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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ABSTRACT

Objective: To investigate the association of metabolic side effects with antipsychotic dose, we conducted a dose-response meta-analysis of randomized controlled trials (RCTs) in which antipsychotics were administered to people with schizophrenia. The primary outcome was mean change in weight. The secondary outcomes were the mean changes in metabolic parameters.

Data Sources: MEDLINE, Embase, PubMed, PsyARTICLES, PsycINFO, Cochrane Database of Systematic Reviews, and different trial registries were searched for articles published in English until February 2021.

Study Selection: We identified fixed-dose RCTs with first- or second-generation antipsychotics. The quality of RCTs was measured with Cochrane's Risk of Bias tool.

Data Extraction: We performed a dose-response meta-analysis.

Results: We retained 52 RCTs including 22,588 participants. With the exception of aripiprazole long-acting injectable (LAI), all investigated antipsychotics presented significant dose-response associations with weight, from lurasidone with a quasi-parabolic shaped curve (9 studies, estimation of 95% effective dose [ED95; 59.93 mg/d] = 0.53 kg/6 wk) to olanzapine LAI with a curve that continued to increase with the dose (1 study, ED95 [15.05 mg/d] = 4.29 kg/8 wk). All curves could be ordered in 3 different classes of shapes—quasi-parabolic, plateau, and ascending.

Conclusions: We found significant dose-response associations for weight and metabolic variables, with a unique signature for each antipsychotic. Weight gain can occur at a relatively low median effective dose, and increasing doses can be associated with greater weight gain for some drugs. Despite several limitations, including the limited number of available studies, our results may provide useful information for preventing weight gain and metabolic disturbance by adapting antipsychotic doses.

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Schizophrenia is a severe mental illness associated with social isolation, occupational disability, and poor physical health.[1] Patients with schizophrenia have a 10- to 25-year reduction in life expectancy[2,] and cardiovascular disease is the strongest contributor to this excess mortality.[3]

Antipsychotic medications are the first-line therapy for schizophrenia and effectively treat positive symptoms.[4] Antipsychotics, particularly second-generation antipsychotics, are often associated with weight gain, lipid disturbance, and glucose dysregulation, thereby contributing to the development of obesity, type 2 diabetes, and metabolic syndrome.[5–8] The combination of these side effects with lifestyle-related cardiovascular risk factors (eg, smoking, sedentary behavior) may explain why patients with schizophrenia are 2 to 3 times more likely to die from cardiovascular disease than the general population.[9–11]

Additionally, patients with schizophrenia receive lower quality of care for cardiovascular disease.[12] Thus, finding a balance between beneficial and adverse effects of antipsychotics is challenging for clinicians.[13–15] Providing personalized treatment to patients with schizophrenia with the fewest possible side effects is important.

For most antipsychotics, whether weight gain and metabolic dysregulation are dose-dependent remains controversial.[16] Although the effect of specific second-generation antipsychotics on weight gain has been explored for olanzapine, paliperidone, and risperidone by Spertus and colleagues,[17] only one study, by Wu and colleagues,[18] has so far examined antipsychotic-induced weight gain in patients with schizophrenia using a dose-response meta-analysis. That important study found pronounced differences in weight dose-response curves between antipsychotics, but did not address metabolic disturbance. Therefore, we conducted a systematic review and a dose-response meta-analysis of fixed-dose randomized controlled trials (RCTs) of

Clinical Points

- Significant dose-response associations were found for weight and metabolic variables, with a unique signature for each antipsychotic.
- Only some second-generation antipsychotics show increasing weight gain across the whole investigated dose range.
- These results may provide useful information for preventing weight gain and metabolic disturbance by adapting antipsychotic doses.

antipsychotics in adult patients with acute schizophrenia to examine antipsychotic-induced weight gain and metabolic disturbance.

METHODS

Registration

Our systematic review followed the updated version of the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement[19] (see the completed PRISMA checklist in Supplementary Appendix 1). The protocol was published on March 16, 2021, in the International Prospective Register of Systematic Reviews (PROSPERO CRD42021176569).

Search Strategy

We included all double-blind RCTs comparing at least one antipsychotic to placebo using any form of administration for acute exacerbation episodes in patients with schizophrenia and related disorders. The retrieved articles were limited to those published in English considering adult patients (18 to 65 years-old).

Two authors (M.S.) and K.P.) independently searched MEDLINE, Embase, PubMed, PsyARTICLES, PsycINFO, Cochrane Database of Systematic Reviews, and different trial registries (ClinicalTrials.gov and clinicaltrialsregister.eu) from inception until September 27, 2022. The search terms used were a combination of keywords and MeSH terms, such as "schizo*" and a list of antipsychotics (eg, "olanzapine," "aripiprazole"). The full list of search terms is available in the PROSPERO protocol.

Inclusion Criteria and Study Selection

We included all RCTs including adult patients with schizophrenia or related disorders and comparing a placebo reference with at least two fixed doses of an antipsychotic in the same trial or with one fixed-dose level of an antipsychotic when at least two trials with different fixed doses were available.

Considering that most of the available RCTs on antipsychotics have been conducted with patients presenting an acute exacerbation of schizophrenia, we focused on short-term administration of antipsychotics (2 to 13 weeks). We excluded maintenance studies to avoid methodological and clinical heterogeneity. In maintenance studies patients are pre-treated with the study drug, which limits the additional weight gain in the randomized phase. In addition, the duration of acute and maintenance studies differs strongly. Furthermore, we performed a separate search for studies from mainland China, because there are indicators that they differ with respect to procedures and patient characteristics from trials conducted in other countries.[20,21] Two reviewers (M.S. and K.P.) independently conducted title/abstract and full-text screening. Any disagreement was resolved by consensus.

Outcome Measures

The primary outcome was the mean ± SD change in weight gain (body weight and/or body mass index [BMI]) between baseline and the study endpoint. The secondary outcomes were the mean ± SD changes in metabolic parameters (fasting glucose, hemoglobin A1c [HbA1c], high-density lipoprotein [HDL] cholesterol, low-density lipoprotein [LDL] cholesterol, total cholesterol, triglycerides, and insulin) between baseline and the study endpoint.

Assessment of Study Quality and Data Extraction

The quality of the included RCTs was measured with the Risk of Bias Tool. The final set of RCTs was subjected to a quality assessment with the use of the bias assessment tool from the Cochrane Collaboration.[22] Two authors (M.S. and K.P.) rated quality independently. For all included RCTs, the following variables were extracted: author, year, country, antipsychotic, dose, duration in weeks, sample size, age, outcome centrality and dispersion measures, diagnostic group and criteria. When needed, the unit for each outcome was converted to a common unit (eg, mg/dL for total cholesterol). Missing standard deviations were estimated from *P* values or with the mean standard deviation of the other included studies.[23]

Data Analysis

To obtain dose-response curves, we estimated flexible dose-response models from sets of correlated differences in means according to the model proposed by Crippa and Orsini.[24] As a measure of effect size, the standardized mean difference (Cohen *d*) was used. A one-stage approach was applied to estimate a combined dose-response association considering the correlation among a set of mean differences.[25] The pooled curve and estimates of between-study heterogeneity were calculated separately for each drug based on the whole set of studies available for the drug.

The dose-response relationship was characterized using a restricted cubic spline model (nonlinear model) with 3 knots located at the 10th, 50th, and 90th percentiles of the overall dose distribution. Estimations of 50% (ED50) and 95% (ED95) effective doses were extracted from the estimated dose-response curves for each antipsychotic. For weight, the ED50 was the mean dose at which half of the possible antipsychotic-induced weight gain effect would occur. The combined dose-response curve was defined by the average population dose-response coefficient β, namely, the coefficients defining the pooled dose-response trend. This

Table 1. Dose Equivalencies for Antipsychotics With Consideration of Near Maximum Weight Gain

Antipsychotic	No. of Studies Included	Patients Included, n	Mean Duration of Trials, wk	Weight Gain ED50, mg/d	Weight Gain ED95, mg/d	Weight Gain (kg) Corresponding to the ED95 Value[a]	Near-Maximum Effective Dose for PANSS Total Score (ED95),[b] mg/d	Mean Dose Across all Studies, mg/d	Chlorpromazine Equivalents (mg) to the ED95 Value
Haloperidol	6	1,138	5.5	1.86	5.00	0.66	6.33	10.1	319.3
Aripiprazole oral	5	1,393	5.2	10.02	27.2	0.88	11.50	18.3	244
Aripiprazole (LAI)[c,d]	2	961	12	9.14 (385.3)	20.1 (830.13)	2.61[e]	7.8 (462)	12.6	167.6
Asenapine	3	986	6	2.28	5.46	1.36	14.97	7	140
Brexpiprazole	4	2,874	6	0.73	1.91	1.11	3.36	2.1	NA
Cariprazine	3	1,496	6	1.2	2.7	0.80	7.6	4.3	NA
Iloperidone	2	1,928	5	4.6	16.7	2.65	20.03	16	266.7
Lurasidone	9	2,969	6	23.08	57.93	0.53	148	70.6	353
Olanzapine oral	8	1,480	5.75	5.68	14.95	3.61	6.47	10.5	210
Olanzapine (LAI)[c,d]	1	404	8	5.41 (113.7)	15.05 (301.1)	4.29	13.8 (277.18)	11.6	232
Paliperidone oral	5	1,789	6	5.3	13.8	1.73	13.35	8	533
Paliperidone (LAI)[c,d]	4	1,422	12	1.6 (28.8)	4 (73.12)	1.54	6.5 (119.97)	4.8	320
Quetiapine IR	6	1,494	6	203.2	579.3	1.67	482.08[f]	470	352.5
Quetiapine ER	6	2,163	6	168.9	390.2	1.40	482.08[f]	575	431
Risperidone oral	6	1,109	5.2	1.24	3.4	1.50	6.26	4.3	215
Risperidone (LAI)[c]	1	400	12	1.70 (23.90)	4.66 (65.37)	1.95	3.2 (36.56)	4.5	225

[a]In the general population, every kg increase in body weight expose to an increase in the cardiovascular disease risk by 3.1% for every kg/m^2 (Willet[83]). This estimated risk does not take in consideration influence of the possible perturbation of metabolic parameters.
[b]The ED95 for the PANSS total score is from Leucht et al.[29]
[c]Approximations of daily dose were obtained by converting each dose of LAI antipsychotic per the published manufacturer monograph for each antipsychotic and using the article by Gopal et al (2010; see reference 40 in the Supplementary Material) for paliperidone.
[d]LAI injections were given every 4 weeks for aripiprazole and paliperidone, every 2 weeks and each 4 weeks for olanzapine LAI, and every 2 weeks and for risperidone LAI. LAI injection values are indicated within parentheses.
[e]A high uncertainty was present for aripiprazole LAI.
[f]Based on results of both quetiapine IR and ER forms.
Abbreviations: ED50 = 50% effective dose, or median effective dose; ED95 = 95% effective dose, or near maximal effective dose; ER = extended release; IR = immediate release; LAI = long-acting injectable; NA = not applicable; PANSS = Positive and Negative Syndrome Scale.

coefficient denotes the steepness of the pooled dose-response trend within the linear mixed model. The hypothesis of no dose-response association H0: $\beta_1 = \ldots = \beta p = 0$ was tested using multivariate extensions of the univariate Wald test.

We also estimated dose-response curves when only one study and few data points were available. Since these data points are calculated from richer data with a sufficiently large number of participants, curves can be fitted with satisfactory precision.[26]

We used a random-effects model to consider between-study variability.[27] Residual heterogeneity was explored using sensitivity analyses excluding studies with a high risk of bias. We assessed heterogeneity with the variance partition coefficient (VPC), which is a multivariate extension of the I^2 value.[25] The VPC can be defined as the ratio of the between-studies component by the total residual.

All meta-analyses were carried out using R software version 3.1 with the metafor[28] and dosresmeta[29] packages.

RESULTS

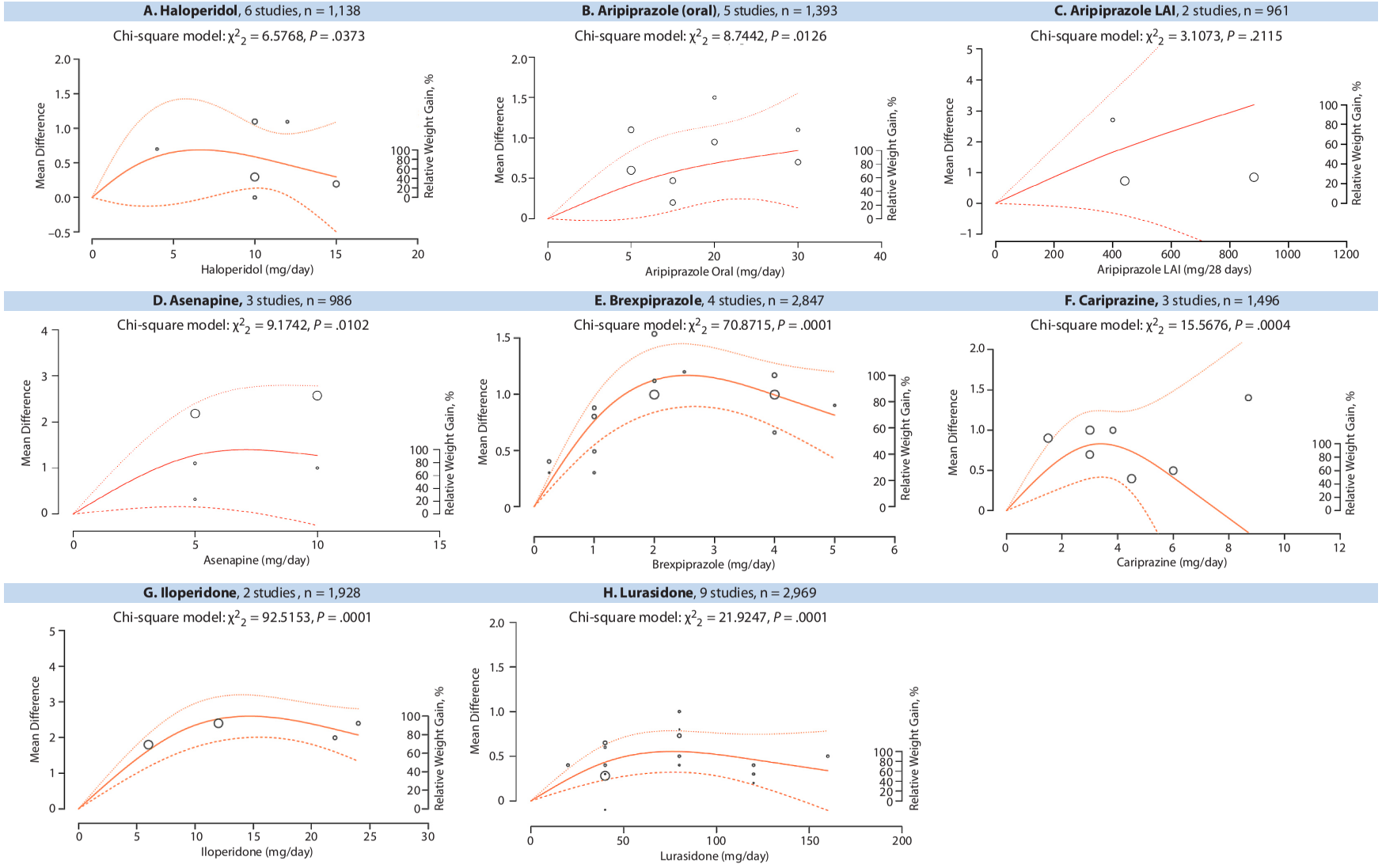
Search Results and Qualitative Analysis

From 6,812 unique citations initially assessed for eligibility, we included 52 RCTs[30–82] that met the inclusion criteria (Supplementary Figure 1 and Supplementary Table 1). These RCTs examined fixed doses of 11 antipsychotics. Data for oral forms were available for aripiprazole (5 studies), asenapine (3 studies), brexpiprazole (4 studies), cariprazine (3 studies), haloperidol (6 studies), iloperidone (2 studies), lurasidone (9 studies), olanzapine (8 studies), paliperidone (5 studies), quetiapine (6 studies), and risperidone (6 studies). Data for long-acting injectable (LAI) formulations were available for aripiprazole (2 studies), olanzapine (1 study), paliperidone (4 studies), and risperidone (1 study). These studies were published between 1996 and 2021. For olanzapine, we retrieved results from an unpublished clinical trial (041-021 SH) on ClinicalTrials.gov.[82] We did not find any study fulfilling inclusion criteria for the following drugs included in our protocol: amisulpride, clozapine, lumateperone, sertindole, ziprasidone, and all first-generation antipsychotics other than haloperidol.

The 52 studies included 22,588 participants, with 16,311 patients taking antipsychotics and 6,277 patients receiving placebo. The study duration ranged from 3 to 13 weeks, with a median duration of 6 weeks. The mean age of the participants was 38.5 years, and 69.2% of participants were men. In addition, the search for articles from mainland China yielded 62 articles, which all had to be excluded because they were not available in English, did not include a placebo arm, or used flexible dosing.

Concerning publication bias, we did not find any registered study fulfilling inclusion criteria for which no results were available. Exploration of publication bias via a funnel plot was not possible due to the limited number of available studies. The overall risk of bias was low in most studies. Twenty-one percent of the studies presented a high risk of bias, which mostly concerned reporting biases (Supplementary Table 2).

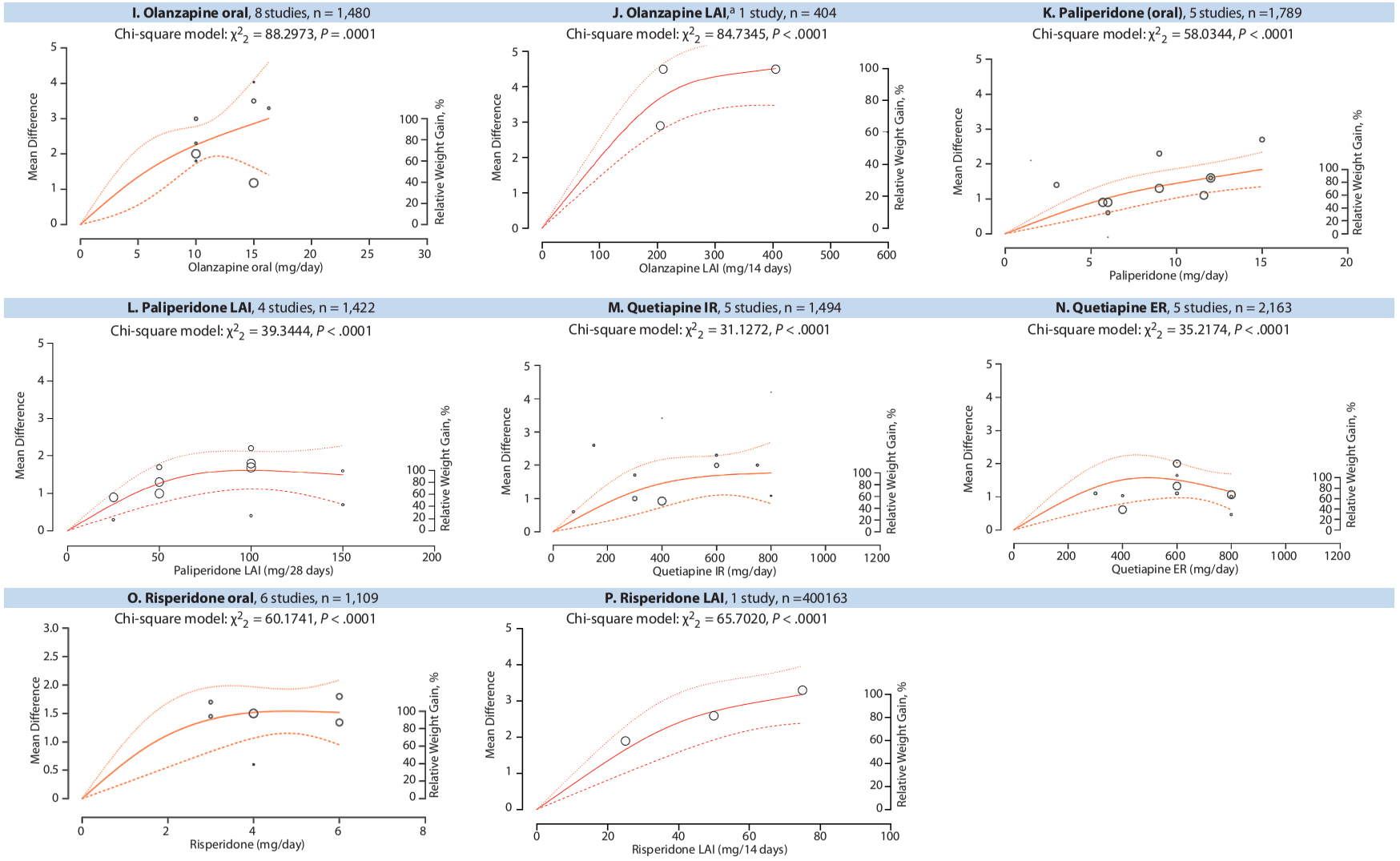
Figure 1. Dose-Response Curves of Antipsychotic-Induced Weight Gain for Aripiprazole, Brexpiprazole, Cariprazine, Asenapine, Iloperidone, and Lurasidone[a]



[a]The figures represent the pooled dose-response association between one or several studies for a same antipsychotic and the mean change in the weight gain (in kg). The antipsychotic dosage is modeled with restricted cubic splines in a random-effects model. Dash lines represent the 95% CIs for the cubic spline model. The placebo group (dose = 0) served as the referent group. Circles indicate observed mean differences in individual studies; size of bubbles is proportional to precision (inverse of variance) of the mean differences. The right y-axis represents percentage of the maximum predicted effect. Predicted mean difference for ED95 weight gain is reported in Table 1.

Abbreviations: ED95 = estimation of the 95% effective dose, LAI = long-acting injectable.

Figure 2. Dose-Response Curves of Antipsychotic-Induced Weight Gain for Olanzapine, Paliperidone, Quetiapine, and Risperidone[a]



[a]In this study, olanzapine LAI doses are used (210 mg and 300 mg each for 2 weeks and 405 mg each for 4 weeks, which correspond approximately to dosages of 10, 15, and 10 mg/day, respectively).
Abbreviations: ER = extended release, IR = immediate release, LAI = long-acting injectable.

Dose-Response Relationship Between Antipsychotic Dose and Weight Gain

All dose equivalencies for the included antipsychotics considering the maximum weight gain are reported in Table 1, and estimated dose-response curves are reported in Figures 1 and 2. The distribution of the ED95 for weight ranged from 0.53 to 4.29 kg with a median of 1.55 for a mean duration of 7 weeks. We added the total score from the Positive and Negative Syndrome Scale (PANSS)[84] near-maximum effective doses (ED95) from a recent dose-response meta-analysis[85] to allow ED95 comparisons with respect to symptoms and weight.

Aripiprazole (oral and LAI). Five RCTs of oral aripiprazole at doses between 10 and 30 mg/d and 2 trials of aripiprazole LAI at doses of 400 and 882 mg/4 weeks were included. Oral aripiprazole exhibited a significant dose-response association for weight ($\chi^2 = 8.744$; $P = .0126$). However, no significant association was found for aripiprazole LAI ($N = 2$; $\chi^2 = 3.107$; $P = .2115$) (Figures 1B and 1C, respectively). Nevertheless, both curves were still ascending at maximum doses.

The oral form of aripiprazole presented an ED95 of 27.2 mg/d for a mean duration of 5.2 weeks (Table 1). At this dose, the average weight gain was 0.88 kg. When considering aripiprazole LAI, the weight gain was 2.61 kg for an ED95 of 20.1 mg/d for a mean duration of 12 weeks. This estimation based on only 2 studies was obtained with important uncertainty.

Asenapine. Three RCTs analyzed doses between 5 and 10 mg/d. A significant association of dose with weight was found ($\chi^2 = 9.17$; $P = .0102$). The curve reached a plateau (Figure 1D) with an ED95 of 5.46 mg/d, corresponding to a predicted weight gain of 1.36 kg over a mean duration of 6 weeks. These results suggest that higher doses are not associated with additional weight gain.

Brexpiprazole. Four RCTs examined doses between 0.25 and 4 mg/d. The estimated curve showed a significant dose-response association ($\chi^2 = 70.87$; $P < .001$) and had a quasi-parabolic shape (Figure 1E), suggesting that a higher dose of brexpiprazole was associated with less weight gain than the ED95 of 1.91 mg/d, which corresponded to a weight gain of 1.11 kg over a mean duration of 6 weeks.

Cariprazine. Three RCTs used doses between 3 and 12 mg/d. The estimated curve showed a significant dose-response relationship ($\chi^2 = 15.57$; $P = .0004$). A quasi-parabolic curve was obtained (Figure 1F), suggesting that a higher dose was associated with less weight gain. The ED95 was 2.7 mg/d, which corresponded to a weight gain of 0.8 kg over a mean duration of 6 weeks.

Haloperidol. Six RCTs using doses between 4 and 15 mg/d were included. The dose-response curve showed a significant dose-response association ($\chi^2 = 6.58$; $P = .037$). Visual inspection of the curve revealed a quasi-parabolic or bell shape, suggesting that higher doses of haloperidol were associated with less weight gain in the short term (Figure 1A). The ED95 was 5 mg/d, and at this dose, the weight gain was 0.66 kg for a mean duration of 5.5 weeks.

Iloperidone. Two RCTs analyzed doses from 6 to 24 mg/d. A significant dose-response association with weight was found ($\chi^2 = 92.52$; $P < .0001$). The estimated curve plateaued (Figure 1G) with an ED95 of 16.7 mg, corresponding to a weight gain of 2.65 kg for a mean duration of 5 weeks.

Lurasidone. Nine RCTs examined doses between 20 and 120 mg/d. The estimated curve revealed a significant dose-response association for weight ($\chi^2 = 21.92$; $P < .0001$) and had a quasi-parabolic shape (Figure 1H). The ED95 was 57.93 mg, which predicted a weight gain of 0.53 kg over a mean duration of 6 weeks.

Olanzapine (oral and LAI). Eight RCTs used doses between 10 and 15 mg/d One study used olanzapine LAI at doses of 200 and 300 mg/2 weeks and 405 mg/4 weeks. Both the oral and olanzapine LAI curves demonstrated a significant dose-response association with weight ($\chi^2 = 88.30$; $P < .0001$ and $\chi^2 = 84.73$; $P < .0001$, respectively). Both curves continued to increase, suggesting that higher doses were associated with an increase in weight gain (Figure 2I and 2J).

Furthermore, the ED95 values were similar (14.95 mg/d and 15.05 mg/d, respectively). For oral olanzapine, the predicted weight gain was 3.61 kg over a mean duration of 5.75 weeks, and that for olanzapine LAI was 4.29 kg over a mean duration of 8 weeks.

Paliperidone (oral and LAI). Nine RCTs were included for paliperidone, with 5 oral and 4 LAI studies. Doses ranged from 3 to 15 mg/d and 25 to 150 mg/4 weeks, respectively. We observed a significant dose-response association with weight for the oral form of paliperidone ($\chi^2 = 58.03$; $P < .0001$) and for paliperidone LAI ($\chi^2 = 39.344$; $P < .0001$). For the oral form, the curve was still increasing at the maximum dose studied (Figure 2K); for paliperidone LAI, the curve plateaued. The ED95 was 13.8 mg/d, corresponding to a weight gain of 1.73 kg over a mean duration of 6 weeks. In contrast, the estimated LAI curves plateaued with an ED95 at 4 mg/d, predicting a weight gain of 1.54 kg over a mean duration of 12 weeks (Figure 2L).

Quetiapine IR. Five RCTs examined doses between 75 and 800 mg/d. A significant dose-response association was found with weight ($\chi^2 = 31.13$; $P < .0001$). The estimated curve plateaued (Figure 2M), and the ED95 was 579.3 mg/d, which corresponded to a weight gain of 1.67 kg for 6 weeks mean duration.

Quetiapine ER. Five RCTs used doses between 300 and 800 mg/d. The estimated curve showed a significant dose-response association with weight ($\chi^2 = 35.22$; $P < .0001$) and had a quasi-parabolic shape (Figure 2N), suggesting that a dose higher than the ED95 of 390 mg was not associated with greater weight gain. This dose was associated with a mean weight gain of 1.40 kg over a mean period of 6 weeks.

Risperidone (oral and LAI). Six RCTs reported oral risperidone at doses from 3 to 6 mg/d, and 1 study reported risperidone LAI at doses of 25, 50, and 75 mg/2 weeks. For both oral and LAI forms, a significant dose-response association with weight was found ($\chi^2 = 60.17$; $P < .0001$ and 65.70; $P < .0001$, respectively). The estimated curve plateaued for oral risperidone (Figure 2O), with an ED95 of 3.4 mg/d,

which corresponded to a weight gain of 1.5 kg over a mean period of 5.2 weeks. The risperidone LAI curve continued to increase, suggesting that a higher dose was associated with greater weight gain (Figure 2P). The ED95 was 4.7 mg/d, predicting a weight gain of 1.95 kg over a mean duration of 12 weeks.

Dose-Response Relationship Between Antipsychotic Dose and Metabolic Disturbance

Mean difference curves for metabolic disturbance and ED95 values were produced (Table 2 and Supplementary Figure 2). Due to the paucity of available data, we were not able to calculate dose-response curves for metabolic parameters for haloperidol and risperidone. For the same reason, we did not calculate dose-response curves for BMI and HbA1c for any drug. These results are summarized in Table 3.

Aripiprazole (oral). For oral aripiprazole, no significant dose-response associations between increasing aripiprazole doses and metabolic parameters were found.

Aripiprazole LAI. Significant dose-response associations of increasing doses of aripiprazole LAI with LDL cholesterol ($\chi^2 = 7.18$; $P = .028$) and HDL cholesterol ($\chi^2 = 15.8$; $P < .001$) were found. Both curves had quasi-parabolic shapes, suggesting that higher doses may be associated with less metabolic disturbance. High uncertainty was identified for the highest doses of aripiprazole.

Asenapine. No significant dose-response associations between increasing asenapine doses and metabolic parameters were found.

Brexpiprazole. Significant dose-response associations were found between increasing doses of brexpiprazole and HDL cholesterol ($\chi^2 = 47.36$; $P < .001$) and total cholesterol ($\chi^2 = 5.75$; $P = .056$). The HDL cholesterol curve presented a quasi-parabolic shape, whereas the total cholesterol curve plateaued.

Cariprazine. Significant dose-response associations of increasing doses of cariprazine with glucose ($\chi^2 = 4.742$; $P = .0934$), LDL cholesterol ($\chi^2 = 20.61$; $P < .0001$) and total cholesterol ($\chi^2 = 18.0$; $P < .0001$) were found. However, the shapes of the curves were not similar: the glucose curve continued to ascend, while the LDL and total cholesterol curves decreased.

Iloperidone. A significant dose-response association was found between increasing doses of iloperidone and glucose concentrations ($\chi^2 = 15.9$; $P < .001$). The glucose curve continued to ascend at the highest doses.

Lurasidone. A significant dose-response association was found for increasing doses of

Table 2. Dose Equivalencies for Antipsychotics With Consideration of Near-Maximum Values Regarding Metabolic Disturbance[a]

Antipsychotic	Mean Duration of Trials, wk	Mean Dose Across all Studies, mg/d	Chlorpromazine Equivalents, mg	Glucose			Insulin			HDL Cholesterol			LDL Cholesterol			Triglycerides			Total Cholesterol		
				No. of Studies	ED95, mg/d	Level, mg/dL	No. of Studies	ED95, mg/d	Level, mg/dL	No. of Studies	ED95, mg/d	Level, mg/dL	No. of Studies	ED95, mg/d	Level, mg/dL	No. of Studies	ED95, mg/d	Level, mg/dL	No. of Studies	ED95, mg/d	Level, mg/dL
Haloperidol	5.5	10.1	336	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Aripiprazole oral[b]	5.2	18.3	244	2	5.5	−8	…	…	…	2	15	−0.18	2	14	−4.1	2	5.9	−8.01	2	14.8	+12.3
Aripiprazole (LAI)[b,c,d]	12	12.6	167.6	2	28.62	+4.29	…	…	…	2	**12.33**	**+3.14**	2	**10.7**	**+3.55**	2	29.5	−7.9	2	12.8	+5.5
Asenapine[b]	6	7	140	2	10	−15.89	2	**9.73**	**+10.2**	…	…	…	…	…	…	1[e]	5.25	−0.38	2	4.83	+24
Brexpiprazole	6	2.1	NA	2	4.82	+2.25	…	…	…	4	**1.8**	**+2.9**	4	4.79	+1.48	4	4.92	+4.95	4	3.39	+4.2
Cariprazine[b]	6	4.3	NA	2	**8.4**	**+9.6**	…	…	…	3	2.93	+1	3	**8.2**	**-10.4**	3	8.4	−2.27	**3**	**8.3**	**-6.4**
Iloperidone	5	16	266.7	1[d]	**19.5**	**+16.9**	…	…	…	…	…	…	…	…	…	2	7.6	+5.7	2	23.1	+4.19
Lurasidone	6	70.6	353	7	128	−0.4	1[e]	120	+1.8	4	**113.66**	**+1.63**	6	5.72	−1.78	4	50.53	+2.53	8	117.14	+2.27
Olanzapine oral	5.75	10.5	210	6	**14.85**	**+9.83**	5	10.76	+2.81	5	14.90	+1.28	5	**5.8**	**+4.68**	6	**12.26**	**+39.2**	6	**8.73**	**+12.3**
Olanzapine (LAI)[c,d]	8	11.6	232	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Paliperidone oral	6	8	533	4	5.5	+1.73	2	4.80	−0.56	4	**14.72**	**+3.2**	4	4.49	+0.55	4	5.91	+7.2	6	8.6	+1.10
Paliperidone (LAI)[c,d]	12	4.8	320	1[e]	**59.68**	**+6.58**	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Quetiapine IR	6	470	352.5	4	**787**	**+6.32**	**3**	**433.8**	**+4.26**	**4**	**777.2**	**+4.53**	**4**	**351**	**+3.6**	**4**	**365.5**	**+43.1**	**4**	**395**	**+13.8**
Quetiapine ER	6	575	431	5	**410.4**	**+3.47**	**4**	**325**	**+5.8**	**5**	**741.6**	**+1.01**	**5**	**423**	**+2.4**	**3**	**638.8**	**+28.1**	**5**	**746**	**+9.37**
Risperidone oral	5.2	4.3	215		…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…
Risperidone (LAI)[c]	12	4.5	225		…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…	…

[a]Significant results ($P < .05$) are highlighted in bold.
[b]A high uncertainty is present for some results concerning high doses of aripiprazole, asenapine, and cariprazine.
[c]Approximations of daily dose were obtained by converting the ED95 per the published manufacturer monograph for each antipsychotic.
[d]LAI injections were given every 4 weeks for aripiprazole and paliperidone, every 2 weeks and every 4 weeks for olanzapine LAI, and every 2 weeks and for risperidone LAI.
[e]Estimated for only one study.
Abbreviations: ED50 = 50% effective dose, or median effective dose; ED95 = 95% effective dose, or near maximal effective dose; ER = extended release; IR = immediate release; LAI = long-acting injectable; NA = not applicable.

Table 3. Association Between Increase in Dose of Antipsychotic, Weight, and Metabolic Disturbance[a]

	Weight Gain		Glucose		Insulin		Triglycerides		HDL Cholesterol[b]		LDL Cholesterol		Total Cholesterol	
	No. of Studies	*P* value	No. of Studies	*P* value	No. of Studies	*P* value	No. of Studies	*P* value	No. of Studies	*P* value	No. of Studies	*P* value	No. of Studies	*P* value
Aripiprazole oral	5	**.012**	2	.209	…	…	2	.83	**2**	.708	2	.390	2	.349
Aripiprazole LAI	2	.211	2	.878	…	…	2	.533	**2**	**<.001**	2	**.027**	2	.189
Asenapine	**3**	**.01**	2	.123	2	.069	1	.272	…	…	…	…	2	.610
Brexpiprazole	4	**<.0001**	2	.188	…	…	4	.269	**4**	**<.001**	4	.818	2	.056
Cariprazine	3	**.0004**	2	.093	…	…	3	.848	3	.308	3	**<.0001**	3	**<.0001**
Haloperidol	6	**.037**	…	…	…	…	…	…	…	…	…	…	…	…
Iloperidone	2	**<.0001**	1	**<.001**	…	…	2	.423	…	…	…	…	2	.595
Lurasidone	**9**	**<.0001**	8	.798	1	.732	4	.234	**4**	**.049**	6	.880	8	.514
Olanzapine (oral)	**8**	**<.0001**	6	**.0001**	5	.238	6	**<.0001**	5	.555	5	**.02**	6	**.003**
Olanzapine LAI	**1**	**<.0001**	…	…	…	…	…	…	…	…	…	…	…	…
Paliperidone (oral)	5	**<.0001**	4	.711	2	.807	4	.272	4	**<.0001**	4	.595	3	.916
Paliperidone LAI	4	**<.0001**	1	**<.0001**	…	…	…	…	…	…	…	…	…	…
Quetiapine IR	5	**<.0001**	**4**	**.001**	**3**	**.006**	**4**	**<.001**	4	**.035**	**4**	**.015**	**4**	**<.0001**
Quetiapine ER	5	**<.0001**	**5**	**.004**	4	**.003**	**4**	**<.001**	**5**	**.001**	**5**	**.0002**	**5**	**.0001**
Risperidone	6	**<.0001**	…		…		…		…		…		…	
Risperidone LAI	1	**<.0001**	…		…		…		…		…		…	
Visual inspection of the curves with significant associations (*P* < .05)	Curves that continue to decrease	Curves with a slight decrease	Curves with a decrease followed by a plateau		Curves with no tendency		Quasi-parabolic curves		Curves with an increase followed by a plateau		Curves with a slight increase		Curves that continue to increase	

[a]Boldface indicates statistical significance. Additional information: For olanzapine LAI and paliperidone LAI studies, data were only/mostly obtained for the weight. In addition, due to the paucity of available data, additional analysis could not be conducted for haloperidol and risperidone. A high uncertainty is present for some results concerning high doses of aripiprazole, of asenapine, and of cariprazine Bell shape was found for aripiprazole HDL and LDL cholesterol, brexpiprazole HDL cholesterol, cariprazine HDL, and paliperidone HDL cholesterol; inverted bell shape was found for brexpiprazole triglycerides, olanzapine glucose, paliperidone glucose, and HDL cholesterol.
[b]For HDL cholesterol, the rise in the curve indicates a potential benefit for the metabolic function; therefore, the colors used are inverted.
Abbreviations: ER = extended release, HDL = high-density lipoprotein, IR = immediate release, LAI = long-acting injectable; LDL = low-density lipoprotein.

lurasidone with HDL cholesterol ($\chi^2 = 6.14$; $P = .045$). The HDL cholesterol curve continued to ascend.

Olanzapine. Olanzapine was the antipsychotic with the most available data. Dose-response associations were found between increasing doses of olanzapine and glucose ($\chi^2 = 18.2$; $P < .0001$), triglycerides ($\chi^2 = 63.8$; $P < .0001$), total cholesterol ($\chi^2 = 11.4$; $P = .003$), and LDL cholesterol ($\chi^2 = 7.8$; $P = .02$). The total cholesterol curve plateaued. The glucose and triglyceride curves continued to ascend, and the LDL cholesterol curve presented a quasi-parabolic shape.

Paliperidone (oral). Increasing doses of oral paliperidone were significantly associated with HDL cholesterol ($\chi^2 = 20.25$; $P < .0001$). The HDL cholesterol values continued to increase.

Paliperidone LAI. Increasing doses of paliperidone LAI were significantly associated with glucose concentrations ($\chi^2 = 161.76$; $P < .0001$). The glucose curve was bell-shaped.

Quetiapine (IR and ER). Significant dose-response associations were found for increasing doses of both quetiapine IR and ER with all variables (glucose, insulin, triglycerides, HDL cholesterol, LDL cholesterol, and total cholesterol).

The glucose curve increased with quetiapine IR, while the quetiapine ER curve plateaued. For insulin, quetiapine IR plateaued, and the quetiapine ER curve was quasi-parabolic. For triglycerides, quetiapine IR presented a quasi-parabolic curve, while the curve for quetiapine ER plateaued. The HDL cholesterol curves increased for both quetiapine IR and quetiapine ER. The LDL cholesterol curve presented a quasi-parabolic shape for quetiapine IR and a plateau for quetiapine ER. Total cholesterol values plateaued for quetiapine and continued to increase for quetiapine ER.

Heterogeneity Assessments

The VPC was retrieved for the primary outcome across each different antipsychotic (Supplementary Figure 3). For aripiprazole, brexpiprazole, lurasidone, paliperidone LAI, quetiapine IR, and risperidone, no heterogeneity was found. A low level of heterogeneity (VPC < 25%) was found for haloperidol, a moderate level (VPC < 50%) was found for iloperidone and quetiapine ER, and a considerable level (VPC > 75%) was found for aripiprazole LAI, asenapine, cariprazine, and olanzapine.

Sensitivity Analyses

We conducted a post hoc analysis for the primary outcome excluding the 6 studies (11 different doses of antipsychotics) with a high risk of bias[40,41,51,53,73,76]; however, the results were not significantly altered (Supplementary Figure 4).

DISCUSSION

To the best of our knowledge, this dose-response meta-analysis including 52 RCTs reporting 22,588 participants and 11 antipsychotics is the first dose-response meta-analysis

focusing on weight gain and metabolic disturbance associated with antipsychotics in patients with acute schizophrenia. Although the overall number of studies and included participants was high, only a limited number of studies were available for each drug, and results have therefore to be interpreted with caution. We found significant dose-response associations for weight and specific metabolic variables, with a unique signature for each antipsychotic. All antipsychotics presented significant dose-response associations with weight except for aripiprazole LAI. For weight gain and metabolic disturbance, we obtained dose-response curves with 3 different shapes: (1) curves that decreased with increasing doses, mostly showing a quasi-parabolic (brexpiprazole, cariprazine, haloperidol, lurasidone, and quetiapine ER); (2) curves that reached a plateau after an initial increase (asenapine, iloperidone, paliperidone LAI, quetiapine IR, and oral risperidone); and (3) curves that continued to ascend at the maximum dose shape (aripiprazole oral and LAI, olanzapine oral and LAI, oral paliperidone, and risperidone LAI). In the following sections, we further discuss the findings structured according to the shape of the dose-response curve for weight.

Regarding the results for weight, it is important to note that we found dose-response curves similar to those reported by Wu and colleagues.[18] Wu and colleagues included more studies than did our dose-response meta-analysis, which is mainly related to differences in inclusion criteria and study selection rather than the search strategy. We used a different inclusion strategy focusing strictly on fixed-dose trials that required no or only very limited imputation of scores. The difference regarding included trials is mainly related to the fact that Wu and colleagues included trials without a placebo group, while we considered the placebo reference as important. In addition, Wu et al included some trials with progressive increase of doses, while we included studies that allowed for doses to vary only across a small range. Finally, imputation of scores is commonly used in meta-analysis, but has so far rarely been employed in dose-response meta-analysis, and its potential consequences are therefore less clearly defined. Thus, although the approach chosen by Wu and colleagues provides very important information, we believe our more restrictive approach provides a valuable and complementary contribution to evaluating the robustness of the results.

Overall, the consistency of the results between the Wu et al study[18] and our own studies is reassuring and suggests that the observed dose-response curves for weight may indeed be robust. In addition to weight, we explored dose-response associations with metabolic disturbances.

Antipsychotics With a Decreasing or a Quasi-Parabolic Dose–Response Curve for Weight

The weight gain curves for brexpiprazole, cariprazine, haloperidol, lurasidone and quetiapine ER were quasi-parabolic. For these antipsychotics, the weight gain ED95 ranged from 0.53 to 1.40 kg, which was lower than the corresponding PANSS total ED95 values (Table 1). Considering the quasi-parabolic shape of these curves, these antipsychotics reach their weight gain ED95 at relatively low median effective doses, and higher doses, which mostly correspond to near-maximum effective doses, may even be associated with less weight gain.

Furthermore, only doses higher than the near-maximum effective dose of brexpiprazole were associated with a small increase in total cholesterol in conjunction with an increase in HDL cholesterol. Similar results were found for lurasidone. Furthermore, cariprazine presented significantly decreasing curves at higher doses for both LDL cholesterol and total cholesterol.

Pillinger and colleagues[5] proposed that the antipsychotics in this group, except for quetiapine, can be considered "metabolically neutral" with low weight gain and metabolic disturbance compared to other antipsychotics. These results are at least partially supported by our dose-response findings.

Antipsychotics With a Plateau-Shaped Curve for Weight

Asenapine, iloperidone, paliperidone LAI, quetiapine IR, and risperidone all presented plateau-shaped curves for weight. For these antipsychotics, the weight gain ED95 ranged from 1.36 to 2.65 kg. For these substances, except for asenapine, the ED95 values for weight gain and for the PANSS total score were comparable.

For both IR and ER quetiapine, similar and significant dose-response associations with all metabolic parameters were found, with a slightly smaller impact noted for the ER form. Notably, no data were available for very low doses of quetiapine that are commonly prescribed, but a recent prospective cohort study[86] suggests that even subtherapeutic doses of quetiapine may be associated with significant metabolic alterations.

Antipsychotic-Induced Weight Gain Curve That Continued to Ascend

Both aripiprazole and olanzapine oral and LAI, risperidone LAI, and oral paliperidone presented weight gain dose-response curves that continued to increase at higher doses, especially for both olanzapine curves. These drugs are generally considered to have different metabolic profiles, as reflected in the ED95 for weight gain, which showed a wide range from 0.88 kg for oral aripiprazole to 4.29 kg for olanzapine LAI.

For aripiprazole, a clear discrepancy in the ED95 was identified between the oral and LAI forms (2.61 kg for the latter). However, high uncertainty exists for the estimation of the dose-response curve for aripiprazole LAI because it is based on only 2 studies with important variance. Nevertheless, higher weight gain was also observed for the LAI formulations of other substances, which is consistent with at least one previous observational study of aripiprazole and paliperidone.[87] If confirmed, this observation raises the question of whether higher adherence to LAI antipsychotics and consequently higher plasma levels can account for this effect.

Among all included antipsychotics, olanzapine presented the most pronounced weight gain, with a clear ascending dose-response curve. In addition, olanzapine presented significant dose-response associations with all metabolic outcomes, particularly the glucose concentration at the highest doses, which is consistent with a recent epidemiologic study reporting that the risk of olanzapine-induced type 2 diabetes seems dose-dependent.[88]

We also observed that the ED95 values for weight were mostly lower than the ED95 values for PANSS total symptom improvement. Pillinger and colleagues[5] have previously reported that improvements in total symptom severity may be associated with weight increases, BMI, total cholesterol and LDL cholesterol concentrations and decreases in HDL cholesterol concentrations. Our results suggest that for some drugs with important metabolic side effects, a lower dose might provide a better combination of high efficacy and reduced metabolic side effects.

Study Limitations

This meta-analysis has several limitations. The one-stage model has the advantage over other models of aggregated dose-response data with considerable flexibility and precision, as curves can be estimated even if individual studies provide a limited number of data points. One limitation is the requirement of placebo as reference, which limits the number of available studies. In dose-response meta-analysis, measures of effect are expressed in terms mean differences using a dose level as reference. In order to have a reference across studies placebo-values for each study are important. However, since a placebo group is used as a reference, the analysis is susceptible to extreme mean placebo changes, which may be of particular concern in relation to reports that the placebo response in many antipsychotic drug trials has increased over the years while the drug response has remained stable.[89] Furthermore, the choice to only include fixed-dose limits our findings, however it avoids dose and response to be confounded, and a selection bias due to the direct comparison of dose groups at any time.[90] Another limitation is our visual inspection of the curves, and their classification according to shape is based on subjective interpretation.

The main limitation is the paucity of data for some drugs, such as first-generations antipsychotics and clozapine, and outcomes, especially metabolic parameters. As stated in the Methods section, the dose-response curve can be estimated when few data points are available, provided those are calculated from sufficiently rich underlying data.[26] Nevertheless, the estimation of non-linear curves may be less precise when very few data points are available. In addition, the limited number of studies for some antipsychotics clearly increase heterogeneity. Therefore, the dose-response curves obtained from only one or two studies should be interpreted with caution. The absence of data for clozapine is an important limitation considering that it is one of the antipsychotics associated with the highest risk of metabolic dysregulation. Due to the paucity of gathered studies, publication bias could not be explored via a funnel plot. In addition, heterogeneity measures should be interpreted with caution when only a few studies are available.

Furthermore, our results are derived from short-term trials with a highly selected population and excluded non-English studies, which limits the generalizability of our results. Eight trials had only a duration of 4 weeks, which may limit the impact on weight and metabolic parameter. We decided to include studies of this short duration, because there is some evidence for very early onset of both weight gain and metabolic dysregulation. The dose-response prediction cannot be simply extrapolated to longer duration of treatments, for example for relapse prevention. Therefore, studies with longer durations of treatments are needed.

Questions arise regarding potential mediating effects on our outcomes, such as variation in adherence, the amount of daily physical activity, lifestyle, or diet, which remain unanswered by our analysis.

A further limitation is the experimental setting of the source of evidence. Complementary evidence synthesis efforts using experimental evidence and real-world data are crucial. For instance, while antipsychotics have been determined to negatively impact weight and metabolic status, real-world evidence has consistently shown that they are associated with lower all-cause and cause-specific mortality,[91] which might be due to higher compliance with cardiometabolic medication prescriptions when patients are taking their medications.[92]

Clinical Relevance

Although our results were limited by the paucity of available data, these results can provide additional information for clinicians aiming to determine the most suitable dose to prevent weight gain and metabolic disturbance in a shared decision-making process with their patients. These results allow prediction of short-term weight gain at a specific antipsychotic dose and comparisons to the average symptom improvement at the same dose.

The present results add to existing concerns about the use of olanzapine as a first-line drug because the drug clearly causes pronounced changes in weight and metabolic parameters that increase with the dose. Whether the use of olanzapine should be restricted to second-line treatment or even treatment-resistant patients requires further discussion.

Overall, our findings may be particularly relevant for patient populations considered at-risk groups, as identified by Pillinger and colleagues,[5] who, in a recent network meta-analysis examining predictors of antipsychotic-induced metabolic changes, found that increased baseline body weight, male sex, and non-White ethnicity predict greater vulnerability to antipsychotic-induced metabolic dysregulation. It would be of high interest to explore the role of these risk factors on dose-response associations, but for this purpose individual patient data would be needed.

CONCLUSIONS

We found significant dose-response associations for weight and metabolic variables, with a unique signature for each antipsychotic. Weight gain can occur at a relatively low median effective dose, and increasing doses can be associated with greater weight gain for some drugs. These results have to be interpreted with caution due several limitations, most notably the limited number of studies that could be included. Future RCTs of antipsychotics should report the full range of weight and metabolic parameters. Furthermore, the assessment of dose-response effects would strongly benefit from studies using doses in the very low and very high ranges. Finally, and most importantly, more RCTs reporting long-term metabolic parameters are needed to evaluate the dose-response effects of continued recommended treatment.

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Additional information: The code used for analysis is available via open access at the following link: https://github.com/alecri/one-stage-dosresmeta The specific adaptation of the code for the present study and the study database are available upon reasonable request addressed to the corresponding author.

Supplementary material: Available at Psychiatrist.com.

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Editor's Note: We encourage authors to submit papers for consideration as a part of our Focus on Psychosis section. Please contact Ann K. Shinn, MD, MPH, at ashinn@psychiatrist.com.

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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

Author(s): Michel Sabe, MD; Konstantinos Pallis, MD; Marco Solmi, MD, PhD; Alessio Crippa, PhD; Othman Sentissi, MD, PhD; and Stefan Kaiser, Prof

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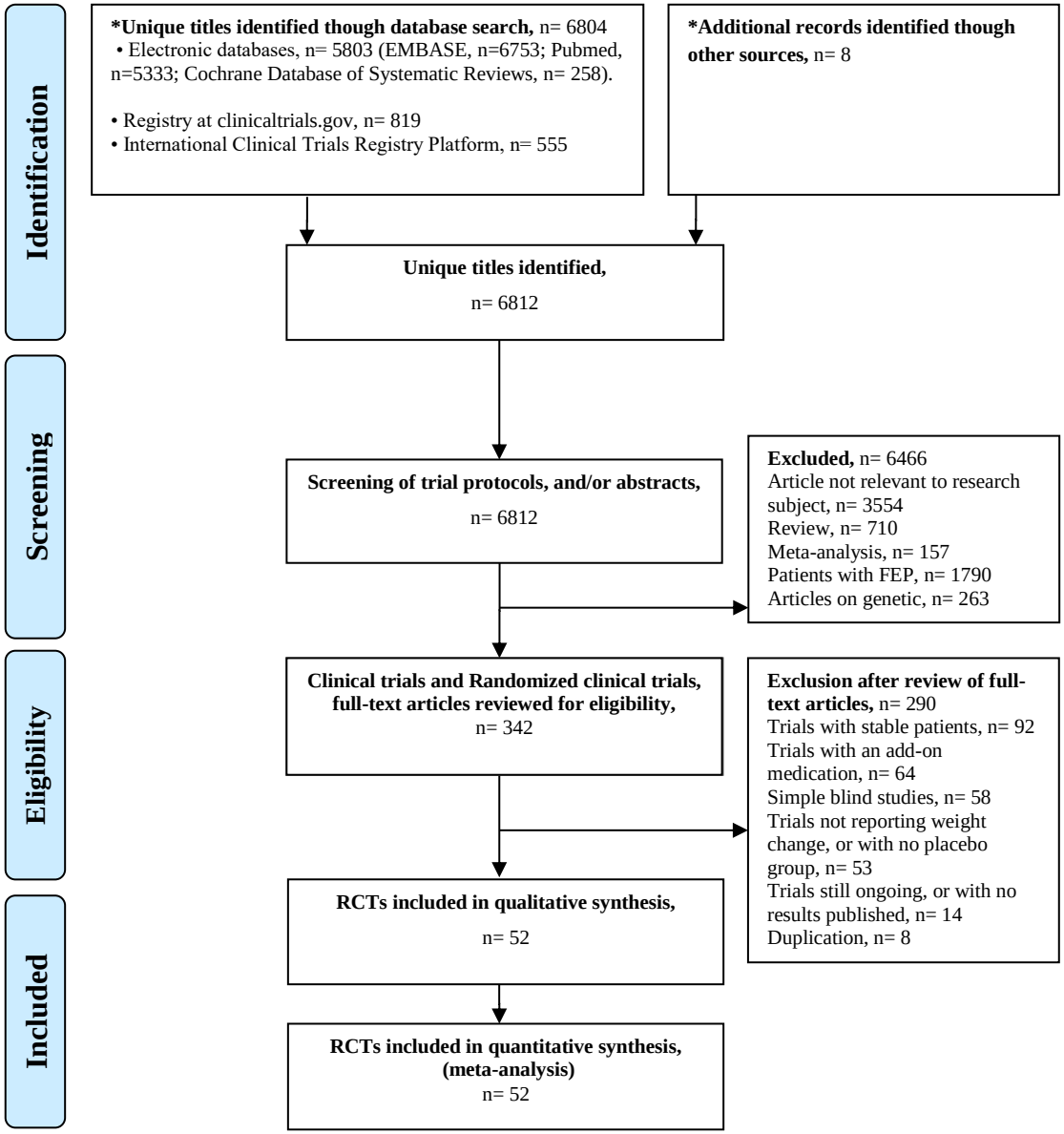
Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

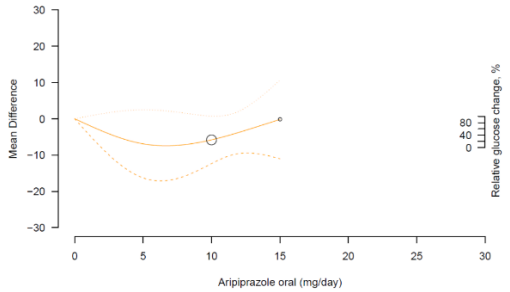
Supplementary Figure 1. Systematic review PRISMA flowchart



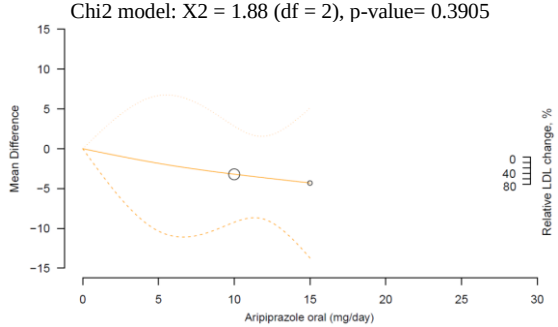
Supplementary Figure 2. Dose-response curves for metabolic disturbance

1. Aripiprazole (oral)

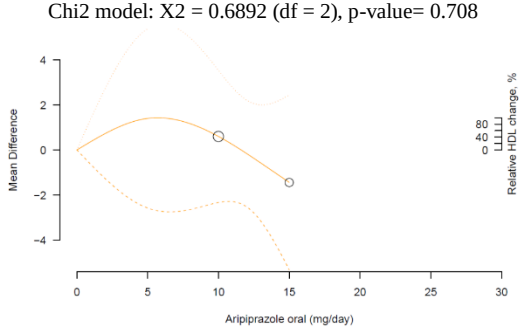
1.a. Glucose concentrations, N= 2, n= 363
Chi2 model: X^2 = 3.1266 (df = 2), p-value= 0.2094



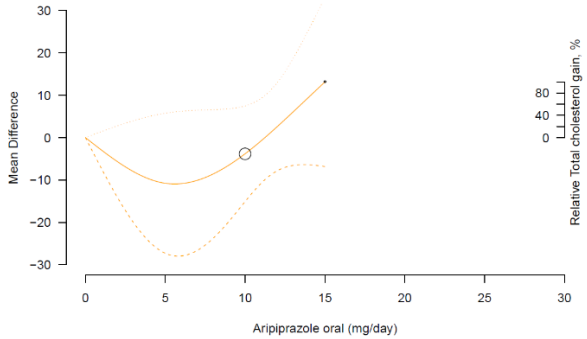
1.b. LDL cholesterol, N= 2, n= 363
Chi2 model: X2 = 1.88 (df = 2), p-value= 0.3905



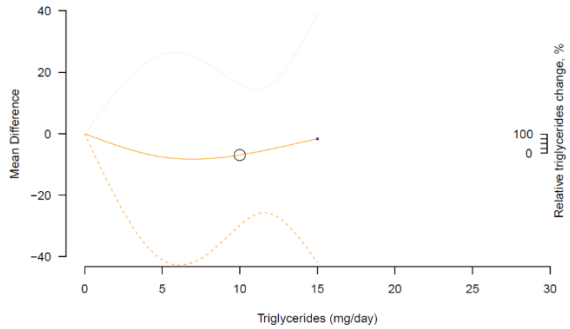
1.c. HDL cholesterol, N= 2, n= 363
Chi2 model: X2 = 0.6892 (df = 2), p-value= 0.708



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

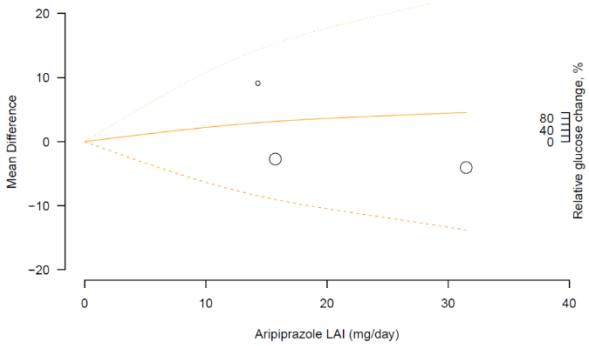


1.e. Triglycerides, N= 2, n= 363
Chi2 model: X2 = 0.3555 (df = 2), p-value= 0.8371

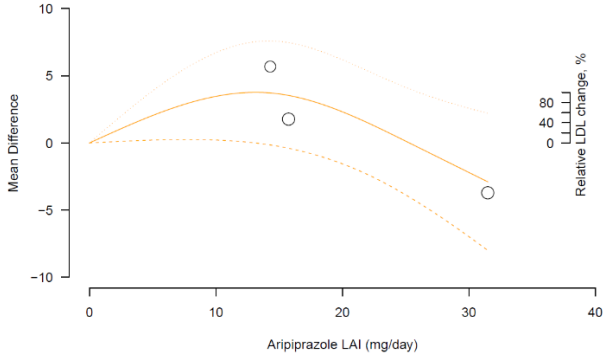


2. Aripiprazole (LAI)

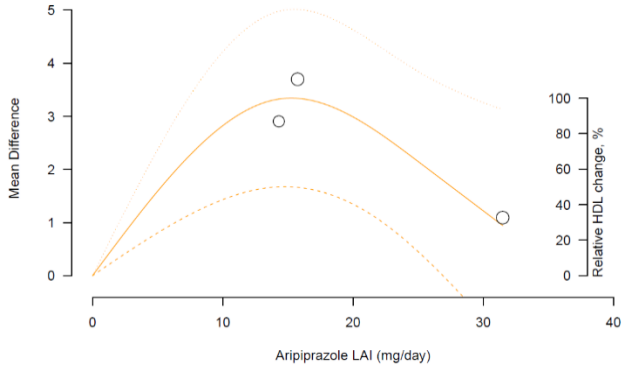
2.a. Glucose concentrations, N= 2, n= 961
Chi2 model: X^2 = 0.2590 (df = 2), p-value= 0.8785



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

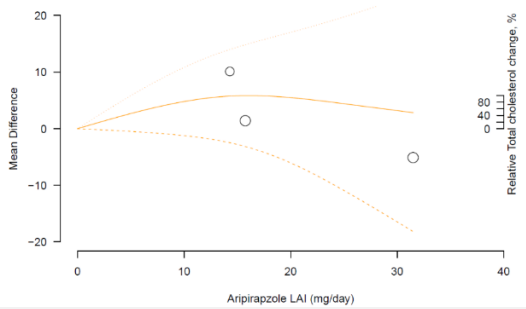


2.c. HDL cholesterol, N= 2, n= 961
Chi2 model: X2 = 15.8 (df = 2), p-value< 0.001



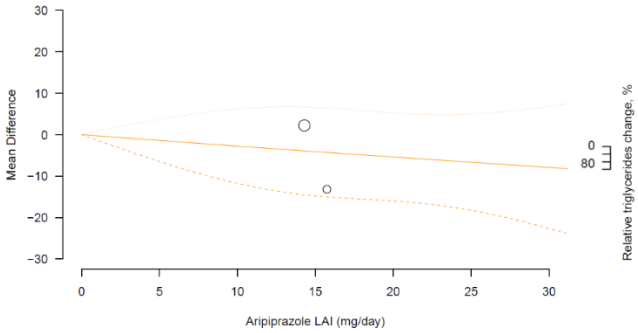
2.d. Total cholesterol, N= 2, n= 961

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



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

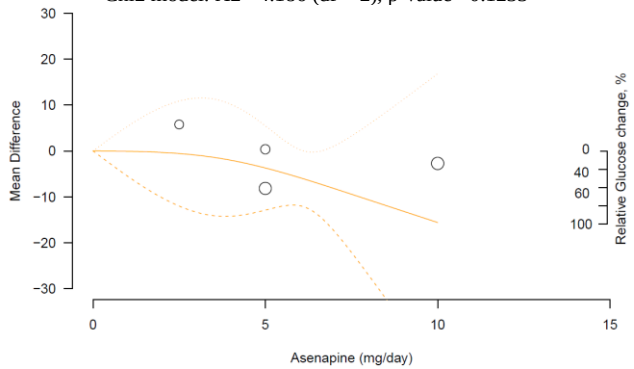
Chi2 model: X2 = 1.2565 (df = 2), p-value= 0.5335



3. Asenapine

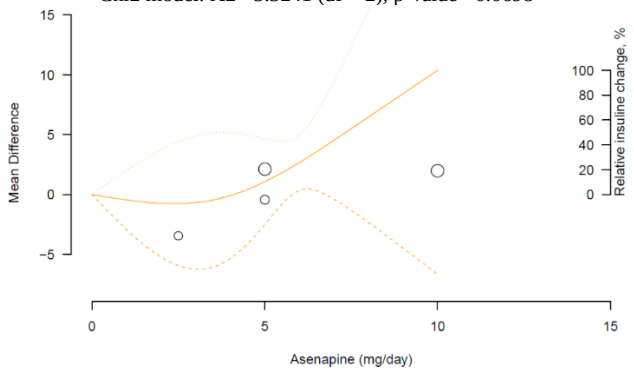
3.a. Glucose, N= 2, n= 819

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



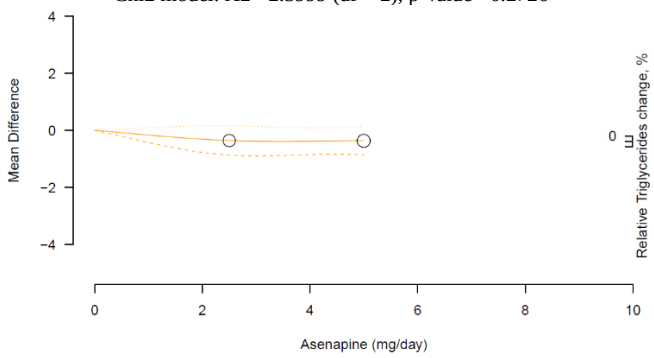
3.b. Insulin, N= 2, n= 819

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



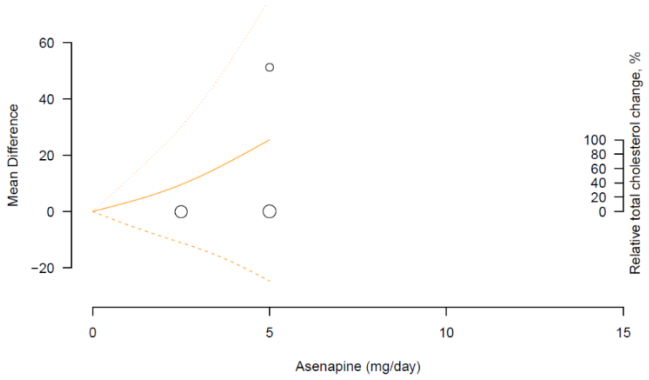
3.c. Triglycerides, N= 1, n= 294

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



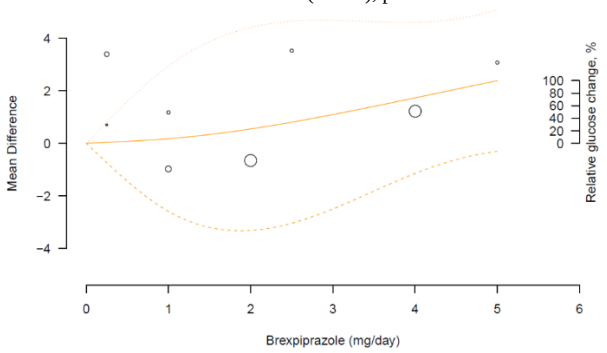
3.d. Total cholesterol, N= 2, n= 415

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

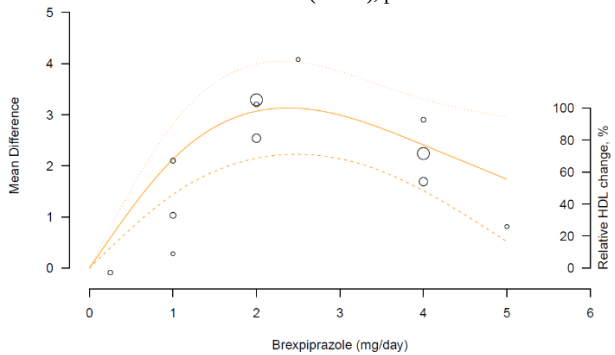


4. Brexpiprazole

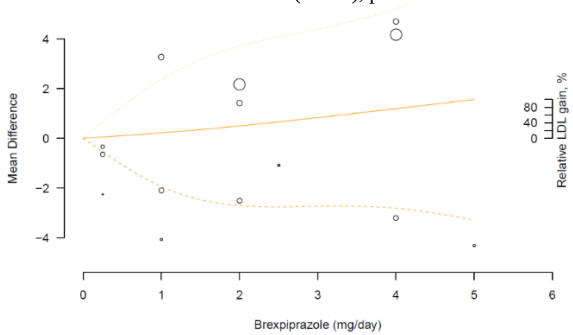
4.a. Glucose, N= 2, n= 1714
Chi2 model: X2= 3.3361 (df = 2), p-value= 0.1886



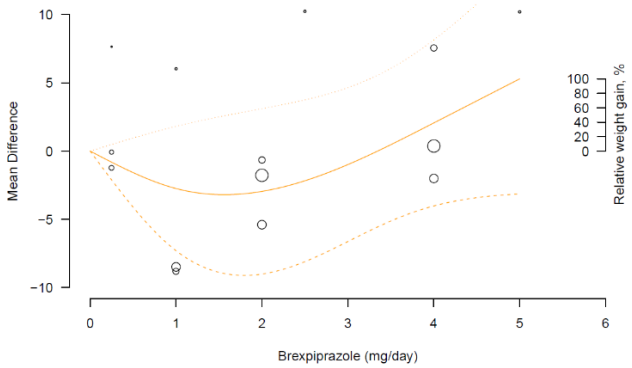
4.b. HDL cholesterol, N= 4, n= 2809
Chi2 model: X2= 47.36 (df = 2), p-value <0.001



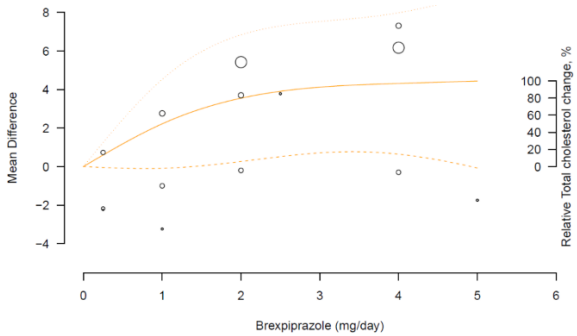
4.c. LDL cholesterol, N= 4, n= 2809
Chi2 model: X2= 0.4016 (df = 2), p-value= 0.8181



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

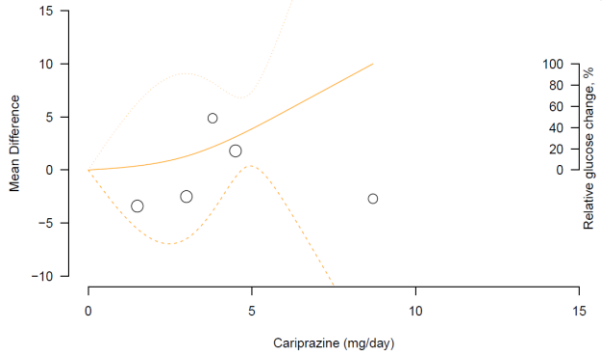


4.e. Total cholesterol, N= 4, n= 2809
Chi2 model: X2= 5.7546 (df = 2), p-value= 0.0563

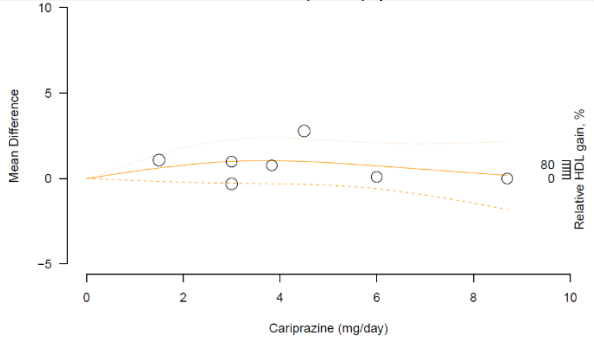


5. Cariprazine

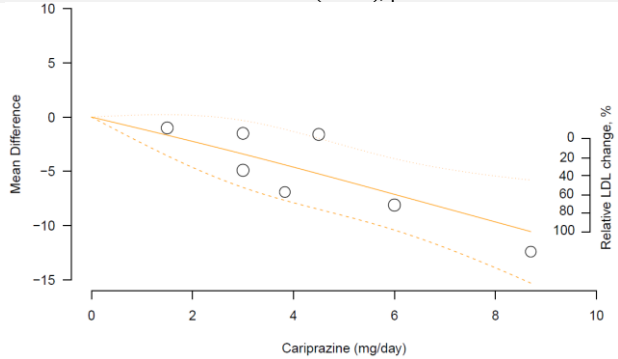
5.a. Glucose, N= 2, n= 1035
Chi2 model: X2= 4.7418(df = 2), p-value= 0.0934



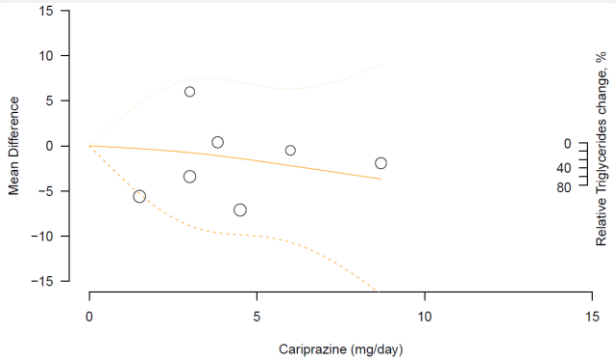
5.b. HDL cholesterol, N= 3, n= 1496
Chi2 model: X2= 2.3538 (df = 2), p-value= 0.308



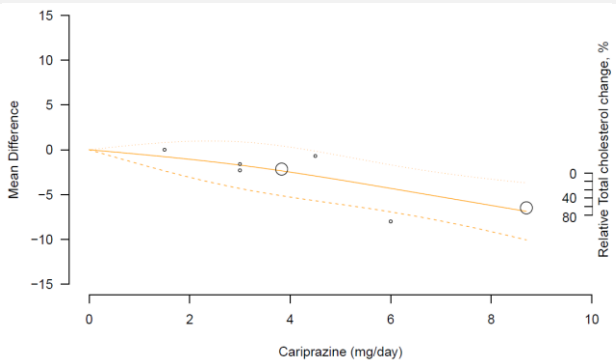
5.c. LDL cholesterol, N= 3, n= 1496
Chi2 model: X2= 20.607 (df = 2), p-value< 0.0001



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

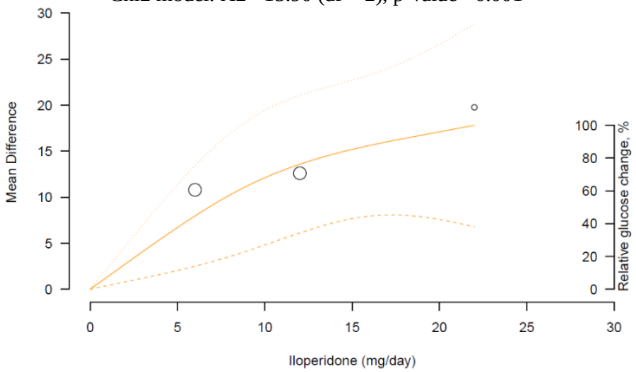


5.e. Total cholesterol, N= 3, n= 1496
Chi2 model: X2= 17.9708 (df = 2), p-value< 0.0001

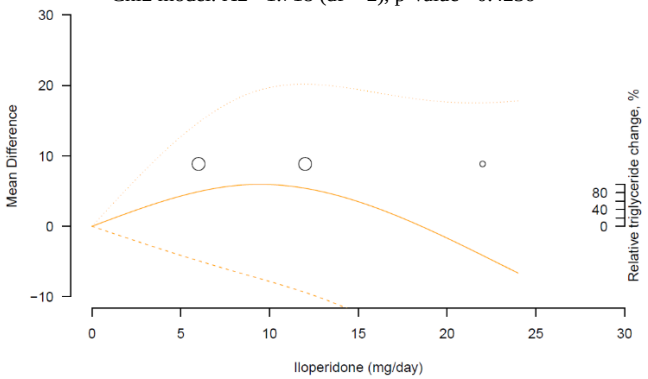


6. Iloperidone

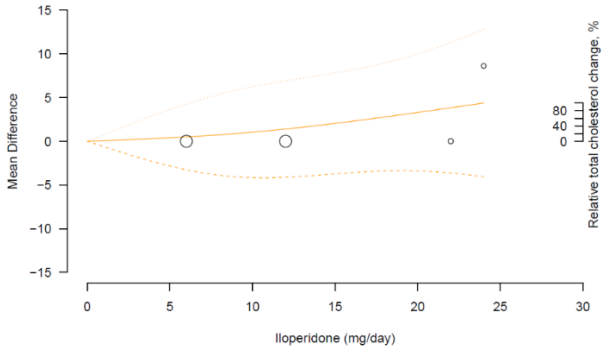
6.a. Glucose, N= 1, n= 1484
Chi2 model: X2= 15.90 (df = 2), p-value< 0.001



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

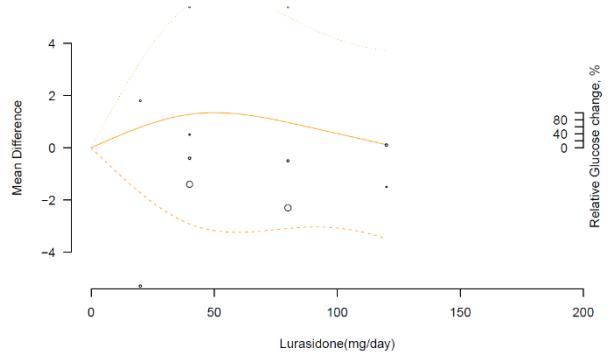


6.c. Total cholesterol, N= 2, n= 1928
Chi2 model: X2= 1.0358 (df = 2), p-value= 0.5958

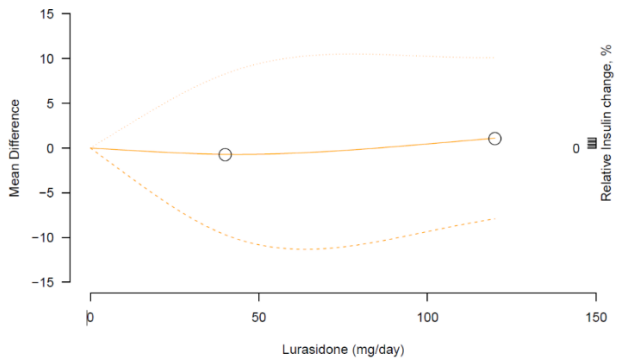


7. Lurasidone

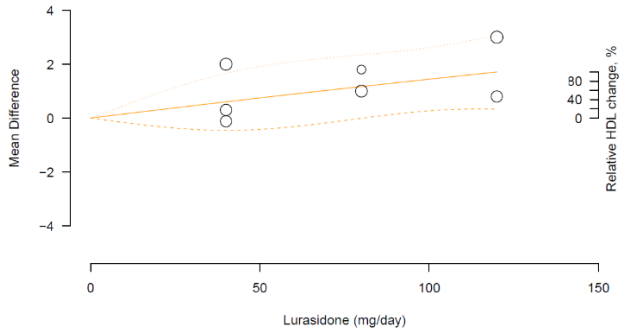
7.a. Glucose, N= 7, n= 2046
Chi2 model: X2= 0.4490 (df = 2), p-value= 0.789



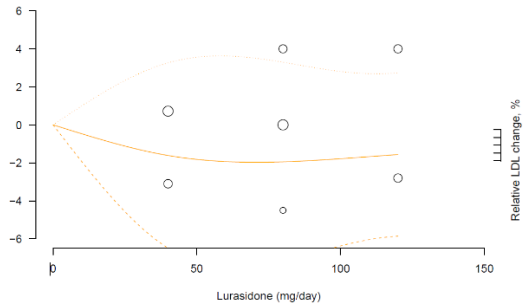
7.b. Insulin, N= 1, n= 353
Chi2 model: X2= 0.6223 (df = 2), p-value= 0.732



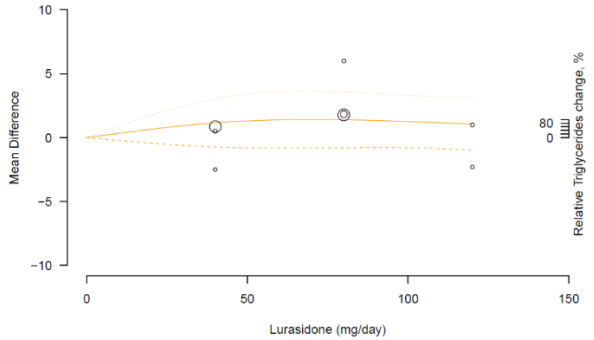
7.c. HDL cholesterol, N= 4, n= 1436
Chi2 model: X2= 6.1364 (df = 2), p-value= 0.045



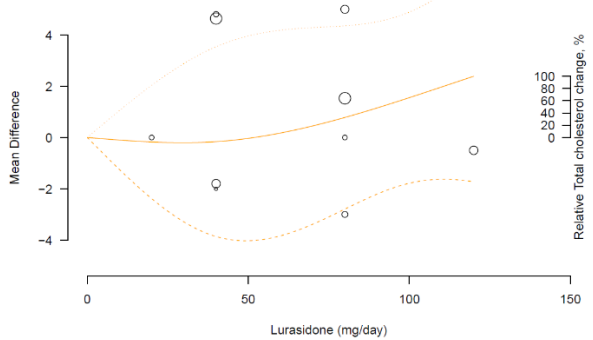
7.d. LDL cholesterol, N= 6, n= 2099
Chi2 model: X2= 0.5792 (df = 2), p-value= 0.7486



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

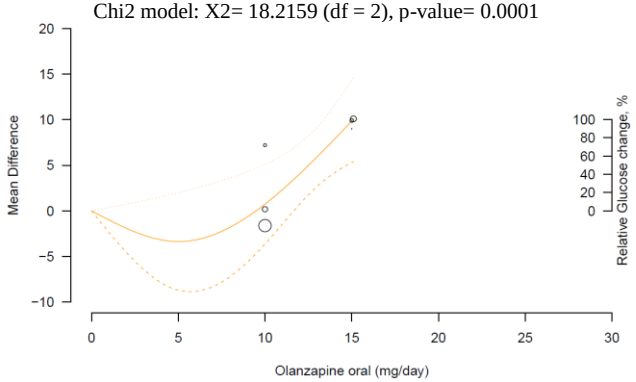


7.f. Total cholesterol, N= 8, n= 2534
Chi2 model: X2= 1.3131 (df = 2), p-value= 0.5186

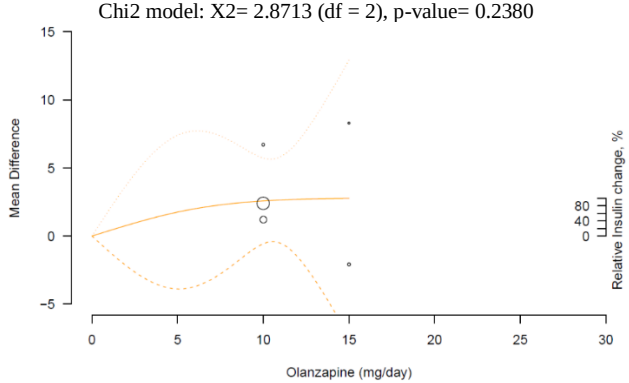


8. Olanzapine oral

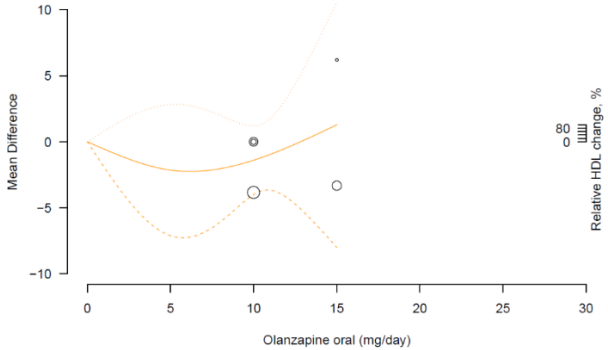
8.a. Glucose, N= 6, n= 1210
Chi2 model: X2= 18.2159 (df = 2), p-value= 0.0001



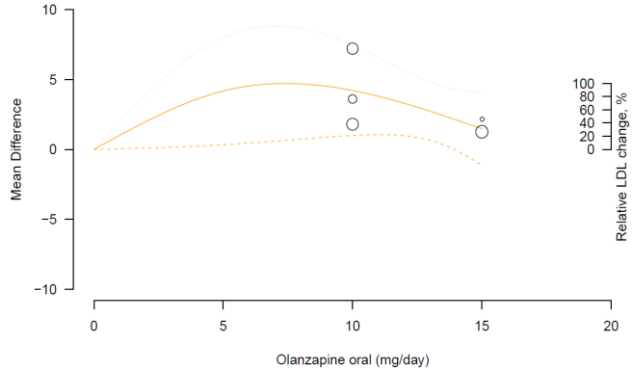
8.b. Insulin, N= 5, n= 1068
Chi2 model: X2= 2.8713 (df = 2), p-value= 0.2380



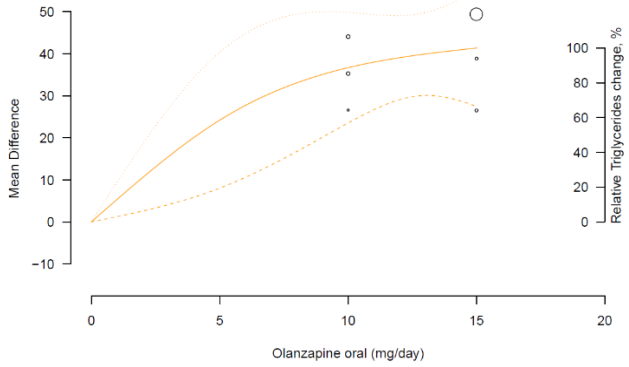
8.c. HDL cholesterol, N= 5, n= 1063
Chi2 model: X2= 1.1768 (df = 2), p-value= 0.5552



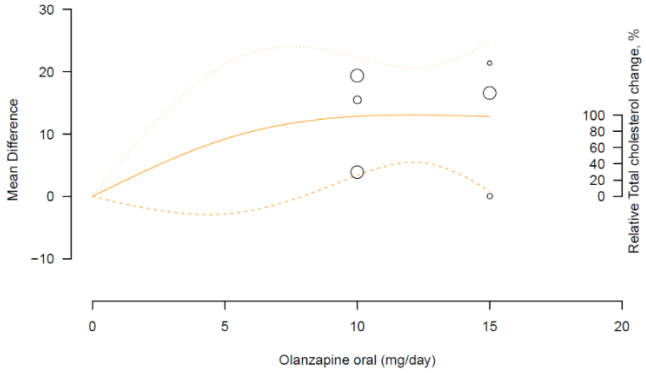
8.d. LDL cholesterol, N= 5, n= 1063
Chi2 model: X2= 7.8019 (df = 2), p-value= 0.02



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

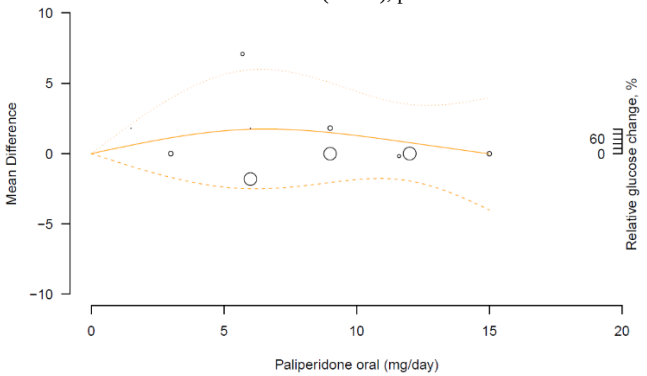


8.f. Total cholesterol, N= 6, n= 1220
Chi2 model: X2= 11.3735 (df = 2), p-value= 0.0034

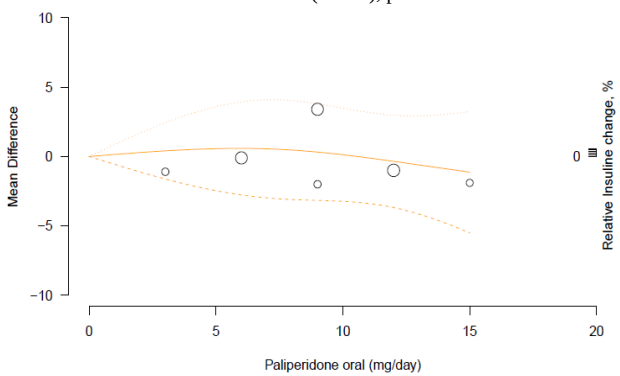


9. Paliperidone (oral)

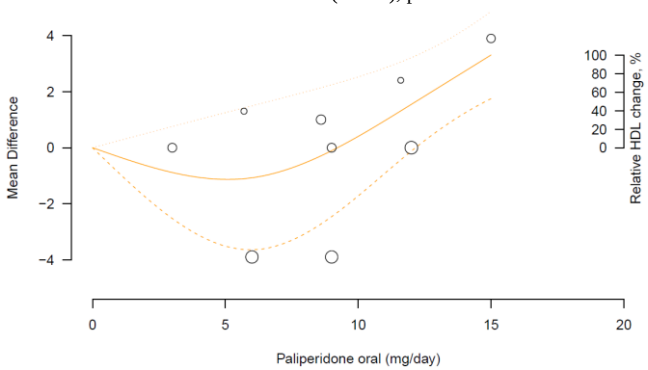
9.a. Glucose, N= 4, n= 1462
Chi2 model: X2= 0.6806 (df = 2), p-value= 0.7116



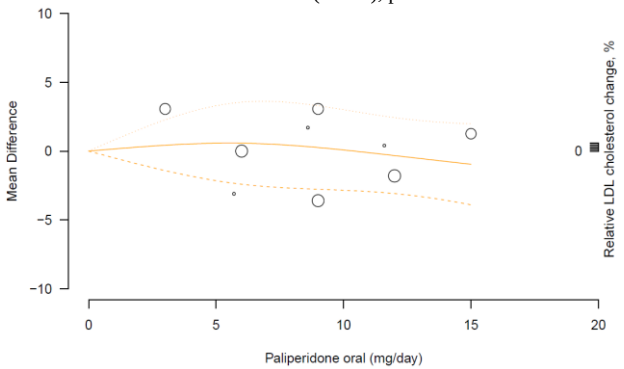
9.b. Insulin, N= 2, n= 979
Chi2 model: X2= 0.4282 (df = 2), p-value= 0.8072



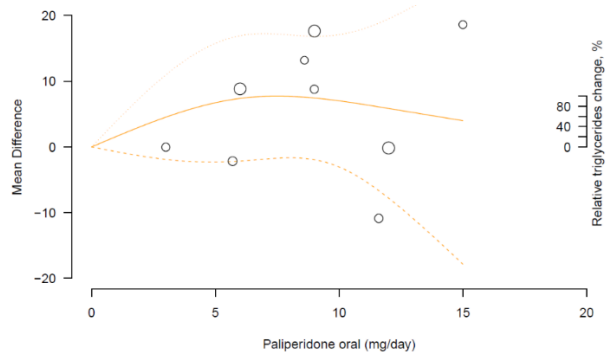
9.c. HDL cholesterol, N= 4, n= 1606
Chi2 model: X2= 20.2450 (df = 2), p-value< 0.0001



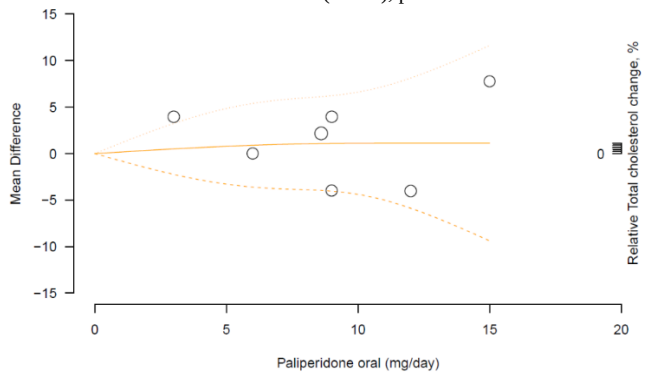
9.d. LDL cholesterol, N= 4, n= 1606
Chi2 model: X2= 1.0383 (df = 2), p-value= 0.5950



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

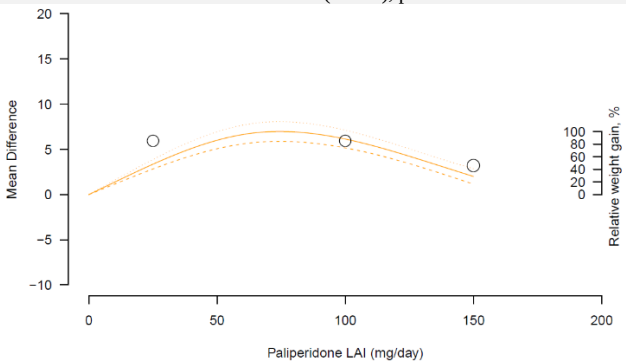


9.f. Total cholesterol, N= 3, n= 1290
Chi2 model: X2= 0.1748(df = 2), p-value= 0.9163



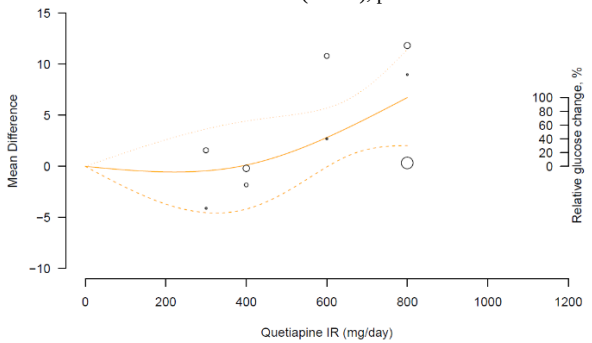
10. Paliperidone LAI

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

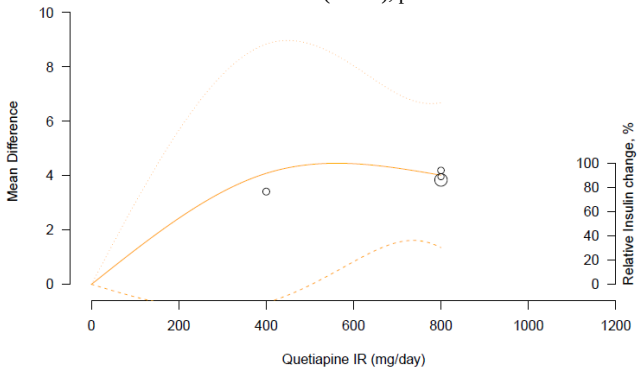


11. Quetiapine IR

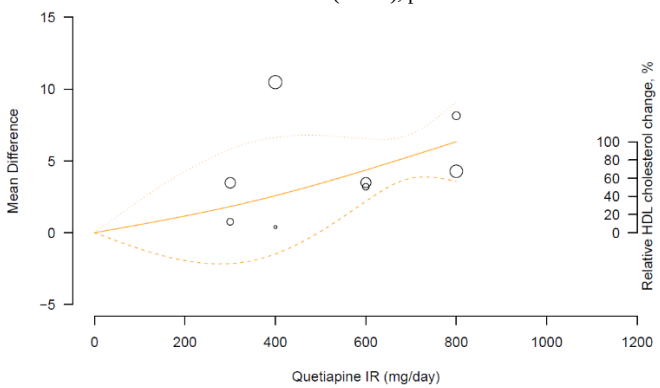
11.a. Glucose, N= 4, n=1680
Chi2 model: X2= 9.2302 (df = 2), p-value= 0.001



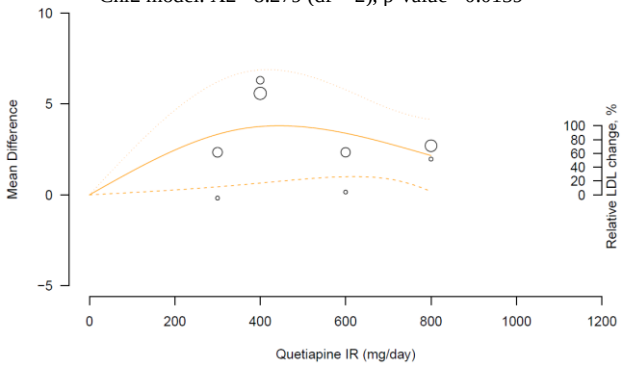
11.b. Insulin, N= 3, n= 1244
Chi2 model: X2= 10.221 (df = 2), p-value= 0.006



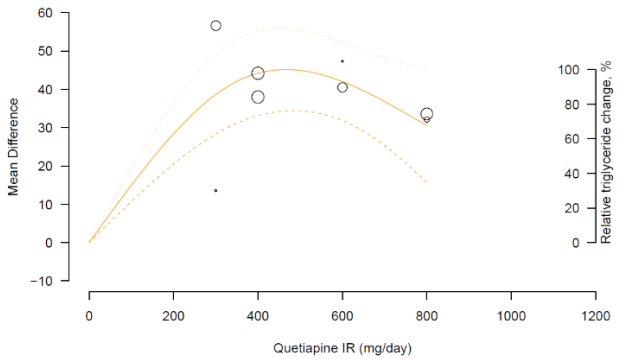
11.c. HDL cholesterol, N= 4, n= 1680
Chi2 model: X2= 6.6920 (df = 2), p-value=0.0352



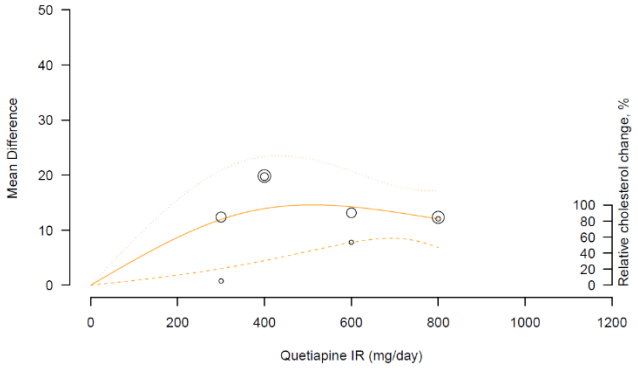
11.d. LDL cholesterol, N= 4, n= 1357
Chi2 model: X2= 8.279 (df = 2), p-value= 0.0159



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

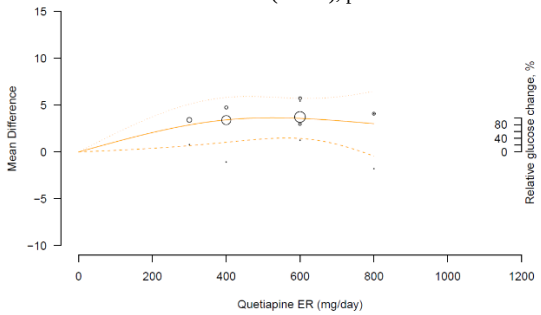


11.f. Total cholesterol, N= 4, n= 1357
Chi2 model: X2 = 30.6207 (df = 2), p-value < 0.0001

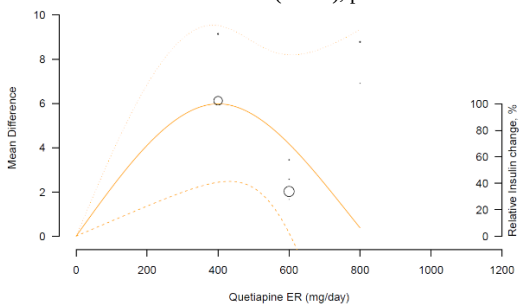


12. Quetiapine ER

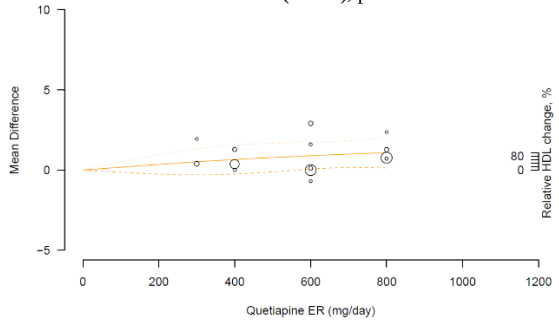
12.a. Glucose, N= 5, n= 2268
Chi2 model: X2= 11.05 (df = 2), p-value= 0.004



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

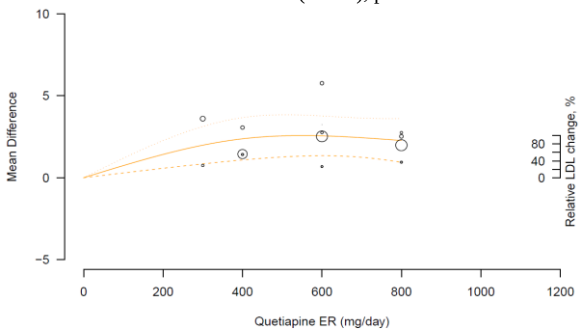


12.c. HDL cholesterol, N= 5, n= 2587
Chi2 model: X2= 5.491 (df = 2), p-value = 0.001



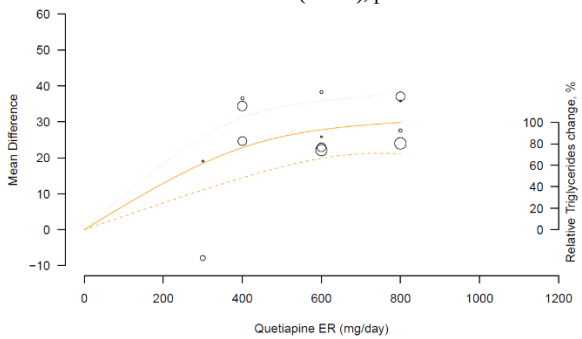
12.d. LDL cholesterol, N= 5, n= 2587

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



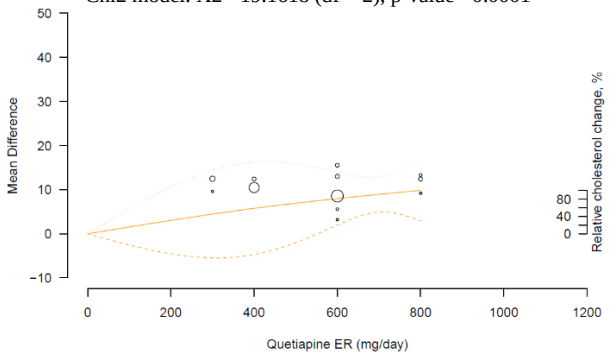
12.e. Triglycerides, N= 4, n= 2351

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



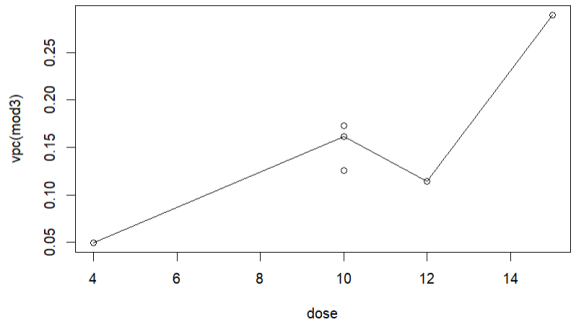
12.f. Total cholesterol, N= 5, n= 2264

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

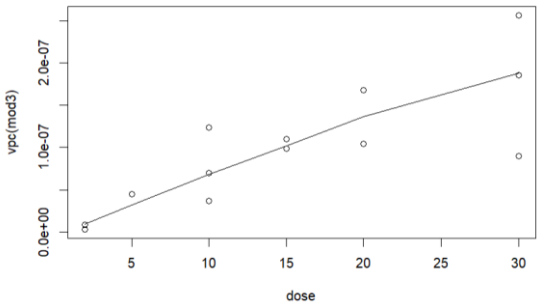


Supplementary Figure 3. Heterogeneity assessments with the variance-partition-coefficient (VPC) for the primary outcome
VPC are expressed as proportion [0-1]. The percentage of heterogeneity can be obtained by multiplying this coefficient by 100.

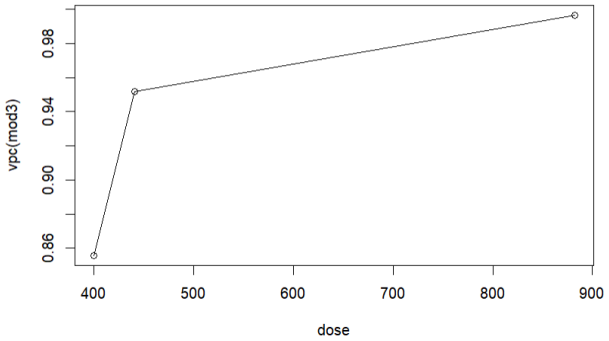
a. Haloperidol, N= 6, n= 1138
VPCs is under 25%, indicating low level of heterogeneity



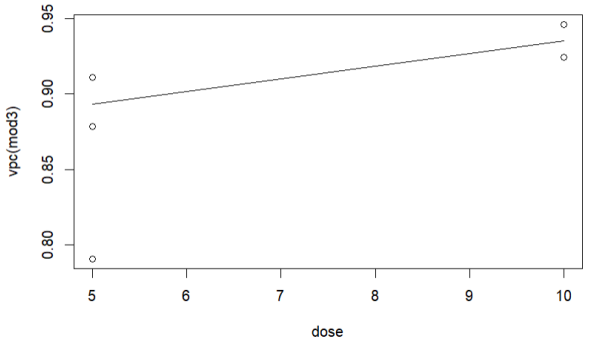
b. Aripiprazole (oral), N= 5, n= 1393
VPCs is 0%, indicating no heterogeneity



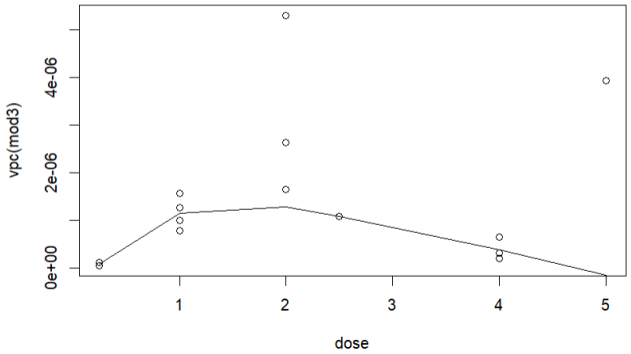
c. Aripiprazole LAI, N= 2, n= 961
There is a considerable level of heterogeneity with VPCs up to 98%



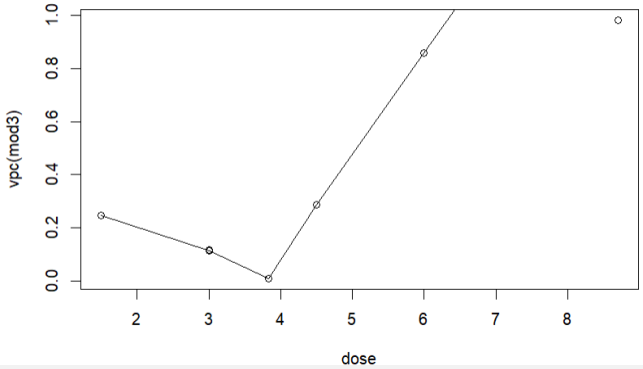
d. Asenapine, N= 3, n= 986
There is a considerable level of heterogeneity with VPCs up to 95%



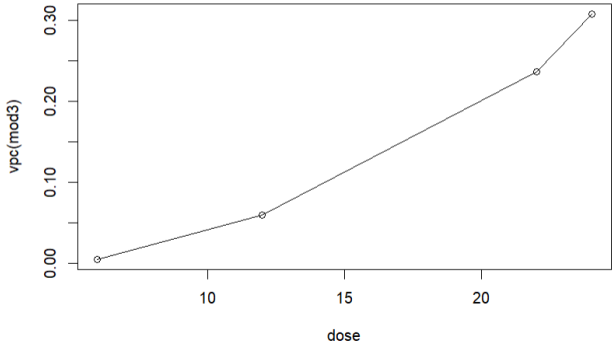
e. Brexpiprazole, N= 4, n= 2847
VPCs is 0%, indicating no heterogeneity



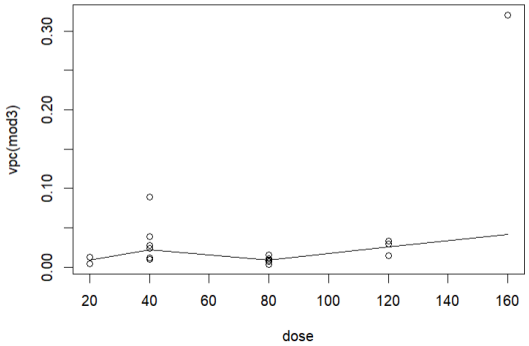
f. Cariprazine, N= 3, n= 1496
There is a considerable level of heterogeneity with VPCs up to 99%



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

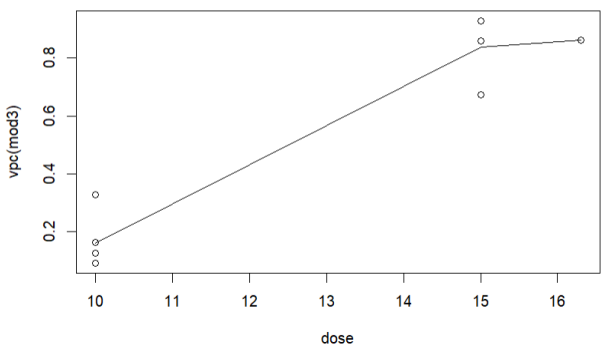


h. Lurasidone, N= 8, n= 2486
VPCs is 0%, indicating no heterogeneity



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

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

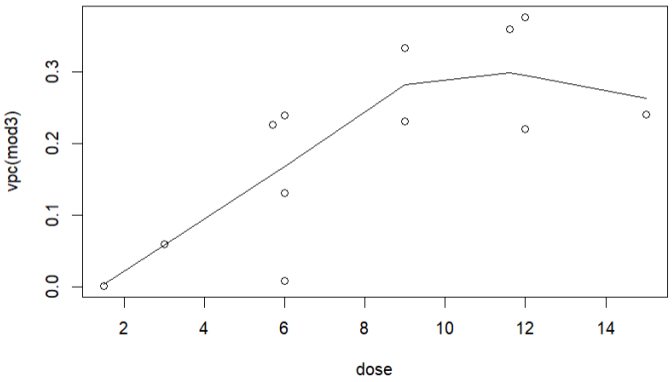


j. Olanzapine LAI[1], N= 1, n= 404

Since only 1 study is available, no heterogeneity was assessed

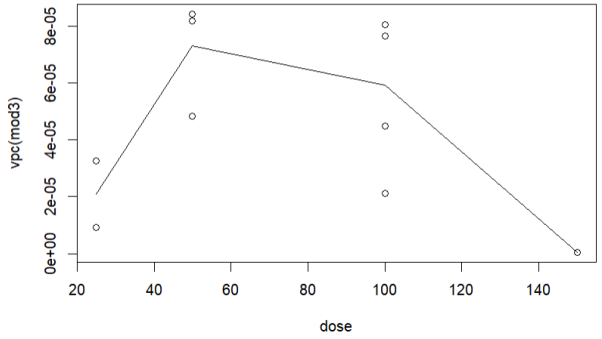
k. Paliperidone (oral), N= 5, n= 1789

VPCs is under 50%, indicating moderate level of heterogeneity



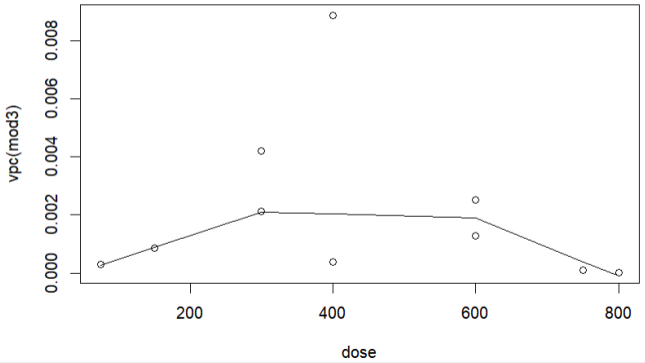
l. Paliperidone LAI, N= 4, n= 1422

VPCs is 0%, indicating no heterogeneity



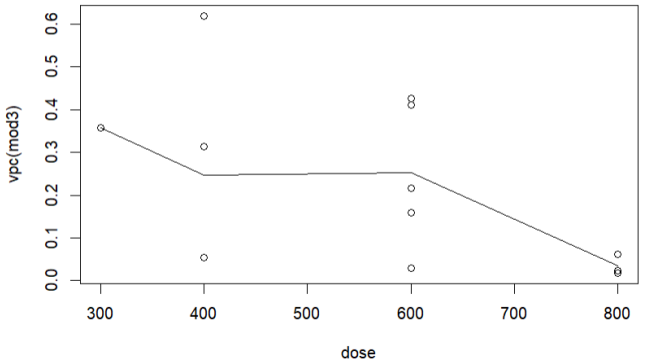
m. Quetiapine IR, N= 5, n= 1494

VPCs is 0%, indicating no heterogeneity



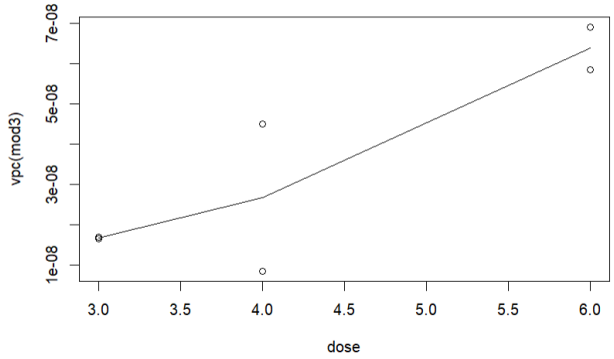
n. Quetiapine ER, N= 5, n= 2163

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

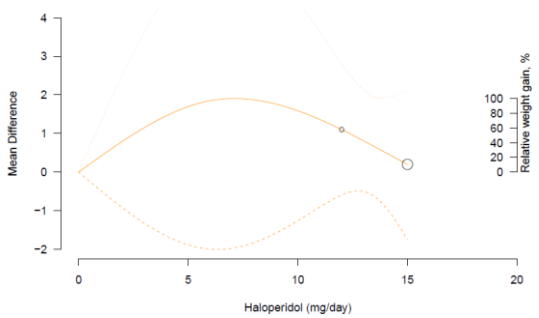
Since only 1 study is available, no heterogeneity was assessed

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.

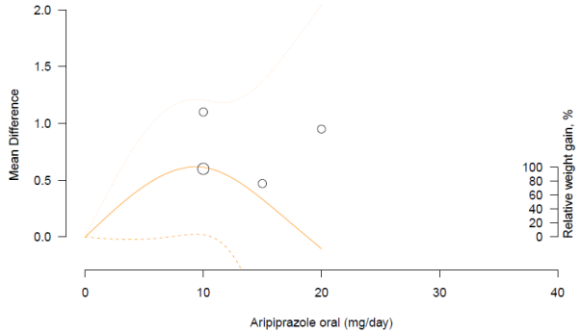
a. Haloperidol, N= 2, n= 354

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



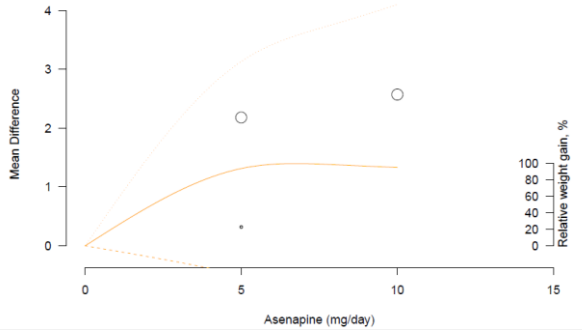
b. Aripiprazole (oral), N= 3, n= 778

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



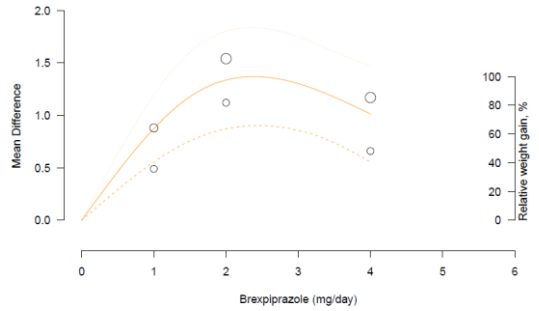
c. Asenapine, N= 2, n= 646

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



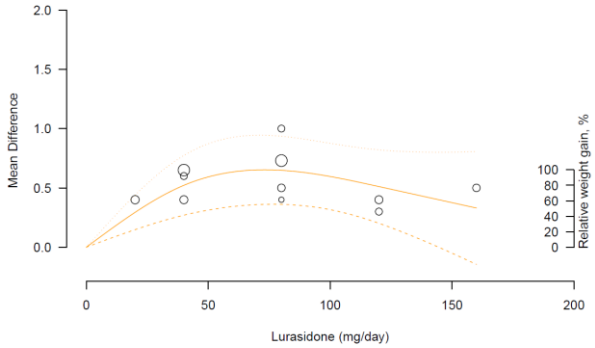
d. Brexpiprazole, N= 2, n= 1133

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



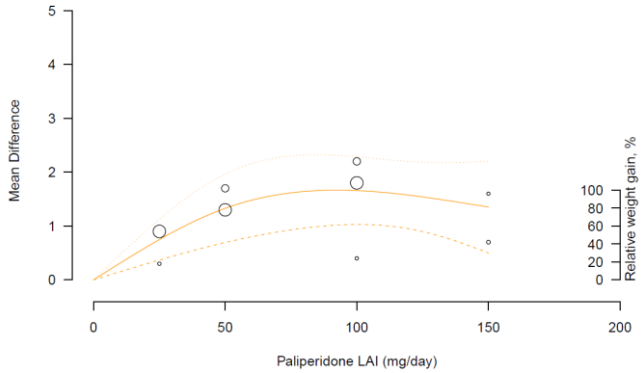
e. Lurasidone, N= 6, n= 2056

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



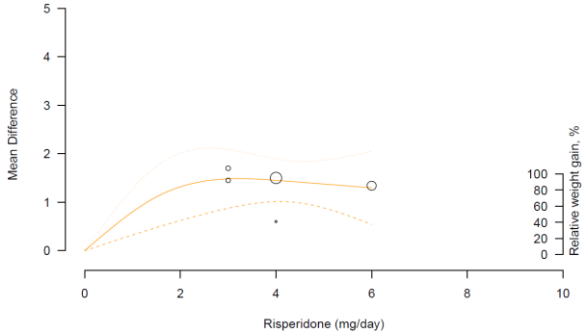
f. Paliperidone LAI, N= 3, n= 1175

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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