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Supplementary Material

Article Title: Comparative Effects of 11 Antipsychotics on Weight Gain and Metabolic Function in Patients With Acute Schizophrenia: A Dose-Response Meta-Analysis

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Disclaimer

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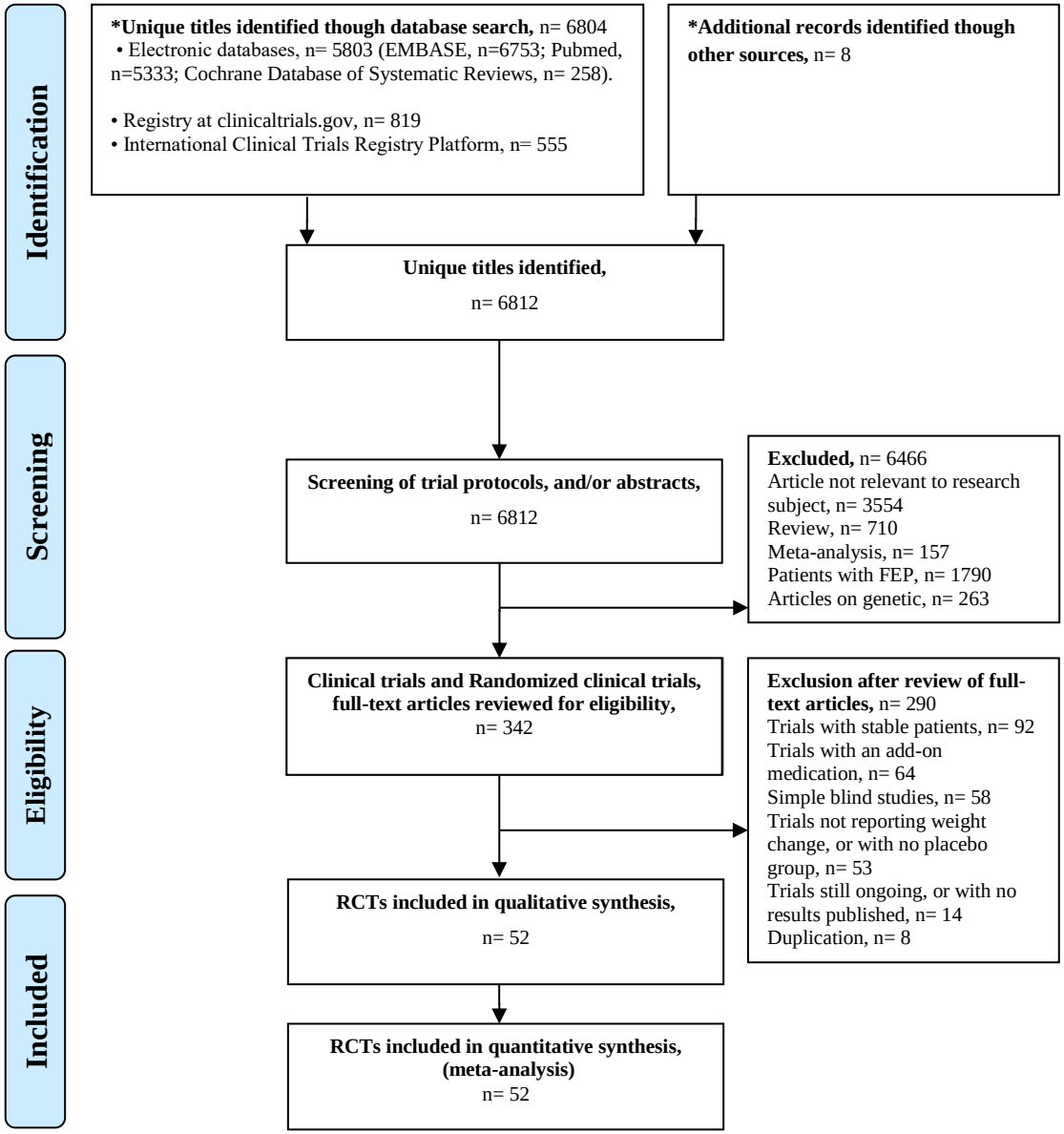
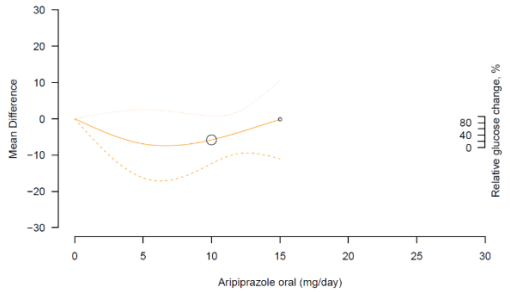
Supplementary Figure 1. Systematic review PRISMA flowchart



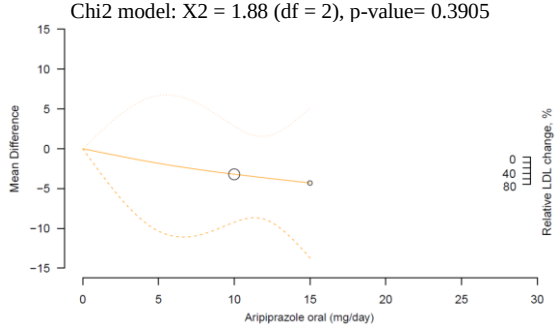
Supplementary Figure 2. Dose-response curves for metabolic disturbance

1. Aripiprazole (oral)

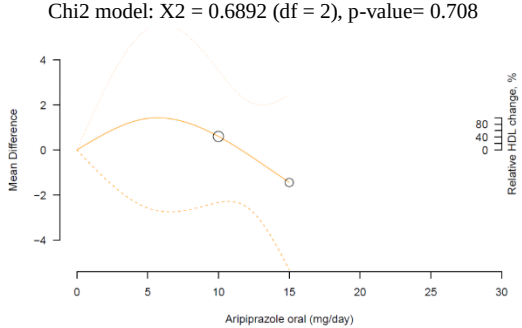
1.a. Glucose concentrations, N= 2, n= 363
Chi2 model: X^2 = 3.1266 (df = 2), p-value= 0.2094



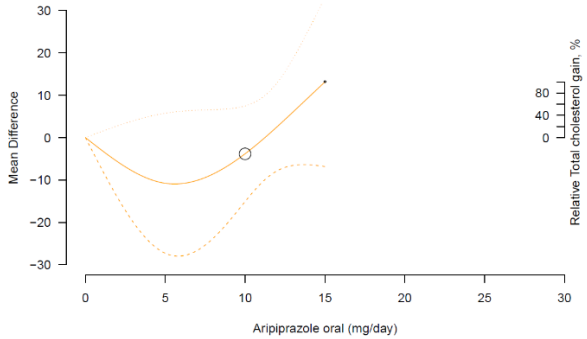
1.b. LDL cholesterol, N= 2, n= 363
Chi2 model: X2 = 1.88 (df = 2), p-value= 0.3905



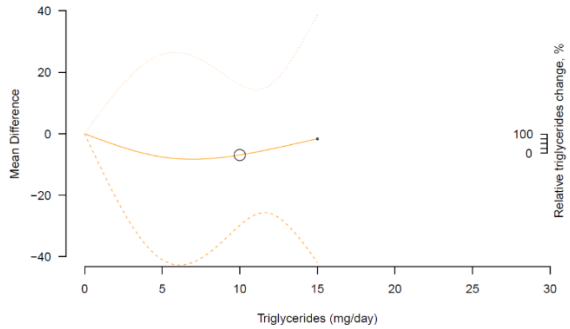
1.c. HDL cholesterol, N= 2, n= 363
Chi2 model: X2 = 0.6892 (df = 2), p-value= 0.708



1.d. Total cholesterol, N= 2, n= 363
Chi2 model: X2 = 2.1001 (df = 2), p-value= 0.3499

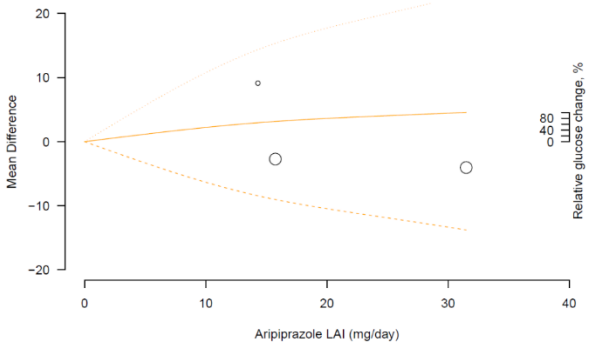


1.e. Triglycerides, N= 2, n= 363
Chi2 model: X2 = 0.3555 (df = 2), p-value= 0.8371

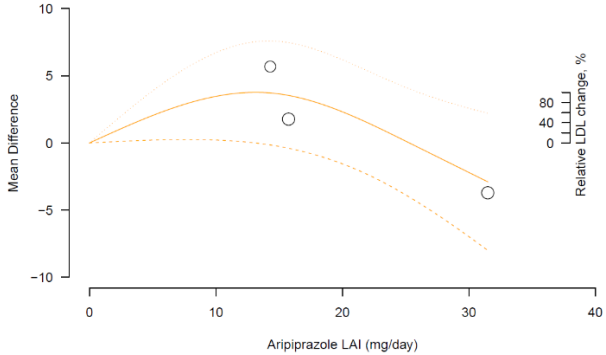


2. Aripiprazole (LAI)

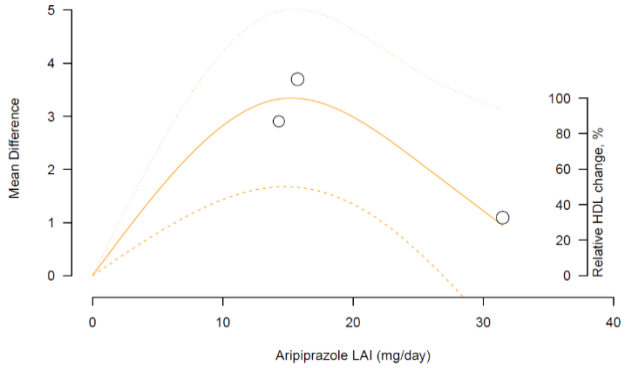
2.a. Glucose concentrations, N= 2, n= 961
Chi2 model: X^2 = 0.2590 (df = 2), p-value= 0.8785



2.b. LDL cholesterol, N= 2, n= 961
Chi2 model: X2 = 7.1761 (df = 2), p-value= 0.0277

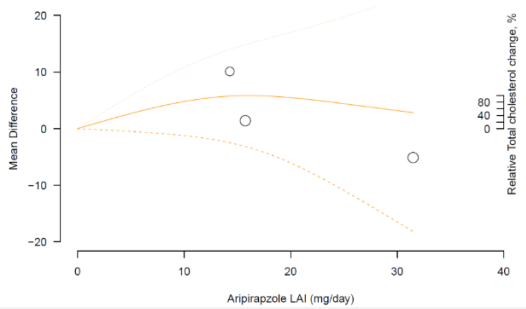


2.c. HDL cholesterol, N= 2, n= 961
Chi2 model: X2 = 15.8 (df = 2), p-value< 0.001



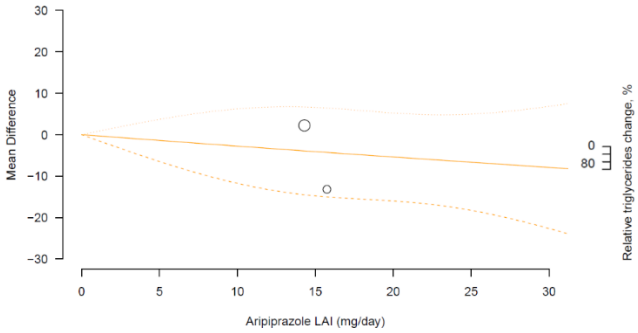
2.d. Total cholesterol, N= 2, n= 961

Chi2 model: X2 = 3.322 (df = 2), p-value= 0.1899



2.e. Triglycerides, N= 2, n= 961

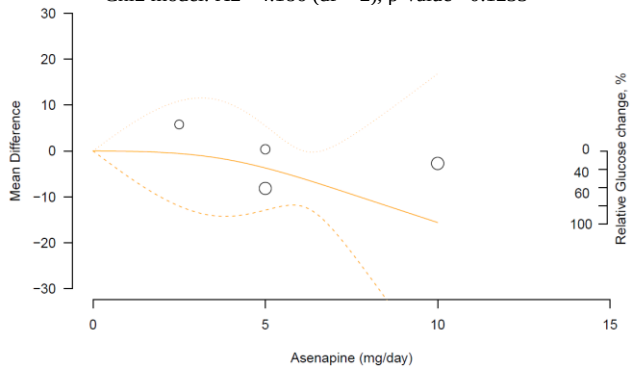
Chi2 model: X2 = 1.2565 (df = 2), p-value= 0.5335



3. Asenapine

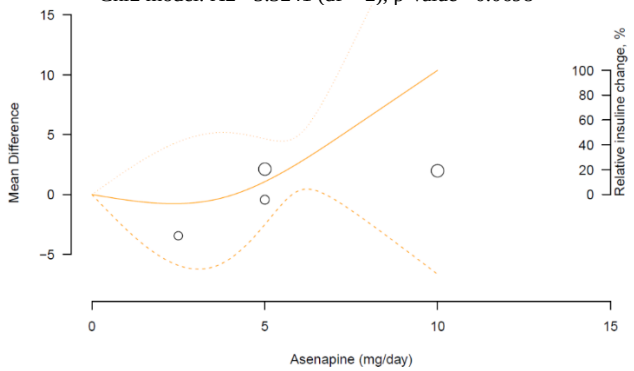
3.a. Glucose, N= 2, n= 819

Chi2 model: X2= 4.186 (df = 2), p-value= 0.1233



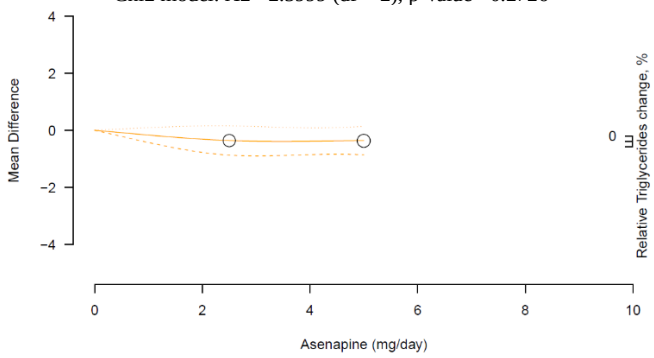
3.b. Insulin, N= 2, n= 819

Chi2 model: X2= 5.3241 (df = 2), p-value= 0.0698



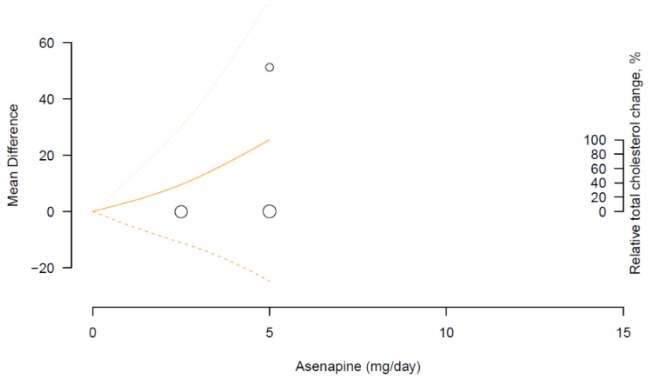
3.c. Triglycerides, N= 1, n= 294

Chi2 model: X2= 2.5999 (df = 2), p-value= 0.2726



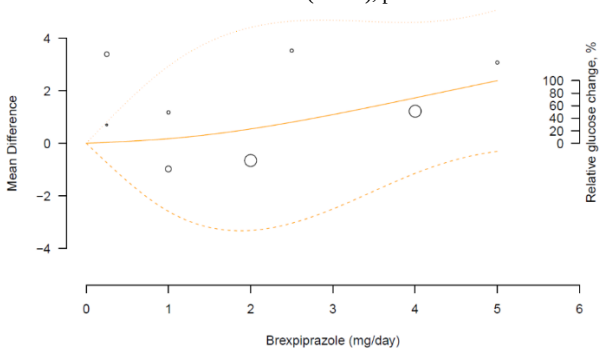
3.d. Total cholesterol, N= 2, n= 415

Chi2 model: X2= 0.9880 (df = 2), p-value= 0.6102

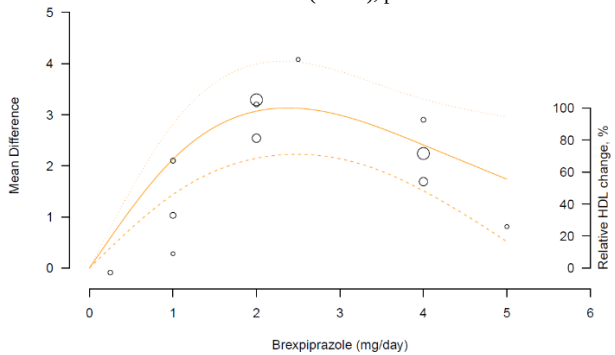


4. Brexpiprazole

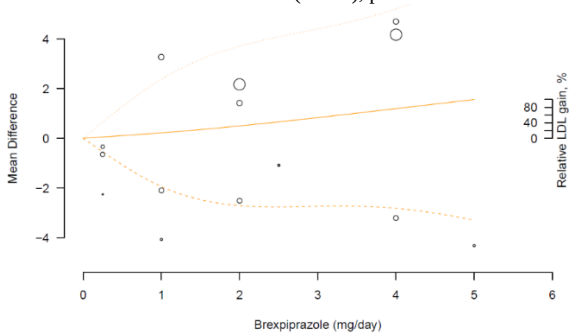
4.a. Glucose, N= 2, n= 1714
Chi2 model: X2= 3.3361 (df = 2), p-value= 0.1886



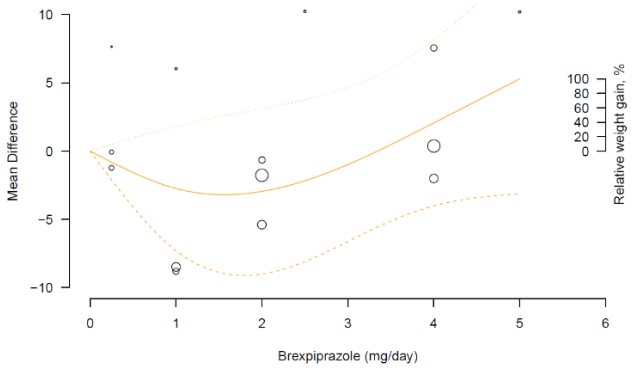
4.b. HDL cholesterol, N= 4, n= 2809
Chi2 model: X2= 47.36 (df = 2), p-value <0.001



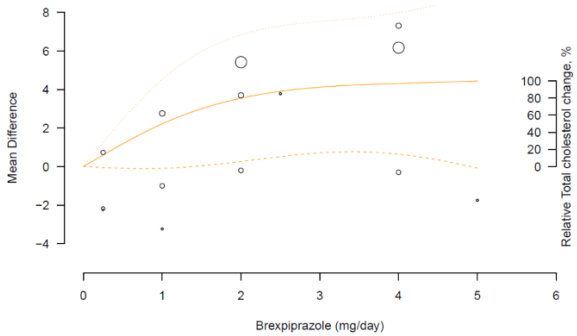
4.c. LDL cholesterol, N= 4, n= 2809
Chi2 model: X2= 0.4016 (df = 2), p-value= 0.8181



4.d. Triglycerides, N= 4, n= 2809
Chi2 model: X2= 2.6216 (df = 2), p-value= 0.2696

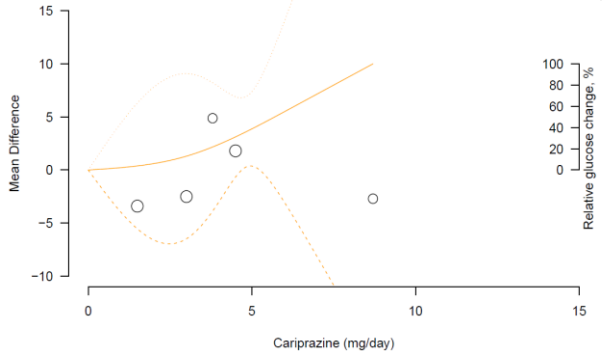


4.e. Total cholesterol, N= 4, n= 2809
Chi2 model: X2= 5.7546 (df = 2), p-value= 0.0563

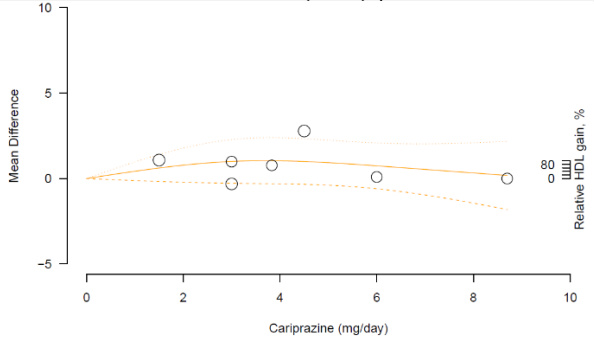


5. Cariprazine

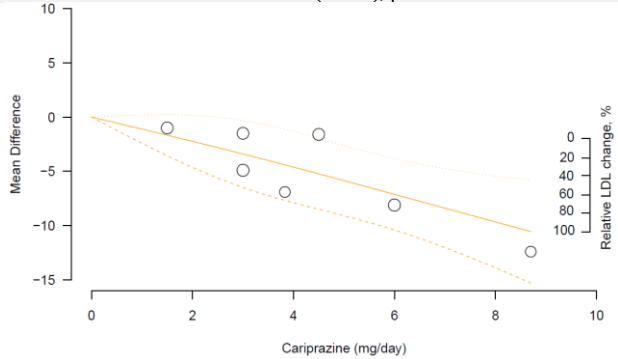
5.a. Glucose, N= 2, n= 1035
Chi2 model: X2= 4.7418(df = 2), p-value= 0.0934



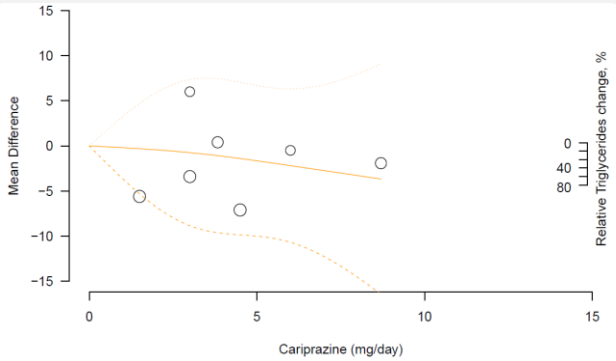
5.b. HDL cholesterol, N= 3, n= 1496
Chi2 model: X2= 2.3538 (df = 2), p-value= 0.308



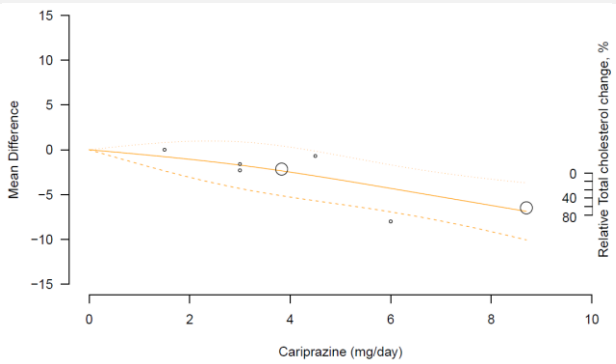
5.c. LDL cholesterol, N= 3, n= 1496
Chi2 model: X2= 20.607 (df = 2), p-value< 0.0001



5.d. Triglycerides, N= 3, n= 1496
Chi2 model: X2= 0.3287 (df = 2), p-value= 0.8485

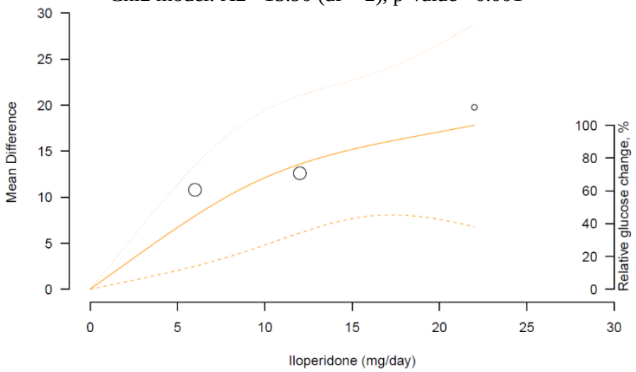


5.e. Total cholesterol, N= 3, n= 1496
Chi2 model: X2= 17.9708 (df = 2), p-value< 0.0001

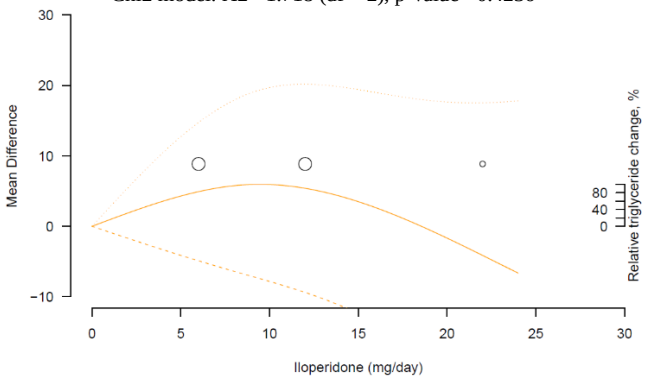


6. Iloperidone

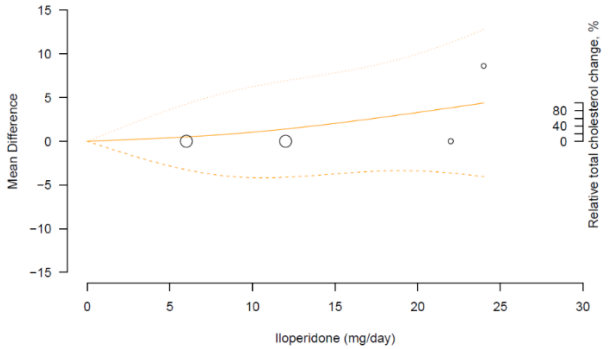
6.a. Glucose, N= 1, n= 1484
Chi2 model: X2= 15.90 (df = 2), p-value< 0.001



6.b. Triglycerides, N= 2, n= 1928
Chi2 model: X2= 1.718 (df = 2), p-value= 0.4236

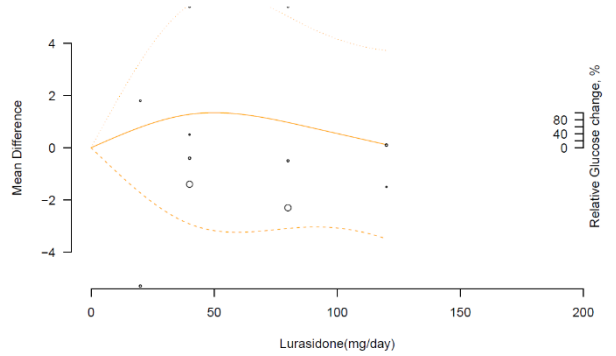


6.c. Total cholesterol, N= 2, n= 1928
Chi2 model: X2= 1.0358 (df = 2), p-value= 0.5958

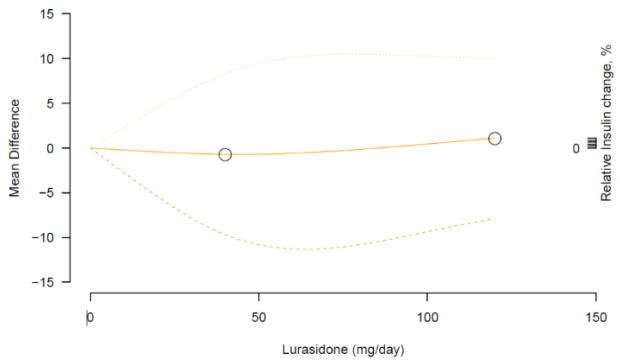


7. Lurasidone

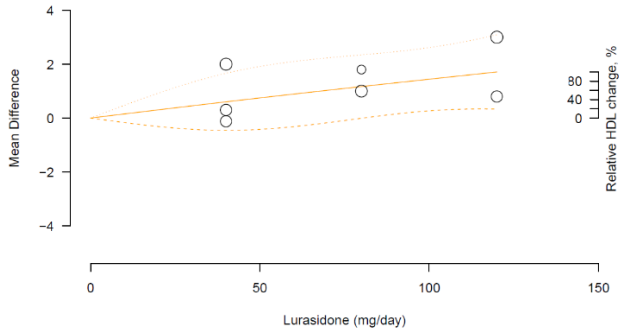
7.a. Glucose, N= 7, n= 2046
Chi2 model: X2= 0.4490 (df = 2), p-value= 0.789



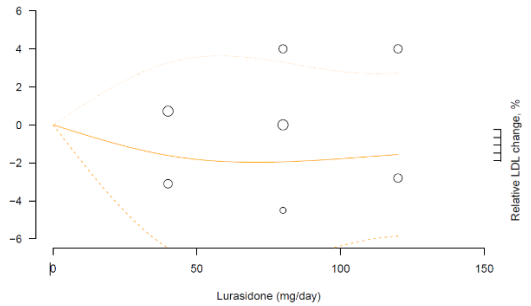
7.b. Insulin, N= 1, n= 353
Chi2 model: X2= 0.6223 (df = 2), p-value= 0.732



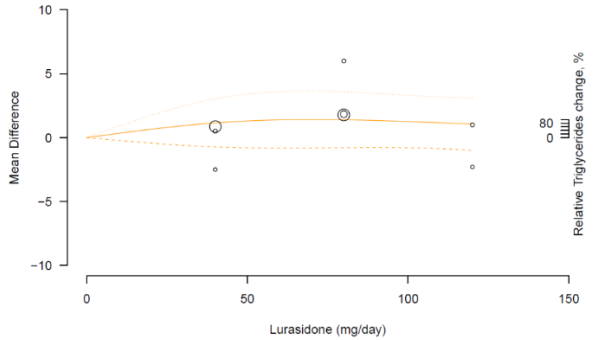
7.c. HDL cholesterol, N= 4, n= 1436
Chi2 model: X2= 6.1364 (df = 2), p-value= 0.045



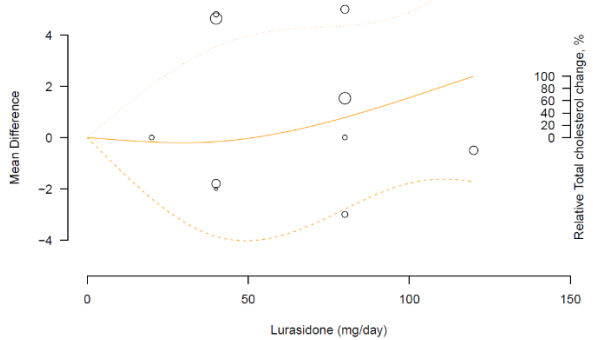
7.d. LDL cholesterol, N= 6, n= 2099
Chi2 model: X2= 0.5792 (df = 2), p-value= 0.7486



7.e. Triglycerides, N= 4, n= 1891
Chi2 model: X2= 2.2544 (df = 2), p-value= 0.3239

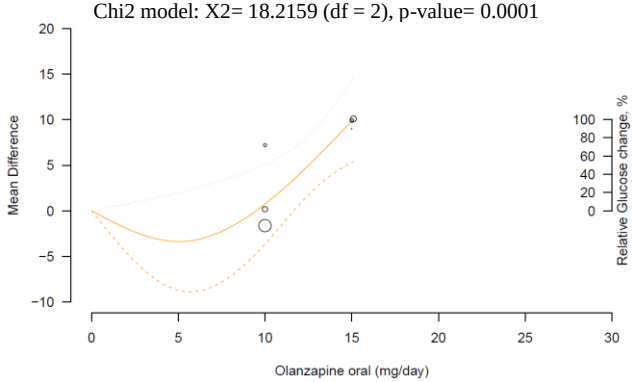


7.f. Total cholesterol, N= 8, n= 2534
Chi2 model: X2= 1.3131 (df = 2), p-value= 0.5186

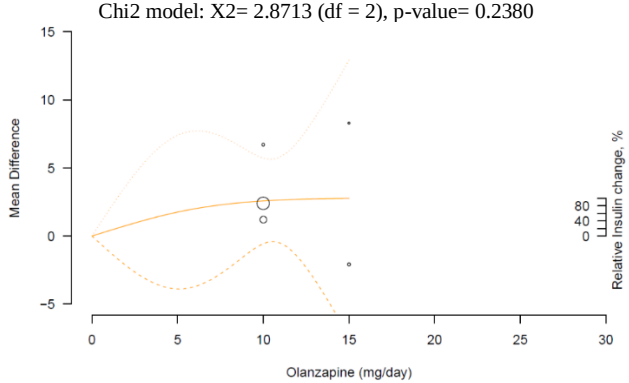


8. Olanzapine oral

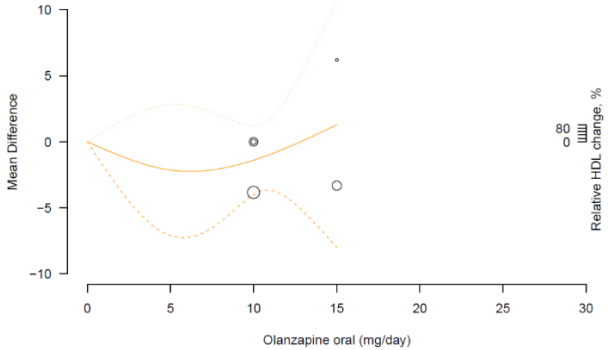
8.a. Glucose, N= 6, n= 1210
Chi2 model: X2= 18.2159 (df = 2), p-value= 0.0001



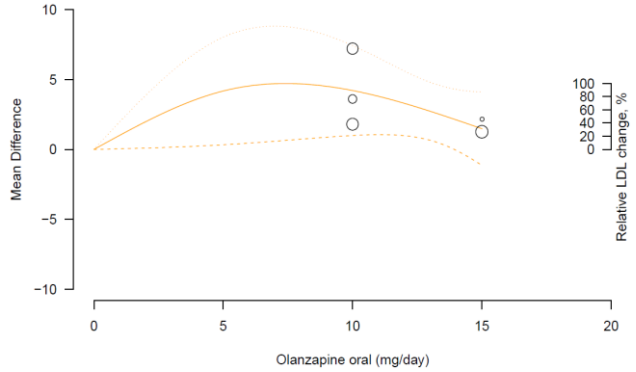
8.b. Insulin, N= 5, n= 1068
Chi2 model: X2= 2.8713 (df = 2), p-value= 0.2380



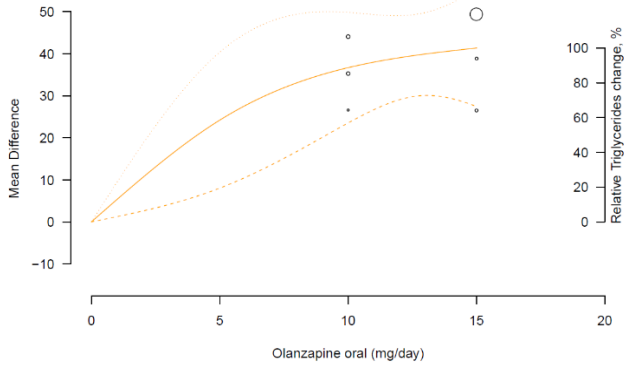
8.c. HDL cholesterol, N= 5, n= 1063
Chi2 model: X2= 1.1768 (df = 2), p-value= 0.5552



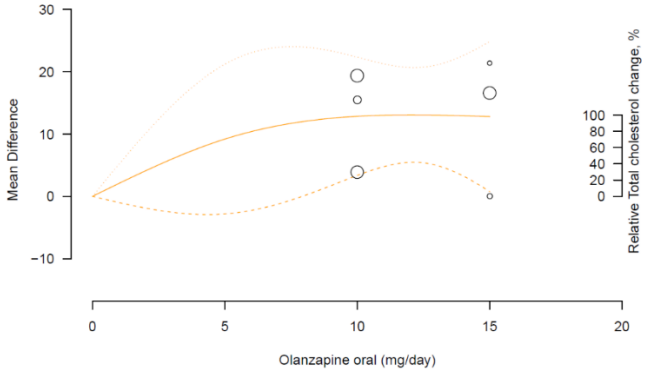
8.d. LDL cholesterol, N= 5, n= 1063
Chi2 model: X2= 7.8019 (df = 2), p-value= 0.02



8.e. Triglycerides, N= 6, n= 1210
Chi2 model: X2= 63.7915 (df = 2), p-value< 0.0001

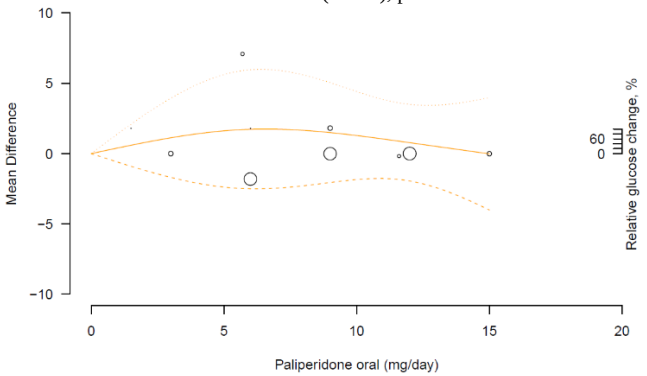


8.f. Total cholesterol, N= 6, n= 1220
Chi2 model: X2= 11.3735 (df = 2), p-value= 0.0034

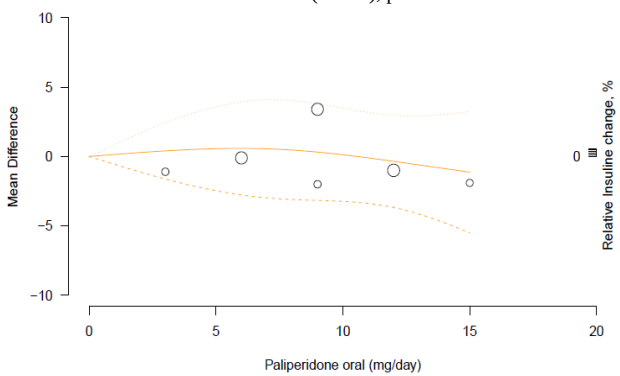


9. Paliperidone (oral)

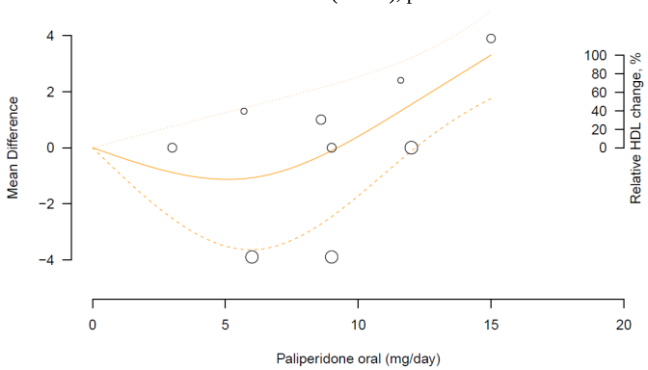
9.a. Glucose, N= 4, n= 1462
Chi2 model: X2= 0.6806 (df = 2), p-value= 0.7116



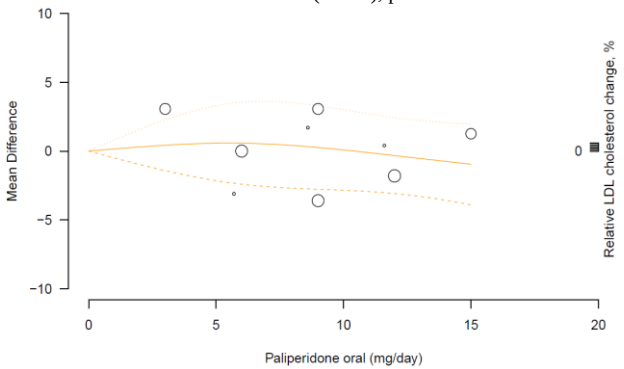
9.b. Insulin, N= 2, n= 979
Chi2 model: X2= 0.4282 (df = 2), p-value= 0.8072



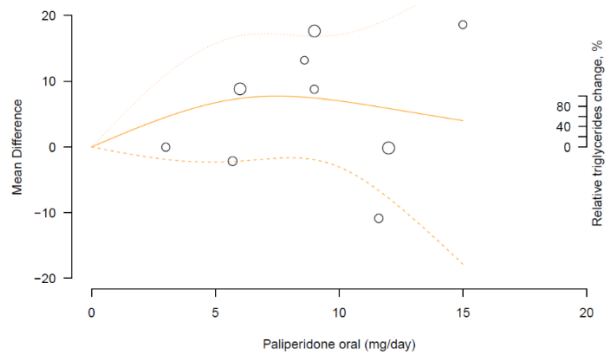
9.c. HDL cholesterol, N= 4, n= 1606
Chi2 model: X2= 20.2450 (df = 2), p-value< 0.0001



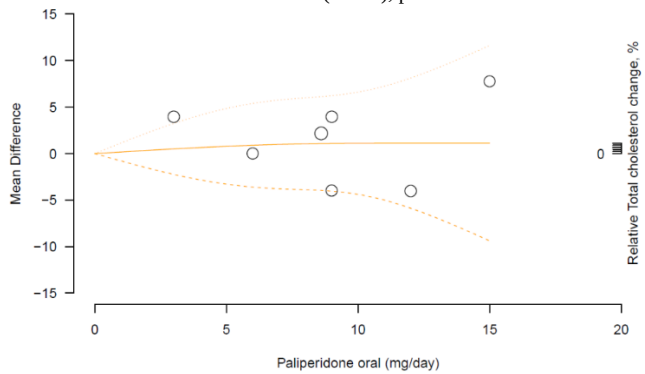
9.d. LDL cholesterol, N= 4, n= 1606
Chi2 model: X2= 1.0383 (df = 2), p-value= 0.5950



9.e. Triglycerides, N= 4, n= 1606
Chi2 model: X2= 2.6013 (df = 2), p-value= 0.2724

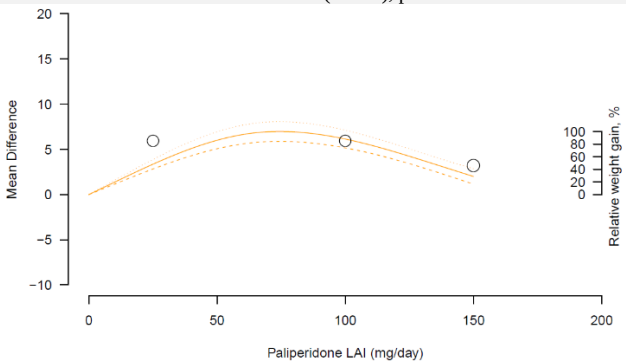


9.f. Total cholesterol, N= 3, n= 1290
Chi2 model: X2= 0.1748(df = 2), p-value= 0.9163



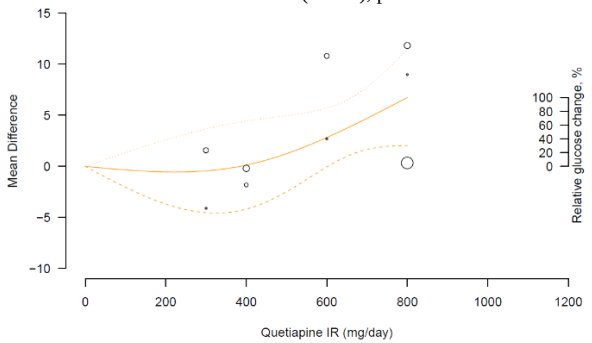
10. Paliperidone LAI

10.a. Glucose, N= 1, n= 312
Chi2 model: X2= 161.7564 (df = 2), p-value< 0.0001

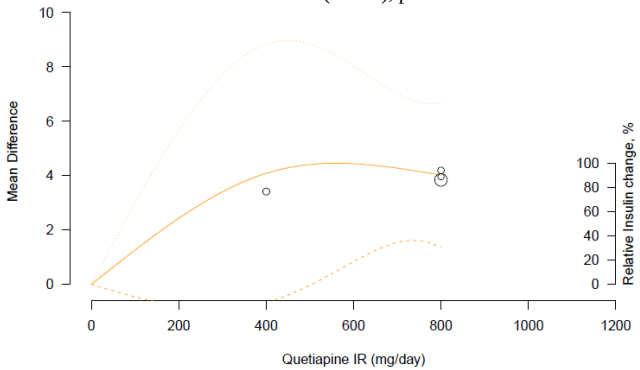


11. Quetiapine IR

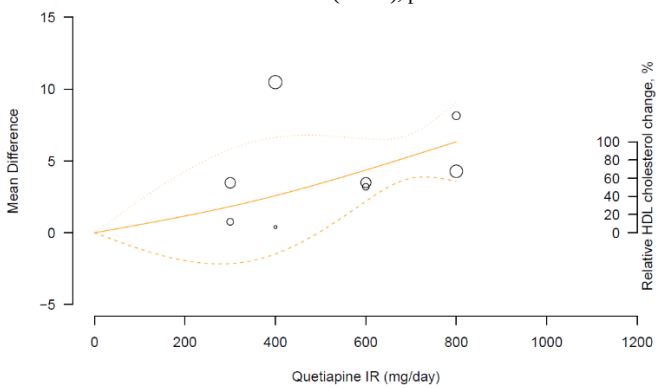
11.a. Glucose, N= 4, n=1680
Chi2 model: X2= 9.2302 (df = 2), p-value= 0.001



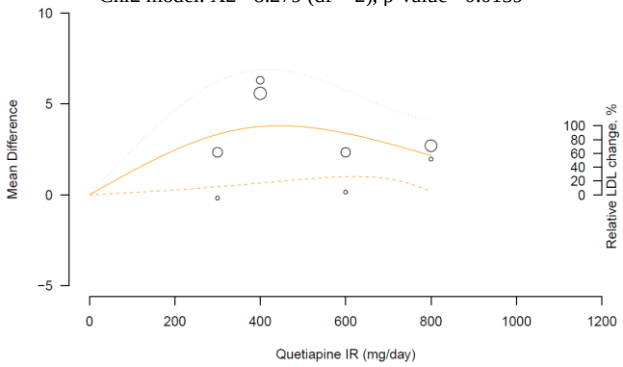
11.b. Insulin, N= 3, n= 1244
Chi2 model: X2= 10.221 (df = 2), p-value= 0.006



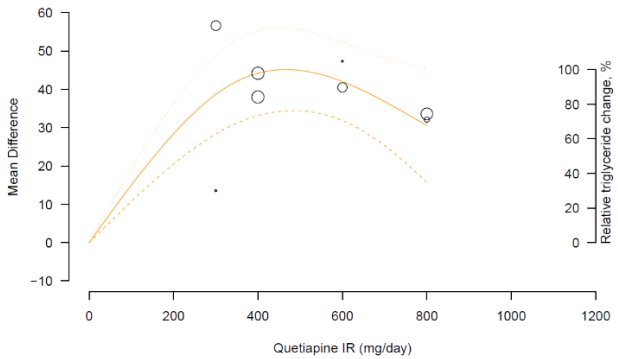
11.c. HDL cholesterol, N= 4, n= 1680
Chi2 model: X2= 6.6920 (df = 2), p-value=0.0352



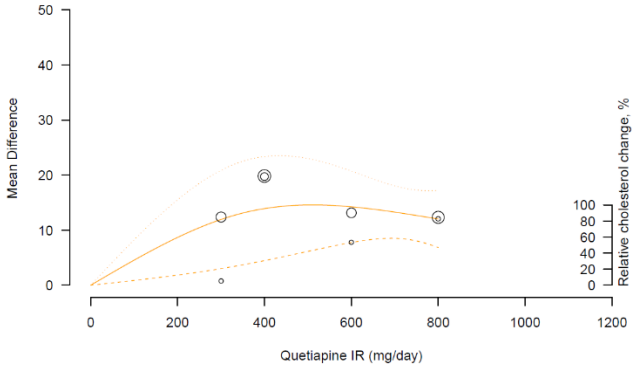
11.d. LDL cholesterol, N= 4, n= 1357
Chi2 model: X2= 8.279 (df = 2), p-value= 0.0159



11.e. Triglycerides, N= 4, n= 1357
Chi2 model: X2 = 70.8 (df = 2), p-value < 0.001

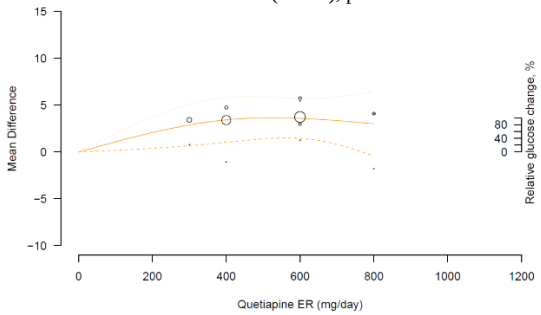


11.f. Total cholesterol, N= 4, n= 1357
Chi2 model: X2 = 30.6207 (df = 2), p-value < 0.0001

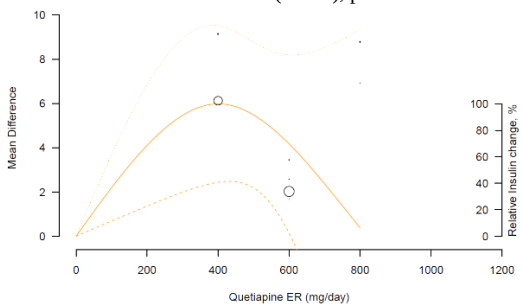


12. Quetiapine ER

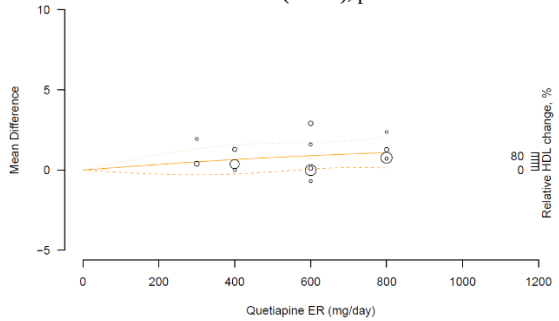
12.a. Glucose, N= 5, n= 2268
Chi2 model: X2= 11.05 (df = 2), p-value= 0.004



12.b. Insulin, N= 4, n= 1821
Chi2 model: X2= 11.4238 (df = 2), p-value= 0.003

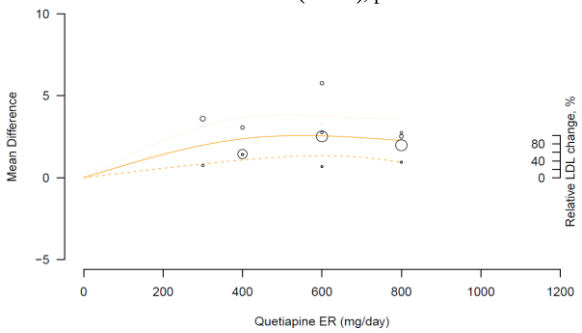


12.c. HDL cholesterol, N= 5, n= 2587
Chi2 model: X2= 5.491 (df = 2), p-value = 0.001



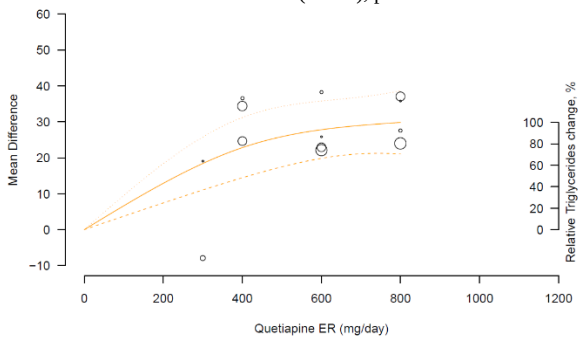
12.d. LDL cholesterol, N= 5, n= 2587

Chi2 model: X2= 17.1911 (df = 2), p-value= 0.0002



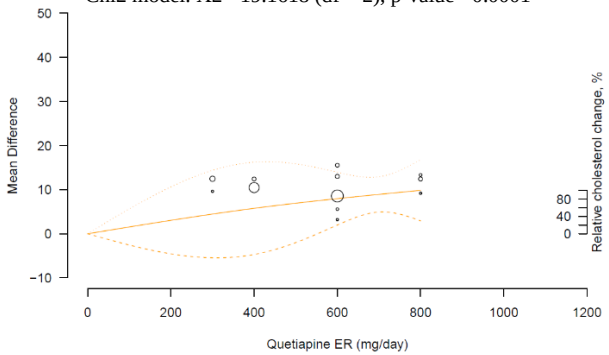
12.e. Triglycerides, N= 4, n= 2351

Chi2 model: X2= 51.798 (df = 2), p-value< 0.001



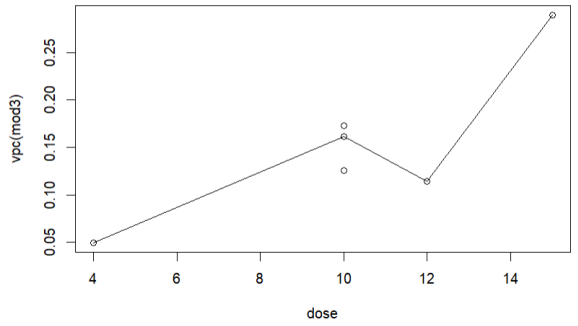
12.f. Total cholesterol, N= 5, n= 2264

Chi2 model: X2= 19.1618 (df = 2), p-value= 0.0001

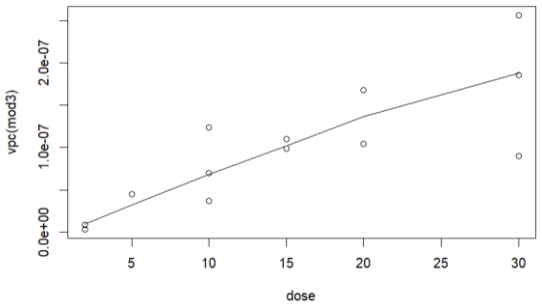


Supplementary Figure 3. Heterogeneity assessments with the variance-partition-coefficient (VPC) for the primary outcome
VPC are expressed as proportion [0-1]. The percentage of heterogeneity can be obtained by multiplying this coefficient by 100.

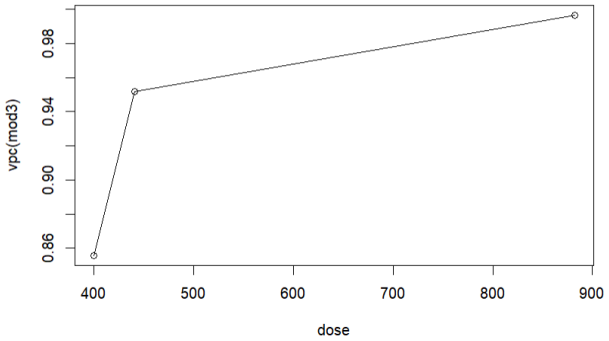
a. Haloperidol, N= 6, n= 1138
VPCs is under 25%, indicating low level of heterogeneity



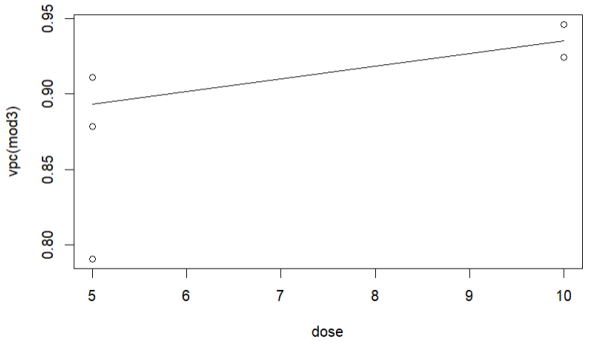
b. Aripiprazole (oral), N= 5, n= 1393
VPCs is 0%, indicating no heterogeneity



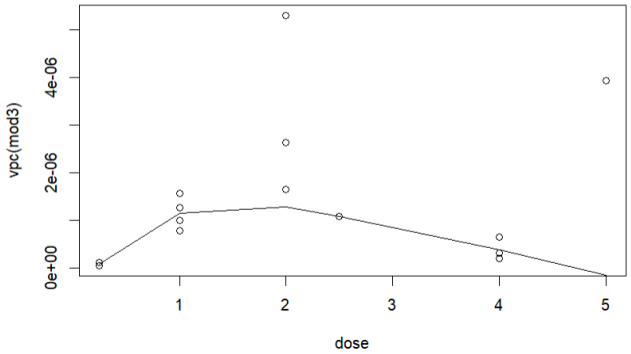
c. Aripiprazole LAI, N= 2, n= 961
There is a considerable level of heterogeneity with VPCs up to 98%



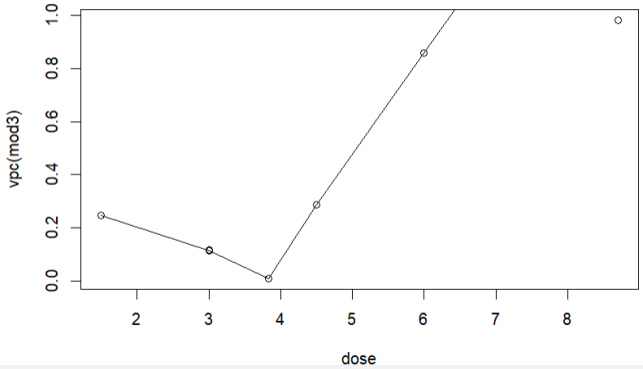
d. Asenapine, N= 3, n= 986
There is a considerable level of heterogeneity with VPCs up to 95%



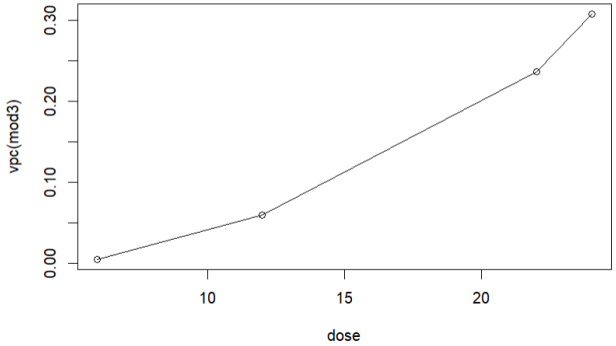
e. Brexpiprazole, N= 4, n= 2847
VPCs is 0%, indicating no heterogeneity



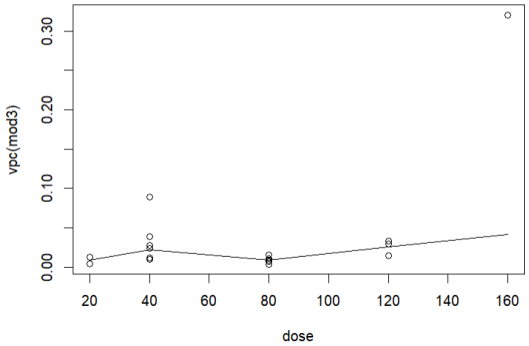
f. Cariprazine, N= 3, n= 1496
There is a considerable level of heterogeneity with VPCs up to 99%



g. Iloperidone, N= 2, n= 1928
VPCs is under 50%, indicating moderate level of heterogeneity

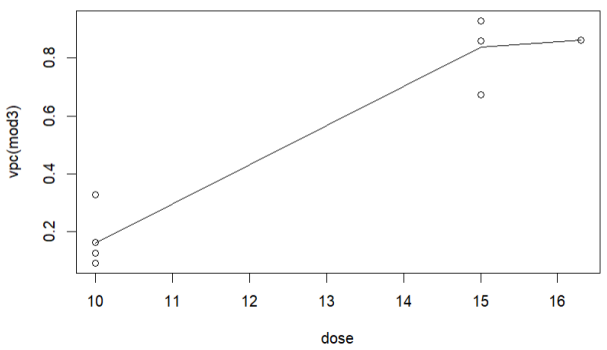


h. Lurasidone, N= 8, n= 2486
VPCs is 0%, indicating no heterogeneity



i. Olanzapine oral, N= 8, n= 1480

There is a considerable level of heterogeneity with VPCs up to 83%

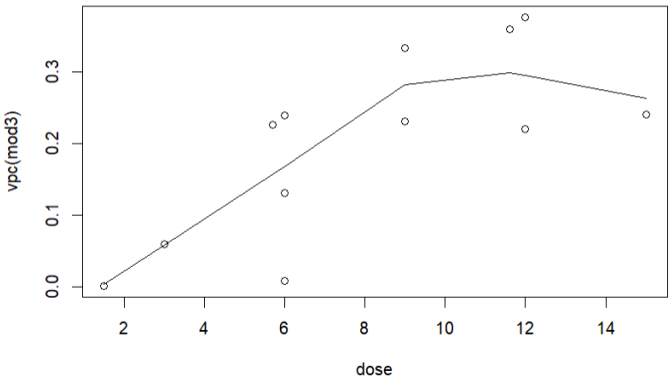


j. Olanzapine LAI[1], N= 1, n= 404

Since only 1 study is available, no heterogeneity was assessed

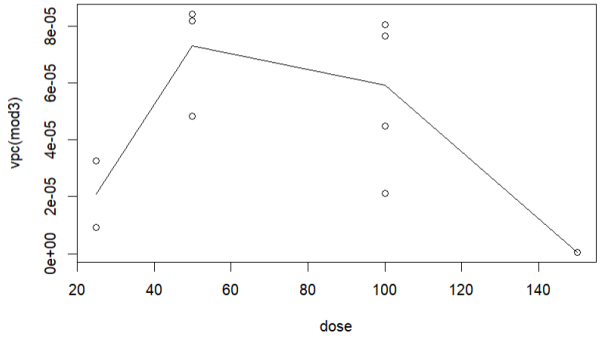
k. Paliperidone (oral), N= 5, n= 1789

VPCs is under 50%, indicating moderate level of heterogeneity



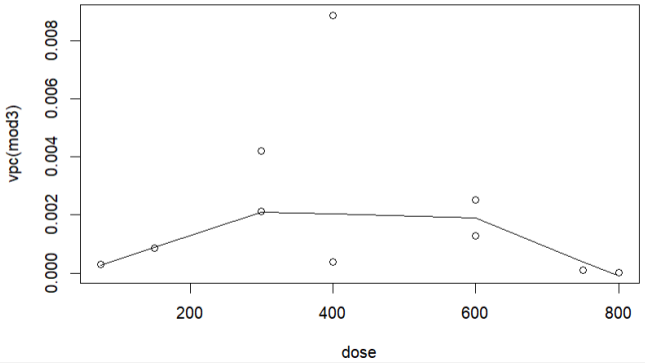
l. Paliperidone LAI, N= 4, n= 1422

VPCs is 0%, indicating no heterogeneity



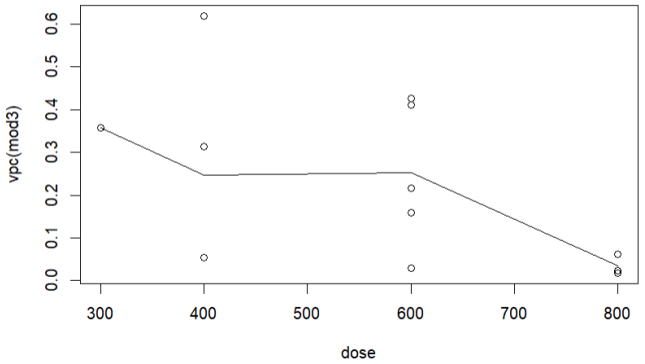
m. Quetiapine IR, N= 5, n= 1494

VPCs is 0%, indicating no heterogeneity



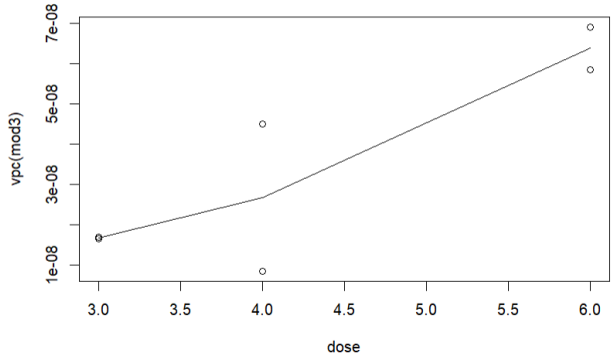
n. Quetiapine ER, N= 5, n= 2163

VPCs is under 50%, indicating moderate level of heterogeneity



o. Risperidone oral, N= 6, n= 1109

VPCs is 0%, indicating no heterogeneity



p. Risperidone LAI, N= 1, n= 400

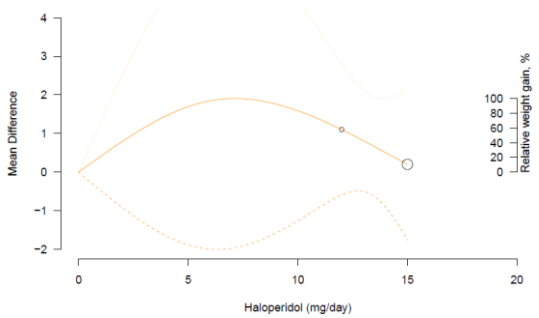
Since only 1 study is available, no heterogeneity was assessed

Supplementary Figure 4. Dose-response curves of antipsychotic-induced weight gain with exclusion of studies presenting a high risk of bias

For haloperidol, 4 studies were excluded (Meltzer et al. 2004; Potkin et al., 2003; Kane et al. 2003; Kane et al., 2010); For aripiprazole 2 studies were excluded (Potkin et al., 2003; Kane et al. 2003). The curve became bell-shaped in presence of a high uncertainty. For asenapine, one study was excluded (Kane et al., 2010). For brexpiprazole, two studies were excluded (Correll et al., 2015; Correll et al., 2016). For Lurasidone, one study was excluded (Ogasa et al., 2013). For risperidone, one study was excluded (Potkin et al., 2003). For these antipsychotics, the shape of the curves did not change; For aripiprazole LAI and Risperdal LAI, the sensitivity analysis could not be conducted, since minimum amount of variable needed for analysis was no more available.

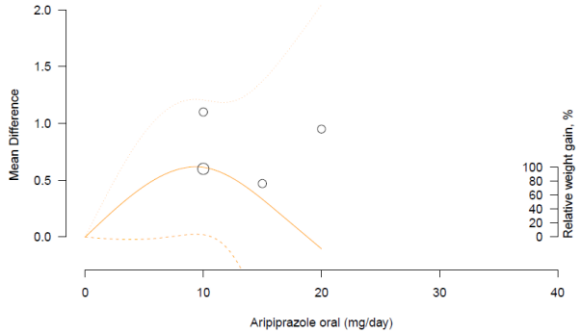
a. Haloperidol, N= 2, n= 354

Chi2 model: X2= 1.663 (df = 2), p-value= 0.4353; ED95= 5.68 mg/day



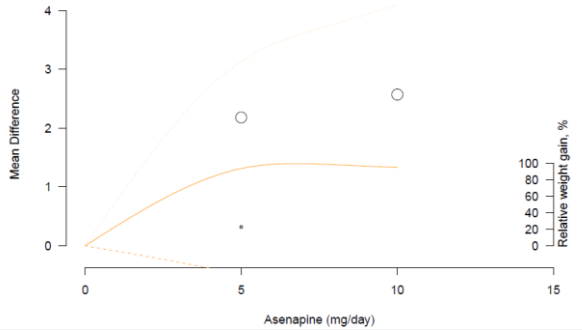
b. Aripiprazole (oral), N= 3, n= 778

Chi2 model: X2= 8.7442 (df = 2), p-value= 0.0126; ED95= 9.5 mg/day



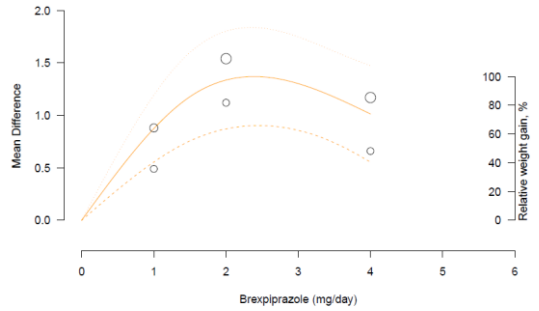
c. Asenapine, N= 2, n= 646

Chi2 model: X2= 3.2804 (df = 2), p-value= 0.1939; ED95= 5.14 mg/day



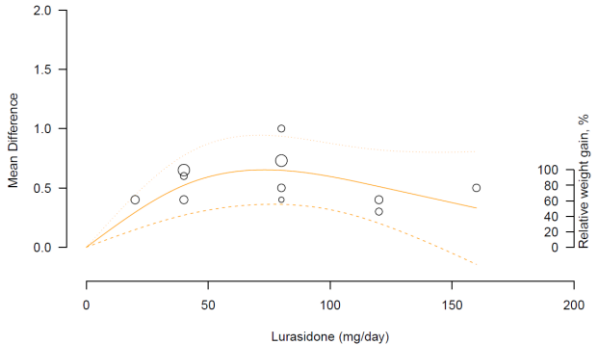
d. Brexpiprazole, N= 2, n= 1133

Chi2 model: X2= 33.4673 (df = 2), p-value< 0.0001; ED95= 1.84 mg/day



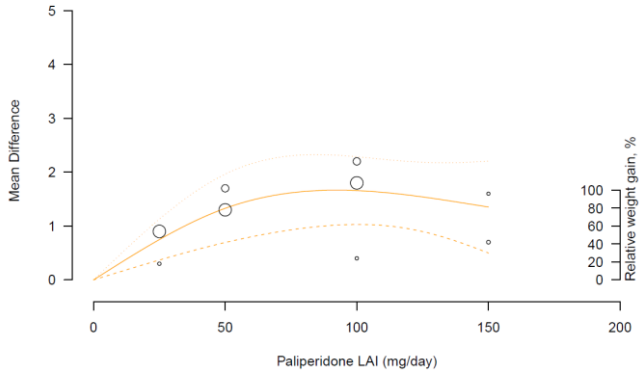
e. Lurasidone, N= 6, n= 2056

Chi2 model: X2= 19.58 (df = 2), p-value< 0.0001; ED95= 55.79 mg/day



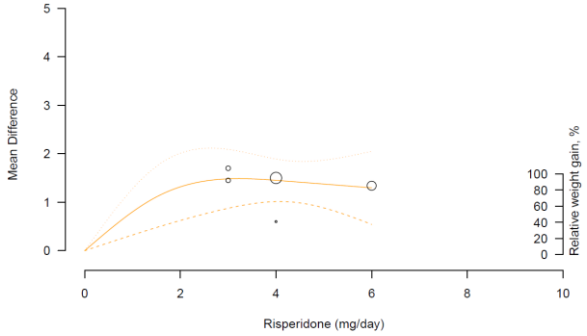
f. Paliperidone LAI, N= 3, n= 1175

Chi2 model: X2= 27.088 (df = 2), p-value< 0.0001; ED95= 70.18 mg/day



g. Risperidone oral, N= 5, n= 907

Chi2 model: X2= 44.06 (df = 2), p-value< 0.0001; ED95= 2.38 mg/day



Supplementary Table 1. Characteristics of included studies

Authors, year	Characteristics of patients (inclusion criteria)	Mean duration of illness in years	Duration of trial	Number of inclusions per group	Fixed doses considered
First generation antipsychotics					
Haloperidol					
Arvanitis et al. 1997 [1]	Included patients presented a diagnosis of acute exacerbation of chronic or subchronic schizophrenia, as defined by the DSM-III-R. Patients were required to have a minimum total score of 27 on the 18-item BPRS (0-6 scoring), a score of 3 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the clinical global impression Severity (CGI-S) of illness item. Inpatients were included (18 to 65-year-old).	n.a.	6 weeks	n= 52 n= 53; 48; 52; 51; 54; 52 n= 51	Haloperidol 12 mg/day Quetiapine 75, 150, 300, 600, 750 mg/day Placebo 0 mg/day
Kane et al. 2002 [2]	Patients had a primary diagnosis of schizophrenia or schizoaffective disorder (DSM-IV criteria). Included patients were hospitalized for an acute relapse (DSM-IV). In addition, patients were to have a PANSS total score of at least 60 and scores of at least 4 (moderate) or any 2 of the items on the psychotic item's subscale (hallucination, delusions, conceptual disorganization, and suspiciousness). Inpatients were included (18 to 65-year-old).	16.3	4 weeks	n= 104 n= 102; 102 n= 106	Haloperidol 10 mg/day Aripiprazole 15, 30 mg/day Placebo 0 mg/day
Meltzer et al. 2004 [3]	Included patients had schizophrenia or schizoaffective disorder diagnosed according to DSM-IV criteria. Patients were required to be hospitalized at baseline through day 15 after random assignment to treatment. Included patients were also required to have a total score on the PANSS greater than 65 at screening and baseline, including a minimum score of 4 (moderate) on at least two of four PANSS positive symptom items (delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution). A minimum severity of illness scores of 4 (moderately ill) on the CGI at screening and baseline was also required. Inpatients were included (18 to 64-year-old).	n.a.	6 weeks	n= 98 n= 98	Haloperidol 10 mg/day Placebo 0 mg/day
Kane et al. 2010 [4]	All patients had a diagnosis of schizophrenia with an acute exacerbation of psychotic symptoms at study enrollment according to the DSM-IV criteria. Other principal inclusion criteria were a PANSS total score of 60 or higher, with scores of 4 or higher on at least 2 of 5 predefined PANSS positive subscale items at the initial screening assessment and at baseline for enrolled patients, and a CGI-S of illness score of min 4 at baseline. Inpatients were included (>18-year-old).	12.5[a]	6 weeks	n= 112 n= 109; 105 n= 122	Haloperidol 4 mg/day Asenapine, 5, 10 mg/day Placebo 0 mg/day
Potkin et al. 2008 [5]	Included patients had a DSM-IV diagnosis of schizophrenia of schizoaffective disorder with acute or subacute exacerbation of schizophrenia and Positive and Negative Syndrome Scale (PANSS) total score of at least 60 at screening and at baseline. Inpatients were included (18 to 65-year-old).	n.a.	6 weeks	n= 124 n= 121; 125; 124 n= 127	Haloperidol 15 mg/day Iloperidone 4, 8, 12 mg/day Placebo 0 mg/day
Potkin et al. 2015 [6]	All patients had a primary diagnosis of DSM-IV schizophrenia of at least one-year duration. Patients were required to have a baseline BPRS total score of 42 or higher with a score of 4 or more on at least two items of the positive symptom subscale and a clinical CGI-S score of moderate or worse (4 or higher). Patients who demonstrated an improvement min 20% in their BPRS score between screening and baseline were excluded. Inpatients were included (18 to 65-year-old).	16.2[a]	8 weeks	n= 72 n= 71; 65; 70 n= 73	Haloperidol 4, 8, 16 mg/day Lurasidone 20, 40 80 mg/day Placebo 0 mg/day
Second generation antipsychotics					
Aripiprazole					
Kane et al. 2002 [2]	Described in the haloperidol section.	16.3	4 weeks	n= 104 n= 102; 102 n= 106	Haloperidol 10 mg/day Aripriprazole 15, 30 mg/day Placebo 0 mg/day
Potkin et al. 2003 [7]	Patients had a primary diagnosis of schizophrenia or schizoaffective disorders (DSM-IV), hospitalized for acute relapse. Patients had to present a PANSS total score of at least 60, and a min score of 4 on at least 2 items of the psychotic item subscale. Inpatients were included (18 to 65-year-old).	n.a.	4 weeks	n= 101; 101; 103 n= 99 n= 103	Aripiprazole 20, 30 mg/day Risperidone 6 mg/day Placebo 0 mg/day
McEnvoy et al. 2007 [8]	Patients had a diagnosis of schizophrenia DSM-IV and were experiencing an acute exacerbation of symptoms that required inpatient hospitalization. In addition, patients were required to have PANSS Total score of 60 or more (1–7 scale) and a score of at least 4 on two or more of the following PANSS items at the baseline assessment: delusions, hallucinatory behavior, conceptual disorganization or suspiciousness/persecution. Inpatients were included (≥18-year-old).	16.4[a]	6 weeks	n= 106; 106; 100 n= 108	Aripiprazole 10, 15, 20 mg/day Placebo 0 mg/day

Cantillon et al. 2017 [9]	Included patients had a diagnosis of acute exacerbation of schizophrenia or schizoaffective disorder according to DSM-IV criteria and by MINI 6.0 for Schizophrenia and Psychotic Disorders Studies. Subjects had been initially diagnosed with schizophrenia or schizoaffective disorder at least 1 year prior to screening and the current exacerbating episode had been no longer than 4 weeks at Screening. Subjects met the following criteria on the BPRS: score N36 and BPRS psychosis cluster ≥4 on at least half of the following items: suspiciousness, conceptual disorganization, hallucinatory behavior, and/or unusual thought content. Inpatients were included (18 to 65-year-old).	8.6	4 weeks	n= 20 n= 58; 59; 58 n= 38	Aripiprazole 15 mg/day RPF063, 15, 30, 50 mg/day Placebo 0 mg/day
Durgam et al. 2015 [10]	Included patients had a DSM-IV-TR criteria for schizophrenia, present for more than one year and with at least one psychotic episode that required hospitalization or change of antipsychotic medication during the past year. To ensure that participants' current psychotic episode was acute, duration of the current episode must be inferior to two weeks. A CGI-S score ≥4, PANSS total score ≥80 and ≤120, and ≥4 on at least 2 of the PANSS positive symptoms of delusions, hallucinatory behavior, conceptual disorganization or suspiciousness/persecution was required. Inpatients were included (18 to 60-year-old).	12.25	6 weeks	n= 152 n= 155; 157 n= 153	Aripiprazole 10 mg/day Cariprazine 3, 6 mg/day Placebo 0 mg/day
Aripiprazole (LAI)					
Kane et al. 2014 [11]	Included patient presented a diagnosis of schizophrenia as defined by the DSM-IV-TR and confirmed by the mini-International Neuropsychiatric interview (MINI) for schizophrenia and psychotic disorders studies. All included patients experienced an acute psychotic episode at screening and baseline, defined as acute exacerbation of psychotic symptoms accompanied by significant deterioration in clinical and/or functional status from their baseline clinical presentation with a PANSS-P total score ≥80 and specific psychotic symptoms on the PANSS with a score>4 on each of 4 specific items (conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, unusual thought content; possible scores ranged from 1 to 7 for each item). Inpatients were included (18 to 65-year-old).	18.2[a]	12 weeks	n= 168 n= 172	Aripiprazole LAI 400mg/4 weeks Placebo 0 mg/day
Nasrallah et al. 2016 [12]	Included patients presented an acute exacerbation or relapse of schizophrenia with an onset Y 2 months prior to screening and ≥2 years had elapsed since the initial onset of symptoms. Patients also were requited to have clinically significant beneficial response to treatment with an antipsychotic medication other than clozapine and to have been an outpatient for > 3months during the past year. At screening and baseline, a PANSS total score of 70 to 120, a score of ≥4 for ≥2 of the PANSS-P items, and a CGI-S score of ≥4 were required. Inpatients were included. These patients could continue the study as outpatients after at least 2 weeks of hospitalization (18 to 70-year-old).	n.a.	12 weeks	n= 207; 208 n= 207	Aripiprazole LAI 441, 882 mg/4weeks Placebo 0 mg/day
Asenapine					
Potkin et al. 2007 [13]	Included patients presented a DSM-IV diagnosis of schizophrenia with symptoms of disorganized, paranoid, catatonic, or undifferentiated subtypes. Acute exacerbation was defined by a baseline CGI-S score of ≥4, and a PANSS total score of ≥ 60. In addition, baseline scores ≥ 4 were required on ≥2 items of the PANSS positive subscale, and the baseline PANSS total score had to be ≥80% of that at prior visits. Inpatients were included (≥18-year-old).	n.a.	6 weeks	n= 59 n= 59 n= 62	Asenapine 5 mg/day Risperidone 3 mg/day Placebo 0 mg/day
Kane et al. 2010 [4]	Described in the haloperidol section.	12.5[a]	6 weeks	n= 109; 105 n= 112 n= 122	Asenapine 5, 10 mg/day Haloperidol 4 mg/day Placebo 0 mg/day
Kinoshita et al. 2016 [14]	Patients had a DSM-IV-TR diagnosis of schizophrenia with an acute exacerbation of psychotic symptoms at study enrollment. The current acute exacerbation of schizophrenia had to be of ≤2 months duration. Other key inclusion criteria were a PANSS total score ≥60, with scores of ≥4 in two or more of five items on the PANSS positive subscale (delusions, conceptual disorganization, hallucinatory behavior, grandiosity, suspiciousness/persecution) at the initial screening assessment and at baseline, and a score of ≥4 on the CGI-S scale at baseline. Inpatients were included (20 to 64-year-old).	n.a.	6 weeks	n= 175; 181 n= 174	Asenapine 5, 10 mg/day Placebo 0 mg/day
Brexpiprazole					
Correll et al. 2016 (NCT00905307) [15]	This paper summarizes three studies. The phase 2 studies do not enter our inclusion criteria since flexible dose of treatment are used. The phase 3 studies have been published as the Correll et al. (2015); Kane et al. (2015) studies with fixed dose of treatment. We extracted the results for the Kane et al. 2015 study. These studies recruited patients according to the DSM-IV-TR criteria for diagnosis of schizophrenia who would benefit from hospitalization or continued hospitalization for treatment of an acute exacerbation. Exacerbation in the Phase 2 study was confirmed at screening and baseline by a PANSS total score ≥ 80 together with a CGI-S score ≥ 4. Patients in the Phase 3 studies had to have a total BPRS ≥ 40 and a score of ≥ 4 on 2 or more of the following BPRS items: hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness, as well as a CGI-S score ≥ 4 (at screening and baseline). Inpatients were included. These patients could continue the study as outpatients (18-65-year-old).	13[a]	6 weeks	n= 87; 117; 359; 359 n= 358	Brexipiprazole 0.25, 1, 2, or 4 mg/day Placebo 0 mg/day
Correll et al. 2015[16]	Described in the brexpiprazole section (Correll et al. 2016 study).	12.8[a]	6 weeks	n= 87; 180; 182 n= 184	Brexipiprazole 0.25, 2, or 4 mg/day Placebo 0 mg/day
Ishigooka et al. 2018 [17]	Patients were diagnosed with DSM-IV-TR for schizophrenia and confirmed by the Mini International Neuropsychiatric Interview assessment for experiencing acute exacerbation of psychotic symptoms, psychotic disorders, and marked deterioration of normal function by meeting the following criteria at screening and baseline: CGI-S score of ≥4, BPRS score of ≥40, and	16.4[a]	6 weeks	n= 115; 115; 113 n= 116	Brexipiprazole 1, 2, 4 mg/day Placebo 0 mg/day

	score of ≥4 for two or more of the BPRS items (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content). Inpatients were included at inclusion, and could continue the study after at least 3 weeks at hospital as outpatients (18 to 65-year-old).				
Kane et al. 2015 [18]	Described in the brexpiprazole section (Correll et al. 2016 study).	12.8[a]	6 weeks	n= 120; 186; 184 n= 184	Brexipiprazole 1, 2, 4 mg/day Placebo 0 mg/day
Cariprazine					
Durgam et al. 2014 [19]	Included patients met the DSM-IV-TR criteria for schizophrenia. Patients had the diagnosis for at least one year, a current exacerbation less than 2 weeks' duration, and at least one psychotic episode requiring hospitalization/antipsychotic medication change/intervention during the preceding year. PANSS total score between 80 and 120, a score≥4 (moderate) on at least 2 of 4 PANSS positive symptoms, and CGI-S rating ≥4 were required. Body mass index between 18 and 35 was also required. Inpatients were included (18 to 60-year-old).	11.3	6 weeks	n= 145; 146; 147 n= 140 n= 151	Cariprazine 1.5, 3, 4.5 mg/day Risperidone 4 mg/day Placebo 0 mg/day
Durgam et al. 2015 [10]	Included patients had a DSM-IV-TR criteria for schizophrenia, present for more than one year and with at least one psychotic episode that required hospitalization or change of antipsychotic medication during the past year. To ensure that participants' current psychotic episode was acute, duration of the current episode must be inferior to two weeks. A CGI-S score ≥4, a PANSS total score ≥80 and ≤120, and a score ≥4 on at least 2 of the PANSS positive symptoms was also required. Inpatients were included. These patients could continue the study as outpatients (18 to 60-year-old).	12.2	6 weeks	n= 155; 157 n= 153	Cariprazine 3, 6 mg/day Placebo 0 mg/day
Durgam et al. 2016 [20]	Include patients had a schizophrenia diagnosis for 1 year or longer based on the DSM-IV-TR, with a current psychotic episode less than 4 weeks in duration and at least one other psychotic episode in the past year that required hospitalization or change in antipsychotic medication. At both screening and randomization, all patients had a PANSS total score of 80–120 (inclusive), a score of 4 or higher on either the PANSS delusions item or the hallucinatory behavior item, a score of 4 or higher on either the PANSS conceptual disorganization item or the suspiciousness/persecution item, and a CGI-S score of 4 or higher. Please note that this study is originally a flexible-dose study, however, since other reported the average dose for each group, we included the study. Inpatients were included. These patients could continue the study as outpatients (18 to 65-year-old).	17.6	6 weeks	n= 128; 134 n= 130	Cariprazine 1.5-4.5, 6-12 mg/day Placebo 0 mg/day
Iloperidone					
Cutler et al. 2008 [21]	Eligible patients had diagnoses of schizophrenia according to DSM-IV criteria, CGI-S 3 scores of 4 or greater at baseline, overall PANSS total scores of 70 or greater at screening and baseline, and a rating of 4 (moderate) or greater on at least 2 of the following PANSS-P symptoms: delusions, conceptual disorganization, hallucinations, and suspiciousness/persecution at screening and baseline. Inpatients were included (18 to 65-year-old).	n.a.	4 weeks	n= 295 n= 149 n= 149	Iloperidone 24 mg/day Ziprasidone 160 mg/day Placebo 0 mg/day
Potkin et al. 2008 [5]	Described in the haloperidol section.	n.a.	6 weeks	n= 121; 125; 124 n= 124 n= 127	Iloperidone 4, 8, 12 mg/day Haloperidol 15 mg/day Placebo 0 mg/day
Lurasidone					
Higuchi et al. 2019 [22]	Included patients presented DSM-IV-TR criteria for schizophrenia with disorganized, paranoid, or undifferentiated subtypes were enrolled in the study. Patients were required to have an exacerbation of psychotic symptoms within 60 days before screening, with a PANSS total score of ≥80, including a score of ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, and unusual thought content at screening and baseline visits. Inpatients were included. These patients could continue the study as outpatients (18 to 74-year-old).	15	6 weeks	n= 150; 154 n= 151	Lurasidone 40, 80 mg/day Placebo 0 mg/day
Iyo et al. 2021 [53]	Included patients were diagnosed with schizophrenia according to a clinical interview using the MINI and the DSM-IV-TR criteria. To be included in the study, patients also had to meet the following key criteria: a PANSS13 total score ≥80; a PANSS item score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, suspiciousness, or unusual thought content at both screening and baseline; a score of 4 (moderately ill) or higher on the CGI-S. Inpatients were included. These patients could continue the study as outpatients (18 to 74-year-old).	10.5	6 weeks	n= 245 n= 233	Lurasidone 40 mg/day Placebo 0 mg/day
Loebel et al. 2013 [23]	Included patients had a DSM-IV-TR criteria for a primary diagnosis of schizophrenia as determined by clinical interview using the Mini International Neuropsychiatric Interview. Subjects were also required to have an illness duration greater than 1 year with the current acute exacerbation of psychotic symptoms no longer than 2 months and, at the Screening and Baseline visits, to have a CGI-S score ≥4 (moderate or greater) and a PANSS total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	11.4	6 weeks	n= 125; 121 n= 119 n= 121	Lurasidone 80, 160 mg/day Quetiapine XR 600 mg/day Placebo 0 mg/day
Loebel et al. 2016a [24]	Included patients presented a diagnosis of schizophrenia for at least 6 months, according to the DSM-IV-TR criteria and experiencing an acute exacerbation (<2months in duration), as indicated by a PANSS total score ≥80; a PANSS items score ≥4 (moderate) on ≥2 of the following items: delusions, conceptual disorganization, hallucinations and unusual thought content; and a CGI-S score ≥4 (moderately ill). Inpatients were included. These patients could continue the study as outpatients (18 to 75-year-old). *Noteworthy, this study included early non-responding patients, therefor we have only included the placebo group and the group receiving 20 mg of lurasidone.	14.2[a]	6 weeks	n= 101 n= 121	Lurasidone 20 mg/day Placebo 0 mg/day

Meltzer et al. 2011 [25]	Enrolled patients met DSM-IV criteria for a primary diagnosis of schizophrenia as determined by the Mini International Neuropsychiatric Interview. Patients were also required to have an illness duration of at least 1 year and to have been hospitalized for ≤2 weeks for an acute exacerbation of psychotic symptoms and, at the screening and baseline visits, to have a CGI-S score ≥4 (moderate or greater) and a PANSS total score ≥80, including a score ≥4 (moderate) on two or more of the following PANSS items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	13.5	6 weeks	n= 118; 118 n= 121 n= 112	Lurasidone 40, 120 mg/day Olanzapine 15 mg/day Placebo 0 mg/day
Nakamura et al. 2009 [26]	Enrolled patients were hospitalized for an acute exacerbation of schizophrenia meeting DSM-IV based on the SCID-CV were enrolled. Patients were also required to have a minimum illness duration of at least 1 year; a BPRS total score, extracted from the PANSS of at least 42, with a score of at least 4 on 2 or more positive symptom items; a CGI-S score ≥ 4; a SAS score of < 2; and an AIMS score of < 3. Inpatients were included (18 to 64-year-old).	n.a.	6 weeks	n= 90 n= 90	Lurasidone 80 mg/day Placebo 0 mg/day
Nasrallah et al. 2013 [27]	Patients were enrolled if they presented a DSM-IV criteria for a primary diagnosis of schizophrenia, as established by structured clinical interview using the MINI, had received a diagnosis of schizophrenia ≥1 year previously, and were currently experiencing an acute exacerbation of psychotic symptoms (lasting ≤2 months). Additional criteria for eligibility included a CGI-S score≥4 (moderate or greater) and PANSS total score ≥80, including a score ≥4 (moderate) on two or more of the following five items: delusions, conceptual disorganization, hallucinations, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	14.1[a]	6 weeks	n= 121; 118; 123 n= 124	Lurasidone 40, 80, 120 mg/day Placebo 0 mg/day
Ogasa et al. 2013 [28]	The study enrolled patients with a DSM-IV criteria for primary diagnosis of schizophrenia, hospitalized for an acute exacerbation. Patients were also required to have illness duration of at least 1 year, no psychiatric hospitalization within the 3 months prior to study entry, a BPRS derived from the PANSS of ≥42, a score of ≥4 on two or more items of the positive symptoms subscale on the PANSS, and a CGI-S score of ≥4 (moderate). Inpatients were included (18 to 64-year-old).	n.a.	6 weeks	n= 50; 49 n= 50	Lurasidone 40, 120 mg/day Placebo 0 mg/day
Potkin et al. 2015 [6]	Described in the haloperidol section.				
	Olanzapine				
Beasley et al. 1996 a [29]	All patients enrolled met the DSM-III-R criteria for schizophrenia with an acute exacerbation, as established by clinical interview and chart review. In addition, patients were required to have a minimum BPRS total score (items scored 0 to 6) of 24. Patients with a diagnosis of a DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry were excluded as were patients at serious suicidal risk. Patients were required to be off oral neuroleptics for at least 2 days and off depot neuroleptics for at least 6 weeks prior to starting the study.	14[a]	6 weeks	n= 65; 64; 69 n= 68	Olanzapine 2.5-7.5, 7.5-12.5, 12.5-17.5 mg/day Placebo 0 mg/day
Beasley et al. 1996 b [30]	All patients enrolled met the DSM-IILR criteria for schizophrenia (295.1-295.3, 295.9) as established by clinical interview and chart review. Residual type 295.6 was excluded. Patients were required to have a minimum BPRS, total score (BPRS items scored 0-6) extracted from the PANSS of at least 24. Also, patients were required to have a CGI-S score >4. Patients with a diagnosis of a DSM-III-R organic mental disorder or substance-use disorder active within 3 months of study entry were excluded as were patients at serious suicidal risk. Inpatients and outpatients were included. Inpatients could continue the study as outpatients (18 to 65-year-old).	12.7[a]	6 weeks	n= 51; 49 n= 49	Olanzapine 1, 10 mg/day Placebo 0 mg/day
Marder et al. 2007 [31]	Patients enrolled presented an acute episode of schizophrenia, represented by a PANSS total score of 70 –120. Patients had to have been diagnosed with schizophrenia according to DSM-IV criteria for ≥ 1 year before screening and to have agreed to voluntary hospitalization for ≥ 14 days. Inpatients and outpatients were included. Inpatients could continue the study as outpatients (≥18-year-old).	n.a.	6 weeks	n= 110 n= 112; 112 n= 110	Olanzapine 10 mg/day Paliperidone ER 6, 12 mg Placebo 0 mg/day
Davidson et al. 2007 [32]	Included patients required a diagnosis of schizophrenia according to DSM-IV criteria for at least 1 year prior to screening and have agreed to voluntary hospitalization for a minimum of 14 days. Patients were initially all hospitalized for a minimum duration of 14 days, and could then continue the study as outpatients (≥18-year-old).	11.7	6 weeks	n= 127; 125; 115 n=126 n= 123	Paliperidone ER 3, 9, 15 mg/day Olanzapine 10 mg/day Placebo 0 mg/day
Kane et al. 2007 [33]	Patients enrolled experienced an acute episode of schizophrenia, as represented by a PANSS total score between 70 and 120. Patients must have been diagnosed with schizophrenia according to DSM-IV criteria for at least 1 year prior to screening. Patients were initially all hospitalized for a minimum duration of 14 days, and could then continue the study as outpatients (≥18-year-old).	10.2	6 weeks	n= 123; 122; 129 n= 128 n= 126	Paliperidone ER 6, 9, 12 mg/day Olanzapine 10 mg/day Placebo 0 mg/day
Meltzer et al. 2011 [25]	Described in the lurasidone section.	13.5	6 weeks	n= 118; 118 n= 121 n= 112	Lurasidone 40, 120 mg/day Olanzapine 15 mg/day Placebo 0 mg/day
Kinon et al. 2011 [34]	Included patients presented a DSM-IV criteria for schizophrenia. To be included in the study, patients had to meet all inclusion criteria including having moderately ill symptom severity or worse, at baseline and randomization, as defined by the following 2 requirements: a BPRS total score, extracted from the PANSS of at least 45 (18-item version, in which 1 indicates ‘‘absent’’ and 7 indicates ‘‘severe’’); item scores of at least 4 were required on 2 of the following BPRS items: conceptual disorganization, suspiciousness, hallucinatory behavior, and/or unusual thought content; and a minimum score of 4 on the CGI-S scale. Patients were initially all hospitalized for a minimum duration of 14 days (18-65-year-old).	n.a.	4 weeks	n= 62 n= 122	Olanzapine 15 mg/day Placebo 0 mg/day

Shen et al. 2014 [35]	Enrolled patients presented a diagnosis of according to the SCI for DSM-IV-TR, and were hospitalized for an acute exacerbation of their schizophrenia. In order to be included in the study, all subjects were required to have a PANSS total score ≥ 70 and ≤120, a PANSS Positive Symptoms Subscale score ≥ 20, and scores of ≥4 on at least two of the following PANSS items: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content. Further, subjects must have had CGI-S scores ≥ 4 at both screening and baseline. Patients were initially all hospitalized for a minimum duration of 14 days, and could then continue the study as outpatients (20-63-year-old).	n.a.	6 weeks	n= 71 n= 71	Olanzapine 15 mg/day Placebo 0 mg/day
Olanzapine (LAI)					
Lauriello et al. 2008 [36]	The study enrolled patients with a DSM-IV or DSM-IV-TR criteria for primary diagnosis of schizophrenia. At enrollment, patient were required to have a PANSS-derived BPRS score of ≥30. For patients treated previously with a depot antipsychotic, the last injection must have been received at least 2 weeks or 1 injection interval, which was longer before double-blind treatment. Inpatients and outpatients were included. Patients were initially all hospitalized, and could then continue the study as outpatients (18 to 75-year-old).	17.1[a]	8 weeks	n= 106; 100; 100 n= 98	Olanzapine LAI 210, 300, 405 mg/day Placebo 0 mg/day
Paliperidone ER					
Davidson et al. 2007 [32]	Described in the olanzapine section.	11.7	6 weeks	n= 127; 125; 115 n=126 n= 123	Paliperidone ER 3, 9, 15 mg/day Olanzapine 10 mg/day Placebo 0 mg/day
Kane et al. 2007 [33]	Described in the olanzapine section.	10.2	6 weeks	n= 123; 122; 129 n= 128 n= 126	Paliperidone ER 6, 9, 12 mg/day Olanzapine 10 mg/day Placebo 0 mg/day
Canuso et al. 2010 [37]	Included patients met the DSM-IV criteria for an acute exacerbation of a schizoaffective disorder. Patients were required to have a PANSS total score of at least 60 and a score ≥4 on at least 2 of the following PANSS items (Pt, P4, G4, G8, G14. In addition, subjects needed to have prominent mood symptoms with a score ≥16 on the Young Mania Rating Scale; and/or on the HDRS 21-item versions. Inpatients were included. Patients were initially all hospitalized (18 to 65-year-old).	4.7[a]	6 weeks	n= 105; 98 n= 107	Paliperidone ER 5.7(0.9), 11.6(1.1) mg/day Placebo 0 mg/day
Coppola et al. 2011 [38]	Enrolled patients presented an established diagnosis of schizophrenia (as per DSM-IV) for at least one year before screening, having an acute exacerbation of the disease, with a documented PANSS total score between 70 and 120 (at screening and baseline). Patients all hospitalized, and could continue the study as outpatients (≥18-year-old).	14.4[a]	6 weeks	n= 55; 59 n= 53	Paliperidone ER 1.5,6 mg/day Placebo 0 mg/day
Marder et al. 2007 [31]	Described in the olanzapine section.	n.a.	6 weeks	n= 110 n= 112; 112 n= 110	Olanzapine 10 mg/day Paliperidone ER 6, 12 mg Placebo 0 mg/day
Paliperidone (LAI)					
Alphs et al. 2011 [39]	Included patients had a diagnosis of schizophrenia per the DSM-IV, established at least 1 year before screening, and if they had a PANSS total score of at least 70 at screening and between 60 and 120, inclusive, at baseline. The criterion for inclusion in this subgroup analysis was a CGI-S score ≥5 at baseline (markedly to severely ill). Patients were initially all hospitalized for a minimum duration of 8 days, and could then continue the study as outpatients (≥18-year-old).	14.65	13 weeks	n= 72; 72; 85 n= 83	Paliperidone palmitate 234/39, 234/156, 234/234 mg/day Placebo 0 mg/day
Gopal et al. 2010 [40]	Included patients presented a diagnosis of schizophrenia for at least 1 year before screening, a PANSS total score at screening and baseline between 70 and 120 (inclusive), and with a body mass index (BMI) >17.0 kg/m2. Patients were initially all hospitalized for a minimum duration of 8 days, and could then continue the study as outpatients (≥18-year-old).	14.5[a]	13 weeks	n= 94; 97; 30 n= 136	Paliperidone LAI 50, 100, 150 mg/day Placebo 0 mg/day
Kramer et al. 2010 [41]	Enrolled patients had a diagnosis of schizophrenia according to DSM-IV criteria for at least 1 year had a PANSS total score of 70–120, inclusive, at screening, and 60–120 inclusive, on day 1 before the start of double-blind study drug, and had a body mass index (BMI) range of 15–35 kg/m2. Patients were initially all hospitalized (18-65 year-old).	12.3[a]	5 weeks	n= 79; 84 n= 84	Paliperidone LAI 50, 100 mg/day Placebo 0 mg/day
Nasrallah et al. 2010 [42]	Eligible patients who met the diagnostic criteria for schizophrenia according to the DSM-IV-TR for at least 1 year before screening. Patients had a PANSS total score at screening and baseline of 70–120 and a body mass index (BMI)>15.0 kg/m2. Patients were initially all hospitalized for a minimum duration of 8 days (≥18-year-old).	13.3[a]	13 weeks	n= 130; 128; 131 n= 125	Paliperidone LAI 25, 50, 100 mg/day Placebo 0 mg/day
Quetiapine					
Arvanitis & Miller, 1997 [43]	On inclusion, patients presented a diagnosis of acute exacerbation of their chronic or subchronic schizophrenia, as defined by the DSM-III-R. Additionally, at trial entry and before randomization, patients were required to have a minimum total score of 27 on the 18-item BPRS (0-6 scoring), a score of 3 (moderate) on at least two items from the BPRS positive symptom cluster (conceptual disorganization, suspiciousness, hallucinatory behavior, unusual thought content), and a score of 4 (moderately ill) on the CGI Severity of illness item. This study gives no information concerning the exact hospitalization duration (18-65-year-old).	14.7[a]	6 weeks	n= 53; 48; 52; 51; 54 n= 51	Quetiapine IR 75, 150, 300, 600, 750 mg/day Placebo 0 mg/day
Kahn et al. 2007 [44]	Included patients presented a DSM-IV diagnosis of acute schizophrenia: diagnosis of catatonic (DSM-IV diagnostic code 295.20), disorganized (295.10), paranoid (295.30), or undifferentiated (295.90). Key inclusion criteria were a PANSS total score ≥70; a CGI-S score ≥4; and in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks; a	8.4	6 weeks	n= 111; 111; 117 n= 115	Quetiapine ER 400, 600, 800 mg/day Placebo 0 mg/day

	PANSS score ≥4 for at least one of the following items: delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/persecution. Both inpatients and outpatients were included. (18-65-year-old).				
Loebel et al. 2013 [23]	Included patients had a DSM-IV-TR criteria for a primary diagnosis of schizophrenia as determined by clinical interview using the MINI. Subjects were also required to have an illness duration greater than 1 year with the current acute exacerbation of psychotic symptoms no longer than 2 months and, at the Screening and Baseline visits, to have a CGI-S score ≥4 and a PANSS total score ≥80, including a score ≥4 on two or more of the following PANSS items: delusions, conceptual disorganization, unusual thought content, and suspiciousness. Inpatients were included (18 to 75-year-old).	11.4	6 weeks	n= 125; 121 n= 119 n= 121	Lurasidone 80, 160 mg/day Quetiapine XR 600 mg/day Placebo 0 mg/day
Lindenmayer et al. 2008 [45]	Patients with a DSM-IV diagnosis of schizophrenia were eligible to participate. To be included in the study, patients had to meet the following criteria: a PANSS total score ≥60; a score of ≥4 for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution; a CGI-S score ≥4 and a worsening of the patient's condition in the previous 3 weeks. Patients screened as outpatients were hospitalized (18-65-year-old).	15.1[a]	6 weeks	n= 85; 80; 85 n= 78	Quetiapine IR 300, 600, 800 mg/day Placebo 0 mg/day
Cutler et al. 2010 [46]	Included patients were a documented DSM-IV diagnosis schizophrenia. Key inclusion criteria were: a PANSS total score ≥70 at enrollment; a score of ≥4 at randomization for at least one of the PANSS items of delusions, conceptual disorganization, hallucinatory behavior, or suspiciousness/ persecution; CGI-S score ≥4; and a worsening of the patient's condition in the previous 3 weeks. Patients were initially all hospitalized for at least of 2 weeks (≥18-year-old).	17.85	6 weeks	n= 40; 44; 45 n= 49	Quetiapine ER 400, 600, 800 mg/day Placebo 0 mg/day
Meulien et al. 2010 [47]	Patients presented a DSM-IV diagnosis of acute schizophrenia. Key inclusion criteria included a PANSS total score ≥70 or ≥ 60, CGI-S score≥4 and, in the opinion of the investigator, a worsening of the patient's condition in the previous 3 weeks; and a PANSS score ≥4 for at least one of the following items: delusions, conceptual disorganization, hallucinatory behaviour or suspiciousness/persecution. In this multicentric study, in one center, patients had to be hospitalized for at least the first 10 days of the study. In other center, patients were outpatients, patients were aged 18 to 65-year-old.	n.a.	6 weeks	n= 91; 227; 310; 323 n= 90; 123; 86; 115 n= 319	Quetiapine ER 300, 400, 600, 800 mg/day Quetiapine IR 300, 400, 600, 800 mg/day Placebo 0 mg/day
Risperidone					
Potkin et al. 2003 [7]	Described in the aripiprazole section	n.a.	4 weeks	n= 101; 101; 103 n= 99 n= 103	Aripiprazole 20, 30 mg/day Risperidone 6 mg/day Placebo 0 mg/day
Potkin et al. 2007 [13]	Described in the asenapine section		6 weeks	n= 59 n= 59 n= 62	Asenapine 5 mg/day Risperidone 3 mg/day Placebo 0 mg/day
Casey et al. 2008 [48]	Enrolled patients presented a current diagnosis of schizophrenia according to the DSM-IV-TR criteria, with an acute exacerbation of the disease. Patients were required to have a total PANSS score between 70 and 120; a baseline (day 1) score ≥4 on at least two of the following PANSS items: conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content; and a CGI—S score ≥4. Patients were initially all hospitalized (18 to 65-year-old).	n.a.	6 weeks	n= 120 n= 119	Risperidone 6 mg/day Placebo 0 mg/day
Durgam et al. 2014 [19]	Described in the cariprazine section.	11.3	6 weeks	n= 145; 146; 147 n= 140 n= 151	Cariprazine 1.5, 3, 4.5 mg/day Risperidone 6 mg/day Placebo 0 mg/day
Litman et al. 2016 [49]	Included patients met criteria for schizophrenia based on clinical psychiatric history and the SCID interview, had a PANSS total score of ≥70, were medically stable, had a history of clinically significant response to prior neuroleptic treatment, had no history of intolerance to olanzapine therapy, and did not meet criteria for substance abuse or substance dependence were eligible for inclusion. Both inpatients and outpatients were included (18 to 65-year-old).	n.a.	6 weeks	n= 31 n= 55	Risperidone 4 mg/day Placebo 0 mg/day
Waillling et al. 2019 [50]	Included patients presented a current diagnosis of schizophrenia according to DSM-IV-TR criteria, confirmed with the MINI. These patients were experiencing an acute exacerbation of schizophrenia that altered their ability to function (<4 weeks' duration; <2 weeks' current hospitalization). Key inclusion criteria included a total PANSS, BPRS 23 score of ≥45 at screening and ≥4 on at least 2 of the 4 core psychosis items (items conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) at screening and baseline, a total score of ≥12 on the 4 BPRS core psychosis items at screening and baseline, and a CGI-S score of ≥4. Patients were initially all hospitalized (18 to 65-year-old).	14.6	4 weeks	n= 36 n= 74	Risperidone 3 mg/day Placebo 0 mg/day
Risperidone (LAI)					
Kane et al. 2003 [51]	Patients with a DSM-IV criteria of schizophrenia were enrolled. Inclusion criteria included a PANSS total score of 60 to 120 and good general health. Inpatients and outpatients were included (18-55-year-old).	n.a.	12 weeks	n= 99; 103; 100; n= 98	Risperidone LAI 25, 50, 75 mg/day Placebo 0 mg/day

a The mean duration of illness was deduced using the mean age at age of onset of the illness (years)

Abbreviations
BPRS: Brief Psychiatric Rating Scale; CGI-S: Clinical Global Impression Severity of Illness; DSM: Diagnostic and Statistical Manual of Mental Disorders; MINI: Mini-International Neuropsychiatric interview for schizophrenia and psychotic disorders studies; PANSS: Positive And Negative Syndrome Scale: SANS: Scale for the Assessment of Negative Symptoms; SCID: Structured Clinical Interview for DSM Disorders interview

Supplementary Table 2. Risk of bias assessment for included RCTs

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 potential biases
Alphs et al. 2011 [39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Arvanitis et al. 1997 [43]	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Beasley et al. 1996a [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Beasley et al. 1996b [30]	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Cantillon et al. 2017 [9]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Canuso et al. 2010a [37]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Casey et al. 2008 [48]	Low risk	unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Coppola et al. 2011 [38]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Cutler et al. 2008 [21]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Cutler et al. 2010 [46]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Correll et al. 2015 [16]	Low risk	Unclear	Unclear	Low risk	Low risk	High risk	This trial was supported by a pharmaceutical company
Correll et al. 2016 (NCT00905307) [15]	Low risk	Unclear	Unclear	Low risk	Low risk	High risk	This trial was supported by a pharmaceutical company
Davidson et al. 2007 [32]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Durgam et al. 2014 [19]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Durgam et al. 2015 [10]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Durgam et al. 2016 [20]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Gopal et al. 2010 [40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Higuchi et al. 2019 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Ishiggoka et al. 2018 [17]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Iyo et al. 2021 [53]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Kahn et al. 2007 [44]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Kane et al. 2002 [2]	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	This trial was supported by a pharmaceutical company
Kane et al. 2003 [51]	Unclear	Unclear	Unclear	Low risk	High risk	Low risk	This trial was supported by a pharmaceutical company
Kane et al. 2007b- [33]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Kane et al. 2010a [4]	Low risk	Unclear	Low risk	Low risk	Unclear	High risk	This trial was supported by a pharmaceutical company
Kane et al. 2010 [4]	Low risk	Unclear	Low risk	Low risk	Low risk	High risk	This trial was supported by a pharmaceutical company

Kane et al. 2014- [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Kane et al. 2015 [18]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Kinon et al. 2011 [52]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Kinoshita et al. 2016 [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company and a private investor
Kramer et al. 2010 [41]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	This trial was supported by a pharmaceutical company and a private investor
Lauriello et al. 2008 [36]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Lindenmayer et al. 2008 [45]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Litman et al. 2016 [49]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Loebel et al. 2013 [23]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Loebel et al. 2016a [24]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Meltzer et al. 2004 [3]	Unclear	Unclear	Unclear	Low risk	High risk	Unclear	This trial was supported by a pharmaceutical company
Marder et al. 2007 [31]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Meltzer et al. 2011 [25]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Meulien et al. 2010 [47]	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
McEnvoy et al. 2007b [8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Nakamura et al. 2009 [26]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Nasrallah et al. 2010 [42]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Nasrallah et al. 2013 [27]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Nasrallah 2016 [12]	Low risk	Unclear	Low risk	Low risk	Low risk	High risk	This trial was supported by a pharmaceutical company
Potkin et al. 2003 [7]	Low risk	Unclear	Low risk	Low risk	Low risk	High risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Potkin et al. 2007c [13]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Potkin et al. 2008 [5]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Ogasa et al. 2013 [28]	Low risk	Unclear	Low risk	Low risk	Low risk	High risk	This trial was supported by a pharmaceutical company
Potkin et al. 2015 [6]	Low risk	Low risk	Low risk	Low risk	Low risk	High risk	No mention of authors conflict of interest. This trial was supported by a pharmaceutical company
Shen et al. 2014 [35]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Wailling et al. 2019 [50]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	This trial was supported by a pharmaceutical company
Study 041-21 SH[a] [53]	-	-	-	-	-	-	This trial was supported by a pharmaceutical company

Criteria for judging risk of bias in the 'Risk of bias' assessment tool:
Low risk: the investigators describe a random component for considered risk
Unclear: insufficient information to permit judgment of 'Low risk' or 'High risk'
High risk: the investigators describe a non-random component; there is a high probability of publication bias.
a- Unpublished trial. Application number 22-117.

Appendix 1. PRISMA checklist

Section/topic	#	Checklist item.	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review.	Title page
ABSTRACT			
ABSTRACT	2	See the PRISMA 2020 for Abstracts checklist (Table 2).	Abstract
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	3,4
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	4,5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	4
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	3,4
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	3,4, Prospero protocol
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	3
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	4
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	4,5
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	4,5
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	5
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	5
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis.	4,5
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	4,5
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	5
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	5
	13e	Describe any methods used to explore possible causes of heterogeneity among study results.	5
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	5
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	5
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	Not applicable
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see Figure 1).	5, Figure S1
	16b	Cite studies that met many but not all inclusion criteria ('near-misses') and explain why they were excluded.	4, 6
Study characteristics	17	Cite each included study and present its characteristics.	Table S1
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Table S1, Table 1, Table 2, Table 3, Figure 1, Figure 2, Figure S2 Page 6, 7, 8, 9, 10, 11.
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	6, 7, 8, 9, 10, 11.
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	6, 7, 8, 9, 10, 11.
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	7, 10, 13

20d		Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Figure S3, 6
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Figure S3, 6
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	6, 7, 8, 9, 10, 11.
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	12, 13
23b		Discuss any limitations of the evidence included in the review.	14
23c		Discuss any limitations of the review processes used.	14
23d		Discuss implications of the results for practice, policy, and future research.	14, 15
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	2
24b		Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	2
24c		Describe and explain any amendments to information provided at registration or in the protocol.	Not applicable
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	15
Competing interests	26	Declare any competing interests of review authors.	15
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	Not applicable

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