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Examination of Dosing of Antipsychotic Drugs for Relapse Prevention in Patients With Stable Schizophrenia
A Meta-analysis

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IMPORTANCE The doses of antipsychotic drugs needed for relapse prevention in schizophrenia is a debated issue.

OBJECTIVE To examine dose-response findings in a meta-analysis of randomized clinical trials.

DATA SOURCES Studies were identified through the Cochrane Schizophrenia Group's Study-Based Register of Trials (March 9, 2020), PubMed (January 1, 2021), and previous reviews. First authors and/or pharmaceutical companies were contacted for additional information.

STUDY SELECTION Two reviewers independently selected randomized clinical trials that compared fixed doses of a second-generation antipsychotic, haloperidol, or fluphenazine for relapse prevention in patients with stable schizophrenia.

DATA EXTRACTION AND SYNTHESIS Using the Preferred Reporting Items for Systematic Reviews and Meta-analyses guideline, all parameters in duplicate were extracted and frequentist dose-response random-effects meta-analyses were conducted.

MAIN OUTCOMES AND MEASURES Study-defined relapse (primary outcome), rehospitalization, Positive and Negative Syndrome Scale or Brief Psychiatric Rating Scale total score reduction from baseline, all-cause discontinuation, and dropouts due to adverse events.

RESULTS Evidence from 72 dose arms from 26 studies with 4776 participants was analyzed. The efficacy-related dose-response curves had a hyperbolic shape meaning that the probability to relapse decreased rapidly with doses of up to 5-mg/d risperidone equivalent (relative relapse risk, 0.43; 95% CI, 0.31-0.57; standardized mean difference for Positive and Negative Syndrome Scale total score reduction, −0.55; 95% CI, −0.68 to −0.41), but flattened thereafter. In contrast, dropouts due to adverse events continued to increase beyond this dose (relative risk at 5 mg/d, 1.38; 95% CI, 0.87-2.55; relative risk at 15 mg/d, 2.68; 95% CI, 1.49-4.62). In a subgroup analysis of patients in remission, a plateau was reached earlier, at approximately 2.5-mg/d risperidone equivalent.

CONCLUSIONS AND RELEVANCE The findings of this meta-analysis suggest that doses higher than approximately 5-mg/d risperidone equivalent may provide limited additional benefit for relapse prevention but more adverse events. For patients in remission or who are receiving high-potency first-generation antipsychotics, doses as low as 2.5-mg/d risperidone equivalent may be sufficient. However, caution is needed at this low dose end when further decreases of dose may be accompanied by a disproportionally higher relapse risk. Moreover, the observations are averages, and factors such as slow or rapid metabolism, age, illness stage, comorbidities, and drug-drug interactions suggest that individual patients will often need higher or lower doses.

Supplemental content

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Antipsychotic drugs are effective for short-term treatment of schizophrenia,[1] and numerous randomized clinical trials have shown that these agents also prevent relapse.[2] However, antipsychotics produce many adverse events.[1] This trade-off is the reason for a debate that has accompanied these drugs since their development in the 1950s. Because patients often need to use antipsychotics for many years, adverse events, such as movement disorders and weight gain, can accumulate and result in even more severe problems, such as tardive dyskinesia[3] or cardiovascular problems. Excess mortality associated with multiple causes is well documented.[4] Therefore, psychiatrists need to know which doses are sufficient for maintenance treatment. If lower doses than needed for short-term treatment were sufficient, the adverse-event burden could be substantially reduced. Bollini et al[5(p307)] reported that "no incremental improvement was found at doses above 375-mg equivalent of chlorpromazine." Similarly, Baldessarini and Davis[6] found no significant dose effect between 100 mg/d and more than 2000 mg/d (median, 310 mg/d) chlorpromazine equivalent. Uchida et al[7] reported that low doses (≥50% daily defined dose [DDD] < 1 DDD) may be as effective as standard doses. Nevertheless, these previous reviews are no longer current, and only one included a few randomized clinical trials on newer, second-generation antipsychotics.[7] Moreover, these reviews did not apply the most appropriate methods to address this issue. Rather, they either assumed linear associations by applying correlations or they compared mean doses below and above more or less arbitrary cutoffs. Dose-response meta-analysis has been successfully applied to identify the optimum doses for the short-term treatment of schizophrenia.[8] In contrast to the above analyses, dose-response meta-analysis does not require a specific shape of the dose-response curve and allows inclusion of more dose arms.[9] We applied this method to provide guidance for clinicians on dosing in relapse prevention for schizophrenia.

Key Points

Question What are the optimum doses for relapse prevention in patients with stable schizophrenia?

Findings In this meta-analysis of 26 studies including 4776 participants, doses higher than approximately 5-mg/d risperidone equivalent were not associated with more efficacy. However, increasing doses were associated with more adverse events.

Meaning In this study, even low doses of antipsychotics appear to have some association with efficacy for relapse prevention in schizophrenia; however, clinicians may need to be cautious when they decrease doses at the lower dose end because further decreases of dose are accompanied by disproportionally higher relapse risk.

Methods

This study followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) reporting guideline for meta-analyses and was registered on Prospero (CRD42020182436) (eAppendix 1 in the Supplement).

We included all fixed-dose, randomized, blinded, or open trials of more than 3 months' duration that compared the following drugs with placebo or at least 1 different dose of the same drug in patients with stable schizophrenia or schizoaffective disorder: amisulpride, aripiprazole (oral, Abilify Maintena and aripiprazole lauroxil), asenapine (oral or transdermal patch), brexpiprazole, cariprazine hydrochloride, clozapine, fluphenazine (oral and long-acting injectable [LAI]), haloperidol (oral and LAI), iloperidone, lumateperone tosylate, lurasidone hydrochloride, olanzapine (oral and LAI), paliperidone (oral, the monthly LAI palmitate, and the 3-monthly LAI Trevicta), quetiapine fumarate (immediate release and extended release), risperidone (oral and the LAIs Consta and Perseris), sertindole, ziprasidone, zotepine. This list comprises all second-generation antipsychotics available in the US and/or Europe. Haloperidol and fluphenazine are first-generation antipsychotics for which pivotal dose-response studies have been conducted and are reported herein. Studies that compared 2 or more dose ranges were also included. Patients had stable states (study defined) of their illness (relapse prevention studies).

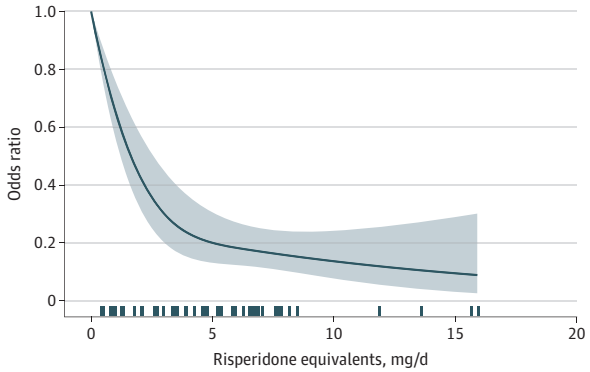
The primary outcome was relapse as defined by the original authors. Secondary outcomes were rehospitalization for psychopathologic factors, the change from baseline to end point on the Positive and Negative Syndrome Scale (PANSS)[10] or the Brief Psychiatric Rating Scale (BPRS),[11] all-cause discontinuation as a measure of overall treatment failure, and dropout due to adverse events as a global tolerability measure. Data on drug-related adverse events vs an exacerbation of schizophrenia were preferred whenever available.

We searched the Cochrane Schizophrenia Group's Study-Based Register of Trials (March 9, 2020) with a term combining the names of the antipsychotics in question and *dosage* in the pairwise comparison field of study records (eAppendix 2 in the Supplement). This register includes regular searches in multiple electronic databases, ClinicalTrials.gov, World Health Organization register of clinical trials, conference reports, and hand searches. An updated search in PubMed was made January 1, 2021 (eAppendix 2 in the Supplement). We also screened the reference lists of included studies, previous reviews,[7,12,13] and a Cochrane protocol on antipsychotic dose reduction.[14] We contacted all authors or pharmaceutical companies for missing data. There were no date, language, document type, or publication status limitations, except for studies from mainland China owing to frequent but usually unrecognizable quality problems.[15] The data were extracted in a Microsoft Access database that allows for automatic comparison of the extractions. Risk of bias for the primary outcome was assessed with a risk of bias tool (Cochrane RoB, version 2; Cochrane Collaboration).[16] Study selection, data extraction, and risk of bias assessment were made independently by 2 of 3 of us (S.L., S.B., or J.S.-T.); in case of doubt, a third reviewer (S.S. or J.M.D.) was involved.

Statistical Analysis

We conducted a 1-step, random-effects, frequentist, dose-response meta-analysis.[9] The association between dose and

Figure 1. Relapse



The dose-response curve for the primary outcome relapse after pooling all drugs using the primary scientific dose-equivalence method (the maximum effective dose method). The marks on the x-axis indicate for which doses data from study arms were available. A total of 26 studies with 71 individual dose arms including 4749 patients were included (1 publication reported on 2 studies).[27,32-55] The shaded areas indicate 95% CIs for the primary outcome.

dichotomous outcomes was measured with odds ratios and on the continuous outcome overall efficacy with standardized mean differences (Cohen *d*). Odds ratios have better mathematical properties than risk ratios,[17] but they are more difficult to interpret. Therefore, odds ratios were also converted to relative risks and absolute numbers for illustration purposes using the meta-analytically pooled placebo rates of each outcome as baseline risks (eAppendix 5 in the Supplement). Values from the BPRS were converted to PANSS units according to Leucht et al.[18] Dose-response curves were fitted with restricted cubic splines.[19] In the primary analysis, we used knots located at the 25th, 50th, and 75th percentiles. Dose-response curves were estimated for all antipsychotics grouped and for each drug separately. For the pooled analysis, the doses of each antipsychotic were converted to risperidone equivalents, primarily according to the maximum effective dose method[8] or, if such equivalents were not available, according to the minimum effective dose method,[20,21] the mean-dose method,[22,23] the DDD method,[24] and based on the international consensus of antipsychotic doses"[25] (fluphenazine long-acting injectable).

In post hoc analyses, we tested with linear splines up to which dose the dose-response curve still showed a significantly increasing slope ($P < .10$). We updated the Uchida et al[7] meta-analysis by comparing standard doses (1 DDD or higher) with low doses (≥50% DDD < 1 DDD), and we compared 3- to 7-mg/d risperidone equivalent with higher doses in pairwise meta-analyses.

In sensitivity analyses, dose conversion was based on the international consensus of antipsychotic doses by Gardner et al.[25] Different knot locations were used: 10%, 50%, and 90% percentiles (as previously recommended[26]) and 2-mg/d (the minimum effective dose for short-term treatment[20]), 4-mg/d, and 8-mg/d (a dose somewhat above the maximum effective dose[8]) risperidone equivalents (post hoc analysis). Studies that compared only a single dose of an antipsychotic with placebo (not designed to examine dose-response) were not described as double blind and were judged to be at high risk of bias (post hoc) and therefore excluded.

We planned separate analyses of children and adolescents, older patients, participants with predominantly negative symptoms, and those with a first episode of schizophrenia, but such trials were not available except for 1 single-dose and thus unanalyzable first-episode study.[27] Post hoc subgroup analyses included patients with remission, oral vs LAI antipsychotics, second-generation vs first-generation antipsychotics, age (median split), and percentage men (median split).

We measured heterogeneity with the variance partition coefficient, which is a multivariate extension of the I^2 value suggested by Crippa et al.[9] Small-trial effects and their potential association with publication bias were explored with the contour-enhanced funnel plot[28] and Egger test.[29] Dose-response meta-analyses were conducted with the dosresmeta[30] package and meta-analyses of the outcomes in placebo arms with meta[31] in R, version 3.6.2 (R Project for Statistical Computing). With 2-sided testing, findings were considered significant at $P < .05$.

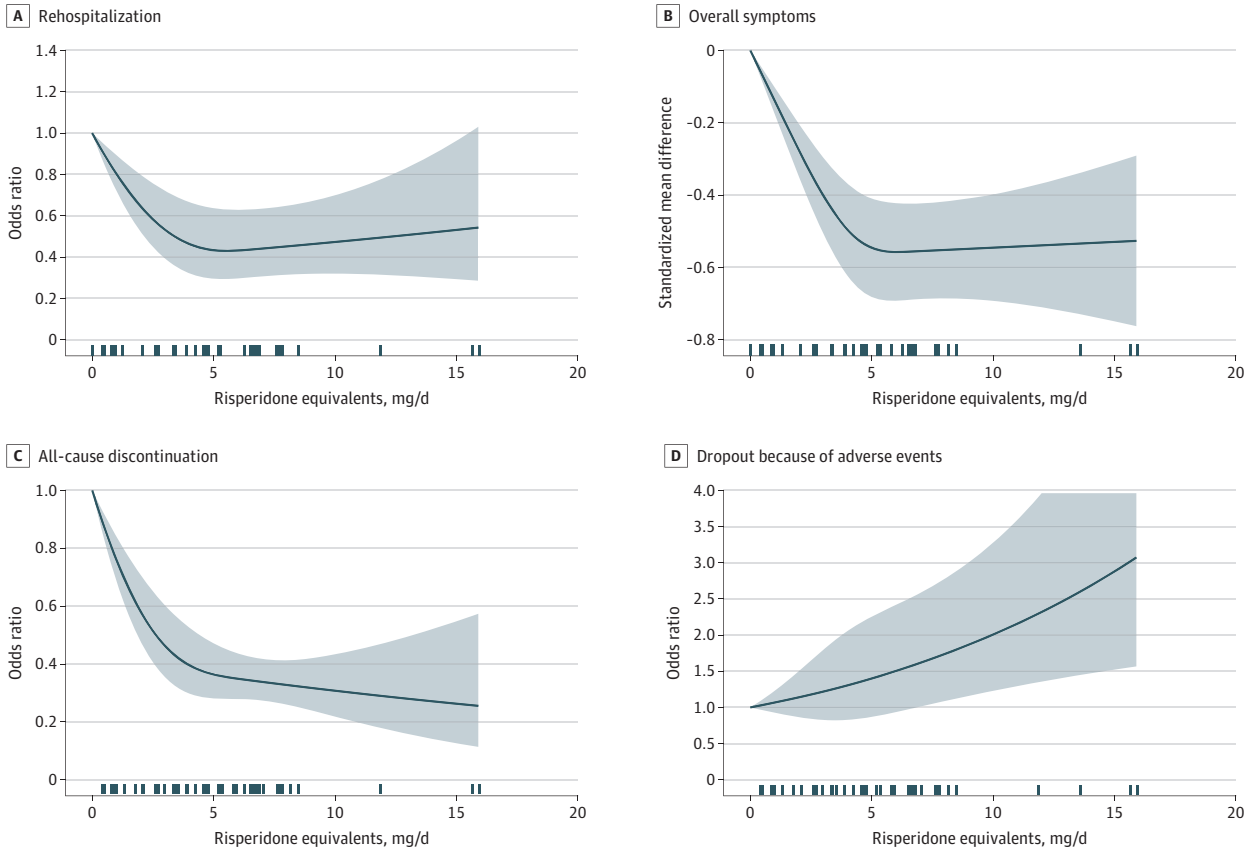
Results

The study selection flowchart, a description of 380 excluded studies and the following 26 included studies with 72 dose arms and 4776 participants are provided in the eFigure, eTable 1, and eTable 2 in the Supplement. The drugs evaluated included oral aripiprazole (2 studies),[32,33] aripiprazole LAI (3 studies),[34-36] fluphenazine LAI (6 studies),[37-42] oral haloperidol (5 studies),[43-46] haloperidol decanoate (3 studies),[47-49] lurasidone (1 study),[50] oral olanzapine (2 studies),[45] olanzapine LAI (1 study),[51] paliperidone LAI (1 study),[52] quetiapine (2 studies),[27,46] risperidone LAI (1 study),[53] ziprasidone (1 study),[54] and zotepine (1 study).[55] Some reports included data on 2 drugs. Nineteen percent of the studies were judged to be of low overall risk of bias, 50% had some concerns of bias, and 31% were considered at high risk for bias (eAppendix 3 in the Supplement).

All but 2 studies[38,44] used operationalized diagnostic criteria (Research Diagnostic Criteria, *DSM-III*, *DSM-III-R*, and *DSM-IV*), and all but 2 were described as double-blind.[36,49] The median study duration was 48 weeks (range, 6 months to 3 years; interquartile range, 33-52 months); a single 3-year study included only 20 participants.[44] In 6 studies, patients were in remission at baseline based on various criteria.[27,39,40,43,44,47]

Figure 1 depicts the primary outcome.[27,32-55] The dose-response curve of relapse, based on 71 dose arms from 26 studies[27,32-55] (1 publication included 2 studies), initially decreased sharply, but it flattened after approximately 5-mg/d risperidone equivalent (odds ratio, 0.20; 95% CI, 0.13-0.31; relative risk, 0.43; 95% CI, 0.31-0.57) (Table 1). **Figure 2** depicts secondary outcomes.[27,32-55] The shapes of the dose-response curves of the secondary efficacy outcomes (rehospitalization, reduction in overall symptoms) and all-cause discontinuation were similar to that of relapse (Figure 2). In

Figure 2. Rehospitalization, Overall Symptoms, All-Cause Discontinuation, and Dropout Owing to Adverse Events



Fourteen studies with 39 arms were available for rehospitalization (A)[27,34,35,37,40-42,45,46,49-51,53]; 16 studies with 44 arms were available for overall symptoms, as measured by the Positive and Negative Syndrome Scale total score or the Brief Psychiatric Rating Scale total score (B)[32-38,45,49-55]; 23 studies with 65 dose arms were available for all-cause discontinuation (C)[27,32,34-43,45-55]; and 18 studies with 50 arms were available for dropouts due to adverse events (D).[27,32-36,38,43-48,50,51,53-55] One publication[45] reported on 2 studies for some of these outcomes. The marks on the x-axis indicate for which doses study arm data were available. The shaded areas indicate 95% CIs.

contrast, the curve for dropouts due to adverse events was monotonic, with higher doses always leading to more adverse events (5 mg/d: odds ratio, 1.4; 95% CI, 0.87-2.25; relative risk, 1.38; 95% CI, 0.87-2.15; 15 mg/d: odds ratio, 2.88; 95% CI, 1.52-5.45; relative risk; 2.68; 95% CI, 1.49-4.62) (Figure 2 and **Table 1**).

Figure 3 depicts sensitivity analyses of the primary outcome.[32-48,50-55] The use of different knot locations (Figure 3A), the exclusion of 9 studies[32,34,38,39,44,48,50,54,55] that compared a single dose with placebo (Figure 3B), exclusion of 2 studies that were not double-blind[36,49] (eAppendix 4 in the Supplement), and 8 studies judged to be of high risk of bias[33,36,40-43,45,52] (Figure 3C) did not produce results that were substantially different from the primary analysis. When doses were converted according to the international consensus of antipsychotic dosing[25] the curve slightly bulged at the left, but generally overlapped with the primary analysis (Figure 3D).

Few dose arms were available for individual drugs, resulting in substantial uncertainty expressed by wide CIs (eAppendix 4 in the Supplement). With this restriction, the dose-response curves of the individual drugs approximately flattened at aripiprazole, 12.5 mg/d (similar for oral and LAI); fluphenazine LAI, 15 mg biweekly; haloperidol, 3 mg/d (similar for oral and LAI); ziprasidone, 80 mg/d; and oral olanzapine, 10 mg/d. A plateau was not reached in a single olanzapine LAI study at 300 mg every 2 weeks (approximately 20 mg/d),[51] as for quetiapine doses of up to 600 mg/d. Risperidone LAI, 50 mg, biweekly was somewhat more effective than 25 mg biweekly,[53] but a dose-response curve could not be constructed, just as little as in single-dose, placebo-controlled studies with lurasidone[50] and zotepine.[55]

Figure 4 depicts subgroup analyses of the primary outcome.[27,32-55] In patients with remission, the dose-response curve plateaued earlier (approximately 2.5-mg/d risperidone equivalent) (Figure 4A). Similarly, the curve for first-generation antipsychotics bulged earlier (approximately 3 mg/d) than that for second-generation antipsychotics, which was similar to the overall analysis (Figure 4B). Oral and LAI antipsychotics plateaued at approximately the same dose, but the odds ratio compared with placebo was lower in the LAI group, meaning the drug had greater superiority compared with placebo (Figure 4C). Although age was not an important

Table. Results per Dose After Conversion of ORs to RRs and of SMDs to PANSS Values

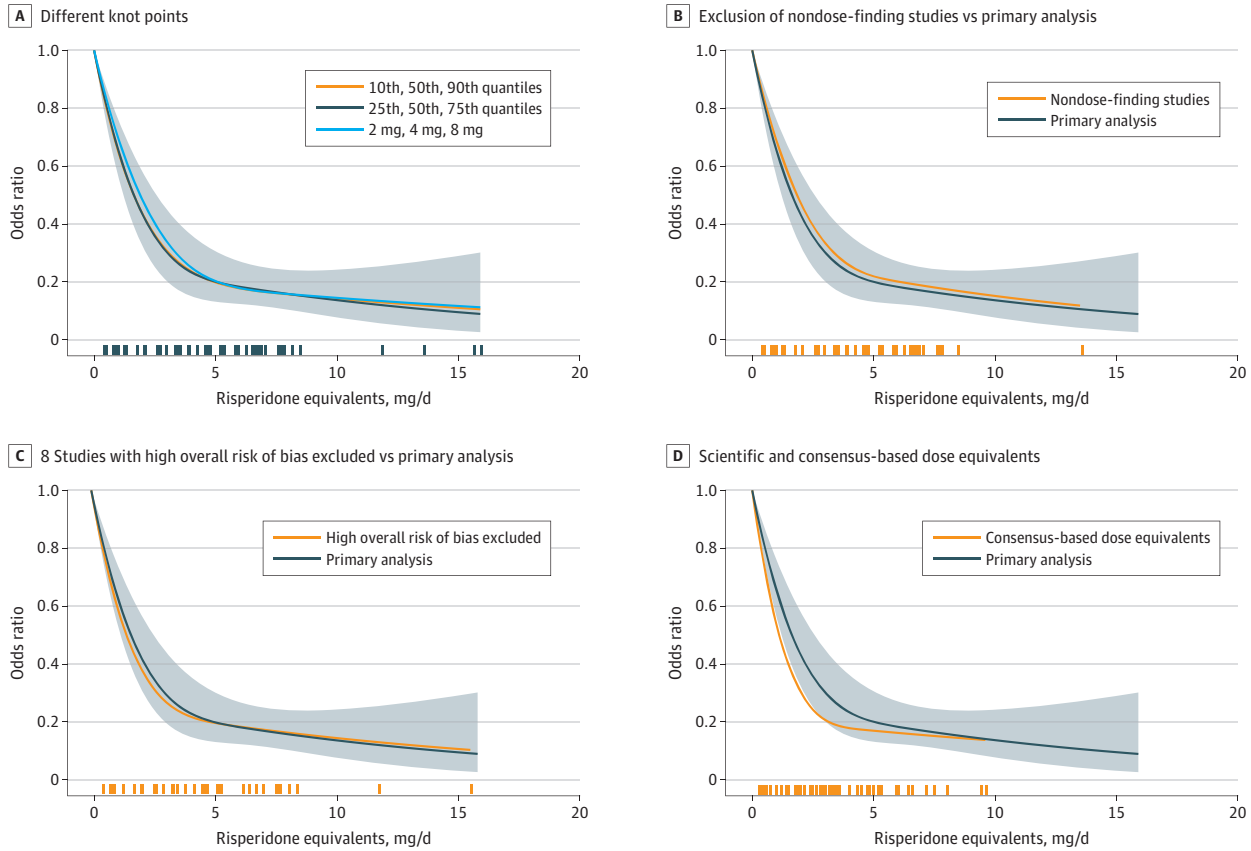
	Relapse			Rehospitalization			All-cause discontinuation			Dropout due to adverse events			Overall symptoms	
Dose, mg[a]	Relapse, % (95% CI)	RR (95% CI)	OR (95% CI)	Rehospitalized, % (95% CI)	RR (95% CI)	OR (95% CI)	Dropout, % (95% CI)	RR (95% CI)	OR (95% CI)	Dropout, % (95% CI)	RR (95% CI)	OR (95% CI)	SMD (95% CI)	PANSS change (95% CI)[b]
Placebo	67	1	1	18	1	1	75	1	1	4	1	1	0	9.6
0.5	62.1 (60.4 to 63.9)	0.93 (0.9 to 0.95)	0.81 (0.75 to 0.87)	16.4 (15.7 to 17.2)	0.91 (0.87 to 0.95)	0.9 (0.85 to 0.94)	72.3 (71.3 to 73.3)	0.96 (0.95 to 0.98)	0.87 (0.83 to 0.92)	4.1 (3.9 to 4.4)	1.03 (0.96 to 1.1)	1.03 (0.96 to 1.11)	−0.07 (−0.09 to −0.05)	8.46 (8.16 to 8.76)
1.0	57 (53.3 to 60.7)	0.85 (0.8 to 0.91)	0.65 (0.56 to 0.76)	15 (13.7 to 16.4)	0.83 (0.76 to 0.91)	0.8 (0.72 to 0.89)	69.5 (67.3 to 71.6)	0.93 (0.9 to 0.95)	0.76 (0.69 to 0.84)	4.3 (3.7 to 4.9)	1.06 (0.93 to 1.22)	1.07 (0.93 to 1.23)	−0.14 (−0.18 to −0.1)	7.31 (6.71 to 7.92)
1.5	51.8 (46.2 to 57.3)	0.77 (0.69 to 0.86)	0.53 (0.42 to 0.66)	13.6 (11.8 to 15.6)	0.76 (0.66 to 0.87)	0.72 (0.61 to 0.84)	66.5 (63.1 to 69.8)	0.89 (0.84 to 0.93)	0.66 (0.57 to 0.77)	4.4 (3.6 to 5.4)	1.1 (0.9 to 1.34)	1.1 (0.89 to 1.36)	−0.21 (−0.26 to −0.15)	6.17 (5.27 to 7.08)
2.0	46.7 (39.6 to 54)	0.7 (0.59 to 0.81)	0.43 (0.32 to 0.58)	12.4 (10.3 to 14.9)	0.69 (0.57 to 0.83)	0.65 (0.52 to 0.8)	63.5 (58.9 to 68)	0.85 (0.78 to 0.91)	0.58 (0.48 to 0.71)	4.5 (3.5 to 5.9)	1.13 (0.87 to 1.47)	1.14 (0.87 to 1.5)	−0.28 (−0.35 to −0.2)	5.05 (3.85 to 6.25)
2.5	42.1 (33.8 to 50.8)	0.63 (0.5 to 0.76)	0.36 (0.25 to 0.51)	11.4 (9 to 14.2)	0.63 (0.5 to 0.79)	0.58 (0.45 to 0.76)	60.7 (54.9 to 66.1)	0.81 (0.73 to 0.88)	0.51 (0.41 to 0.65)	4.7 (3.4 to 6.4)	1.17 (0.85 to 1.61)	1.18 (0.84 to 1.65)	−0.34 (−0.43 to −0.25)	3.98 (2.5 to 5.45)
3.0	38 (29.2 to 47.7)	0.57 (0.44 to 0.71)	0.3 (0.2 to 0.45)	10.5 (8 to 13.7)	0.58 (0.44 to 0.76)	0.53 (0.39 to 0.72)	58.1 (51.5 to 64.4)	0.77 (0.69 to 0.86)	0.46 (0.35 to 0.6)	4.8 (3.3 to 7)	1.21 (0.83 to 1.74)	1.22 (0.83 to 1.79)	−0.4 (−0.51 to −0.3)	2.99 (1.27 to 4.72)
3.5	34.7 (25.7 to 44.9)	0.52 (0.38 to 0.67)	0.26 (0.17 to 0.4)	9.8 (7.2 to 13.2)	0.54 (0.4 to 0.73)	0.49 (0.35 to 0.69)	55.9 (48.9 to 62.7)	0.75 (0.65 to 0.84)	0.42 (0.32 to 0.56)	5 (3.3 to 7.4)	1.25 (0.83 to 1.86)	1.26 (0.82 to 1.93)	−0.45 (−0.57 to −0.34)	2.13 (0.19 to 4.07)
4.0	32.2 (23.4 to 42.4)	0.48 (0.35 to 0.63)	0.23 (0.15 to 0.36)	9.2 (6.6 to 12.7)	0.51 (0.37 to 0.71)	0.46 (0.32 to 0.67)	54.3 (47.2 to 61.2)	0.72 (0.63 to 0.82)	0.4 (0.3 to 0.53)	5.2 (3.3 to 7.9)	1.29 (0.83 to 1.97)	1.3 (0.83 to 2.05)	−0.5 (−0.62 to −0.37)	1.42 (−0.67 to 3.52)
4.5	30.3 (22 to 40.2)	0.45 (0.33 to 0.6)	0.21 (0.14 to 0.33)	8.9 (6.3 to 12.5)	0.49 (0.35 to 0.69)	0.44 (0.3 to 0.65)	53.1 (46.2 to 59.8)	0.71 (0.62 to 0.8)	0.38 (0.29 to 0.5)	5.3 (3.4 to 8.3)	1.33 (0.85 to 2.07)	1.35 (0.84 to 2.16)	−0.53 (−0.66 to −0.39)	0.91 (−1.29 to 3.11)
5.0	28.9 (21.1 to 38.3)	0.43 (0.31 to 0.57)	0.2 (0.13 to 0.31)	8.7 (6.1 to 12.3)	0.48 (0.34 to 0.68)	0.43 (0.3 to 0.64)	52.2 (45.7 to 58.6)	0.7 (0.61 to 0.78)	0.36 (0.28 to 0.47)	5.5 (3.5 to 8.6)	1.38 (0.87 to 2.15)	1.4 (0.87 to 2.25)	−0.55 (−0.68 to −0.41)	0.6 (−1.64 to 2.84)
5.5	27.9 (20.5 to 36.7)	0.42 (0.31 to 0.55)	0.19 (0.13 to 0.29)	8.6 (6.1 to 12.2)	0.48 (0.34 to 0.68)	0.43 (0.29 to 0.63)	51.6 (45.6 to 57.5)	0.69 (0.61 to 0.77)	0.36 (0.28 to 0.45)	5.7 (3.6 to 8.9)	1.43 (0.9 to 2.22)	1.45 (0.9 to 2.34)	−0.55 (−0.69 to −0.42)	0.45 (−1.79 to 2.69)
6.0	27.1 (20.1 to 35.5)	0.4 (0.3 to 0.53)	0.18 (0.12 to 0.27)	8.7 (6.1 to 12.1)	0.48 (0.34 to 0.67)	0.43 (0.3 to 0.63)	51.2 (45.6 to 56.7)	0.68 (0.61 to 0.76)	0.35 (0.28 to 0.44)	5.9 (3.8 to 9.1)	1.47 (0.94 to 2.29)	1.5 (0.94 to 2.42)	−0.56 (−0.69 to −0.42)	0.4 (−1.82 to 2.62)
6.5	26.4 (19.6 to 34.5)	0.39 (0.29 to 0.51)	0.18 (0.12 to 0.26)	8.7 (6.2 to 12.2)	0.49 (0.35 to 0.68)	0.44 (0.3 to 0.63)	50.8 (45.5 to 56)	0.68 (0.61 to 0.75)	0.34 (0.28 to 0.42)	6.1 (3.9 to 9.4)	1.52 (0.97 to 2.36)	1.56 (0.97 to 2.5)	−0.56 (−0.69 to −0.42)	0.42 (−1.78 to 2.61)
7.0	25.7 (19 to 33.7)	0.38 (0.28 to 0.5)	0.17 (0.12 to 0.25)	8.8 (6.3 to 12.2)	0.49 (0.35 to 0.68)	0.44 (0.31 to 0.63)	50.4 (45.1 to 55.6)	0.67 (0.6 to 0.74)	0.34 (0.27 to 0.42)	6.3 (4 to 9.7)	1.58 (1.01 to 2.43)	1.62 (1.01 to 2.58)	−0.55 (−0.69 to −0.42)	0.44 (−1.74 to 2.63)
7.5	25 (18.3 to 33.2)	0.37 (0.27 to 0.5)	0.16 (0.11 to 0.24)	8.9 (6.4 to 12.3)	0.5 (0.36 to 0.68)	0.45 (0.31 to 0.64)	50 (44.6 to 55.4)	0.67 (0.59 to 0.74)	0.33 (0.27 to 0.41)	6.5 (4.2 to 10)	1.63 (1.05 to 2.51)	1.68 (1.05 to 2.67)	−0.55 (−0.69 to −0.42)	0.47 (−1.72 to 2.66)
8.0	24.3 (17.4 to 32.9)	0.36 (0.26 to 0.49)	0.16 (0.1 to 0.24)	9 (6.5 to 12.4)	0.5 (0.36 to 0.69)	0.45 (0.31 to 0.65)	49.6 (43.8 to 55.3)	0.66 (0.58 to 0.74)	0.33 (0.26 to 0.41)	6.8 (4.3 to 10.4)	1.69 (1.08 to 2.59)	1.74 (1.09 to 2.78)	−0.55 (−0.69 to −0.42)	0.5 (−1.71 to 2.7)
8.5	23.7 (16.5 to 32.7)	0.35 (0.25 to 0.49)	0.15 (0.1 to 0.24)	9.1 (6.5 to 12.6)	0.51 (0.36 to 0.7)	0.46 (0.32 to 0.66)	49.2 (42.9 to 55.5)	0.66 (0.57 to 0.74)	0.32 (0.25 to 0.42)	7 (4.5 to 10.7)	1.75 (1.12 to 2.68)	1.8 (1.12 to 2.89)	−0.55 (−0.69 to −0.41)	0.52 (−1.72 to 2.76)
9.0	23 (15.6 to 32.7)	0.34 (0.23 to 0.49)	0.15 (0.09 to 0.24)	9.2 (6.5 to 12.8)	0.51 (0.36 to 0.71)	0.46 (0.32 to 0.67)	48.8 (41.9 to 55.7)	0.65 (0.56 to 0.74)	0.32 (0.24 to 0.42)	7.2 (4.6 to 11.1)	1.8 (1.15 to 2.78)	1.87 (1.16 to 3.01)	−0.55 (−0.69 to −0.41)	0.55 (−1.74 to 2.84)
9.5	22.4 (14.6 to 32.8)	0.33 (0.22 to 0.49)	0.14 (0.08 to 0.24)	9.3 (6.6 to 13)	0.52 (0.36 to 0.72)	0.47 (0.32 to 0.68)	48.4 (40.8 to 56.1)	0.65 (0.54 to 0.75)	0.31 (0.23 to 0.43)	7.5 (4.7 to 11.6)	1.87 (1.19 to 2.89)	1.94 (1.2 to 3.14)	−0.55 (−0.69 to −0.4)	0.57 (−1.78 to 2.93)
10.0	21.8 (13.6 to 33)	0.32 (0.2 to 0.49)	0.14 (0.08 to 0.24)	9.4 (6.6 to 13.3)	0.52 (0.36 to 0.74)	0.47 (0.32 to 0.7)	48 (39.6 to 56.5)	0.64 (0.53 to 0.75)	0.31 (0.22 to 0.43)	7.7 (4.9 to 12)	1.93 (1.22 to 3)	2.01 (1.23 to 3.28)	−0.55 (−0.69 to −0.4)	0.6 (−1.82 to 3.03)
15.0	16.2 (6 to 37)	0.24 (0.09 to 0.55)	0.1 (0.03 to 0.29)	10.4 (6.1 to 17.4)	0.58 (0.34 to 0.97)	0.53 (0.29 to 0.96)	44.1 (27.5 to 62.2)	0.59 (0.37 to 0.83)	0.26 (0.13 to 0.55)	10.7 (6 to 18.5)	2.68 (1.49 to 4.62)	2.88 (1.52 to 5.45)	−0.53 (−0.75 to −0.31)	0.86 (−2.76 to 4.48)

Abbreviations: OR, odds ratio; PANSS, Positive and Negative Syndrome Scale total score change from baseline to end point; RR, relative risk; SMD, standardized mean difference for PANSS change from baseline drug vs placebo.

[a] Dose is indicated in risperidone equivalents.

[b] Positive values indicate worsening; negative values indicate improvement.

Figure 3. Sensitivity Analyses of the Primary Outcome



A, Different knot points were used in the statistical analysis. B, Studies that compared a single dose of an antipsychotic with placebo were excluded.[32,34,38,39,44,48,50,54,55] C, The results of 8 studies judged to be at high risk of bias [33,36,40-43,45,52] were excluded and the remaining studies were compared with the overall results. D, The results of primary scientific dose-equivalence method were compared with the consensus-based dose equivalents. The marks on the x-axis indicate for which doses study-arm data were available. The shaded areas indicate 95% CIs.

moderator, studies with more men seemed to use lower doses; because the latter 2 analyses were based on methodologically less-sound median splits, we present them in eAppendix 4 in the Supplement.

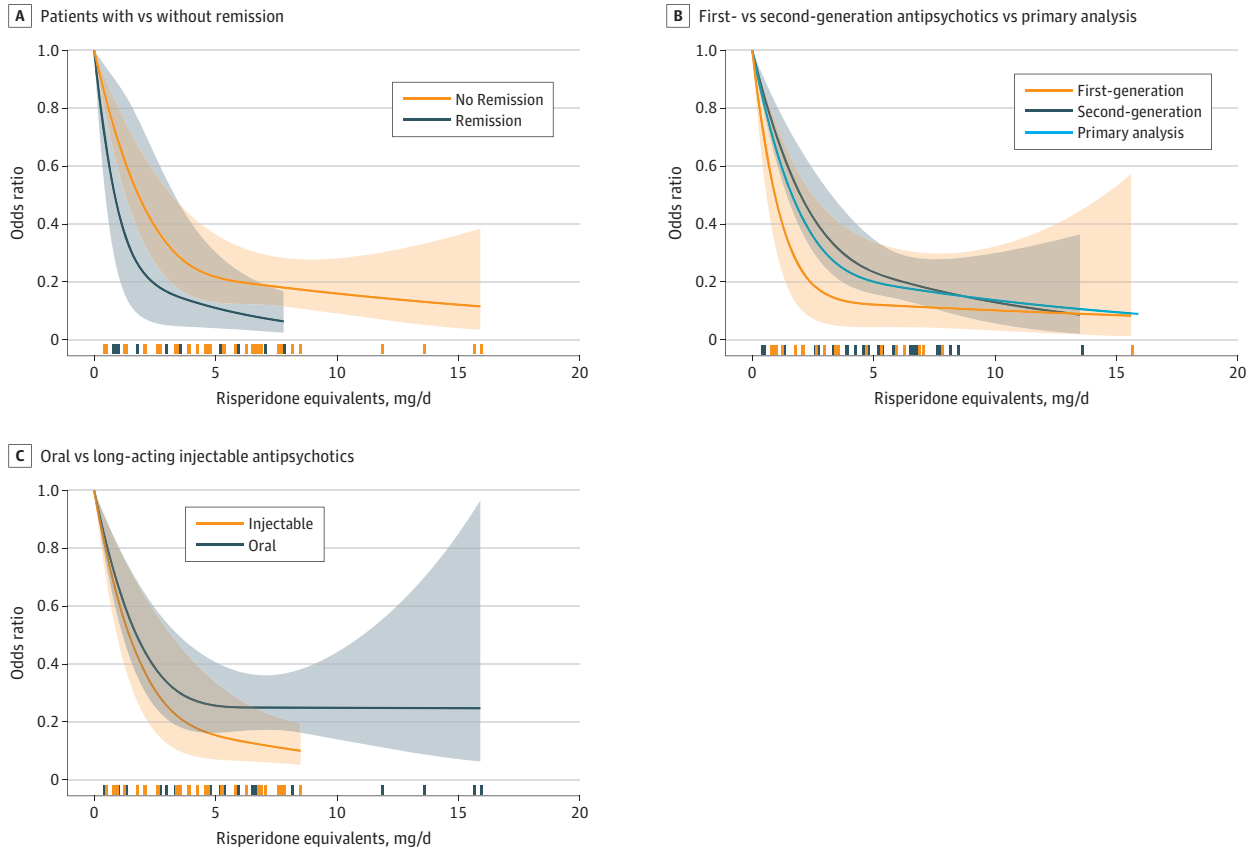
The average percentages in the placebo groups, based on meta-analyses of the included studies, were 67% for relapse, 18% for rehospitalization, 75% for all-cause discontinuation, and 4% for dropouts due to adverse events (Table); details about their calculation are provided in eAppendix 5 in the Supplement. Compared with baseline, the PANSS total score worsened by a weighted average of 9 points in the placebo groups.

A dose of 2.5 mg/d risperidone equivalent reduced the risk to relapse from 67% to 42.1%, in relative terms, by approximately 40% (relative risk, 0.63; relative risk reduction = 1 − relative risk; thus, 1 − 0.63 = 0.37 [ie, 37%]) (Table). The mean relative risk reduction for rehospitalization was the same as that for relapse, and mean relative risk reduction for all-cause discontinuation was 25%. Dropouts due to adverse events increased by 17% (relative risk, 1.17). The standardized mean difference for overall association with efficacy compared with placebo was −0.36.

Further gains in terms of reduction of relapse risk, rehospitalization, and improvement or stabilization of symptoms were achieved by doses of approximately 5-mg/d risperidone equivalent: mean relative risk reduction of 57% for relapse, 52% for rehospitalization, 30% for all-cause discontinuation, and an effect size of −0.55 compared with placebo. Some additional gains in relapse prevention beyond 5 mg/d can be an artifact of few dose arms with very high doses being available (as indicated with marks on the x-axis in Figures 1 and 2). Rehospitalization and symptoms did not show such an association; in post hoc analyses, the slope was no longer substantially increasing above 3.5 mg/d, and very high doses were not more effective than 3- to 7-mg/d risperidone equivalent (eAppendix 7 in the Supplement). In contrast, dropouts due to adverse events continued to increase (eg, 38% relative increase compared with placebo at 5 mg/d vs 74% at 8 mg/d). The average dopamine receptor occupancies for the respective risperidone doses from another meta-analysis[56] appears in eTable 3 in the Supplement, which we added for a discussion of relapse risk related to this parameter.

There were moderate levels of heterogeneity, with variance partition coefficients usually below 50% across doses and

Figure 4. Subgroup Analyses of the Primary Outcome



A, The results of 6 studies in patients with remission [27,39,40,43,44,47] were compared with patients without remission. B, Second-generation antipsychotics[27,32-36,45,46,50-55] were compared with first-generation antipsychotics[37-45,47-49] and the primary analysis. C, Oral formulations were compared with long-acting injectable medications.

outcomes (Figures 1 and 2; eAppendix 6 in the Supplement). The Egger test for small-study effects bias was not significant, but the contour-enhanced funnel plot of the primary outcome was somewhat asymmetrical (eAppendix 6 in the Supplement).

Discussion

Our main findings were that 2.5-mg/d risperidone equivalents were associated with a relative reduction in schizophrenia relapse rates by 40%, and beyond approximately 5-mg/d risperidone equivalent there were no substantial gains in association with efficacy. In contrast, adverse events continued increasing with higher doses. The shapes of the dose-response curves were hyperbolic, meaning disproportionally higher relapse rates at the lower doses.

How do these findings compare with previous findings, which were either mainly based on first-generation antipsychotics,[5,6,57] were outdated,[5-7] were based on a small number of studies,[7] and/or did not use the more appropriate method of dose-response meta-analysis?[5-7,57] For first-generation antipsychotics, Bollini et al[5] found no further gain beyond 375-mg/d chlorpromazine equivalent and Baldessarini and Davis[6] found no further gain beyond 310-mg/d chlorpromazine equivalent. Risperidone, 5 mg, corresponds to chlorpromazine, 313 mg,[8,58] which is similar to the previous findings. Uchida et al[7] reported that standard doses (1 DDD or higher) are more effective than very low doses (<50% DDD), but not statistically significantly more than low doses (≥50% < 1 DDD). However, when we updated their meta-analysis, standard doses outperformed low doses (12 studies, odds ratio, 1.46; 95% CI, 1.04-2.04; $P = .03$) (eAppendix 7 in the Supplement).[7] This finding suggests that low doses are more effective than placebo (Table), but less effective than standard doses (updated Uchida et al[7] and Table). In addition, Tani et al[57] reported that doses can be reduced as long as the remaining dose is higher than 200-mg/d chlorpromazine equivalents (shown in their figure). However, only 1 small study (31 participants) in Japanese patients, who are usually smaller and weigh less (eg, 62 kg in a large trial[59]) than current US or European patients, came close to 200 mg/d of chlorpromazine equivalents (Takeuchi et al,[60] approximately 210 mg/d); all other studies had higher doses (mean in the dose-reduction group 450-mg/d chlorpromazine equivalents).

The relapse curve still decreased slightly above risperidone, 5 mg/d (Figure 1, Table). However, there is no reason to

believe that the average dose for relapse prevention should be higher than that for short-term treatment, which is 5 mg/d, as well.[8] Reviews have suggested that even in the acute phase, very high doses are not more effective than standard doses.[61,62] There was no significant difference between 3- and 7-mg/d risperidone equivalent and higher doses, and the curve's slope no longer significantly increased above 3.5 mg/d (eAppendix 7 in the Supplement). Most importantly, the dose-response curves for rehospitalization and overall symptoms clearly plateaued at 5 mg/d (Figure 2). Rehospitalization and PANSS and BPRS scores are not subject to the problem of differences in relapse definitions and therefore more robust measures. Thus, because only 4 dose arms were available above 8 mg/d, the most likely explanation is that the tail of the curve was sensitive to random extreme observations.

Patients who experienced remission at baseline plateaued earlier (approximately 2.5 mg/d risperidone). Only 6 studies in patients with remission were available,[27,39,40,43,44,47] 3 of which used operationalized criteria focusing on positive symptoms[27,40,47]; the other 3 used broad criteria, including aspects such as vocational functioning, but were not operationalized[39,43,44] (eTable 1 in the Supplement). As a caveat, 3 of these studies[27,43,44] were conducted in Asian patients (ie, usually smaller and lighter), and 3 used LAIs with their advantages for adherence (Figure 3). The fact that the curve for first-generation antipsychotics plateaued at approximately 3 mg is plausible because haloperidol and fluphenazine are high-potency first-generation antipsychotics, which are strong antagonists of dopamine receptors. Although the curve of LAI antipsychotics plateaued at the same dose as that of oral antipsychotics (approximately 5 mg), their difference compared with placebo was larger. Better adherence may account for this difference. Although these findings are plausible, subgroup analyses are subject to confounders and they were conducted post hoc. These results, therefore, should be interpreted with great caution.

These results can also be considered with regard to the trade-off between avoiding relapses vs adverse events and supersensitivity effects. Several studies have shown that, after a relapse, not all patients return to their psychopathologic state before the relapse.[63-67] Relapses should therefore be avoided. Conversely, treatment with antipsychotics can lead to supersensitivity of dopamine receptors, which may make patients more prone to relapse in the long run. Supersensitivity effects have been reported in animal studies.[68] In patients, the clearest proof is tardive dyskinesia.[3] In view of this dilemma, the use of low doses is a pragmatic solution. However, owing to the hyperbolic shape of the curve, lower doses are associated with disproportionally higher relapse risks (Figure). This finding is also supported by the results of a meta-analysis of plasma level studies and relative dopamine receptor occupancy available as eTable 3 in the Supplement and which we added for examples to the information in the Table.[56] For example, the difference in relapse risk between 7.5 mg/d risperidone equivalents and 5 mg/d risperidone equivalents is very small (28.9% − 25.0% = 3.9%), and so is the difference in dopamine receptor occupancy (81% − 76% = 6%). The difference is larger between 5 mg/d and 2.5 mg/d (absolute difference in relapse rates, 42.1% − 28.9% = 13.3%, receptor occupancy 76% − 64% = 13.2%). This variance means that it should be safe to reduce excessive doses, but caution needs to be taken at the low dose end.

Based on similar, but theoretical, considerations, Horowitz et al[69] suggested reducing doses by 10 percentage points of the drug's D_2-blockade every 3 to 6 months (an early consensus guideline made similar recommendations[70]), with even smaller steps for the lower the dose owing to the hyperbolic dose-response function. Our data, however, suggest that antipsychotic drugs dosages should not be completely withdrawn and the safest procedure would be to stay around 5 mg/d, in particular, if there are no important adverse events. At 2 mg/d, receptor occupancy falls below the 65% threshold, which is considered to be the minimum of a postulated 65% to 80% range. Because a systematic review found only 12 studies with 70 patients, this threshold has a weak foundation.[71] Moreover, if other factors, such as stress or irregular lifestyle intervene, relapses may result despite 65% dopamine occupancy.

Strengths and Limitations

Strengths of the analysis are the use of dose-response meta-analysis. Previous reviews only compared the means of higher and lower doses or applied linear regression,[5-7,57] but our results suggest that dose-response associations are not linear. Our results were consistent across various measures of efficacy and effectiveness, and they were robust when a consensus method rather than a method based on empirical data for dose equivalence was applied. Although we consider the maximum effective dose method to be the most appropriate one, all these methods have limitations as has been discussed elsewhere.[8,20-24]

Limitations of the meta-analysis are that dose equivalence could be avoided if several dose-finding studies were available for each antipsychotic, but these are unlikely to be available in the foreseeable future. A discussion of the results of individual antipsychotic drugs is presented in eAppendix 4 in the Supplement. We included only the first-generation antipsychotics haloperidol and fluphenazine, but according to Uchida et al,[7] additional data would have been available only for propericyazine (24 patients) and pimozide (24 patients),[43,44] and the Cochrane review on chlorpromazine dose identified only 1 study, which was a mix of an acute- and maintenance-phase study. Due to the expectable lack of data,[1] old drugs were not included in our dose-equivalence analyses,[8,20-24] and change of trial methods[72] would have made the comparison with newer drugs difficult. Relapses can occur with a delay of several months. Therefore, the difference between drug and placebo may increase over time, making the median trial duration of 1 year a limitation. Publication bias is possible. In addition, only severe adverse events led to study discontinuation so that the dropouts due to adverse events reported in the Table underestimate the true adverse event burden.

Conclusions

The results of our meta-analysis may provide some guidance based on average patients with chronic disease. The dose-

response associations in specific populations are likely to be different. For example, doses might be lower for patients with a first episode of schizophrenia and higher for treatment-resistant patients. Moreover, the substantial interindividual variability in all these outcomes is important to consider. Individual dosing decisions should be guided by patient wishes. For many patients, adverse events may be a priority, and for many others, avoidance of relapse may be more important. Several factors should be considered in dosing of antipsychotic drugs to prevent relapse. These include patient characteristics, such as degree of residual symptoms; physical and psychiatric comorbidities, such as kidney damage or substance abuse; slow or ultrarapid metabolism due to polymorphisms of cytochrome enzymes; doses that were effective in the acute phase and/or for relapse prevention in the past; the severity of previous relapses (higher doses may be recommendable if relapses could be disastrous); the properties of each drug (eg, pharmacodynamic and pharmacokinetic properties, adverse event profile), and concomitant treatment with psychiatric and nonpsychiatric drugs which, by interaction, can affect drug plasma levels.[73]

ARTICLE INFORMATION

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Additional Information: The work is part of the dissertation of Ms Bauer at the Technical University of Munich, School of Medicine (degree, Dr Med). A calculator for determining daily defined doses of antipsychotic agents is available at http://www.cfdm.de/media/doc/Antipsychotic%20dose%20conversion%20calculator.xls.

REFERENCES

1. Huhn M, Nikolakopoulou A, Schneider-Thoma J, et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019; 394(10202):939-951. doi:10.1016/S0140-6736(19)31135-3

2. Leucht S, Tardy M, Komossa K, et al. Antipsychotic drugs versus placebo for relapse prevention in schizophrenia: a systematic review and meta-analysis. *Lancet*. 2012;379(9831):2063-2071. doi:10.1016/S0140-6736(12)60239-6

3. Carbon M, Kane JM, Leucht S, Correll CU. Tardive dyskinesia risk with first- and second-generation antipsychotics in comparative randomized controlled trials: a meta-analysis. *World Psychiatry*. 2018;17(3):330-340. doi:10.1002/wps.20579

4. Saha S, Chant D, McGrath J. A systematic review of mortality in schizophrenia: is the differential mortality gap worsening over time? *Arch Gen Psychiatry*. 2007;64(10):1123-1131. doi:10.1001/archpsyc.64.10.1123

5. Bollini P, Pampallona S, Orza MJ, Adams ME, Chalmers TC. Antipsychotic drugs: is more worse? a meta-analysis of the published randomized control trials. *Psychol Med*. 1994;24(2):307-316. doi:10.1017/S003329170002729X

6. Baldessarini RJ, Davis JM. What is the best maintenance dose of neuroleptics in schizophrenia? *Psychiatry Res*. 1980;3(2):115-122. doi:10.1016/0165-1781(80)90028-1

7. Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC. Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. *Schizophr Bull*. 2011; 37(4):788-799. doi:10.1093/schbul/sbp149

8. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-response meta-analysis of antipsychotic drugs for acute schizophrenia. *Am J Psychiatry*. 2020;177(4):342-353. doi:10.1176/appi.ajp.2019.19010034

9. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. *Stat Methods Med Res*. 2019; 28(5):1579-1596. doi:10.1177/0962280218773122

10. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. *Schizophr Bull*. 1987;13(2):261-276. doi:10.1093/schbul/13.2.261

11. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. *PsycholRep*. 1962;10:790-812.

12. Ceraso A, Lin JJ, Schneider-Thoma J, et al. Maintenance treatment with antipsychotic drugs for schizophrenia. *Cochrane Database Syst Rev*. 2020;8:CD008016. doi:10.1002/14651858.CD008016.pub3

13. Tani H, Uchida H, Suzuki T, Fujii Y, Mimura M. Interventions to reduce antipsychotic polypharmacy: a systematic review. *Schizophr Res*. 2013;143(1):215-220. doi:10.1016/j.schres.2012.10.015

14. Bighelli I, Samara MT, Rodolico A, Hansen W-P, Leucht S. Antipsychotic dose reduction compared to dose continuation for people with schizophrenia. *Cochrane Database Syst Rev*. 2021. Accessed July 17, 2021 doi:10.1002/14651858.CD014384

15. Tong Z, Li F, Ogawa Y, Watanabe N, Furukawa TA. Quality of randomized controlled trials of new generation antidepressants and antipsychotics identified in the China National Knowledge Infrastructure (CNKI): a literature and telephone interview study. *BMC Med Res Methodol*. 2018;18 (1):96. doi:10.1186/s12874-018-0554-2

16. Higgins JPT, Thomas J, Chandler J, et al Cochrane Handbook for Systematic Reviews of Interventions, version 6.1. September 2020. Accessed November 15, 2020. http://www.training.cochrane.org/handbook

17. Bakbergenuly I, Hoaglin DC, Kulinskaya E. Pitfalls of using the risk ratio in meta-analysis. *Res Synth Methods*. 2019;10(3):398-419. doi:10.1002/jrsm.1347

18. Leucht S, Rothe P, Davis JM, Engel RR. Equipercentile linking of the BPRS and the PANSS. *Eur Neuropsychopharmacol*. 2013;23(8):956-959. doi:10.1016/j.euroneuro.2012.11.004

19. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med*. 1989;8(5):551-561. doi:10.1002/sim.4780080504

20. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. *Schizophr Bull*. 2014;40(2): 314-326. doi:10.1093/schbul/sbu001

21. Rothe PH, Heres S, Leucht S. Dose equivalents for second generation long-acting injectable antipsychotics: the minimum effective dose method. *Schizophr Res*. 2018;193:23-28. doi:10.1016/j.schres.2017.07.033

22. Leucht S, Samara M, Heres S, et al. Dose equivalents for second-generation antipsychotic

drugs: the classical mean dose method. *Schizophr Bull*. 2015;41(6):1397-1402. doi:10.1093/schbul/sbv037

23. Davis JM. Dose equivalence of the antipsychotic drugs. *J Psychiatr Res*. 1974;11:65-69. doi:10.1016/0022-3956(74)90071-5

24. Leucht S, Samara M, Heres S, Davis JM. Dose equivalents for antipsychotic drugs: the DDD method. *Schizophr Bull*. 2016;42(suppl 1):S90-S94. doi:10.1093/schbul/sbv167

25. Gardner DM, Murphy AL, O'Donnell H, Centorrino F, Baldessarini RJ. International consensus study of antipsychotic dosing. *Am J Psychiatry*. 2010;167(6):686-693. doi:10.1176/appi.ajp.2009.09060802

26. Harrell FE. *Regression Modeling Strategies With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis*. Springer International Publishing; 2015. doi:10.1007/978-3-319-19425-7

27. Chen EYH, Hui CLM, Lam MML, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. *BMJ*. 2010;341:c4024. doi:10.1136/bmj.c4024

28. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. *J Clin Epidemiol*. 2008;61(10):991-996. doi:10.1016/j.jclinepi.2007.11.010

29. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634. doi:10.1136/bmj.315.7109.629

30. Crippa A, Orisini N. Multivariate dose-response meta-analysis: the dosresmeta R package. *J Statistical Software*. 2016;72(1):1-15.

31. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health*. 2019;22(4):153-160. doi:10.1136/ebmental-2019-300117

32. Pigott TA, Carson WH, Saha AR, Torbeyns AF, Stock EG, Ingenito GG; Aripiprazole Study Group. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry*. 2003;64(9):1048-1056. doi:10.4088/JCP.v64n0910

33. McEvoy JP, Daniel DG, Carson WH Jr, McQuade RD, Marcus RN. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. *J Psychiatr Res*. 2007;41(11):895-905. doi:10.1016/j.jpsychires.2007.05.002

34. Kane JM, Sanchez R, Perry PP, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week, multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2012;73(5):617-624. doi:10.4088/JCP.11m07530

35. Fleischhacker WW, Sanchez R, Perry PP, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. *Br J Psychiatry*. 2014;205(2):135-144. doi:10.1192/bjp.bp.113.134213

36. Mallikaarjun S, Kane JM, Bricmont P, et al. Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: an open-label, parallel-arm, multiple-dose study. *Schizophr Res*. 2013;150(1):281-288. doi:10.1016/j.schres.2013.06.041

37. Carpenter WT Jr, Buchanan RW, Kirkpatrick B, Lann HD, Breier AF, Summerfelt AT. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. *Am J Psychiatry*. 1999;156(3):412-418.

38. Dotti A, Bersani G, Rubino IA, Eliseo C. Double-blind trial of fluphenazine decanoate against placebo in ambulant maintenance treatment of chronic schizophrenics. *Rivista di Psichiatria*. 1979;14:374-383.

39. Kane JM, Rifkin A, Quitkin F, et al. Low dose fluphenazine decanoate in maintenance treatment of schizophrenia. *Psychiatry Res*. 1979;1(3):341-348. doi:10.1016/0165-1781(79)90016-7

40. Kane JM, Rifkin A, Woerner M, et al. Low-dose neuroleptic treatment of outpatient schizophrenics—I: preliminary results for relapse rates. *Arch Gen Psychiatry*. 1983;40(8):893-896. doi:10.1001/archpsyc.1983.01790070083010

41. Marder SR, Van Putten T, Mintz J, et al. Costs and benefits of two doses of fluphenazine. *Arch Gen Psychiatry*. 1984;41(11):1025-1029. doi:10.1001/archpsyc.1983.01790220015002

42. Schooler NR, Keith SJ, Severe JB, et al. Relapse and rehospitalization during maintenance treatment of schizophrenia: the effects of dose reduction and family treatment. *Arch Gen Psychiatry*. 1997;54(5):453-463. doi:10.1001/archpsyc.1997.01830170079011

43. Nishikawa T, Tsuda A, Tanaka M, Hoaki Y, Koga I, Uchida Y. Prophylactic effect of neuroleptics in symptom-free schizophrenics: a comparative dose-response study of haloperidol and propericiazine. *Psychopharmacology (Berl)*. 1984;82(3):153-156. doi:10.1007/BF00427763

44. Nishikawa T, Tsuda A, Tanaka M, Koga I, Uchida Y. Prophylactic effect of neuroleptics in symptom-free schizophrenics. *Psychopharmacology (Berl)*. 1982;77(4):301-304. doi:10.1007/BF00432759

45. Dellva MA, Tran P, Tollefson GD, Wentley AL, Beasley CM Jr. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. *Psychiatr Serv*. 1997;48(12):1571-1577. doi:10.1176/ps.48.12.1571

46. Velligan DI, Newcomer J, Pultz J, et al. Does cognitive function improve with quetiapine in comparison to haloperidol? *Schizophr Res*. 2002;53(3):239-248. doi:10.1016/S0920-9964(01)00268-7

47. Kane JM, Davis JM, Schooler N, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. *Am J Psychiatry*. 2002;159(4):554-560. doi:10.1176/appi.ajp.159.4.554

48. Eklund K, Forsman A. Minimal effective dose and relapse—double-blind trial: haloperidol decanoate vs. placebo. *Clin Neuropharmacol*. 1991;14(suppl 2):S7-S12.

49. Huttunen MO, Piepponen T, Rantanen H, Larmo I, Nyholm R, Raitasuo V. Risperidone versus zuclopenthixol in the treatment of acute schizophrenic episodes: a double-blind parallel-group trial. *Acta Psychiatr Scand*. 1995;91(4):271-277. doi:10.1111/j.1600-0447.1995.tb09781.x

50. Tandon R, Cucchiaro J, Phillips D, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. *J Psychopharmacol*. 2016;30(1):69-77. doi:10.1177/0269881115620460

51. Kane JM, Detke HC, Naber D, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. *Am J Psychiatry*. 2010;167(2):181-189. doi:10.1176/appi.ajp.2009.07081221

52. Hough D, Lindenmayer JP, Gopal S, et al. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009;33(6):1022-1031. doi:10.1016/j.pnpbp.2009.05.014

53. Simpson GM, Mahmoud RA, Lasser RA, et al. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry*. 2006;67(8):1194-1203. doi:10.4088/JCP.v67n0804

54. Arato M, O'Connor R, Meltzer HY; ZEUS Study Group. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. *Int Clin Psychopharmacol*. 2002;17(5):207-215. doi:10.1097/00004850-200209000-00001

55. Cooper SJ, Butler A, Tweed J, Welch C, Raniwalla J. Zotepine in the prevention of recurrence: a randomised, double-blind, placebo-controlled study for chronic schizophrenia. *Psychopharmacology (Berl)*. 2000;150(3):237-243. doi:10.1007/s002130000452

56. Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K. Estimating dopamine D_2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis. *J Clin Psychopharmacol*. 2013;33(5):675-681. doi:10.1097/JCP.0b013e3182983ffa

57. Tani H, Takasu S, Uchida H, Suzuki T, Mimura M, Takeuchi H. Factors associated with successful antipsychotic dose reduction in schizophrenia: a systematic review of prospective clinical trials and meta-analysis of randomized controlled trials. *Neuropsychopharmacology*. 2020;45(5):887-901. doi:10.1038/s41386-019-0573-7

58. Davis JM. Comparative doses and costs of antipsychotic medication. *Arch Gen Psychiatry*. 1976;33(7):858-861. doi:10.1001/archpsyc.1976.01770070088010

59. Ishigooka J, Iwashita S, Tadori Y. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: a 6-week, randomized, double-blind, placebo-controlled study. *Psychiatry Clin Neurosci*. 2018;72(9):692-700. doi:10.1111/pcn.12682

60. Takeuchi H, Suzuki T, Remington G, et al. Effects of risperidone and olanzapine dose reduction on cognitive function in stable patients with schizophrenia: an open-label, randomized, controlled, pilot study. *Schizophr Bull*. 2013;39(5):993-998. doi:10.1093/schbul/sbt090

61. Samara MT, Klupp E, Helfer B, Rothe PH, Schneider-Thoma J, Leucht S. Increasing antipsychotic dose for non response in schizophrenia. *Cochrane Database Syst Rev*. 2018;5:CD011883. doi:10.1002/14651858.CD011883.pub2

62. Baldessarini RJ, Cohen BM, Teicher MH. Significance of neuroleptic dose and plasma level in the pharmacological treatment of psychoses. *Arch*

Gen Psychiatry. 1988;45(1):79-91. doi:10.1001/archpsyc.1988.01800250095013

63. Takeuchi H, Siu C, Remington G, et al. Does relapse contribute to treatment resistance? antipsychotic response in first- vs. second-episode schizophrenia. *Neuropsychopharmacology*. 2019;44(6):1036-1042. doi:10.1038/s41386-018-0278-3

64. Emsley R, Nuamah I, Hough D, Gopal S. Treatment response after relapse in a placebo-controlled maintenance trial in schizophrenia. *Schizophr Res*. 2012;138(1):29-34. doi:10.1016/j.schres.2012.02.030

65. Emsley R, Chiliza B, Asmal L. The evidence for illness progression after relapse in schizophrenia. *Schizophr Res*. 2013;148(1-3):117-121. doi:10.1016/j.schres.2013.05.016

66. Emsley R, Oosthuizen P, Koen L, Niehaus D, Martinez L. Comparison of treatment response in second-episode versus first-episode schizophrenia. *J Clin Psychopharmacol*. 2013;33(1):80-83. doi:10.1097/JCP.0b013e31827bfcc1

67. Pollack S, Lieberman JA, Fleischhacker WW, et al. A comparison of European and American dosing regimens of schizophrenic patients on clozapine: efficacy and side effects. *Psychopharmacol Bull*. 1995;31(2):315-320.

68. Joyce JN. D_2 but not D_3 receptors are elevated after 9 or 11 months chronic haloperidol treatment: influence of withdrawal period. *Synapse*. 2001;40(2):137-144. doi:10.1002/syn.1035

69. Horowitz MA, Murray RM, Taylor D. Tapering antipsychotic treatment. *JAMA Psychiatry*. 2021;78(2):125-126. doi:10.1001/jamapsychiatry.2020.2166

70. Kissling W, Kane JM, Barnes TR, et al Guidelines for neuroleptic relapse prevention in schizophrenia: towards consensus view. In: Kissling W, ed. *Guidelines for Neuroleptic Relapse Prevention in Schizophrenia*. Springer; 1991:155-163. doi:10.1007/978-3-642-86922-8_19

71. Uchida H, Takeuchi H, Graff-Guerrero A, Suzuki T, Watanabe K, Mamo DC. Dopamine D_2 receptor occupancy and clinical effects: a systematic review and pooled analysis. *J Clin Psychopharmacol*. 2011;31(4):497-502. doi:10.1097/JCP.0b013e3182214aad

72. Brunoni AR, Tadini L, Fregni F. Changes in clinical trials methodology over time: a systematic review of six decades of research in psychopharmacology. *PLoS One*. 2010;5(3):e9479. doi:10.1371/journal.pone.0009479

73. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(1-02):9-62. doi:10.1055/s-0043-116492

Supplementary Online Content

Leucht S, Bauer S, Siafis S, et al. Examination of dosing of antipsychotic drugs for relapse prevention in patients with stable schizophrenia: a meta-analysis. JAMA Psychiatry. Published online August 18, 2021. doi:10.1001/jamapsychiatry.2021.2130

eAppendix 1. Dose Response Meta-analysis of Antipsychotic Drugs for Relapse Prevention in Schizophrenia (protocol)

eAppendix 2. Description of the Search Strategy

eFigure. PRISMA Diagram of the Search

eTable 1. Characteristics of Included Studies

eTable 2. Characteristics of Excluded Studies

eReferences

eAppendix 3. Assessment With the Cochrane Risk of Bias Tool, Version 2

eAppendix 4. Individual Drugs and Additional Sensitivity/Subgroup Analyses

eAppendix 5. Conversion to Absolute Rates, Relative Risks, and PANSS Units

eAppendix 6. Heterogeneity and Small Trial/Publication Bias

eAppendix 7. Update of the Meta-analysis of Uchida et al (2011) and Additional Analyses of Doses Higher Than Standard Doses (≥5mg Risperidone Equivalent per Day)

eTable 3. Average Dopamine Receptor Occupancies for Risperidone Doses

This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Dose response meta-analysis of antipsychotic drugs for relapse prevention in schizophrenia

Sofia Bauer, Tasnim Hamza, Spyridon Siafis, Hui Wu, MD, Johannes Schneider-Thoma, MD, Georgia Salanti, PhD, John M Davis, MD, Stefan Leucht, MD

Review question

Antipsychotic drugs are the mainstay of treatment of schizophrenia. The antipsychotic doses which are effective for the acute treatment of the disorder have been relatively well established (Leucht et al. American Journal of Psychiatry 2019;177:342-53). It is, however, unclear whether lower doses are sufficient for maintenance treatment (relapse prevention) than in the acute phase. To know this would be important due reduce the side-effects of antipsychotics to a minimum. We aim to fill this gap by dose-response meta-analysis of randomized controlled trials. Two separate publications are planned. One on efficacy with the primary outcome relapse (study defined) and one on the major side-effects of antipsychotics drugs, i.e. 1) at least one side-effect (primary outcome), 2) weight gain, 3) extrapyramidal side-effects, 4) prolactin increase, 5) QTc prolongation, 6) sedation.

Searches

1. Electronic databases: We will search the Cochrane Schizophrenia Group's Study-Based Register of Trials. The search strategy is: (*Amisulpride Dosage* OR *Aripiprazole Dosage* OR *Asenapine Dosage* OR *Brexpiprazole Dosage* OR *Cariprazine Dosage* OR *Clozapine Dosage* OR *Haloperidol Decanoate Dosage* OR *Haloperidol Dosage* OR *Iloperidone Dosage* OR *Lumateperone Dosage* OR *Lurasidone Dosage* OR *Olanzapine Dosage* OR *Paliperidone Dosage* OR *Paliperidone Palmitate Dosage* OR *Quetiapine Dosage* OR *Risperidone Dosage* OR *Sertindole Dosage* OR *Ziprasidone Dosage* OR *Zotepine Dosage*) in Pairwise Comparison Field of Study Records. This register is compiled of regular searches in multiple electronic databases, clinicaltrials.gov, WHO register of clinical trials and more. Details on the register can be found in (Shokraneh and Adams Systematic Reviews 2019;8:129, Shokraneh and Adams BioImpacts : BI 2017;7:209-17, Health Information and Libraries Journal 2020, Schizophrenia Bulletin Open 2020).
2. Previous reviews: We will search the studies of a Cochrane review on the effects of antipsychotic drugs for maintenance treatment in general (Leucht et al. Cochrane Database Syst Rev 2012;Cd008016, Ceraso et al. Cochrane Database Syst Rev 2020). For this review exhaustive searches had been undertaken.
3. Reference searching: Reference lists of newly included records will be hand-searched for potentially relevant studies.
4. We will contact authors or pharmaceutical companies for missing data of studies published from 1990 onward as long as e-mail addresses were available.

There will be no date/time, language, document type, and publication status limitations. All publications will be selected independently by at least two reviewers. In case of doubt, a third reviewer (SL and JST) will be involved. If this procedure does not lead to resolution of the issue, the study authors will be contacted.

Search strategy

Types of study to be included

- Randomized controlled trials (RCTs) with at least one fixed, antipsychotic dose versus a placebo (active or inactive, e.g. a benzodiazepine) or RCTs which compared at least two fixed doses of the same antipsychotic will be included.
- Both open and blinded trials.
- In case of crossover trials, only data from the first of cross-over phase will be used in order to avoid carry-over effects (Elbourne et al. Int J Epidemiol 2002;31:140-9)

- Cluster randomized trials will be excluded due to the unit-of-analysis-problems associated with this design (Whiting-O'Keefe et al. Med Care 1984;22:1101-14).
- Studies with a high risk of bias in terms of randomization according the Cochrane risk of bias tool will be excluded.
- There will be no language restriction. Studies from mainland China will be excluded due to frequent quality problems (Tong et al. BMC Med Res Methodol 2018;18:96). The reports are usually short making it impossible to detect these problems and authors often do not reply to requests in our experience. Studies conducted in China by international companies will be accepted.
- The minimum study duration will at least 14 weeks. The rational of this cutoff is to exclude short-term trials which usually examine acutely ill patients with schizophrenia. The purpose of the cutoff therefore is to reduce clinical and methodological heterogeneity. It corresponds to the category for short-term trials of the Cochrane Schizophrenia Group (https://schizophrenia.cochrane.org). There will be no a priori defined maximum duration, although we expect that few studies will last longer than 1 year and that the longest trial duration will be 3 years (Ceraso et al. Cochrane Database Syst Rev 2020).
- We will include both, studies which randomize participants in their maintenance phase, and so-called continuation studies, as long as all acute phase responders could be followed up. Continuation are studies in which patients are randomized in the acute phase, and the responders in the acute phase are then followed up and examined for relapse prevention. Designs that allow that participants switch from one randomised group to the other will be excluded. This kind of trials is, for example, often used in cost effectiveness studies, but it is not appropriate to compare the effects of different doses of one drug.
- Studies on the acute treatment of schizophrenia will be excluded.

Condition or domain being studied

Schizophrenia and schizophrenia-related disorder

Participants/population

- Participants with a diagnosis of schizophrenia or schizophrenia-related disorders, e.g. schizophreniform or schizoaffective disorders. We will accept both clinical diagnosis and diagnosis based on operationalized diagnostic criteria. Studies including participants with a diagnosis other than schizophrenia-related disorders will be accepted when the at least 80% of the participants had diagnoses with schizophrenia-related disorders.
- Participants must be in the stable phase of their illness, we will exclude studies in acutely ill patients. Any definition of “stability” will be accepted, because no uniform definition is available.
- Studies in children and adolescents, in elderly patients, in participants with predominant negative symptoms and in participants with a first-episode of schizophrenia will be analyzed separately, because there is evidence that such patients need lower doses, at least in the acute phase (Oosthuizen et al. Int J Neuropsychopharmacol 2004;7:125-31, Krause et al. Eur Neuropsychopharmacol 2018;28:659-74, Krause et al. Eur Arch Psychiatry Clin Neurosci 2018;268:625-39, Krause et al. Eur Neuropsychopharmacol 2018;28:1360-70). It is planned to analyze these populations in separate publications. Studies in treatment resistant patients and in patients with concomitant substance abuse will be analyzed together with the studies on general adults with schizophrenia, but they will be excluded in a sensitivity analysis (Krause et al. Eur Neuropsychopharmacol 2019;29:32-45).
- There will be no other restriction in terms of setting, gender, nationality and ethnicity.

Intervention(s), exposure(s)

- Any of the following antipsychotic drugs will be eligible: amisulpride, aripiprazole (oral, depot formulations of maintena and lauroxil), asenapine (oral and transdermal), brexpiprazole, cariprazine, clozapine, haloperidol (oral and depot), fluphenazine, iloperidone, lumateperone, lurasidone, olanzapine (oral and depot), quetiapine, paliperidone (oral and depot), risperidone (oral, depot formulations of consta and RBP-7000), sertindole, ziprasidone, zotepine. This selection comprises all so-called second-generation antipsychotic drugs available in Europe and/or the US. Haloperidol will also be examined, because it was the gold standard in many countries before these

more recent drugs had been developed. As the depot formulation of fluphenazine was the best investigated drug for dose-response before the advent of the second-generation antipsychotics, we included this other standard first-generation antipsychotic, as well.

- There will be no restriction in terms of route of administration (except for short-acting injections and intranasal forms that are used for acute agitation). Antipsychotic compounds given via different route of administration will be considered as separate compounds. For example, oral aripiprazole, aripiprazole maintena and aripiprazole lauroxil will be considered as three separate antipsychotic interventions. In a similar vein for oral asenapine/transdermal asenapine, oral paliperidone/paliperidone depot once monthly, risperidone/risperidone consta/risperidone RBP-7000, olanzapine/olanzapine depot.
- Fixed-dose schedules, and studies in which patients are randomised to different, narrow, non-overlapping, fixed dose range, for example olanzapine 5mg/day +/- 2.5 mg/day versus olanzapine 10mg/day +/-2.5mg/day. Flexible-dosing schedules will not be eligible.

Comparator(s)/control

Placebo, active of non-active.

Context

We will include studies in outpatient and in inpatient settings as long as the patients are stable at baseline. We will not generally exclude inpatient studies, because there might be studies which have been conducted in long-term wards for stable patients. The detailed in- and exclusion criteria are listed above.

Main outcome(s)

We plan two separate publications, one with a focus on efficacy, the other one on different side-effects. We wrote one protocol, because the overall methodology and the searches will be the same. The following are the outcomes for the efficacy focused review.

The number of participants relapsed (study defined)

We will accept any definition of relapse. Different definitions have been used in the literature and that there is no consensus as to which is the most appropriate one. We will, however, prefer relapse criteria which are operationalized by rating scales rather than other criteria that we will extract following this hierarchy a) ‘patient relapsed by the judgment of the clinician/rater’, b) need for additional antipsychotic medication c) dropout due to inefficacy d) re-hospitalisation and e) and other.

The primary outcome relapse will be extracted at 6 months, 9 months, 12 months and longer than 12 months. We will statistically analyze the outcome closest to 12 months. All other outcomes will be measured at study endpoint.

* Measures of effect

Relapse will be analyzed with odds ratios. Also see section ‘strategy for data synthesis’.

Additional outcome(s)

The following secondary outcomes will be analysed in the review.

1. Mean change from baseline to endpoint of overall symptoms of schizophrenia as measured by the Positive and Negative Syndrome Scale (Kay et al. Schizophr Bull 1987;13:261-76), the Brief Psychiatric Rating Scale (Overall and Gorham Psychological Reports 1962;10:799-812) or any other published scale to measure the symptoms of schizophrenia.
2. Premature study discontinuation due to any reason. This outcome is actually a measure of effectiveness, because it comprises dropouts due to side-effects, inefficacy and others.
3. Rehospitalisation for psychiatric reasons
4. Premature study discontinuation due to adverse events, where dropouts due to side-effects were preferred whenever available.

* Measures of effect

Rating scales of schizophrenia symptoms will be analyzed with the standardized mean difference, because we expect that different scales have been used in the studies. All other outcomes are dichotomous for which odds ratios will be use as measures of effect. Also see section 'strategy for data synthesis'.

Data extraction (selection and coding)

1. Selection of trials: At least two reviewers will independently inspect the titles and abstracts of non-duplicated references identified through the search and will exclude those not pertinent. Discrepancies between the two reviewers will be resolved by discussion. If doubts still remain, the full text will be obtained and eligibility will be assessed. Full texts of included references will be obtained and independently assessed by two reviewers for eligibility. Again, disagreements will be resolved by discussion and, if needed, a third author will be involved (SL or JST). When required, further information will be requested from study authors.

2. Data extraction: Two authors will independently extract data from all selected trials in a Microsoft Access database. When disagreement arises, we will resolve it by discussion and, if needed, involving a third senior author (SL or JST). Where this is not sufficient, we will contact the study authors.

- When authors of original studies used imputation methods to handle missing data, we will prefer them to completers' data. For the outcome relapse we will prefer data based on survival analysis rather than the absolute number of participants relapsed. In terms of continuous data mixed-models of repeated measurement (MMRM), multiple imputation will be preferred over last-observation carried forward (LOCF), if available.
- For dichotomous outcomes, if only completer analyses are presented, we will assume that participants lost to follow-up did not have the outcome. We think that another assumption would overestimate the risk.
- For continuous outcomes, we will prefer change scores to follow-up data, but we will also accept the latter when the former are not available.
- Missing SDs will be calculated from 1) standard error (SE), 2) other measures of variability (95% confidence intervals, ranges etc), 3) test statistics 4) imputed from the SDs of the other studies using a validated method (Furukawa et al. J Clin Epidemiol 2006;59:7-10) according to the Cochrane Handbook (Higgins and Green 2011;4).

Risk of bias (quality) assessment

Two independent review authors will assess the risk of bias in the selected studies using the 'Cochrane Collaboration risk of bias' tool version 2 (Sterne et al. Bmj 2019;366:l4898). When disagreement arises we will resolve it by discussion and, if needed, involving a third senior author.

Strategy for data synthesis

- In the efficacy publication we will – in addition to analyzing each antipsychotic separately - pool all studies after converting the doses to risperidone equivalents based on the following criteria: Dose equivalence based on 95% Effective Doses (Leucht et al. American Journal of Psychiatry 2019;177:342-53), if not available Minimum Effective Dose method (Leucht et al. Schizophr Bull 2014;40:314-26, Rothe et al. Schizophr Res 2018;193:23-8), if not available Mean Dose method (Leucht et al. Schizophr Bull 2015;41:1397-402, Davis J Psychiatr Res 1974;11:65-9), if not available Daily Defined Dose method (Leucht et al. Schizophr Bull 2016;42 Suppl 1:S90-4) if not available based on the International Consensus of Antipsychotic Doses (David M. Gardner et al. American Journal of Psychiatry 2010;167:686-93). In a secondary analysis we will convert doses based on the expert opinions according to the International Consensus of Antipsychotic Doses (David M. Gardner et al. American Journal of Psychiatry 2010;167:686-93) supplemented by similar judgements by the reviewer team for drugs that were not reported in the consensus statement.

- The effect sizes for dichotomous outcomes will be the odds ratio (OR). The effect sizes for continuous rating scales for efficacy we will use the standardized mean difference (SMD as Hedges' g), because we expect that various scales have been used in the studies to measure the same concepts. All effect sizes will be accompanied by their 95% confidence intervals.
- We will conduct a one-stage dose response meta-analysis in a frequentist framework using restricted-cubic splines with the R package 'dosresmeta' developed by Crippa et al (Crippa et al. Stat Methods Med Res 2019;28:1579-96, Crippa and Orsini Journal of Statistical Software 2016;72). We will use knot points at the 25th, 50th and 75th percentile.
- We will produce absolute dose-response curves: we will synthesize the effects in the placebo arms and we will transform the relative dose-response curves estimated in previous steps to absolute curves.
- For drugs with enough data we will use the Wald statistic to explore whether there is evidence of an overall dose-response relationship and we will report the p-values.
- We will use the dose-response curves to estimate the 95% effective dose (ED95) and 50% effective dose (ED50) as is customary in dose-response analysis (1, 4). The ED50 is the mean dose that produces 50% of the maximum relapse prevention compared with placebo, and the ED95 is the mean dose that produces 95% of the maximum reduction. The ED50 and the ED95 will be calculated for each drug separately and for all drugs pooled.
- Small study effects and the possibility of publication bias will be assessed with funnel plots and Egger's test, when there are at least 10 studies available.

Analysis of subgroups or subsets

Predefined sensitivity analyses of the primary outcomes will be:

- In the primary analysis, we will synthesize studies that compared at least two doses of a compound with placebo. In a sensitivity analysis we will exclude studies that compared only a single dose of an antipsychotic with placebo, because such studies were not designed to address dose-response and could therefore produce methodological heterogeneity.
- Immediate (IR) and extended release (XR) formulations will be analyzed separately (i.e. for quetiapine).
- We will exclude open RCTs for subjective outcomes.
- We will examine the subgroup of patients in remitted (added post-hoc).

References

1. Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. American Journal of Psychiatry. 2019;177:342-53.
2. Shokraneh F, Adams CE. Study-based registers reduce waste in systematic reviewing: discussion and case report. Systematic Reviews. 2019;8:129.
3. Shokraneh F, Adams CE. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. BioImpacts : BI. 2017;7:209-17.
4. Shokraneh F, Adams CE. Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis. Health Information and Libraries Journal. 2020.
5. Shokraneh F, Adams CE. Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials: Development and Content Analysis. Schizophrenia Bulletin Open. 2020.
6. Leucht S, Tardy M, Komossa K, Heres S, Kissling W, Davis JM. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev. 2012:Cd008016.
7. Ceraso A, Lin J, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, Heres S, Kisslin W, Davis JM, Leucht S. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev. 2020.
8. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol. 2002;31:140-9.
9. Whiting-O'Keefe QE, Henke C, Simborg DW. Choosing the correct unit of analysis in Medical Care experiments. Med Care. 1984;22:1101-14.
10. Tong Z, Li F, Ogawa Y, Watanabe N, Furukawa TA. Quality of randomized controlled trials of new generation antidepressants and antipsychotics identified in the China National Knowledge Infrastructure (CNKI): a literature and telephone interview study. BMC Med Res Methodol. 2018;18:96.

11. Oosthuizen P, Emsley R, Jadri Turner H, Keyter N. A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. Int J Neuropsychopharmacol. 2004;7:125-31.
12. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Chaimani A, Leucht S. Efficacy, acceptability, and tolerability of antipsychotics in children and adolescents with schizophrenia: A network meta-analysis. Eur Neuropsychopharmacol. 2018;28:659-74.
13. Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A, Leucht S. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. Eur Arch Psychiatry Clin Neurosci. 2018;268:625-39.
14. Krause M, Huhn M, Schneider-Thoma J, Rothe P, Smith RC, Leucht S. Antipsychotic drugs for elderly patients with schizophrenia: A systematic review and meta-analysis. Eur Neuropsychopharmacol. 2018;28:1360-70.
15. Krause M, Huhn M, Schneider-Thoma J, Bighelli I, Gutsmiedl K, Leucht S. Efficacy, acceptability and tolerability of antipsychotics in patients with schizophrenia and comorbid substance use. A systematic review and meta-analysis. Eur Neuropsychopharmacol. 2019;29:32-45.
16. Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13:261-76.
17. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychological Reports. 1962;10:799-812.
18. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl. 1970;212:11-9.
19. Chouinard G, Margolese HC. Manual for the Extrapyramidal Symptom Rating Scale (ESRS). Schizophr Res. 2005;76:247-65.
20. Barnes TRE. A rating scale for drug-induced akathisia. Br J Psychiatry. 1989;154:672-6.
21. Schooler NR, Kane JM. Research diagnoses for tardive dyskinesia. Arch Gen Psychiatry. 1982;39:486-7.
22. Furukawa TA, Barbui C, Cipriani A, Brambilla P, Watanabe N. Imputing missing standard deviations in meta-analyses can provide accurate results. J Clin Epidemiol. 2006;59:7-10.
23. Higgins JPT, Green S: Cochrane handbook for systematic reviews of interventions, John Wiley & Sons; 2011.
24. Sterne JAC, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernan MA, Hopewell S, Hrobjartsson A, Junqueira DR, Juni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. Bmj. 2019;366:l4898.
25. Leucht S, Samara M, Heres S, Patel MX, Woods SW, Davis JM. Dose equivalents for second-generation antipsychotics: the minimum effective dose method. Schizophr Bull. 2014;40:314-26.
26. Rothe PH, Heres S, Leucht S. Dose equivalents for second generation long-acting injectable antipsychotics: The minimum effective dose method. Schizophr Res. 2018;193:23-8.
27. Leucht S, Samara M, Heres S, Patel MX, Furukawa T, Cipriani A, Geddes J, Davis JM. Dose Equivalents for Second-Generation Antipsychotic Drugs: The Classical Mean Dose Method. Schizophr Bull. 2015;41:1397-402.
28. Davis JM. Dose equivalence of the antipsychotic drugs. J Psychiatr Res. 1974;11:65-9.
29. Leucht S, Samara M, Heres S, Davis JM. Dose Equivalents for Antipsychotic Drugs: The DDD Method. Schizophr Bull. 2016;42 Suppl 1:S90-4.
30. David M. Gardner, Pharm.D., M.Sc. ,, Andrea L. Murphy, Pharm.D. ,, Heather O'Donnell, B.Sc. Pharm. ,, Franca Centorrino, M.D. , and, Ross J. Baldessarini, M.D. International Consensus Study of Antipsychotic Dosing. American Journal of Psychiatry. 2010;167:686-93.
31. Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Backers L, Rothe P, Cipriani A, Davis J, Salanti G, Leucht S. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. Lancet. 2019;394:939-51.
32. Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res. 2019;28:1579-96.
33. Crippa A, Orsini N. Multivariate Dose-Response Meta-Analysis: The dosresmeta R Package. Journal of Statistical Software. 2016;72.

Changes to the original protocol published in Prospero

- This version refers to the efficacy focussed review, additional ones on specific side-effects are planned. This decision was made a priori, see first paragraph of the protocol.

- We added a subgroup analysis of patients in remission at baseline. The single first-episode study was analysed together with the studies in chronic patients, but excluded in a sensitivity analysis. Similarly, due to a relative scarcity of data we pooled oral and depot formulations, but we also analysed both separately (data not shown).
95% and 50% effective doses were not calculated.
- The outcome rehospitalisation for psychiatric reasons was analysed separately in addition to its analysis as an indicator for relapse.
- Following reviewer requests we tested with linear splines up to which dose the dose-response curve still showed a significantly increasing slope, and added subgroup analyses on long-acting injectable versus oral medications, first-generation versus second-generation antipsychotics, percentage male and age.

eAppendix 2. . Description of the search strategy

1 Database

Cochrane Schizophrenia Group's Study-Based Register of Trials. Details are also described on the Cochrane Schizophrenia Group's website https://schizophrenia.cochrane.org/.

2 Date of search

9th March 2020

3 Search Strategy

Strategy: (*Amisulpride Dosage* OR *Aripiprazole Dosage* OR *Asenapine Dosage* OR *Brexpiprazole Dosage* OR *Cariprazine Dosage* OR *Clozapine Dosage* OR *Fluphenazine Dosage* OR *Haloperidol Decanoate Dosage* OR *Haloperidol Dosage* OR *Iloperidone Dosage* OR *Lumateperone Dosage* OR *Lurasidone Dosage* OR *Olanzapine Dosage* OR *Paliperidone Dosage* OR *Paliperidone Palmitate Dosage* OR *Quetiapine Dosage* OR *Risperidone Dosage* OR *Sertindole Dosage* OR *Ziprasidone Dosage* OR *Zotepine Dosage*) in Pairwise Comparison Field of Study Records

4 Search Results

There were 1306 references from 390 studies.

5 References to database details

1. Shokraneh, Farhad; Adams, Clive E. Classification of all pharmacological interventions tested in trials relevant to people with schizophrenia: A study-based analysis. Health Information and Libraries Journal 2020; Accepted

2. Shokraneh, Farhad; Adams, Clive E. Cochrane Schizophrenia Group's Study-Based Register of Randomized Controlled Trials: Development and Content Analysis. Schizophrenia Bulletin Open 2020; Under Review.

3. Shokraneh, Farhad; Adams, Clive E. Study-based registers reduce waste in systematic reviewing: discussion and case report. Systematic Reviews 2019; 8: 129. DOI 10.1186/s13643-019-1035-3

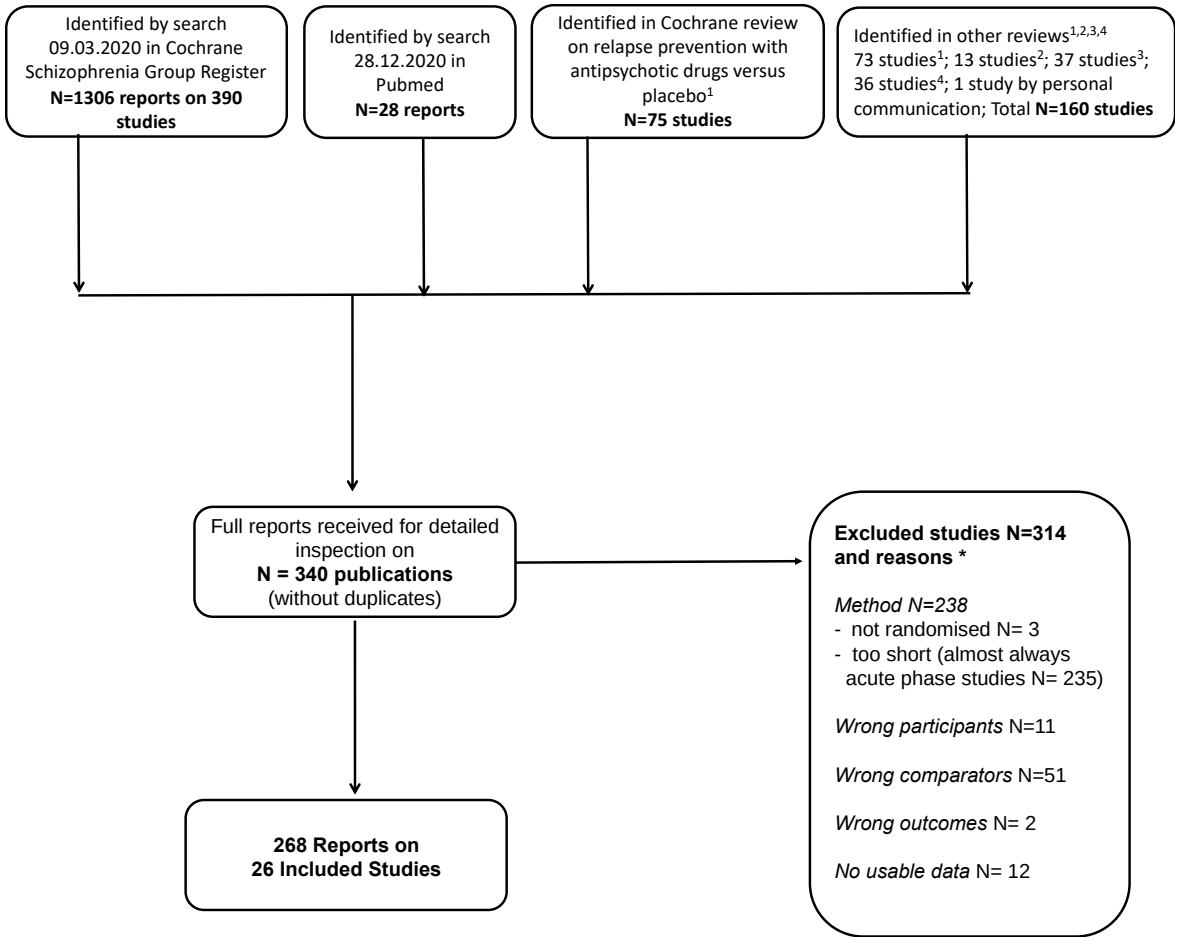
4. Shokraneh, Farhad; Adams, Clive E. Study-based registers of randomized controlled trials: Starting a systematic review with data extraction or meta-analysis. BioImpacts 2017; 7(4): 209-217. DOI 10.15171/bi.2017.25

5 Update search in Pubmed January 1st 2021

Search: (amisulpride OR aripiprazole OR asenapine OR brexpiprazole OR cariprazine OR clozapine OR fluphenazine OR haloperidol* OR iloperidone OR lumateperone OR lurasidone OR olanzapine OR paliperidone OR quetiapine OR risperidone OR sertindole OR ziprasidone OR zotepine) Filters: Randomized Controlled Trial, From 2020/1/1 to 2021/1/1

28 selected items

eFigure. PRISMA diagram of the search



N = number of studies, * some publications provided data on two studies

References

1. Ceraso A, Lin J, Schneider-Thoma J, Siafis S, Tardy M, Komossa K, Heres S, Kisslin W, Davis JM, Leucht S. Maintenance treatment with antipsychotic drugs for schizophrenia. Cochrane Database Syst Rev. 2020.
2. Rothe PH, Heres S, Leucht S. Dose equivalents for second generation long-acting injectable antipsychotics: The minimum effective dose method. Schizophr Res Jul 21 2017.
3. Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC. Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. Schizophr Bull. 2011;37(4):788-99.
4. Tani H, Takasu S, Uchida H, Suzuki T, Mimura M, Takeuchi H. Factors associated with successful antipsychotic dose reduction in schizophrenia: a systematic review of prospective clinical trials and meta-analysis of randomized controlled trials. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2020;45(5):887-901.
5. Leucht S, Samara M, Rodolico A, Bauer I, Bäckers L, Bighelli I. S204. Reduction of antipsychotic doses and polypharmacy: two Cochrane reviews. Schizophrenia Bulletin. 2020;46(Supplement_1):S116-S.

eTable1: Characteristics of Included Studies

Study	Year of Publicationm	Degree of blinding	Duration (wks)	Diagnostic term (diagnostic criteria)	Interventions	Application	Dosing interval	Dose mean and range mg	Number of patients randomized	Mean age in years
Arato et al 2002(1)	2002	double blind	52	Schizophrenia (DSM-III-R)	Placebo	oral	-	-	71	48.7
					Ziprasidone 160mg	oral	daily	160 (160-160)	67	49.6
					Ziprasidone 40mg	oral	daily	40 (40-40)	72	50.8
					Ziprasidone 80mg	oral	daily	80 (80-80)	68	49.8
Velligan et al 2002(2) (unpublished data obtained)	1995	double blind	52	Schizophrenia (DSM-III-R)	Haloperidol	oral	daily	12 (12-12)	41	37
					Quetiapine 300mg	oral	daily	300 (300-300)	88	37
					Quetiapine 600mg	oral	daily	600 (600-600)	87	38
					Quetiapine 75mg	oral	daily	75 (75-75)	85	39
Beasley et al 1996a (Study F1M-MC-HGAD)(3) (unpublished data obtained)	1996	double blind	46	Schizophrenia (DSM-III-R)	Haloperidol 15±5mg	oral	daily	15.8 (10-20)	10	36.1
					Olanzapine 10±2.5mg	oral	daily	11.6 (7.5-12.5)	9	40.9
					Olanzapine 15±2.5mg	oral	daily	15.8 (12.5-17.5)	22	34.4
					Olanzapine 5±2.5mg	oral	daily	6.3 (2.5-7.5)	14	33.5
					Placebo	oral	-	-	13	36.1
Beasley et al 1997 (Study	1997	double blind	46	Schizophrenia (DSM-III-R)	Haloperidol 15±5mg	oral	daily		28	34.9

F1D-EW-E003)(3) (unpublished data obtained)					Olanzapine 1±2.5mg	oral	daily	1 (1-1)	33	34.0
					Olanzapine 10±2.5mg	oral	daily	11.3 (7.5-12.5)	40	36.5
					Olanzapine 15±5mg	oral	daily	16.1(12.5-17.5)	43	37.6
					Olanzapine 5±2.5mg	oral	daily	6.6 (2.5-7.5)	31	35.2
Carpenter et al 1999(4)	1999	double blind	54	Schizophrenia or schizoaffective disorder (DSM-III-R)	Fluphenazine 25mg/2 weeks	depot	every 2 weeks	25 (25-25)	25	34.7
					Fluphenazine 25mg/6 weeks	depot	every 6 weeks	25 (25-25)	25	36.2
Chen et al 2010(5)#	2010	double blind	52	First-episode outpatients with schizophrenia or related disorders (DSM-IV). Remission criteria: no history of relapse in the last 12 months (defined as any increase in positive symptoms leading to adjustement of drug treatment or readmission to hospital, ascertained with information from patients, carers, case managers, clinicians, and clinical records). All were non-psychotic at study entry as defined by having below threshold scores on five	Placebo	oral	-	-	89	24.9
					Quetiapine	oral	daily	400 (400-400)	89	23.5

				key psychotic symtpoms on the PANSS: P1 delusions ≤2, P2 conceptual disorganization ≤ 3, P3 hallucinatory behavior ≤ 2, P6 suspiciousness ≤ 4, G9 Unusual thought content ≤3; and ≤2 (borderline or questionable illness) on the CGI severity.						
Cooper et al 2000(6)	2000	double blind	26	Schizophrenia (DSM-III-R)	Placebo	oral	-	-	58	41.6
					Zotepine	oral	daily	n.i. (150-300)	63	43
Dotti et al 1979(7)	1979	double blind	39	Schizophrenia (Clinical diagnosis)	Fluphenazine	depot	every 4 weeks	n.i. (25-50)	10	n.i.
					Placebo	depot	-	-	10	n.i.
Eklund et al 1991(8)	1991	double blind	48	Schizophrenia (Research Diagnostic Criteria (RDC))	Haloperidol	depot	every 4 weeks	60 (60-60)	20	51.7
					Placebo	depot	-	-	23	51.7
Fleischhacker et al 2014(9)	2014	double blind	38	Schizophrenia (DSM-IV-TR)	Aripiprazole LAI 400mg/4weeks	depot	every 4 weeks	392 (300-400)	265	41.7
					Aripiprazole LAI 50mg/4weeks	depot	every 4 weeks	50 (25-50)	131	40.2
Hough et al 2009(10)	2009	double blind	25	Schizophrenia (DSM-IV)	Paliperidone 100mg	depot	every 4 weeks	100 (100-100)	86	43
					Paliperidone 50mg	depot	every 4 weeks	50 (50-50)	82	43
					Paliperidone 75mg	depot	every 4 weeks	75 (75-75)	84	43
Huttunen et al 1996(11)	1996	open-label	104	Schizophrenia (DSM-III-R)	Haloperidol 150mg	depot	every 4 weeks	150 (150-150)	13	n.i.

					Haloperidol 25mg	depot	every 4 weeks	25 (25-25)	13	n.i.
Kane et al 1979(12)#	1979	double blind	26	Schizophrenia, any subtype (RDC) in good remission with no evidence for significant psychopathology and with reasonably good social and vocational functioning for at least 6 months during a prospective open non-randomised trial with fluphenazine decanoate. All patients were being successfully maintained in the community.	Fluphenazine	depot	every 2 weeks	n.i. (1.25-5)	8	26.5
					Placebo	depot	-	-	8	26.9
Kane et al 1983(13)#	1983	double blind	52	Outpatients with schizophrenia or schizoaffective disorder (RDC) in remission or partial remission defined by GAS ≥ 35; BPRS ≤ 4 on conceptual disorganization and hallucinatory behavior, ≤ 5 on suspiciousness, and ≤3 on unusual thought content. No fluctuation in either direction by more than 10 on the GAS and by more than 1 on any of the BPRS items	Fluphenazine 1.25-5mg	depot	every 2 weeks	3.125 (1.25-5)	66	28.9
					Fluphenazine 12.5-50mg	depot	every 2 weeks	31.25 (12.5-50)	66	28.9

				mentioned. Patients were required to maintain this stability while receiving a constant IM dose of fluphenazine-decanoate within the range of 12.5 to 50mg/2week. Average number of weeks from hospital discharge to study entry 63.9+-78.5 weeks.						
Kane et al 2002b(14)#	2002	double blind	52	Schizophrenia or schizoaffective disorder (DSM-III) outpatients with a baseline state of relative remission for at least 3 months during maintenance treatment with antipsychotic medication and a BPRS ≤3 on conceptual disorganization and unusual thought content and ≤4 on hallucinatory behavior and suspiciousness	Haloperidol 100mg	depot	every 4 weeks	100 (100-100)	31	38
					Haloperidol 200mg	depot	every 4 weeks	200 (200-200)	29	40
					Haloperidol 25mg	depot	every 4 weeks	25 (25-25)	29	38
					Haloperidol 50mg	depot	every 4 weeks	50 (50-50)	30	38
Kane et al 2010(15)	2010	double blind	24	Schizophrenia (DSM-IV or DSM-IV-TR)	Olanzapine LAI 150mg/2weeks	depot	every 2 weeks	150 (150-150)	140	37.7
					Olanzapine LAI 300mg/2weeks	depot	every 2 weeks	300 (300-300)	141	39.5

					Olanzapine LAI 405mg/4weeks	depot	every 4 weeks	405 (405-405)	318	39
					Olanzapine LAI 45mg/4weeks	#NV	n.i.	n.i. (n.i.-n.i.)	#NV	n.i.
Kane et al 2012(16)	2012	double blind	52	Schizophrenia (DSM-IV-TR)	Aripiprazole	depot	every 4 weeks	396.3 (300-400)	269	40.1
					Placebo	depot	-	-	134	41.7
Mallikaarjun et al 2013(17)	2013	open-label	24	Schizophrenia (DSM-IV-TR)	Aripiprazole 200mg	depot	every 4 weeks	200 (200-200)	11	46
					Aripiprazole 300mg	depot	every 4 weeks	300 (300-300)	16	43.3
					Aripiprazole 400mg	depot	every 4 weeks	400 (400-400)	14	46.8
Marder et al 1984(18)	1984	double blind	104	Schizophrenia (DSM-III)	Fluphenazine 25mg	depot	every 2 weeks	25 (25-25)	31	38.1
					Fluphenazine 5mg	depot	every 2 weeks	5 (5-5)	35	35.1
McEvoy et al 2007 extension (19) (unpublished data obtained)	2005	double blind	46	Schizophrenia (DSM-IV)	Aripiprazole 10-15mg	oral	daily	n.i. (10-15)	88	n.i.
					Aripiprazole 20-30mg	oral	daily	n.i. (20-30)	88	n.i.
Nishikawa et al 1982(20)#	1982	double blind	156	Fully remitted schizophrenic outpatients who were working in society	Haloperidol	oral	daily	3 (3-3)	10	33
					Placebo	oral	-	-	10	33.6
Nishikawa et al 1984(21)#	1984	double blind	52	Symptom free outpatients Schizophrenia (DSM-III) in the recovery stage of remission or residual phase	Haloperidol 1mg	oral	daily	1 (1-1)	13	40
					Haloperidol 3mg	oral	daily	3 (3-3)	12	36.3
					Haloperidol 6mg	oral	daily	6 (6-6)	12	42.8
					Placebo	oral	-	-	13	38.8
	2016		28	Schizophrenia	Lurasidone	oral	daily	78.9 (40-80)	144	43

Tandon et al 2016(22)		double blind		(DSM-IV-TR)	Placebo	oral	-	-	141	42.4
Pigott et al 2003(23)	2003	double blind	26	Schizophrenia (DSM-IV)	Aripiprazole	oral	daily	15 (15-15)	155	42.2
					Placebo	oral	-	-	155	41.7
Schooler et al 1997(24)	1997	double blind	104	Schizophrenia (any subtype), schizoaffective disorder or schizophreniform (DSM-III-R)	Fluphenazine 12.5-50mg	depot	every 2 weeks	27.47353 (12.5-50)	55	29.6
					Fluphenazine 2.5-10mg	depot	every 2 weeks	13.775 (2.5-10)	52	29.6
					Placebo	depot	-	-	49	29.6
Simpson et al 2006(25)	2006	double blind	52	Schizophrenia or schizoaffective disorder (DSM-IV)	Risperidone 25mg	depot	every 2 weeks	25 (25-25)	163	41.7
					Risperidone 50mg	depot	every 2 weeks	50 (50-50)	161	40.2

n.i. = not indicated, DSM = Diagnostic and Statistical Manual, RDC = Research diagnostic criteria , # studies in remitted patients.

eTable2: Characteristics of Excluded Studies

Author	Reason for exclusion
Agid et al 2007(26)	Method: short-term
Agid et al 2008(27)	Method: short-term
Anderson et al 1976(28)	Method: short-term
Andrews et al 1976(29)[i]	Method: randomized Participants: schizophrenia Intevention: flexible dose ranges
Anonymus 1994(30)	Method: short-term
Anonymus 2001(31)	Method: short-term
Aravagiri et al 1994(32)	Method: randomized Participants: schizophrenia Intevention: fixed dose Outcome: not relapse prevention
Arvanitis et al 1997(33)	Method: short-term
Assion et al 2008(34)	Method: short-term
Auby et al 2002(35)	Method: short-term
Bark et al 1996(36)	Method: short-term
Barnas et al 2001(37)	Method: short-term
Bateman et al 1979(38)	Method: short-term
Beasley et al 1996 (Study F1D-MC-HGAP)(39)	Method: randomized Participants: schizophrenia Intervention: no fixed doses
Beasley et al 2003(40)	Method: randomized Participants: schizophrenia Intevention: flexible dose range
Berger et al 2008(41)	Method: short-term
Berwaerts et al 2015(42)	Method: randomized Participants: schizophrenia Intevention: not all participants received the same dosages of paliperidone palimtate
Bitter et al 1989(43)	Method: short-term
Bjorndal et al 1980(44)	Method: short-term
Boyer et al 1987(45)	Method: short-term
Brambilla et al 1987(46)	Method: randomized Participants: chronic schizophrenia Intevention: combination of drugs
Bristol-Myers 2004/CN138114(47)	Method: short-term
Bristol-Myers 2005/CN138050(48)	Method: short-term
Bunney et al 2010(49)	Method: short-term
Cada et al 2004(50)	Method: short-term
Canuso et al 2010(51)	Method: short-term
Cetin et al 1999(52)	Method: short-term
Chang et al 1991(53)	Method: short-term
Channabasavanna et al 1987(54)	Method: short-term
Chapel et al 2009(55)	Method: short-term
Chavda et al 2004(56)	Method: short-term
Citome et al 2019(57)	Method: short-term
Clark et al 1975(58)	Method: randomized Participants: chronic schizophrenia Intevention: flexible dosage
Clerc et al 1989(59)	Method: short-term
Coppola et al 2011(60)	Method: short-term

Correll et al 2015(61)	Method: short-term
Correll et al 2020(62)	Method: short-term
Ctri-2014-04-004521(63)	Method: short-term
Cutler et al 2006(64)	Method: short-term
Cutler et al 2010(65)	Method: short-term
Czobor et al 1993(66)	Method: short-term
Daniel et al 1999(67)	Method: short-term
Daniel et al 2001(68)	Method: short-term
Daniel et al 2001a(69)	Method: short-term
Davidson et al 2007(70)	Method: short-term
Davis et al 1985(71)	Method: short-term
De Buck et al 1973(72)	Method: short-term
DelBello et al 2008(73)	Method: short-term
Dencker et al 1978(74)	Method: short-term, cross over design, 4 wks each
Denijs et al 1973(75)	Method: randomized Population: stable schizophrenics Intervention: no fixed dosage
do Carmo Borges 2012(76)	Method: short-term
Donlon et al 1978(77)	Method: short-term
Donlon et al 1980(78)	Method: short-term
Dubitsky et al 2002(79)	Method: randomized Population: stable schizophrenia Intervention: no fixed dose
Dubovsky et al 2012(80)	Method: short-term
Durgam et al 2014(81)	Method: short-term
Durgam et al 2015(82)	Method: short-term
Durgam et al 2016(83)	Method: short-term
Durgam et al 2016a(84)	Method: randomized Population: stable schizophrenia Intervention: no fixed dose
Dutoit et al 1995(85)	Method: short-term
Eerdekens et al 2004(86)	Method: short-term
Eli Lilly 2008(87)	Method: not adequately randomized
EMEA 2007(88)	Method: pooled data
Euctr2006-006434-17(89)	Method: short-term
Findling et al 2008(90)	Method: short-term
Findling et al 2015(91)	Method: short-term
Findling et al 2015a(92)	Method: short-term
Fleischhacker et al 2003(93)	Method: randomization issues
Fleischhacker et al 2017(94)	Method: randomized Population: stable schizophrenia Intervention: no fixed dose
Freeman et al 1962(95)	Method: randomized Population: stable schizophrenia Intervention: flexible doses
Fu et al 2015(96)	Method: randomized Population: schizoaffective disorder Intervention: flexible doses
Gallant et al 1974(97)	Method: randomized Population: severly ill schizophrenics Intervention: flexible doses of penfluridol
Gitlin et al 1988(98)	Method: short-term cross over phases
Gitlin et al 2001(99)	Method: short-term cross over phases

Goff et al 2013(100)	Method: short-term
Goldman et al 2017(101)	Method: short-term
Good et al 1958(102)	Method: short-term cross over phases
Gopal et al 2009(103)	Method: short-term
Grosset al 1974(104)	Method: randomized Population: chronic schizophrenia Intervention: wrong medication (pimozide, trifluoperazine)
Gutierrez et al 1996(105)	Method: short-term
H. Lundbeck 2009(106)	Method: short-term
Haas et al 2009(107)	Method: short-term
Hale et al 2012(108)	Method: short-term
Hard et al 2017(109)	Method: randomized Population: schizophrenia Intervention: All groups received the same dosage over time but in different divisions
Hard et al 2018(110)	Method: short-term
Harvey et al 2009(111)	Method. Randomized Population: schizophrenia Intervention: no fixed dose
Harvey et al 2010(112)	Method: randomized Population: schizophrenia Intervention: no fixed dose in continuitation phase
Hershon et al 1972(113)	Method: randomized Population: schizophrenia Intervention: wrong medication (trifluoperazine)
Higuchi et al 2019(114)	Method: short-term
Higuchi et al 2019a(115)	Method: short-term
Hirsch et al 1973(116)	Method: randomized Population: chronic schizophrenia Intervention: no fixed dosage
Hirsch et al 1989(117)	Method: randomized Population: chronic schizophrenia Intervention: no fixed dosage
Hirsch et al 1996(118)	Method: randomization issues
Hirschowitz et al 1997(119)	Method: short-term
Hogarty et al 1974(120)	Method: randomized Population: schizophrenia Intervention: flexible doses
Hogarty et al 1988(121)	Method: randomized Population: schizophrenia Intervention: no fixed dosages
Hogarty et al 1995(122)	Method: short-term
Horner et al 2012(123)	Method: short-term
Hough et al 2010(124)	Method: randomized Population: schizophrenia Intervention: flexible doses
Hough et al 2011(125)	Method: short-term
Huber et al 1971(126)	Method: randomized Population: schizophrenia Intervention: no fixed dosages
Inderbitzin et al 1994(127)	Method: randomized Population: schizophrenia

	Intervention: no fixed doses
Ishigooka et al 2018(128)	Method: short-term
Itil et al 1970(129)	Method: short-term
Itil et al 1971(130)	Method: short-term
Jhee 2003(131)	Method: short-term
Johns 1990(132)	Other: no study, pooled data
JPRN-JapicCTI-050092(133)	Method: short-term
JPRN-JapicCTI-101146(134)	Method: short-term
Kahn et al 2007(135)	Method: short-term
Kane 1993(136)	Method: Short term
Kane et al 2002a(137)	Method: short-term
Kane et al 2003(138)	Method: short-term
Kane et al 2007(139)	Method: short-term
Kane et al 2010a(140)	Method: short-term
Kane et al 2011(141)	Method: randomized Population: schizophrenia Intervention: flexible
Kane et al 2015(142)	Method: short-term
Kane et al 2015a(143)	Method: short-term
Kapur et al 1998(144)	Method: short-term
Kapur et al 2000(145)	Method: short-term
Kapur et al 2000a(146)	Method: short-term
Karpouzian-Rogers et al 2020(147)	Method: randomized Population: schizophrenia Intervention: flexibly dosed
Kato et al 2012(148)	Method: randomized Population: Schizophrenia Intervention: flexible dosages in extension phase
Keck et al 2001(149)	Method: short-term
Keskiner et al 1968(150)	Method: randomized Population: schizophrenia Intervention: flexible
Khanna et al 1997(151)	Method: randomized Population: acutely ill
King et al 1979(152)	Method: short-term
King et al 1998(153)	Method: short-term
Kinon et al 1993(154)	Method: short-term
Kinon et al 2001(155)	Other: only pooled data available
Kinon et al 2004(156)	Method: randomized Population: schizophrenia Intervention: no fixed dosage
Kinon et al 2008(157)	Method: short-term
Kinon et al 2010(158)	Method: short-term
Kinoshita et al 2016(159)	Method: short-term
Klieser et al 1987(160)	Method: short-term
Klieser et al 1996(161)	Method: short-term
Ko et al 1995(162)	Method: short-term
Kramer et al 2007(163)	Method: short-term
Kryzhanovskaya et al 2009(164)	Method: short-term
Kudo et al 1985(165)	Method: unclear Population: schizophrenia Intervention: flexible
Kurland et al 1975(166)	Method: short-term
Laffont et al 2015(167)	Method: short-term

Lan et al 2007(168)	Method: short-term
Landbloom et al 2017(169)	Method: short-term
Lane et al 2001(170)	Method: short-term
Lecrubier et al 1988(171)	Method: short-term
Lecrubier et al 2006(172)	Method: short-term
Lee et al 2002(173)	Method: short-term
Lee et al 2012(174)	Method: short-term
Lehmann et al 1980(175)	Method: short-term
Lesem et al 2001(176)	Method: short-term
Levin et al 1996(177)	Method: short-term
Levinson et al 1992(178)	Method: short-term
Levy et al 1983(179)	Method: short-term
Li et al 2014(180)	Method: short term
Li et al 2014a(181)	Method: short-term
Liebermann et al 2016(182)	Method: short-term
Lindenmayer et al 2009(183)	Method: short-term
Lindenmayer et al 2011(184)	Method: randomized Population: chronic schizophrenia Intervention Galantamine augmentation
Llaudo et al 2016(185)	Method: short-term
Loebel et al 2013(186)	Method: short-term
Loebel etal 2015(187)	Method: short-term
Louza Neto et al 1988(188)	Method: short-term
Mahal et al 1975(189)	Method: short-term
Mamo et al 2004(190)	Method: short-term
Mamo et al 2007(191)	Method: short-term
Marder et al 1994(192)	Method: randomized Participants: schizophrenia Intervention: flexibly dosed
Marder et al 2007(193)	Method: short-term
Marinkovic et al 2006(194)	Method: short-term
Martin et al 2019(195)	Method: short-term
Mathur et al 1981(196)	Method: randomized Population: chronic schizophrenia Intervention: probably flexible doses, unclear Outcome: no usable data
Matsumoto et al 2018(197)	Method: randomized Population: schizophrenia Intervention: flexible dosed
Mauri et al 2006(198)	Method: short-term
Mavroidids et al 1983(199)	Method: short-term
Mavroidis et al 1984(200)	Method: short-term
McClelland et al 1974(201)	Method: randomized Population: treatment resistant = not stable
McDonnel et al 2008(202)	Method: short-term
McEvoy et al 1991(203)	Method: short-term
McEvoy et al 1996(204)	Method: short-term
McGorry et al 2011(205)	Method: short-term
Meltzer et al 2011(206)	Method: short-term
Meltzer et al 2012(207)	Method: short-term
Meltzer et al 2014(208)	Method: randomized Population: treatment resistant = not stable
Meltzer et al 2015(209)	Method: randomized Population: schizophrenics

	Intervention: no monotherapy
Meltzer et al 2015a(210)	Method: short-term
Merlo et al 2002(211)	Method: short-term
Miceli et al 1998(212)	Method: short-term
Mitchell et al 2003(213)	Method: short-term
Mitchell et al 2006(214)	Method: short-term
Modestin et al 1983(215)	Method: short-term
Mosholder et al: Study 0008(216)	Method: short-term
Mosholder et al: Study 0012(216)	Method: short-term
Mosholder et al: Study 0013(216)	Method: short-term
Nair et al 1998(217)	Method: randomized Population: treatment refractory =not stable
Nakamura et al 2016(218)	Method: short-term
Nasrallah et al 2010(219)	Method: short-term
Nasrallah et al 2013(220)	Method: short-term
Nasser et al 2016(221)	Method: short-term
NCT 00044044(222)	Method: short-term
NCT 00650611(223)	Method: short-term
NCT00044005(224)	Other: no usable data
NCT00074477(225)	Other: no usable data
NCT00077714 Published in Meltzer et al 2008(226)	Method: short-term
NCT00078039 Published in Meltzer et al 2008(226)	Method: short-term
NCT00083668 Published in Meltzer et al 2008(226)	Method: short-term
NCT00085748(227)	Other: no usable data
NCT00088075(228)	Method: short-term
NCT00210548(229)	Method: short-term
NCT00210717(230)	Method: randomized Participants: schizophrenia Intervention: flexibly dosed
NCT00232687(231)	Method: short-term
NCT00237939(232)	Method: short-term
NCT00297947(233)	Method: short-term
NCT00485810(234)	Method: short-term
NCT00653406(235)	Method: short-term
NCT00704509(236)	Method: short-term
NCT00711269(237)	Method: short-term
NCT00796081(238)	Method: short-term
NCT00862992(239)	Method: short-term
NCT00892528(240)	Method: short-term
NCT00905307(241)	Method: short-term
NCT01082250(242)	Method: short-term
NCT01142596(243)	Other: no usable data
NCT01377233(244)	Method: short-term
NCT01423916(245)	Method: short-term
NCT01493726(246)	Other: No usable data
NCT01606254(247)	Method: short-term
NCT01625000(248)	Method: short-term
NCT01625897(249)	Method: randomized Population: schizophrenia Intervention: after 4 first weeks flexibly dosed
NCT01626456(250)	Method: randomized

(Meltzer 2015_Ex)	Participants: not stable
NCT01626859(251)	Method: short-term
NCT01626872(252)	Method: randomized Population: schizophrenia, but unclear how stable the participants were Outcome: no useable data
NCT01942382(253)	Method: short-term
NCT02146547(254)	Method: randomized Population: schizophrenia Intervention: no fixed doses
NCT02174510(255)	Method: short-term
NCT03751488(256)	Method: short-term
NCT03817502(257)	Method: short-term
NCT03870880(258)	Method: randomized Population: probably not stable but (still) acutely ill
NCT03872596(259)	Method: short-term
NCT04030143(260)	Method: randomized Population: not 80% schizophrenia, also bipolar I
Neborsky et al 1981(261)	Method: short-term
Odejide et al 1982(262)	Method: randomized Population: acute schizophrenia
Ogasa et al 2013(263)	Method: short-term
Ono et al 2006(264)	Method: short-term
Ono et al 2008(265)	Method: short-term
Oostuizen et al 2004(266)	Method: short-term
Oren et al 2007(267)	Method: short-term
Ortega-Soto et al 1994(268)	Method: short-term
Ota et al 1973(269)	Method: short-term
Palao et al 1994(270)	Method: short-term
Pandina et al 2010(271)	Method: short-term
Petrie et al 1997(272)	Method: short-term
Peuskens et al 2007(273)	Method: randomized Population: chronic schizophrenia Intervention: flexible doses
Potkin et al 1985(274)	Method: short-term
Potkin et al 1994(275)	Method: short-term
Potkin et al 2003(276)	Method: short-term
Potkin et al 2008(277)	Method: short-term
Potkin et al 2013(278)	Method: short-term
Potkin et al 2014(279)	Method: short-term
Prien et al 1968(280)	Method: short-term
Prien et al 1969(281)	Method: randomized Population: chronic schizophrenia Intervention: wrong medication
Puech et al 1998(282)	Method: short-term
Quitkin et al 1975(283)	Method: Short term Population: treatment resistant = not stable
Ravenstijn et al 2016(284)	Method: randomized Population: schizophrenia Intervention: single dose design
Rein et al 1996(285)	Method: short-term
Reschke et al 1974(286)	Method: short-term
Rifkin et al 1977(287)	Method: randomized

	Population: chronic schizophrenia Intervention: flexible doses
Rifkin et al 1991(288)	Method: short-term
Rodriguez et al 2004(289)	Method: randomized Population: chronic schizophrenia or schizoaffective disorder Intervention: fixed medication doses Outcome: no usable data
Roelofs et al 1974(290)	Method: randomized Population: chronic schizophrenia Intervention: wrong medication
Rossenu et al 2008(291)	Method: short-term
Rui et al 2014(292)	Method: variable duration in double blind treatment phase
Ruiz et al 1975(293)	Method: short-term
Ruskin et al 1991(294)	Method: randomized Population: chronic schizophrenia Intervention: no fixed doses, individual dosages
Sampath et al 1992(295)	Method: randomized Population: chronic schizophrenia Intervention: no fixed doses, individual dosages continued
Santos et al 1989(296)	Method: short-term
Sarin et al 2004(297)	Method: short-term
Schooler et al 2000(298)	Method: short-term
Shawver et al 1959(299)	Method: randomized Population: chronic schizophrenia Intervention: fixed doses Outcome: no relapse prevention, no measurement of symptoms
Sim et al 1989(300)	Method: short-term
Simpson et al 1967(301)	Method: short-term
Simpson et al 1999(302)	Method: randomized Population: treatment refractory = not stable
Singh et al 1990(303)	Method: short-term
Singh et al 2011(304)	Method: short-term
Smith et al 1984(305)	Method: short-term
Smith et al 1987(306)	Method: short-term
Soria et al 1994(307)	Method, randomized Population: chronic schizophrenia Intervention: no fixed dose
Stewart et al 2009(308)	Method: randomized Population: not 80% schizophrenia
Stone et al 1995(309)	Method: short-term
Sun et al 2018(310)	Method: short-term
Svestka et al 2003(311)	Method: short-term
Swift et al 2002(312)	Method: short-term
Takeuchi et al 2014(313)	Method: randomized Population: Schizophrenia Intervention: dose reduction by half = no fixed dose
Turncliff et al 2012(314)	Method: short-term
Uzun et al 2002(315)	Method: short-term
Van Erp et al 2020(316)	Method: short-term

Van Kammern et al 1996(317)	Method: short-term
Van Putten et al 1986(318)	Method: short-term
Van Putten et al 1990(319, 320)	Method: short-term
Van Putten et al 1991(321)	Method: short-term
Vandecasteele et al 1974(322)	Method: randomized Population: schizophrenia Intervention: wrong medication, no fixed doses
Vanover et al 2016(323)	Method: short-term
Vanover et al 2016(324)	Method: short-term
Vinar et al 1970(325)	Method: short-term
Walling et al 2018(326)	Method: short-term
Wehnert et al 1999(327)	Method: short-term
Weiden et al 2016(328)	Method: randomized Population: chronic schizophrenia Intervention: flexible doses
Wessels et al 1991(329)	Method: short-term
Wiles et al 1980(330)	Method: short-term
Winter et al 1984(331)	Method: short-term
Witte et al 2012(332)	Method: short-term
Yamagami et al 1990(333)	Method: randomized Population: schizophrenia Intervention: no fixed doses
Younis et al 2012(334)	Method: short-term
Zimbroff et al 1997(335)	Method: short-term
Zissis et al 1982(336)	Method: randomized Population: schizophrenia Intervention: no fixed doses

eReferences

In sum there were 340 studies, 26 were included and 314 were excluded. Please note that some publications reported on two studies so that there are only 336 references.

1. Arato M, O'Connor R, Meltzer HY. A 1-year, double-blind, placebo-controlled trial of ziprasidone 40, 80 and 160 mg/day in chronic schizophrenia: the Ziprasidone Extended Use in Schizophrenia (ZEUS) study. International clinical psychopharmacology. 2002;17(5):207-15.
2. Velligan D, Newcomer J, Pultz J, Csernansky J, Hoff A, Mahurin R, et al. Does cognitive function improve with quetiapine in comparison to haloperidol? Schizophrenia research. 2002;53:239-48.
3. Dellva MA, Tran P, Tollefson GD, Wentley AL, Beasley CM, Jr. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. Psychiatric services (Washington, DC). 1997;48(12):1571-7.
4. Carpenter WT, Jr., Buchanan RW, Kirkpatrick B, Lann HD, Breier AF, Summerfelt AT. Comparative effectiveness of fluphenazine decanoate injections every 2 weeks versus every 6 weeks. Am J Psychiatry. 1999;156(3):412-8.
5. Chen EYH, Hui CLM, Lam MML, Chiu CPY, Law CW, Chung DWS, et al. Maintenance treatment with quetiapine versus discontinuation after one year of treatment in patients with remitted first episode psychosis: randomised controlled trial. BMJ. 2010;341:c4024.
6. Cooper SJ, Butler A, Tweed J, Welch C, Raniwalla J. Zotepine in the prevention of recurrence: a randomised, double-blind, placebo-controlled study for chronic schizophrenia. Psychopharmacology. 2000;150(3):237-43.
7. Dotti A, Bersani G, Rubino IA, Eliseo C. Studio in doppio cieco della flufenazina decanoato versus placebo nella terapia ambulatiorale di mantenimento di pazienti schizofrenici cronici. Rivista di Psichiatria. 1979;5:374-83.
8. Eklund K, Forsman A. Minimal effective dose and relapse-double-blind trial: haloperidol decanoate vs. placebo. Clinical neuropharmacology. 1991;14 Suppl 2:S7-12; discussion S-5.
9. Fleischhacker WW, Sanchez R, Perry PP, Jin N, Peters-Strickland T, Johnson BR, et al. Aripiprazole once-monthly for treatment of schizophrenia: double-blind, randomised, non-inferiority study. Br J Psychiatry. 2014;205(2):135-44.
10. Hough D, Lindenmayer JP, Gopal S, Melkote R, Lim P, Herben V, et al. Safety and tolerability of deltoid and gluteal injections of paliperidone palmitate in schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(6):1022-31.
11. Huttunen MO, Tuhkanen H, Haavisto E, Nyholm R, Pitkanen M, Raitasuo V, et al. Low- and standard-dose depot haloperidol combined with targeted oral neuroleptics. Psychiatric services (Washington, DC). 1996;47(1):83-5.
12. Kane J, Rifkin A, Quitkin F, Nayak D, Saraf K, Ramos-Lorenzi J, et al., editors. Low Dose Fluphenazine Decanoate in Treatment of Schizophrenia. 1979.
13. Kane JM, Rifkin A, Woerner M, Reardon G, Sarantakos S, Schiebel D, et al. Low-Dose Neuroleptic Treatment of Outpatient Schizophrenics: I. Preliminary Results for Relapse Rates. Archives of General Psychiatry. 1983;40(8):893-6.
14. Kane JM, Davis JM, Schooler N, Marder S, Casey D, Brauzer B, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. Am J Psychiatry. 2002;159(4):554-60.
15. Kane JM, Detke HC, Naber D, Sethuraman G, Lin DY, Bergstrom RF, et al. Olanzapine long-acting injection: a 24-week, randomized, double-blind trial of maintenance treatment in patients with schizophrenia. The American journal of psychiatry. 2010;167(2):181-9.
16. Kane JM, Sanchez R, Perry PP, Jin N, Johnson BR, Forbes RA, et al. Aripiprazole intramuscular depot as maintenance treatment in patients with schizophrenia: a 52-week,

multicenter, randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2012;73(5):617-24.
17. Mallikaarjun S, Kane JM, Bricmont P, McQuade R, Carson W, Sanchez R, et al. Pharmacokinetics, tolerability and safety of aripiprazole once-monthly in adult schizophrenia: an open-label, parallel-arm, multiple-dose study. Schizophr Res. 2013;150(1):281-8.
18. Marder SR, Van Putten T, Mintz J, McKenzie J, Lebell M, Faltico G, et al. Costs and benefits of two doses of fluphenazine. Arch Gen Psychiatry. 1984;41(11):1025-9.
19. McEvoy JP, Daniel DG, Carson WH, Jr., McQuade RD, Marcus RN. A randomized, double-blind, placebo-controlled, study of the efficacy and safety of aripiprazole 10, 15 or 20 mg/day for the treatment of patients with acute exacerbations of schizophrenia. Journal of psychiatric research. 2007;41(11):895-905.
20. Nishikawa T, Tsuda A, Tanaka M, Koga I, Uchida Y. Prophylactic effect of neuroleptics in symptom-free schizophrenics. Psychopharmacology (Berl). 1982;77(4):301-4.
21. Nishikawa T, Tsuda A, Tanaka M, Hoaki Y, Koga I, Uchida Y. Prophylactic effect of neuroleptics in symptom-free schizophrenics: a comparative dose-response study of haloperidol and propericiazine. Psychopharmacology (Berl). 1984;82(3):153-6.
22. Tandon R, Cucchiaro J, Phillips D, Hernandez D, Mao Y, Pikalov A, et al. A double-blind, placebo-controlled, randomized withdrawal study of lurasidone for the maintenance of efficacy in patients with schizophrenia. J Psychopharmacol. 2016;30(1):69-77.
23. Pigott TA, Carson WH, Saha AR, Torbeyns AF, Stock EG, Ingenito GG. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. The Journal of clinical psychiatry. 2003;64(9):1048-56.
24. Schooler NR, Keith SJ, Severe JB, Matthews SM, Bellack AS, Glick ID, et al. Relapse and rehospitalization during maintenance treatment of schizophrenia. The effects of dose reduction and family treatment. Arch Gen Psychiatry. 1997;54(5):453-63.
25. Simpson GM, Mahmoud RA, Lasser RA, Kujawa M, Bossie CA, Turkoz I, et al. A 1-year double-blind study of 2 doses of long-acting risperidone in stable patients with schizophrenia or schizoaffective disorder. The Journal of clinical psychiatry. 2006;67(8):1194-203.
26. Agid O, Mamo D, Ginovart N, Vitcu I, Wilson AA, Zipursky RB, et al. Striatal vs extrastriatal dopamine D2 receptors in antipsychotic response--a double-blind PET study in schizophrenia. Int J Neuropsychopharmacol. 2007;32(6):1209-15.
27. Agid O, Kapur S, Warrington L, Loebel A, Siu C. Early onset of antipsychotic response in the treatment of acutely agitated patients with psychotic disorders. Schizophrenia research. 2008;102(1-3):241-8.
28. Anderson WH, Kuehnle JC, Catanzano DM. Rapid treatment of acute psychosis. The American journal of psychiatry. 1976;133(9):1076-8.
29. Andrews P, Hall JN, Snaith RP. A controlled trial of phenothiazine withdrawal in chronic schizophrenic patients. The British journal of psychiatry : the journal of mental science. 1976;128:451-5.
30. Anonymus. Risperidone vs clozapine. Biological Therapies in Psychiatry. USA1994. p. 47-8.
31. Anonymus. Ziprasidone hydrochloride approved for treatment of schizophrenia, but with major warning. American Journal of Health-System Pharmacy. 2001;58(9):758.
32. Aravagiri M, Marder SR, Van Putten T, Marshall BD. Simultaneous determination of plasma haloperidol and its metabolite reduced haloperidol by liquid chromatography with electrochemical detection Plasma levels in schizophrenic patients treated with oral or intramuscular depot haloperidol. Journal of Chromatography B: Biomedical Sciences and Applications. 1994;656(2):373-81.
33. Arvanitis LA, Miller BG. Multiple fixed doses of "Seroquel" (quetiapine) in patients with acute exacerbation of schizophrenia: a comparison with haloperidol and placebo. The Seroquel Trial 13 Study Group. Biological psychiatry. 1997;42(4):233-46.
34. Assion HJ, Reinbold H, Lemanski S, Basilowski M, Juckel G. Amisulpride augmentation in patients with schizophrenia partially responsive or unresponsive to

clozapine. A randomized, double-blind, placebo-controlled trial. Pharmacopsychiatry. 2008;41(1):24-8.
35. Auby P, Saha A, Ali M, Ingenito G, Wilber R, Bramer S. Safety and tolerability of aripiprazole at doses higher than 30 mg. Eur Neuropsychopharmacol. 2002;12(Supplement 3):S288.
36. Bark N, Mack R, Zobrowsky J, Morris D, Sebree T, Shook S, et al. Efficacy and safety of three doses of sertindole and haloperidol in schizophrenic patients. Biological psychiatry. 1996;39:597.
37. Barnas C, Quiner S, Tauscher J, Hilger E, Willeit M, Küfferle B, et al. In vivo 123I IBZM SPECT imaging of striatal dopamine 2 receptor occupancy in schizophrenic patients. Psychopharmacology. 2001;157(3):236-42.
38. Bateman DN, Dutta DK, McClelland HA, Rawlins MD. Metoclopramide and haloperidol in tardive dyskinesia. The British journal of psychiatry : the journal of mental science. 1979;135:505-8.
39. Beasley CM, Jr., Sanger T, Satterlee W, Tollefson G, Tran P, Hamilton S. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology. 1996;124(1-2):159-67.
40. Beasley CM, Jr., Sutton VK, Hamilton SH, Walker DJ, Dossenbach M, Taylor CC, et al. A double-blind, randomized, placebo-controlled trial of olanzapine in the prevention of psychotic relapse. Journal of clinical psychopharmacology. 2003;23(6):582-94.
41. Berger GE, Proffitt TM, McConchie M, Kerr M, Markulev C, Yuen HP, et al. Dosing quetiapine in drug-naive first-episode psychosis: a controlled, double-blind, randomized, single-center study investigating efficacy, tolerability, and safety of 200 mg/day vs. 400 mg/day of quetiapine fumarate in 141 patients aged 15 to 25 years. The Journal of clinical psychiatry. 2008;69(11):1702-14.
42. Berwaerts J, Liu Y, Gopal S, Nuamah I, Xu H, Savitz A, et al. Efficacy and Safety of the 3-Month Formulation of Paliperidone Palmitate vs Placebo for Relapse Prevention of Schizophrenia: A Randomized Clinical Trial. JAMA psychiatry. 2015;72(8):830-9.
43. Bitter I, Jaeger J, Agdeppa J, Volavka J. Subjective symptoms: part of the negative syndrome of schizophrenia? Psychopharmacology bulletin. 1989;25(2):180-4.
44. Bjørndal N, Bjerre M, Gerlach J, Kristjansen P, Magelund G, Oestrich IH, et al. High dosage haloperidol therapy in chronic schizophrenic patients: a double-blind study of clinical response, side effects, serum haloperidol, and serum prolactin. Psychopharmacology. 1980;67(1):17-23.
45. Boyer P, Puech AJ. Determinants for clinical activity of neuroleptic drugs: chemical substances, doses, assessment tools. Psychiatry and Psychobiology. 1987;2(4):296-305.
46. Brambilla F, Facchinetti F, Petraglia F, Smeraldi E, Bellodi L, Brancato V, et al. Effects of neuroleptic treatments on peripheral opioid secretion. Neuropsychobiology. 1987;18(2):68-73.
47. Bristol-Myers_Squibb. Synopsis. Clinical Study Report CN138114. 2004 [updated 26.04.2004. Available from: https://benmeg.com/archives/rxarchives.org/uploads/2/4/4/6/24466638/cn138-114_st_online.pdf.
48. Bristol-Myers_Squibb. Synopsis. Clinical Study Report CN138050. 2005 [updated 16.09.2005. Available from: https://benmeg.com/archives/rxarchives.org/aripiprazole%20(Abilify)/CN138-050_online.pdf.
49. Bunney W, Keator D, Fallon J, Kesler-West ML, Predna A, Nguyen D, et al. Ziprasidone D2 Receptor Occupancy at Doses of 120 to 240 mg/day Measured with 18F-Fallypride PET Support Once-A-Day Dosing. Int J Neuropsychopharmacol. 2010;35(Suppl 1):S96.
50. Cada DJ, Levien T, Baker DE. Risperidone Long-Acting Injection. Hospital Pharmacy. 2004;39(4):353-63.
51. Canuso CM, Schooler N, Carothers J, Turkoz I, Kosik-Gonzalez C, Bossie CA, et al. Paliperidone extended-release in schizoaffective disorder: a randomized, controlled study

comparing a flexible dose with placebo in patients treated with and without antidepressants and/or mood stabilizers. J Clin Psychopharmacol. 2010;30(5):487-95.
52. Çetin M, Ebrinç S, Bçargün M, Bb_pçlu C, Can S. Determination of the optimal dose of risperidone in patients with schizophrenia. Eur Neuropsychopharmacol. 1999;9:254-5.
53. Chang WH, Jann MW, Hwu HG, Chen TY, Lin SK, Wang JM, et al. Ethnic comparison of haloperidol and reduced haloperidol plasma levels: Taiwan Chinese versus American non-Chinese. Journal of the Formosan Medical Association = Taiwan yi zhi. 1991;90(6):572-8.
54. Channabasavanna SM, Michael A. Penfluridol maintenance therapy in schizophrenia: a controlled study. Indian J Psychiatry. 1987;29(4):333-6.
55. Chapel S, Hutmacher MM, Haig G, Bockbrader H, de Greef R, Preskorn SH, et al. Exposure-response analysis in patients with schizophrenia to assess the effect of asenapine on QTc prolongation. Journal of clinical pharmacology. 2009;49(11):1297-308.
56. Chavda RK, Laxmi L, Nair BS, Gandewar K. Efficacy and tolerability of aripiprazole in patients with schizophrenia & schizoaffective disorders. Indian J Psychiatry. 2004;46(2):150-5.
57. Citrome L, Walling D, Zeni C, Komaroff M, Park A. Efficacy and Safety of an Asenapine Transdermal Patch (Asenapine Transdermal System, HP-3070) in the Treatment of Adults With Schizophrenia: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, 6-Week Inpatient Study. Biological psychiatry. 2019;85:S126.
58. Clark ML, Huber WK, Hill D, Wood F, Costiloe JP. Pimozide in chronic schizophrenic outpatients. Dis Nerv Syst. 1975;36(3):137-41.
59. Clerc G. Double-blind study of amisulpride at different dosages in negative schizophrenic patients. Semaine des Hôpitaux de Paris. 1989;65(17):1079-82.
60. Coppola D, Melkote R, Lannie C, Singh J, Nuamah I, Gopal S, et al. Efficacy and Safety of Paliperidone Extended Release 1.5 mg/day-A Double-blind, Placebo- and Active-Controlled, Study in the Treatment of Patients with Schizophrenia. Psychopharmacology bulletin. 2011;44(2):54-72.
61. Correll CU, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. The American journal of psychiatry. 2015;172(9):870-80.
62. Correll CU, Davis RE, Weingart M, Saillard J, O'Gorman C, Kane JM, et al. Efficacy and Safety of Lumateperone for Treatment of Schizophrenia: A Randomized Clinical Trial. JAMA psychiatry. 2020;77(4):349-58.
63. Clinical_trials_registry_India. CTRI/2014/04/004521 2018 [updated 30.11.2018. Available from: http://www.ctri.nic.in/Clinicaltrials/pdf_generate.php?trialid=8566&EncHid=&modid=&compid=%27,%278566det%27.
64. Cutler AJ, Marcus RN, Hardy SA, O'Donnell A, Carson WH, McQuade RD. The efficacy and safety of lower doses of aripiprazole for the treatment of patients with acute exacerbation of schizophrenia. CNS spectrums. 2006;11(9):691-702; quiz 19.
65. Cutler AJ, Tran-Johnson T, Kalali A, Astrom M, Brecher M, Meulien D. A failed 6-week,randomized, double-blind, placebo-controlled study of once-daily extended release quetiapine fumarate in patients with acute schizophrenia: lessons learned. Psychopharmacol Bull. 2010;43(4):37-69.
66. Czobor R, Volavka J. Quantitative electroencephalogram examination of effects of risperidone in schizophrenic patients. Journal of clinical psychopharmacology. 1993;13(5):332-42.
67. Daniel DG, Zimbroff DL, Potkin SG, Reeves KR, Harrigan EP, Lakshminarayanan M. Ziprasidone 80 mg/day and 160 mg/day in the acute exacerbation of schizophrenia and schizoaffective disorder: a 6-week placebo-controlled trial. Ziprasidone Study Group. Int J Neuropsychopharmacol. 1999;20(5):491-505.
68. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. Psychopharmacology. 2001;155(2):128-34.

69. Daniel DG, Potkin SG, Reeves KR, Swift RH, Harrigan EP. Intramuscular (IM) ziprasidone 20 mg is effective in reducing acute agitation associated with psychosis: a double-blind, randomized trial. Psychopharmacology. 2001;155(2):128-34.
70. Davidson M, Emsley R, Kramer M, Ford L, Pan G, Lim P, et al. Efficacy, safety and early response of paliperidone extended-release tablets (paliperidone ER): results of a 6-week, randomized, placebo-controlled study. Schizophr Res. 2007;93(1-3):117-30.
71. Davis JM, Ericksen SE, Hurt S, Chang SS, Javaid JI, Dekirmenjian H, et al. Haloperidol plasma levels and clinical response: basic concepts and clinical data. Psychopharmacology bulletin. 1985;21(1):48-51.
72. De Buck RP, editor Relative safety and efficacy of high and low dose administration of fluphenazine-HCL to psychotic patients. CINP Congress 1972.
73. DelBello MP, Versavel M, Ice K, Keller D, Miceli J. Tolerability of oral ziprasidone in children and adolescents with bipolar mania, schizophrenia, or schizoaffective disorder. Journal of child and adolescent psychopharmacology. 2008;18(5):491-9.
74. Dencker SJ, Johansson R, Lundin L, Malm U. High doses of fluphenazine enanthate in schizophrenia: a controlled study. Acta Psychiatrica Scandinavica. 1978;57(5):405-14.
75. Denijs EL, Vereecken JL. Pimozide (orap, R 6238) in residual schizophrenia. A clinical evaluation with long-term double-blind follow-up. Psychiatria, neurologia, neurochirurgia. 1973;76(1):47-59.
76. do Carmo Borges NC, Astigarraga RB, Sverdloff CE, Galvinas PR, Borges BC, Moreno RA. Comparative bioavailability of two oral formulations of clozapine in steady state administered in schizophrenic volunteers under individualized dose regime. Current clinical pharmacology. 2012;7(4):241-53.
77. Donlon PT, Meadow A, Tupin JP, Wahba M. High vs standard dosage fluphenazine HCL in acute schizophrenia. The Journal of clinical psychiatry. 1978;39(11):800-4.
78. Donlon PT, Hopkin JT, Tupin JP, Wicks JJ, Wahba M, Meadow A. Haloperidol for acute schizophrenic patients. An evaluation of three oral regimens. Archives of general psychiatry. 1980;37(6):691-5.
79. Dubitsky GM, Harris R, Laughren T, Hardeman S. Abilify (aripiprazole) tablets; medical review part 3. http://wwwfdagov/cder/foi/nda/2002/21-436_Abilifyhtm: U.S. Food and Drug Administration CDER; 2002. p. 111-75.
80. Dubovsky SL, Frobose C, Phiri P, de Greef R, Panagides J. Short-term safety and pharmacokinetic profile of asenapine in older patients with psychosis. International Journal of Geriatric Psychiatry. 2012;27(5):472-82.
81. Durgam S, Starace A, Li D, Migliore R, Ruth A, Nemeth G, et al. An evaluation of the safety and efficacy of cariprazine in patients with acute exacerbation of schizophrenia: a phase II, randomized clinical trial. Schizophr Res. 2014;152(2-3):450-7.
82. Durgam S, Cutler AJ, Lu K, Migliore R, Ruth A, Laszlovszky I, et al. Cariprazine in acute exacerbation of schizophrenia: a fixed-dose, phase 3, randomized, double-blind, placebo- and active-controlled trial. The Journal of clinical psychiatry. 2015;76(12):e1574-82.
83. Durgam S, Litman RE, Papadakis K, Li D, Németh G, Laszlovszky I. Cariprazine in the treatment of schizophrenia: a proof-of-concept trial. International clinical psychopharmacology. 2016;31(2):61-8.
84. Durgam S, Earley W, Li R, Li D, Lu K, Laszlovszky I, et al. Long-term cariprazine treatment for the prevention of relapse in patients with schizophrenia: A randomized, double-blind, placebo-controlled trial. Schizophrenia research. 2016;176(2-3):264-71.
85. Dutoit D, Thomas P, Leroux JM, Vaiga G, Pommery J, Cottencin O, et al. [Erythrocyte ketone reductase activity, total plasma haloperidol and acute psychoses]. L'Encephale. 1995;21(6):417-24.
86. Eerdekens M, Van Hove I, Remmerie B, Mannaert E. Pharmacokinetics and tolerability of long-acting risperidone in schizophrenia. Schizophrenia research. 2004;70(1):91-100.
87. EliLilly. A study to assess safety, tolerability, and pharmacokinetics of single and multiple doses of an intramuscular formulation of depot olanzapine (pamoate salt) in stable schizophrenic subjects. https://wwwClinicalstudyresultsorg/2008.

88. European_Medical_Agency. Abilify H-C-471; European Public Assessment Report; Scientific discussion. https://wwwemeaeuropaeu/humandocs/. 7 ed2007.
89. Janssen-Cilag_International_N.V. EU Clinical Trials Register Euctr2006-006434-17 2006 [Available from: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2006-006434-17.
90. Findling RL, Robb A, Nyilas M, Forbes RA, Jin N, Ivanova S, et al. A multiple-center, randomized, double-blind, placebo-controlled study of oral aripiprazole for treatment of adolescents with schizophrenia. The American journal of psychiatry. 2008;165(11):1432-41.
91. Findling RL, Landbloom RP, Mackle M, Pallozzi W, Braat S, Hundt C, et al. Safety and Efficacy from an 8 Week Double-Blind Trial and a 26 Week Open-Label Extension of Asenapine in Adolescents with Schizophrenia. Journal of child and adolescent psychopharmacology. 2015;25(5):384-96.
92. Findling R, Chiu YY, Silva R, Goldman R, Jin F, Pikalov A, et al. Pharmacokinetic and Safety Evaluation of Lurasidone in Pediatric Patients with Psychiatric Disorders. European Psychiatry. 2015;30:1202.
93. Fleischhacker WW, Eerdekens M, Karcher K, Remington G, Llorca PM, Chrzanowski W, et al. Treatment of schizophrenia with long-acting injectable risperidone: a 12-month open-label trial of the first long-acting second-generation antipsychotic. The Journal of clinical psychiatry. 2003;64(10):1250-7.
94. Fleischhacker WW, Hobart M, Ouyang J, Forbes A, Pfister S, McQuade RD, et al. Efficacy and Safety of Brexpiprazole (OPC-34712) as Maintenance Treatment in Adults with Schizophrenia: a Randomized, Double-Blind, Placebo-Controlled Study. Int J Neuropsychopharmacol. 2017;20(1):11-21.
95. Freeman LS, Alson E. Prolonged withdrawal of chlorpromazine in chronic patients. Diseases of the nervous system. 1962;23:522-5.
96. Fu DJ, Turkoz I, Simonson RB, Walling DP, Schooler NR, Lindenmayer JP, et al. Paliperidone palmitate once-monthly reduces risk of relapse of psychotic, depressive, and manic symptoms and maintains functioning in a double-blind, randomized study of schizoaffective disorder. J Clin Psychiatry. 2015;76(3):253-62.
97. Gallant DM, Mielke DH, Spirtes MA, Swanson WC, Bost R. Penfluridol: an efficacious long-acting oral antipsychotic compound. The American journal of psychiatry. 1974;131(6):699-702.
98. Gitlin MJ, Midha KK, Fogelson D, Nuechterlein K. Persistence of fluphenazine in plasma after decanoate withdrawal. Journal of clinical psychopharmacology. 1988;8(1):53-6.
99. Gitlin M, Nuechterlein K, Subotnik KL, Ventura J, Mintz J, Fogelson DL, et al. Clinical outcome following neuroleptic discontinuation in patients with remitted recent-onset schizophrenia. The American journal of psychiatry. 2001;158(11):1835-42.
100. Goff DC, McEvoy JP, Citrome L, Mech AW, Bustillo JR, Gil R, et al. High-dose oral ziprasidone versus conventional dosing in schizophrenia patients with residual symptoms: the ZEBRAS study. J Clin Psychopharmacol. 2013;33(4):485-90.
101. Goldman R, Loebel A, Cucchiaro J, Deng L, Findling RL. Efficacy and Safety of Lurasidone in Adolescents with Schizophrenia: A 6-Week, Randomized Placebo-Controlled Study. Journal of child and adolescent psychopharmacology. 2017;27(6):516-25.
102. Good WW, Sterling M, Holtzman WH. Termination of chlorpromazine with schizophrenic patients. The American journal of psychiatry. 1958;115(5):443-8.
103. Gopal S, Hough DW, Xu H, Lull JM, Gassmann-Mayer C, Remmerie BM, et al. Efficacy and safety of paliperidone palmitate in adult patients with acutely symptomatic schizophrenia: a randomized, double-blind, placebo-controlled, dose-response study. Int Clin Psychopharmacol. 2010;25(5):247-56.
104. Gross HS. A double-blind comparison of once-a-day pimozide, trifluoperazine, and placebo in the maintenance care of chronic schizophrenic outpatients. Current therapeutic research, clinical and experimental. 1974;16(7):696-705.
105. Gutierrez R, Potkin S. Efficacy and safety of once-daily dosing with risperidone in patients with schizophrenia. 35th Annual Meeting of the American College of Neuropsychopharmacology; San Juan, Puerto Rico1996. p. 259.

106. H.Lundbeck. Efficacy of Bifeprunox in Patients With Schizophrenia 2008 [Available from: https://www.clinicaltrials.gov/ct2/show/NCT00658645.
107. Haas M, Eerdekens M, Kushner S, Singer J, Augustyns I, Quiroz J, et al. Efficacy, safety and tolerability of two dosing regimens in adolescent schizophrenia: double-blind study. The British journal of psychiatry : the journal of mental science. 2009;194(2):158-64.
108. Hale AS, Azorin JM, Lemming OM, Mæhlum E. Sertindole in the long-term treatment of schizophrenia. International clinical psychopharmacology. 2012;27(4):231-7.
109. Hard ML, Mills RJ, Sadler BM, Wehr AY, Weiden PJ, von Moltke L. Pharmacokinetic Profile of a 2-Month Dose Regimen of Aripiprazole Lauroxil: A Phase I Study and a Population Pharmacokinetic Model. CNS drugs. 2017;31(7):617-24.
110. Hard ML, Wehr AY, Du Y, Weiden PJ, Walling D, von Moltke L. Pharmacokinetic Evaluation of a 1-Day Treatment Initiation Option for Starting Long-Acting Aripiprazole Lauroxil for Schizophrenia. Journal of clinical psychopharmacology. 2018;38(5):435-41.
111. Harvey PD, Pappadopulos E, Lombardo I, Kremer CM. Reduction of functional disability with atypical antipsychotic treatment: A randomized long term comparison of ziprasidone and haloperidol. Schizophrenia research. 2009;115(1):24-9.
112. Harvey PD, Murasaki M, Cucchiaro J, Ogasa M, Loebel A. A three arm dose finding study of lurasidone: efficacy and tolerability data. Schizophrenia research. 2010;117(2):374-5.
113. Hershon HI, Kennedy PF, McGuire RJ. Persistence of extra-pyramidal disorders and psychiatric relapse after withdrawal of long-term phenothiazine therapy. The British journal of psychiatry : the journal of mental science. 1972;120(554):41-50.
114. Higuchi T, Ishigooka J, Iyo M, Yeh CB, Ebenezer EG, Liang KY, et al. Lurasidone in the treatment of schizophrenia: Results of a double-blind, placebo-controlled trial in Asian patients. Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists. 2019;11(2):e12352.
115. Higuchi T, Iyo M, Kwon JS, Chou YH, Chen HK, Chen JY, et al. Randomized, double-blind, placebo, and risperidone-controlled study of lurasidone in the treatment of schizophrenia: Results of an inconclusive 6-week trial. Asia-Pacific psychiatry : official journal of the Pacific Rim College of Psychiatrists. 2019;11(3):e12354.
116. Hirsch SR, Gaind R, Rohde PD, Stevens BC, Wing JK. Outpatient maintenance of chronic schizophrenic patients with long-acting fluphenazine: double-blind placebo trial. Report to the Medical Research Council Committee on Clinical Trials in Psychiatry. British medical journal. 1973;1(5854):633-7.
117. Hirsch SR, Jolley AG. The Dysphoric Syndrome in Schizophrenia and its Implications for Relapse. British Journal of Psychiatry. 1989;155(S5):46-50.
118. Hirsch S, Bowen J, Emami J, Cramer P, Jolley A, Haw C, et al. A One Year Prospective Study of the Effect of Life Events and Medication in the Aetiology of Schizophrenic Relapse. British Journal of Psychiatry. 1996;168(1):49-56.
119. Hirschowitz J, Hitzemann R, Piscani K, Burr G, Frecska E, Culliton D, et al. The Dose Reduction in Schizophrenia (DORIS) Study: a final report. Schizophrenia research. 1997;23(1):31-43.
120. Hogarty GE, Goldberg SC, Schooler NR, Ulrich RF. Drug and sociotherapy in the aftercare of schizophrenic patients. II. Two-year relapse rates. Archives of general psychiatry. 1974;31(5):603-8.
121. Hogarty GE, McEvoy JP, Munetz M, DiBarry AL, Bartone P, Cather R, et al. Dose of fluphenazine, familial expressed emotion, and outcome in schizophrenia. Results of a two-year controlled study. Archives of general psychiatry. 1988;45(9):797-805.
122. Hogarty GE, McEvoy JP, Ulrich RF, DiBarry AL, Bartone P, Cooley S, et al. Pharmacotherapy of Impaired Affect in Recovering Schizophrenic Patients. Archives of general psychiatry. 1995;52(1):29-41.
123. Honer WG, MacEwan GW, Gendron A, Stip E, Labelle A, Williams R, et al. A randomized, double-blind, placebo-controlled study of the safety and tolerability of high-dose quetiapine in patients with persistent symptoms of schizophrenia or schizoaffective disorder. J Clin Psychiatry. 2012;73(1):13-20.

124. Hough D, Gopal S, Vijapurkar U, Lim P, Morozova M, Eerdekens M. Paliperidone palmitate maintenance treatment in delaying the time-to-relapse in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Schizophrenia research. 2010;116(2-3):107-17.
125. Hough DW, Natarajan J, Vandebosch A, Rossenu S, Kramer M, Eerdekens M. Evaluation of the effect of paliperidone extended release and quetiapine on corrected QT intervals: a randomized, double-blind, placebo-controlled study. International clinical psychopharmacology. 2011;26(1):25-34.
126. Huber W, Serafetinides EA, Colmore JP, Clark M. Pimozide in chronic schizophrenic patients. The Journal of clinical pharmacology and new drugs. 1971;11(4):304-9.
127. Inderbitzin LB, Lewine RR, Scheller-Gilkey G, Swofford CD, Egan GJ, Gloersen BA, et al. A double-blind dose-reduction trial of fluphenazine decanoate for chronic, unstable schizophrenic patients. The American journal of psychiatry. 1994;151(12):1753-9.
128. Ishigooka J, Iwashita S, Tadori Y. Efficacy and safety of brexpiprazole for the treatment of acute schizophrenia in Japan: A 6-week, randomized, double-blind, placebo-controlled study. Psychiatry and clinical neurosciences. 2018;72(9):692-700.
129. Itil T, Keskiner A, Heinemann L, Han T, Gannon P, Hsu W. Treatment of resistant schizophrenics with extreme high dosage fluphenazine hydrochloride. Psychosomatics. 1970;11(5):456-63.
130. Itil TM, Saletu B, Hsu W, Kiremitci N, Keskiner A. Clinical and quantitative EEG changes at different dosage levels of fluphenazine treatment. Acta Psychiatrica Scandinavica. 1971;47(4):440-51.
131. Jhee S, Guarino J, Ogasa M, Kimura T, Kassem R, Shiovitz T, et al. A maximum tolerated dose study of SM13496 in patients with schizophrenia. Schizophrenia research. 2003;60:287-.
132. Johns CA, Mayerhoff DI, Lieberman JA, Kane JM. Schizophrenia: alternative neuroleptic strategies. In: Angrist B, Schulz SC, editors. The Neuroleptic-Nonresponsive Patient: Characterization and Treatment. Washington, DC, USA: American Psychiatric Press Inc; 1990. p. 53-66.
133. Dainippon Sumitomo Pharma Co. L. JPRN-JapicCTI-050092 2005 [updated 12.09.2005. Available from: https://rctportal.niph.go.jp/en/detail?trial_id=JapicCTI-050092.
134. Otsuka Pharmaceutical Co. L. A short treatment study of aripiprazole in pediatric patients with schizophrenia 2017 [updated 06.01.2017. Available from: https://www.clinicaltrials.jp/cti-user/trial/ShowDirect.jsp?japicId=JapicCTI-101146.
135. Kahn RS, Schulz SC, Palazov VD, Reyes EB, Brecher M, Svensson O, et al. Efficacy and tolerability of once-daily extended release quetiapine fumarate in acute schizophrenia: a randomized, double-blind, placebo-controlled study. The Journal of clinical psychiatry. 2007;68(6):832-42.
136. Kane JM, Kinon B, Johns C. Alternative strategies for treating neuroleptic non responsive patients. Schizophrenia Research. 1993;9:240.
137. Kane JM, Carson WH, Saha AR, McQuade RD, Ingenito GG, Zimbroff DL, et al. Efficacy and safety of aripiprazole and haloperidol versus placebo in patients with schizophrenia and schizoaffective disorder. The Journal of clinical psychiatry. 2002;63(9):763-71.
138. Kane JM, Eerdekens M, Lindenmayer JP, Keith SJ, Lesem M, Karcher K. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry. 2003;160(6):1125-32.
139. Kane J, Canas F, Kramer M, Ford L, Gassmann-Mayer C, Lim P, et al. Treatment of schizophrenia with paliperidone extended-release tablets: a 6-week placebo-controlled trial. Schizophrenia research. 2007;90(1-3):147-61.
140. Kane JM, Cohen M, Zhao J, Alphs L, Panagides J. Efficacy and safety of asenapine in a placebo- and haloperidol-controlled trial in patients with acute exacerbation of schizophrenia. Journal of clinical psychopharmacology. 2010;30(2):106-15.

141. Kane JM, Mackle M, Snow-Adami L, Zhao J, Szegedi A, Panagides J. A randomized placebo-controlled trial of asenapine for the prevention of relapse of schizophrenia after long-term treatment. The Journal of clinical psychiatry. 2011;72(3):349-55.
142. Kane JM, Zukin S, Wang Y, Lu K, Ruth A, Nagy K, et al. Efficacy and Safety of Cariprazine in Acute Exacerbation of Schizophrenia: Results From an International, Phase III Clinical Trial. Journal of clinical psychopharmacology. 2015;35(4):367-73.
143. Kane JM, Skuban A, Ouyang J, Hobart M, Pfister S, McQuade RD, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with acute schizophrenia. Schizophrenia research. 2015;164(1-3):127-35.
144. Kapur S, Zipursky RB, Remington G, Jones C, DaSilva J, Wilson AA, et al. 5-HT2 and D2 receptor occupancy of olanzapine in schizophrenia: a PET investigation. The American journal of psychiatry. 1998;155(7):921-8.
145. Kapur S, Zipursky R, Jones C, Shammi CS, Remington G, Seeman P. A positron emission tomography study of quetiapine in schizophrenia: a preliminary finding of an antipsychotic effect with only transiently high dopamine D2 receptor occupancy. Archives of general psychiatry. 2000;57(6):553-9.
146. Kapur S, Zipursky R, Jones C, Remington G, Houle S. Relationship between dopamine D(2) occupancy, clinical response, and side effects: a double-blind PET study of first-episode schizophrenia. Am J Psychiatry. 2000;157(4):514-20.
147. Karpouzian-Rogers T, Stocks J, Meltzer HY, Reilly JL. The effect of high vs. low dose lurasidone on eye movement biomarkers of prefrontal abilities in treatment-resistant schizophrenia. Schizophrenia research. 2020;215:314-21.
148. Kato M, Ogasa M, Ogo H, Ishige Y, Sawabe H, Siu C, et al. Long-term treatment with lurasidone in schizophrenia: Results of an 8-week double-blind acute study followed by a 44-week open-label extension. Schizophrenia research. 2012;136(Supplement 1):351.
149. Keck PE, Jr., Reeves KR, Harrigan EP. Ziprasidone in the short-term treatment of patients with schizoaffective disorder: results from two double- blind, placebo-controlled, multicenter studies. Journal of clinical psychopharmacology. 2001;21(1):27-35.
150. Keskiner A, Holden JM, Itil TM. Maintenance treatment of schizophrenic outpatients with a depot phenothiazine. Psychosomatics. 1968;9(3):166-71.
151. Khanna A, Lal N, Dalal PK, Khalid A, Trivedi JK. Treatment of acute and transient psychotic disorders with low and high doses of oral haloperidol. Indian J Psychiatry. 1997;39(2):136-42.
152. King CE, Goldstein MJ. Therapist Ratings of Achievement of Objectives in Psychotherapy With Acute Schizophrenics*. Schizophrenia bulletin. 1979;5(1):118-29.
153. King DJ, Link CGG, Kowalcyk B. A comparison of bd and tid dose regimens of quetiapine (Seroquel) in the treatment of schizophrenia. Psychopharmacology. 1998;137(2):139-46.
154. Kinon BJ, Kane JM, Johns C, Perovich R, Ismi M, Koreen A, et al. Treatment of neuroleptic-resistant schizophrenic relapse. Psychopharmacology bulletin. 1993;29(2):309-14.
155. Kinon BJ, Wang L, Gilmore JA. Exploration of a dose-response relationship in schizophrenia with the novel antipsychotic drug olanzapine. Eur Neuropsychopharmacol. 2001;11(3):277.
156. Kinon BJ, Jeste DV, Kollack-Walker S, Stauffer V, Liu-Seifert H. Olanzapine treatment for tardive dyskinesia in schizophrenia patients: a prospective clinical trial with patients randomized to blinded dose reduction periods. Progress in neuro-psychopharmacology & biological psychiatry. 2004;28(6):985-96.
157. Kinon BJ, Volavka J, Stauffer V, Edwards SE, Liu-Seifert H, Chen L, et al. Standard and higher dose of olanzapine in patients with schizophrenia or schizoaffective disorder: a randomized, double-blind, fixed-dose study. J Clin Psychopharmacol. 2008;28(4):392-400.
158. Kinon BJ, Chen L, Ascher-Svanum H, Stauffer VL, Kollack-Walker S, Zhou W, et al. Early Response to Antipsychotic Drug Therapy as a Clinical Marker of Subsequent

Response in the Treatment of Schizophrenia. Int J Neuropsychopharmacol. 2010;35(2):581-90.
159. Kinoshita T, Bai Y-M, Kim J-H, Miyake M, Oshima N. Efficacy and safety of asenapine in Asian patients with an acute exacerbation of schizophrenia: a multicentre, randomized, double-blind, 6-week, placebo-controlled study. Psychopharmacology. 2016;233(14):2663-74.
160. Klieser E, Lehmann E. Experimental comparison of the effectivity of individually adapted and standardized dosages of haloperidol. Neuropsychobiology. 1987;18(3):122-6.
161. Klieser E, Lehmann E, Heinrich K. Risperidone in Comparison with Various Treatments of Schizophrenia. Serotonin in Antipsychotic Treatment Mechanisms and Clinical Practice Edited by JM Kane, H-J Moller and F Awouters, Marcel Dekker Inc, New York, Basel, Hong Kong. 1996:331-43.
162. Ko G, Goff D, Herz H, Wilner K, Posever T, Howard H, et al. Status report: ziprasidone. Schizophrenia Research. 1995;15(1):154.
163. Kramer M, Simpson G, Maciulis V, Kushner S, Vijapurkar U, Lim P, et al. Paliperidone extended-release tablets for prevention of symptom recurrence in patients with schizophrenia: a randomized, double-blind, placebo-controlled study. Journal of clinical psychopharmacology. 2007;27(1):6-14.
164. Kryzhanovskaya L, Schulz SC, McDougle C, Frazier J, Dittmann R, Robertson-Plouch C, et al. Olanzapine versus placebo in adolescents with schizophrenia: a 6-week, randomized, double-blind, placebo-controlled trial. Journal of the American Academy of Child and Adolescent Psychiatry. 2009;48(1):60-70.
165. Kudo Y. Multi-Clinical Study of Haloperidol Decanoate on Schizophrenia. Japanese Journal of Neuropsychopharmacology. 1985;7:947-60.
166. Kurland AA, Ota KY, Slotnick VB. Penfluridol: a long-acting oral neuroleptic. A controlled study. Journal of clinical pharmacology. 1975;15(8-9):611-21.
167. Laffont CM, Gomeni R, Zheng B, Heidbreder C, Fudala PJ, Nasser AF. Population pharmacokinetic modeling and simulation to guide dose selection for RBP-7000, a new sustained-release formulation of risperidone. Journal of clinical pharmacology. 2015;55(1):93-103.
168. Lan T, Chiu H, Hu T, Huang H, Wu B, Tuan Y. Prolactin level as an indicator to clinical psychopathological severity in aripiprazole treated schizophrenia. Eur Neuropsychopharmacol. 2007;18(Supplement 4):S440.
169. Landbloom R, Mackle M, Wu X, Kelly L, Snow-Adami L, McIntyre RS, et al. Asenapine for the treatment of adults with an acute exacerbation of schizophrenia: results from a randomized, double-blind, fixed-dose, placebo-controlled trial with olanzapine as an active control. CNS spectrums. 2017;22(4):333-41.
170. Lane HY, Chang WH, Chiu CC, Huang MC, Lee SH, Chen JY. A pilot double-blind, dose-comparison study of risperidone in drug-naive first-episode schizophrenia. The Journal of clinical psychiatry. 2001;62(12):994-5.
171. Lecrubier Y, Puech AJ, Aubin F, Boyer P, Deyrieux B. Improvement by amisulpride of the negative syndrome in non-psychotic subjects : a preliminary study. Psychiatry and Psychobiology. 1988;3(5):329-33.
172. Lecrubier Y, Quintin P, Bouhassira M, Perrin E, Lancrenon S. The treatment of negative symptoms and deficit states of chronic schizophrenia: olanzapine compared to amisulpride and placebo in a 6-month double-blind controlled clinical trial. Acta Psychiatrica Scandinavica. 2006;114(5):319-27.
173. Lee HS, Kim CH, Kim YH, Yoon DJ, Lee MS, Suh HS, et al. Effective titration of risperidone in patients with schizophrenia: open multicenter randomized comparative 8 weeks study. Korean Journal of Psychopharmacology. 2002;13(4):276-88.
174. Lee SJ, Lee JH, Jung SW, Koo BH, Choi TY, Lee KH. A 6-week, randomized, multicentre, open-label study comparing efficacy and tolerability of amisulpride at a starting dose of 400 mg/day versus 800 mg/day in patients with acute exacerbations of schizophrenia. Clinical drug investigation. 2012;32(11):735-45.

175. Lehmann E, Quadbeck H, Tegeler J, Fararuni M, Heinrich K. Drug-response differences of high and standard dosage of fluphenazine-decanoate in relation to schizophrenic symptoms. Pharmakopsychiatrie, Neuro-Psychopharmakologie. 1980;13(3):117-29.
176. Lesem MD, Zajecka JM, Swift RH, Reeves KR, Harrigan EP. Intramuscular ziprasidone, 2 mg versus 10 mg, in the short-term management of agitated psychotic patients. The Journal of clinical psychiatry. 2001;62(1):12-8.
177. Levin ED, Wilson W, Rose JE, McEvoy J. Nicotine-haloperidol interactions and cognitive performance in schizophrenics. Int J Neuropsychopharmacol. 1996;15(5):429-36.
178. Levinson DF, Singh H, Simpson GM. Timing of Acute Clinical Response to Fluphenazine. British Journal of Psychiatry. 1992;160(3):365-71.
179. Levy DL, Lipton RB, Holzman PS, Davis JM. Eye tracking dysfunction unrelated to clinical state and treatment with haloperidol. Biological psychiatry. 1983;18(7):813-9.
180. Li Q, Su YA, Liu Y, Chen JX, Tan YL, Yang FD, et al. Pharmacokinetics and tolerability of extended-release quetiapine fumarate in Han Chinese patients with schizophrenia. Clinical pharmacokinetics. 2014;53(5):455-65.
181. Li M, Heidbreder C, Fudala P, Nasser A. A model-based approach to characterize risperidone release, absorption, and disposition afteradministration of RBP-7000 in schizophrenic patients. Clinical Pharmacology and Therapeutics. 2014;95:S77.
182. Lieberman JA, Davis RE, Correll CU, Goff DC, Kane JM, Tamminga CA, et al. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. Biological psychiatry. 2016;79(12):952-61.
183. Lindenmayer JP, Liu-Seifert H, Kulkarni PM, Kinon BJ, Stauffer V, Edwards SE, et al. Medication nonadherence and treatment outcome in patients with schizophrenia or schizoaffective disorder with suboptimal prior response. The Journal of clinical psychiatry. 2009;70(7):990-6.
184. Lindenmayer J-P, Khan A. Galantamine augmentation of long-acting injectable risperidone for cognitive impairments in chronic schizophrenia. Schizophrenia research. 2011;125(2):267-77.
185. Llaudó J, Anta L, Ayani I, Martínez J, Schronen J, Morozova M, et al. Phase I, open-label, randomized, parallel study to evaluate the pharmacokinetics, safety, and tolerability of one intramuscular injection of risperidone ISM at different dose strengths in patients with schizophrenia or schizoaffective disorder (PRISMA-1). International clinical psychopharmacology. 2016;31(6):323-31.
186. Loebel A, Cucchiaro J, Sarma K, Xu L, Hsu C, Kalali AH, et al. Efficacy and safety of lurasidone 80 mg/day and 160 mg/day in the treatment of schizophrenia: a randomized, double-blind, placebo- and active-controlled trial. Schizophr Res. 2013;145(1-3):101-9.
187. Loebel A, Citrome L, Correll CU, Xu J, Cucchiaro J, Kane JM. Treatment of early non-response in patients with schizophrenia: assessing the efficacy of antipsychotic dose escalation. BMC psychiatry. 2015;15:271.
188. Louza Neto MR, Müller-Spahn F, Rüther E, Scherer J. Haloperidol plasma level after a test dose as predictor for the clinical response to treatment in acute schizophrenic patients. Pharmacopsychiatry. 1988;21(5):226-31.
189. Mahal AS, Janakiramaiah NN. A Double-Blind Placebo Controlled Trial Of Pimozide(R6238) On 49 Hospitalized Chronic Schizophrenics. Indian J Psychiatry. 1975;17(1):45-55.
190. Mamo D, Kapur S, Shammi CM, Papatheodorou G, Mann S, Therrien F, et al. A PET study of dopamine D2 and serotonin 5-HT2 receptor occupancy in patients with schizophrenia treated with therapeutic doses of ziprasidone. The American journal of psychiatry. 2004;161(5):818-25.
191. Mamo D, Graff A, Mizrahi R, Shammi CM, Romeyer F, Kapur S. Differential effects of aripiprazole on D(2), 5-HT(2), and 5-HT(1A) receptor occupancy in patients with schizophrenia: a triple tracer PET study. The American journal of psychiatry. 2007;164(9):1411-7.

192. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. The American journal of psychiatry. 1994;151(6):825-35.
193. Marder SR, Kramer M, Ford L, Eerdekens E, Lim P, Eerdekens M, et al. Efficacy and safety of paliperidone extended-release tablets: results of a 6-week, randomized, placebo-controlled study. Biological psychiatry. 2007;62(12):1363-70.
194. Marinkovic D, Totic S, Marjanovic M. Is risperidone an atypical antipsychotic? Eur Neuropsychopharmacol. 2006;16(Suppl 4):S424.
195. Martin WF, Correll CU, Weiden PJ, Jiang Y, Pathak S, DiPetrillo L, et al. Mitigation of Olanzapine-Induced Weight Gain With Samidorphan, an Opioid Antagonist: A Randomized Double-Blind Phase 2 Study in Patients With Schizophrenia. The American journal of psychiatry. 2019;176(6):457-67.
196. Mathur S, Hall JN. Phenothiazine withdrawal in schizophrenics in a hostel. The British journal of psychiatry : the journal of mental science. 1981;138:271-2.
197. Matsumoto H, Ishigooka J, Ono H, Tadori Y. Safety and efficacy from a 6-week double-blind study and a 52-week open-label extension of aripiprazole in adolescents with schizophrenia in Japan. Psychiatry and clinical neurosciences. 2018;72(9):701-12.
198. Mauri MC, Colasanti A, Rossattini M, Moliterno D, Baldi ML, Papa P. A single-blind, randomized comparison of olanzapine at a starting dose of 5 mg versus 20 mg in acute schizophrenia. Clinical neuropharmacology. 2006;29(3):126-31.
199. Mavroidis ML, Kanter DR, Hirschowitz J, Garver DL. Clinical response and plasma haloperidol levels in schizophrenia. Psychopharmacology. 1983;81(4):354-6.
200. Mavroidis ML, Kanter DR, Hirschowitz J, Garver DL. Fluphenazine plasma levels and clinical response. J Clin Psychiatry. 1984;45(9):370-3.
201. McClelland HA, Blessed G, Bhate S, Ali N, Clarke PA. The abrupt withdrawal of antiparkinsonian drugs in schizophrenic patients. The British journal of psychiatry : the journal of mental science. 1974;124(579):151-9.
202. McDonnell D, Lauriello J, Lambert T, Andersen S, Lin D, Detke H. Olanzapine long-acting injection: An 8-week double-blind. randomized, placebo-controlled study in acutely-ill patients with schizophrenia. Schizophrenia research. 2008;102:251.
203. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of neuroleptic in acute schizophrenia. A controlled study of the neuroleptic threshold and higher haloperidol dose. Archives of general psychiatry. 1991;48(8):739-45.
204. McEvoy JP, Lindgren J. Smoking and schizophrenia. Drug Development Research. 1996;38(3-4):263-6.
205. McGorry P, Cocks J, Power P, Burnett P, Harrigan S, Lambert T. Very Low-Dose Risperidone in First-Episode Psychosis: A Safe and Effective Way to Initiate Treatment. Schizophr Res Treatment. 2011;2011:631690.
206. Meltzer HY, Cucchiaro J, Silva R, Ogasa M, Phillips D, Xu J, et al. Lurasidone in the treatment of schizophrenia: a randomized, double-blind, placebo- and olanzapine-controlled study. Am J Psychiatry. 2011;168(9):957-67.
207. Meltzer HY, Elkis H, Vanover K, Weiner DM, van Kammen DP, Peters P, et al. Pimavanserin, a selective serotonin (5-HT)2A-inverse agonist, enhances the efficacy and safety of risperidone, 2mg/day, but does not enhance efficacy of haloperidol, 2mg/day: Comparison with reference dose risperidone, 6mg/day. Schizophrenia research. 2012;141(2):144-52.
208. Meltzer HY, Lindenmayer JP, Kwentus J, Share DB, Johnson R, Jayathilake K. A six month randomized controlled trial of long acting injectable risperidone 50 and 100mg in treatment resistant schizophrenia. Schizophrenia research. 2014;154(1-3):14-22.
209. Meltzer H, Share B, Jayathilake K. Lurasidone is an effective treatment for treatment resistant schizophrenia. Int J Neuropsychopharmacol. 2015;40:S546.
210. Meltzer HY, Risinger R, Nasrallah HA, Du Y, Zummo J, Corey L, et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. The Journal of clinical psychiatry. 2015;76(8):1085-90.

211. Merlo MC, Hofer H, Gekle W, Berger G, Ventura J, Panhuber I, et al. Risperidone, 2 mg/day vs. 4 mg/day, in first-episode, acutely psychotic patients: treatment efficacy and effects on fine motor functioning. The Journal of clinical psychiatry. 2002;63(10):885-91.
212. Miceli J, Preskorn S, Wilner K, Folger C, Tensfeld T. Characterization of the intramuscular pharmacokinetics of ziprasidone in schizophrenic patients. European Psychiatry. 1998;13(S4):304s-5s.
213. Mitchell M, Earley W, Bari M, Riesenberg R, Marquez E, Kurtz D, et al. P.2.081 A preliminary study of the pharmacokinetics and tolerability of higher dose oral olanzapine (20, 30, or 40mg/day) in stable patients with serious mental disorders. Eur Neuropsychopharmacol. 2003;13.
214. Mitchell M, Riesenberg R, Bari MA, Marquez E, Kurtz D, Falk D, et al. A double-blind, randomized trial to evaluate the pharmacokinetics and tolerability of 30 or 40 mg/d oral olanzapine relative to 20 mg/d oral olanzapine in stable psychiatric subjects. Clinical therapeutics. 2006;28(6):881-92.
215. Modestin J, Toffler G, Pia M, Greub E. Haloperidol in acute schizophrenic inpatients. A double-blind comparison of two dosage regimens. Pharmacopsychiatria. 1983;16(4):121-6.
216. Mosholder AD. Review and evaluation of clinical data: NDA 20-639; quetiapine fumarate (seroquel). Food and Drug Administration, US Department of Health and Human Services 1996.
217. Nair CJ, Abraham G, Stanilla JK, Tracy JI, de Leon J, Simpson GM, et al. Therapeutic effects of clozapine on tardive dyskinesia. Cognitive and Behavioral Practice. 1998;5(1):123-31.
218. Nakamura T, Kubota T, Iwakaji A, Imada M, Kapás M, Morio Y. Clinical pharmacology study of cariprazine (MP-214) in patients with schizophrenia (12-week treatment). Drug design, development and therapy. 2016;10:327-38.
219. Nasrallah HA, Gopal S, Gassmann-Mayer C, Quiroz JA, Lim P, Eerdekens M, et al. A controlled, evidence-based trial of paliperidone palmitate, a long-acting injectable antipsychotic, in schizophrenia. Int J Neuropsychopharmacol. 2010;35(10):2072-82.
220. Nasrallah HA, Silva R, Phillips D, Cucchiaro J, Hsu J, Xu J, et al. Lurasidone for the treatment of acutely psychotic patients with schizophrenia: a 6-week, randomized, placebo-controlled study. J Psychiatr Res. 2013;47(5):670-7.
221. Nasser AF, Henderson DC, Fava M, Fudala PJ, Twumasi-Ankrah P, Kouassi A, et al. Efficacy, Safety, and Tolerability of RBP-7000 Once-Monthly Risperidone for the Treatment of Acute Schizophrenia: An 8-Week, Randomized, Double-Blind, Placebo-Controlled, Multicenter Phase 3 Study. Journal of clinical psychopharmacology. 2016;36(2):130-40.
222. Sunovion. A Comparison of Study Drug With Placebo and Haloperidol in Patients With Schizophrenia 2011 [updated 17.04.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT00044044.
223. Pfizer. A Study of the Safety and Tolerability of Oral Ziprasidone in Children and Teens With Psychotic Disorders 2008 [updated 10.04.2008. Available from: https://clinicaltrials.gov/ct2/show/NCT00650611.
224. Sunovion. Safety and Tolerability Study of Drug to Treat Schizophrenia 2011 [updated 17.04.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT00044005.
225. de Haan L, van Bruggen M, Lavalaye J, Booij J, Dingemans PM, Linszen D. Subjective experience and D2 receptor occupancy in patients with recent-onset schizophrenia treated with low-dose olanzapine or haloperidol: a randomized, double-blind study. AmJPsychiatry. 2003;160:303-9.
226. Meltzer HY, Bobo WV, Nuamah IF, Lane R, Hough D, Kramer M, et al. Efficacy and tolerability of oral paliperidone extended-release tablets in the treatment of acute schizophrenia: pooled data from three 6-week, placebo-controlled studies. The Journal of clinical psychiatry. 2008;69(5):817-29.
227. Johnson & Johnson Pharmaceutical Research & Development LLC. Safety Study With Paliperidone ER Extended-Release (ER) Tablets in Geriatric Patients With Schizophrenia 2004 [updated 08.06.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00085748.

228. Johnson & Johnson Pharmaceutical Research & Development LLC. Investigate Risperidone for the Treatment of Schizophrenia in Adolescents 2004 [updated 08.06.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00088075.
229. Johnson & Johnson Pharmaceutical Research & Development LLC. A Study to Evaluate the Effectiveness and Safety of 3 Doses of Paliperidone Palmitate in Treating Subjects With Schizophrenia 2005 [updated 08.06.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00210548.
230. Johnson & Johnson Pharmaceutical Research & Development LLC. A Study to Compare the Effectiveness and Safety of Flexibly Varied Doses of Paliperidone Palmitate and Risperidone in Treating Patients With Schizophrenia 2005 [updated 08.06.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00210717.
231. Otsuka Pharmaceutical Development & Commercialization I. A Switch Study of BMS-337039 in Schizophrenic Out-patients 2005 [updated 08.11.2013. Available from: https://clinicaltrials.gov/ct2/show/NCT00232687.
232. Otsuka Pharmaceutical Development & Commercialization I. A Study of Aripiprazole in the Management of Patients With Schizophrenia in the General Psychiatric Practices 2005 [updated 08.11.2013. Available from: https://clinicaltrials.gov/ct2/show/NCT00237939.
233. Lindenmayer JP. High Dose of Quetiapine in Treating Subjects With Treatment Refractory Schizophrenia or Schizoaffective Disorder (HDQ) 2006 [updated 17.04.2015. Available from: https://clinicaltrials.gov/ct2/show/NCT00297947.
234. EliLilly. Examining Rapid Acting Intra-Muscular Olanzapine in Japanese Patients With Schizophrenia 2007 [updated 13.06.2007. Available from: https://clinicaltrials.gov/ct2/show/NCT00485810.
235. JanssenPharmaceutical. A Pharmacokinetic and Safety Study of Risperidone Long Acting Injectable in Schizophrenic Patients 2008 [updated 17.05.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00653406.
236. H.Lundbeck. Efficacy of Bifeprunox in Patients With Schizophrenia 2008 [updated 27.09.2010. Available from: https://clinicaltrials.gov/ct2/show/NCT00704509.
237. Sumitomo Dainippon Pharma Co. L. Study of SM-13496 (Lurasidone HCl) in Patients With Schizophrenia 2008 [updated 19.10.2018. Available from: https://clinicaltrials.gov/ct2/show/NCT00711269.
238. Johnson & Johnson Pharmaceutical Research & Development LLC. A Safety and Pharmacokinetic Study of ER OROS Paliperidone in Pediatric Patients With Schizophrenia, Schizoaffective Disorder, or Schizophreniform Disorder 2008 [updated 08.06.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT00796081.
239. Mitsubishi_Tanabe_Pharma_Corporation. Safety, Pharmacokinetics and Efficacy Study of MP-214 in Patients With Schizophrenia 2009 [updated 10.09.2009. Available from: https://clinicaltrials.gov/ct2/show/NCT00862992.
240. ForestLaboratories. Safety and Efficacy of Cariprazine (RGH-188) in the Acute Exacerbation of Schizophrenia 2008 [updated 12.06.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT00694707.
241. Otsuka Pharmaceutical Development & Commercialization I. Study to Evaluate the Efficacy, Safety, and Tolerability of Oral OPC-34712 and Aripiprazole for Treatment of Acute Schizophrenia (STEP 203) 2009 [updated 20.10.2015. Available from: https://clinicaltrials.gov/ct2/show/NCT00905307.
242. Sunovion. The Bioequivalence Of Two Different Lurasidone Formulations In Patients 2010 [updated 08.09.2011. Available from: https://clinicaltrials.gov/ct2/show/NCT01082250.
243. Dohme-_Corp. MS. Long-term Extension Trial of Asenapine in Subjects With Schizophrenia (Study P06125) 2016 [updated 17.10.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT01142596.
244. H.Lundbeck. Study of the Safety, Tolerability, and Pharmacokinetics of Once Weekly Zicronapine in Patients With Schizophrenia 2016 [updated 22.03.2016. Available from: https://clinicaltrials.gov/ct2/show/NCT01377233.
245. Otsuka Pharmaceutical Development & Commercialization I. Trial to Evaluate the Effects of OPC-34712 on QT/QTc in Subjects With Schizophrenia or Schizoaffective

Disorder 2015 [updated 29.10.2015. Available from: https://clinicaltrials.gov/ct2/show/NCT01423916.
246. Alkermes. A Study of ALKS 9072 in Subjects With Chronic Stable Schizophrenia 2018 [updated 29.08.2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01493726.
247. Janssen_Pharmaceutical_K.K. A Pharmacokinetic and Safety Study of Paliperidone Palmitate (JNS010) in Participants With Schizophrenia 2013 [updated 05.06.2013. Available from: https://clinicaltrials.gov/ct2/show/NCT01606254.
248. Mitsubishi_Tanabe_Pharma_Corporation. Safety and Efficacy of MP-214 in Patients With Schizophrenia 2016 [Available from: https://clinicaltrials.gov/ct2/show/NCT01625000.
249. Mitsubishi_Tanabe_Pharma_Corporation. A Long-Term Study of MP-214 in Patients With Chronic Phase or Elderly Schizophrenia 2015 [Available from: https://clinicaltrials.gov/ct2/show/NCT01625897.
250. Alkermes. A Long-term Safety Study of ALKS 9072 (Also Known as ALKS 9070) 2016 [updated 25.09.2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01626456.
251. Mitsubishi_Tanabe_Pharma_Corporation. A Pharmacokinetic Study of MP-214 in Patients With Schizophrenia 2014 [Available from: https://clinicaltrials.gov/ct2/show/NCT01626859.
252. Mitsubishi_Tanabe_Pharma_Corporation. Long-Term Study of MP-214 in Patients With Schizophrenia 2017 [updated 06.04.2017. Available from: https://clinicaltrials.gov/ct2/show/NCT01626872.
253. Janssen_Pharmaceutical_K.K. A Clinical Pharmacology Study of JNS010 (Paliperidone Palmitate) in Patients With Schizophrenia 2013 [updated 16.09.2013. Available from: https://clinicaltrials.gov/ct2/show/NCT01942382.
254. Kahn RS. European Long-acting Antipsychotics in Schizophrenia Trial (EULAST): UMC Utrecht; 2020 [updated 01.09.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT02146547.
255. Sumitomo Pharmaceutical (Suzhou) Co. L. A Pharmacokinetic Study of Lurasidone After Single Oral Administration in Healthy Subjects 2019 [updated 11.01.2019. Available from: https://clinicaltrials.gov/ct2/show/NCT02174510.
256. Luye_Pharma_Group_Ltd. A Study to Determine Pharmacokinetic Characteristics of LY03010 Versus INVEGA SUSTENNA® in Schizophrenia Patients 2019 [updated 13.08.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03751488.
257. Allergan. Efficacy and Safety of Cariprazine in the Treatment of Adolescent Participants (13 to 17 Years of Age) With Schizophrenia 2019 [updated 29.10.2020. Available from: https://www.clinicaltrials.gov/ct2/show/NCT03817502.
258. Rovi_Pharmaceuticals_Laboratories. Study to Evaluate the Efficacy and Safety of Risperidone ISM® in Patients With Acute Schizophrenia: Open Label Extension (PRISMA-3_OLE) 2019 [updated 05.02.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03870880.
259. Otsuka Pharmaceutical Development & Commercialization I. Trial to Assess the Bioavailability of Quetiapine Versus Seroquel® in Subjects With Schizophrenia or Bipolar Disorder 2019 [updated 02.09.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT03872596.
260. Otsuka Pharmaceutical Development & Commercialization I. A Trial of Multiple-doses of Aripiprazole in Adults With Schizophrenia or Bipolar 1 Disorder 2019 [updated 02.09.2020. Available from: https://clinicaltrials.gov/ct2/show/NCT04030143.
261. Neborsky R, Janowsky D, Munson E, Depry D. Rapid treatment of acute psychotic symptoms with high- and low-dose haloperidol. Behavioral considerations. Archives of general psychiatry. 1981;38(2):195-9.
262. Odejide OA, Aderounmu AF. Double-blind placebo substitution: withdrawal of fluphenazine decanoate in schizophrenic patients. The Journal of clinical psychiatry. 1982;43(5):195-6.
263. Ogasa M, Kimura T, Nakamura M, Guarino J. Lurasidone in the treatment of schizophrenia: a 6-week, placebo-controlled study. Psychopharmacology. 2013;225(3):519-30.

264. Ono H, Murasaki M, Sasaki Y, Bille A. Open-label, randomized, exploratory study showed rapid-acting intramuscular olanzapine 7,5 mg and 10 mg were effective in agitated Japanese schizophrenia patients. Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology. 2006;9(Suppl 1):S266.
265. Ono H, Fujikoshi S, Oka T, Sugiura M, Takahashi M. A double-blind dose-response study comparing rapid acting intramuscular olanzapine and placebo in agitated schizophrenia. Eur Neuropsychopharmacol. 2008;18(Supplement 4):S410.
266. Oosthuizen P, Emsley R, Jadri Turner H, Keyter N. A randomized, controlled comparison of the efficacy and tolerability of low and high doses of haloperidol in the treatment of first-episode psychosis. Int J Neuropsychopharmacol. 2004;7(2):125-31.
267. Oren DA, Manos G, Markovic O, McQuade RD. Intramuscular aripiprazole for the treatment of acute agitation associated with schizophrenia: Sub-analysis of a double-blind, controlled, dose-ranging study. European Psychiatry. 2007;22(S1):S124.
268. Ortega-Soto H, Brunner E, Apiquian R, de la Torre P. Therapeutic Minimum Dose of Haloperidol (HLP) in Schizophrenia. Int J Neuropsychopharmacol. 1994;10(3S):140S.
269. Ota KY, Kurland AA. A double-blind comparison of haloperidol oral concentrate, haloperidol solutabs and placebo in the treatment of chronic schizophrenia. The Journal of clinical pharmacology and new drugs. 1973;13(2):99-110.
270. Palao DJ, Arauxo A, Brunet M, Bernardo M, Haro JM, Ferrer J, et al. Haloperidol: therapeutic window in schizophrenia. Journal of clinical psychopharmacology. 1994;14(5):303-10.
271. Pandina GJ, Lindenmayer JP, Lull J, Lim P, Gopal S, Herben V, et al. A randomized, placebo-controlled study to assess the efficacy and safety of 3 doses of paliperidone palmitate in adults with acutely exacerbated schizophrenia. Journal of clinical psychopharmacology. 2010;30(3):235-44.
272. Petrie JL, Saha AR, McEvoy JP. Aripiprazole, a new typical antipsychotic: Phase 2 clinical trial result. Eur Neuropsychopharmacol. 1997;7(1002):S227.
273. Peuskens J, Trivedi J, Malyarov S, Brecher M, Svensson O, Miller F, et al. Prevention of schizophrenia relapse with extended release quetiapine fumarate dosed once daily: a randomized, placebo-controlled trial in clinically stable patients. Psychiatry (Edgmont). 2007;4(11):34-50.
274. Potkin SG, Shen YC, Zhou DF, Pardes H, Shu L, Phelps B, et al. Does a therapeutic window for plasma haloperidol exist?: Preliminary Chinese data. Psychopharmacology bulletin. 1985;21(1):59-61.
275. Potkin SG, Bera R, Gulasekaram B, Costa J, Hayes S, Jin Y, et al. Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. The Journal of clinical psychiatry. 1994;55 Suppl B:133-6.
276. Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, et al. Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs placebo in patients with schizophrenia and schizoaffective disorder. Archives of general psychiatry. 2003;60(7):681-90.
277. Potkin SG, Litman RE, Torres R, Wolfgang CD. Efficacy of iloperidone in the treatment of schizophrenia: initial phase 3 studies. Journal of clinical psychopharmacology. 2008;28(2 Suppl 1):S4-11.
278. Potkin SG, Preskorn S, Hochfeld M, Meng X. A thorough QTc study of 3 doses of iloperidone including metabolic inhibition via CYP2D6 and/or CYP3A4 and a comparison to quetiapine and ziprasidone. Journal of clinical psychopharmacology. 2013;33(1):3-10.
279. Potkin SG, Keator DB, Kesler-West ML, Nguyen DD, van Erp TG, Mukherjee J, et al. D2 receptor occupancy following lurasidone treatment in patients with schizophrenia or schizoaffective disorder. CNS spectrums. 2014;19(2):176-81.
280. Prien RF CJ. High dose chlorpromazine therapy in chronic schizophrenia. Report of National Institute of Mental Health--psychopharmacology research branch collaborative study group. Archives of general psychiatry. 1968;18(4):482-95.
281. Prien RF, Levine J, Cole JO. High dose trifluoperazine therapy in chronic schizophrenia. The American journal of psychiatry. 1969;126(3):305-13.

282. Puech A, Fleurot O, Rein W. Amisulpride, and atypical antipsychotic, in the treatment of acute episodes of schizophrenia: a dose-ranging study vs. haloperidol. The Amisulpride Study Group. Acta Psychiatrica Scandinavica. 1998;98(1):65-72.
283. Quitkin F, Rifkin A, Klein DF. Very high dosage vs standard dosage fluphenazine in schizophrenia. A double-blind study of nonchronic treatment-refractory patients. Archives of general psychiatry. 1975;32(10):1276-81.
284. Ravenstijn P, Remmerie B, Savitz A, Samtani MN, Nuamah I, Chang CT, et al. Pharmacokinetics, safety, and tolerability of paliperidone palmitate 3-month formulation in patients with schizophrenia: A phase-1, single-dose, randomized, open-label study. Journal of clinical pharmacology. 2016;56(3):330-9.
285. Rein W, Turjanski S, Fleurot O. Amilsulpride in the treatment of deficit schizophrenia. Proceeding of the 10th World Concress of Psychiatry; 1996 Aug 23-28; Madrid, Spain1996.
286. Reschke RW. Parenteral haloperidol for rapid control of severe, disruptive symptoms of acute schizophrenia. Diseases of the nervous system. 1974;35(3):112-5.
287. Rifkin A, Quitkin F, Rabiner CJ, Klein DF. Fluphenazine decanoate, fluphenazine hydrochloride given orally, and placebo in remitted schizophrenics. I. Relapse rates after one year. Archives of general psychiatry. 1977;34(1):43-7.
288. Rifkin A, Doddi S, Karajgi B, Borenstein M, Wachspress M. Dosage of haloperidol for schizophrenia. Archives of general psychiatry. 1991;48(2):166-70.
289. Rodriguez S, Lasser R, Turkoz I, Urioste R, Burks EJ, Gharabawi G. Long-term long-acting risperidone: QoL and functioning in schizophrenia. Proceedings of the 157th Annual Meeting of the American Psychiatric Assosiation; 2004 May 1-6; New York, USA 2004.
290. Roelofs GA. Penfluridol (R 16 341) as a maintenance therapy in chronic psychotic patients: a double-blind clinical evaluation. Acta Psychiatrica Scandinavica. 1974;50(2):219-24.
291. Rossenu S, Cleton A, Talluri K, Francetic I, Canuso C, Remmerie B, et al. Pharmacodynamics of paliperidone extended-release tablets and immediate-release risperidone in schizophrenia. Schizophrenia research. 2008;98:159.
292. Rui Q, Wang Y, Liang S, Liu Y, Wu Y, Wu Q, et al. Relapse prevention study of paliperidone extended-release tablets in Chinese patients with schizophrenia. Progress in neuro-psychopharmacology & biological psychiatry. 2014;53:45-53.
293. Ruiz M, Quintana LM, Vilalta JS. Estudio clinico con pimocide en las esquizofrenias de evolucion cronica. Revista de Psiquiatria y Pscologia Medicina. 1975;4:247-56.
294. Ruskin PE, Nyman G. Discontinuation of neuroleptic medication in older, outpatient schizophrenics. A placebo-controlled, double-blind trial. The Journal of nervous and mental disease. 1991;179(4):212-4.
295. Sampath G, Shah A, Krska J, Soni SD. Neuroleptic discontinuation in the very stable schizophrenic patient: Relapse rates and serum neuroleptic levels. Human Psychopharmacology: Clinical and Experimental. 1992;7(4):255-64.
296. Santos JL, Cabranes JA, Vazquez C, Fuentenebro F, Almoguera I, Ramos JA. Clinical response and plasma haloperidol levels in chronic and subchronic schizophrenia. Biological psychiatry. 1989;26(4):381-8.
297. Sarin A, Nagpal J, Bohra NK, Jiloha RC, Rao GP, Sharma SK, et al. Open labeled, randomized, switch-over study of two fixed doses (10/15mg) of aripiprazole : to evaluate its safety and efficacy in the treatment of Indian patients of schizophrenia. Indian J Psychiatry. 2004;46(1):64-71.
298. Schooler NR, Siu C. Ziprasidone's effect on anxiety in a group of oupatients with stable schizophrenia. Int J Neuropsychopharmacol. 2000;3(Suppl 1):S104.
299. Shawver JR, Gorham DR, Leskin LW, Good WW, Kabnick DE. Comparison of chlorpromazine and reserpine in maintenance drug therapy. Diseases of the nervous system. 1959;20:452-7.
300. Sim CB, Lee YC, Hwang JP. Haloperidol for schizophrenic inpatients with three dose regimens. Psychiatry Today. 1989:817.
301. Simpson GM, Angus JW, Edwards JG. A controlled study of haloperidol in chronic schizophrenia. Curr Ther Res Clin Exp. 1967;9(8):407-12.

302. Simpson GM, Josiassen RC, Stanilla JK, de Leon J, Nair C, Abraham G, et al. Double-blind study of clozapine dose response in chronic schizophrenia. The American journal of psychiatry. 1999;156(11):1744-50.
303. Singh H, Levinson DF, Simpson GM, Lo ES, Friedman E. Acute dystonia during fixed-dose neuroleptic treatment. Journal of clinical psychopharmacology. 1990;10(6):389-96.
304. Singh J, Robb A, Vijapurkar U, Nuamah I, Hough D. A Randomized, Double-Blind Study of Paliperidone Extended-Release in Treatment of Acute Schizophrenia in Adolescents. Biological psychiatry. 2011;70(12):1179-87.
305. Smith RC, Baumgartner R, Misra CH, Mauldin M, Shvartsburd A, Ho BT, et al. Haloperidol. Plasma levels and prolactin response as predictors of clinical improvement in schizophrenia: chemical v radioreceptor plasma level assays. Archives of general psychiatry. 1984;41(11):1044-9.
306. Smith RC. Plasma Haloperidol Levels and Clinical Response. Archives of general psychiatry. 1987;44(12):1110-2.
307. Soria JM, Santiuste MA, Salorio P. Efecto de la medicacion neuroleptica sobre la conducta en la esquizofrenia cronica. Psiquis. 1994;15(3):21-5.
308. Stewart M, DelBello MP, Versavel M, Keller D. Psychosocial functioning and health-related quality of life in children and adolescents treated with open-label ziprasidone for bipolar mania, schizophrenia, or schizoaffective disorder. Journal of child and adolescent psychopharmacology. 2009;19(6):635-40.
309. Stone CK, Garve DL, Griffith J, Hirschowitz J, Bennett J. Further evidence of a dose-response threshold for haloperidol in psychosis. The American journal of psychiatry. 1995;152(8):1210-2.
310. Sun L, McDonnell D, von Moltke L. Pharmacokinetics and Short-term Safety of ALKS 3831, a Fixed-dose Combination of Olanzapine and Samidorphan, in Adult Subjects with Schizophrenia. Clinical therapeutics. 2018;40(11):1845-54.e2.
311. Švestka J. Intramuscular ziprasidone - A rapid-acting antipsychotic of the 2nd generation. Psychiatrie. 2003;7:110-6.
312. Swift RH, Harrigan EP, Cappelleri JC, Kramer D, Chandler LP. Validation of the behavioural activity rating scale (BARS): a novel measure of activity in agitated patients. J Psychiatr Res. 2002;36(2):87-95.
313. Takeuchi H, Suzuki T, Remington G, Watanabe K, Mimura M, Uchida H. Lack of effect of risperidone or olanzapine dose reduction on subjective experiences in stable patients with schizophrenia. Psychiatry research. 2014;218(1-2):244-6.
314. Turncliff R, Potocka E, Corey L, Lowy A, Marandi M, DeSomer M, et al. ALKS 9070, a novel once monthly prodrug of aripiprazole, achieves therapeutic levels and is well-tolerated in adults with schizophrenia. European Neuropsychopharmacology. 2012;22(Suppl. 2):S330-S1.
315. Uzun S, Folnegović-Šmalc V, Mimica N, Ljubin Golub T, Makarić G, Ivezić S, et al. Ziprasidone clinical trials conducted in Croatia. Schizophrenia research. 2002;53(Suppl 3):182.
316. van Erp TG, Baker RA, Cox K, Okame T, Kojima Y, Eramo A, et al. Effect of brexpiprazole on control of impulsivity in schizophrenia: A randomized functional magnetic resonance imaging study. Psychiatry research Neuroimaging. 2020;301:111085.
317. van Kammen DP, McEvoy JP, Targum SD, Kardatzke D, Sebree TB. A randomized, controlled, dose-ranging trial of sertindole in patients with schizophrenia. Psychopharmacology. 1996;124(1-2):168-75.
318. Van Putten T, Marder S. Low-Dose Treatment Strategies. The Journal of clinical psychiatry. 1986;47(Suppl 5):12-6.
319. Van Putten T, Marder SR, May PR, Poland RE, O'Brien RP. Plasma levels of haloperidol and clinical response. Psychopharmacology bulletin. 1985;21(1):69-72.
320. Van Putten T, Marder SR, Mintz J. A controlled dose comparison of haloperidol in newly admitted schizophrenic patients. Archives of general psychiatry. 1990;47(8):754-8.

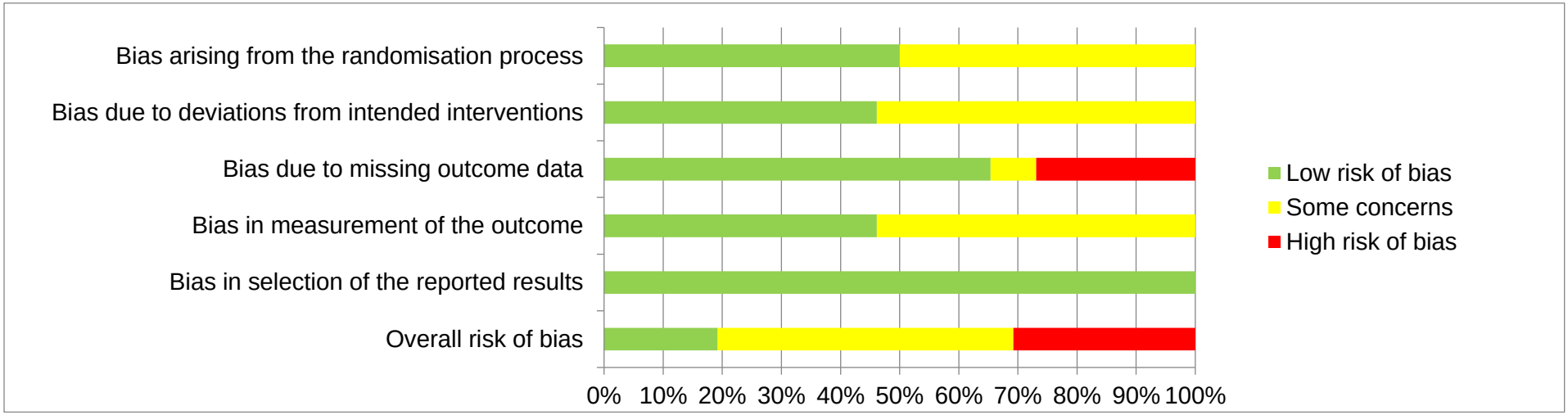
321. Van Putten T, Aravagiri M, Marder SR, Wirshing WC, Mintz J, Chabert N. Plasma fluphenazine levels and clinical response in newly admitted schizophrenic patients. Psychopharmacology bulletin. 1991;27(2):91-6.
322. Vandecasteele AJA, Vereecken JLTM. A double-blind clinical evaluation of penfluridol (R 16 341) as maintenance therapy in schizophrenia. Acta Psychiatrica Scandinavica. 1974;50(3):346-53.
323. Vanover K, Glass S, O'Gorman C, Saillard J, Weingart M, Correll C, et al. Advancing the Clinical Development of ITI-007 - Update on Efficacy for the Treatment of Schizophrenia. Int J Neuropsychopharmacol. 2016;41:S232-3.
324. Vanover KE, Davis RE, O'Gorman C, Saillard J, Weingart M, Mates S. Unique Pharmacology of ITI-007 Confers Efficacy in the Treatment of Schizophrenia at Low Striatal D2 Receptor Occupancy Levels. Biological psychiatry. 2016;79:S354-S5.
325. Vinar O, Taussigová D, Bastecký J, Boleloucký Z. Long acting peroral fluphenazine and its dosage in psychoses. Activitas nervosa superior. 1970;12(3):248-9.
326. Walling D, Hard M, Wehr A, Du Y, Weiden P, Moltke L. F197. Aripiprazole Lauroxil NanoCrystal® Dispersion: A Potential 1-Day Initiation Regimen for Long-Acting Aripiprazole Lauroxil. Biological psychiatry. 2018;83:S315.
327. Wehnert A, Rasmussen C. Sertindole improves cognitive functioning in schizophrenic patients: results of a five-factor component analysis of sertindole. Schizophrenia research. 1999;36(1-3):301.
328. Weiden PJ, Manning R, Wolfgang CD, Ryan JM, Mancione L, Han G, et al. A Randomized Trial of Iloperidone for Prevention of Relapse in Schizophrenia: The REPRIEVE Study. CNS drugs. 2016;30(8):735-47.
329. Wessels WH, Gagiano CA, Emsley RA, Hart GAD, Daubenton F, Bodemer W, et al. Risperidone (64766) in the treatment of chronic schizophrenic patients. Biological psychiatry. 1991;29:705S-22S.
330. Wiles D, Franklin M, Dencker SJ, Johansson R, Lundin L, Malm U. Plasma fluphenazine and prolactin levels in schizophrenic patients during treatment with low and high doses of fluphenazine enanthate. Psychopharmacology. 1980;71(2):131-6.
331. Winter M, Lehmann E, Scholz OB. Effects of high and low dosage of haloperidol on the brain in relation to schizophrenic thought disorder. Neuropsychobiology. 1984;12(2-3):115-21.
332. Witte MM, Case MG, Schuh KJ, Ascher-Svanum H. Effects of olanzapine long-acting injection on levels of functioning among acutely ill patients with schizophrenia. Current medical research and opinion. 2012;28(3):315-23.
333. Yamagami S, Mui K, Koide K, Okuno M, Onishi H, Hirayama E. A correlation among clinical response, plasma levels of haloperidol and prolactin in chronic schizophrenia. Proceedings of the 17th Collegium Internationale Neuro-Psychopharmacologicum Congress: 1990 Sep 1014; Kyoto, Japan 1990.
334. Younis IR, Laughren TP, Wang Y, Mathis M, Gobburu JV. Learn-apply approach for establishing dosing recommendations: paliperidone for the treatment of adolescent schizophrenia. Clinical pharmacology and therapeutics. 2012;91:S54-S5.
335. Zimbroff DL, Kane JM, Tamminga CA, Daniel DG, Mack RJ, Wozniak PJ, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Sertindole Study Group. The American journal of psychiatry. 1997;154(6):782-91.
336. Zissis NP, Psaras M, Lyketsos G. Haloperidol decanoate, a new long-acting antipsychotic, in chronic schizophrenics: Double-blind comparison with placebo. Current Therapeutic Research - Clinical and Experimental. 1982;31(4):650-5.

eAppendix 3. Assessment with the Cochrane Risk of bias tool, version2 : judgements about each bias item for each study for the primary outcome relapse

Study name	Bias arising from the randomisation process	Bias due to deviations from intended interventions	Bias due to missing outcome data	Bias in measurement of the outcome	Bias in selection of the reported results	Overall risk of bias
Arato 2002	Low	Some concerns	Low	Some concerns	Low	Some concerns
Velligan 2002	Low	Low	Low	Low	Low	Low
Beasley 1996b_Extension	Some concerns	Low	Some concerns	Low	Low	Some concerns
Beasley 1997_Extension	Some concerns	Low	High	Low	Low	High
Carpenter 1999	Some concerns	Low	Low	Low	Low	Some concerns
Chen 2010	Low	Some concerns	Low	Some concerns	Low	Some concerns
Cooper 2000b	Low	Some concerns	Low	Some concerns	Low	Some concerns
Dotti 1979	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Eklund 1991	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Fleischhacker 2014	Low	Low	Low	Low	Low	Low
Hough 2009	Low	Low	High	Low	Low	High

Huttunen 1996	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Kane 1979	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Kane 1983	Some concerns	Low	High	Low	Low	High
Kane 2002b	Low	Low	Low	Low	Low	Low
Kane 2010c	Low	Low	Low	Low	Low	Low
Kane 2012	Low	Some concerns	Low	Some concerns	Low	Some concerns
Mallikaarjun 2013	Low	Some concerns	High	Some concerns	Low	High
Marder 1984	Some concerns	Low	High	Low	Low	High
McEvoy 2007b_Extension	Some concerns	Low	High	Low	Low	High
Nishikawa 1982	Some concerns	Some concerns	Low	Some concerns	Low	Some concerns
Nishikawa 1984	Some concerns	Some concerns	Some concerns	Some concerns	Low	High
Pigott 2003	Low	Some concerns	Low	Some concerns	Low	Some concerns
Schooler 1993	Some concerns	Some concerns	High	Some concerns	Low	High
Simpson 2006	Low	Low	Low	Low	Low	Low

Tandon 2016	Low	Some concerns	Low	Some concerns	Low	Some concerns

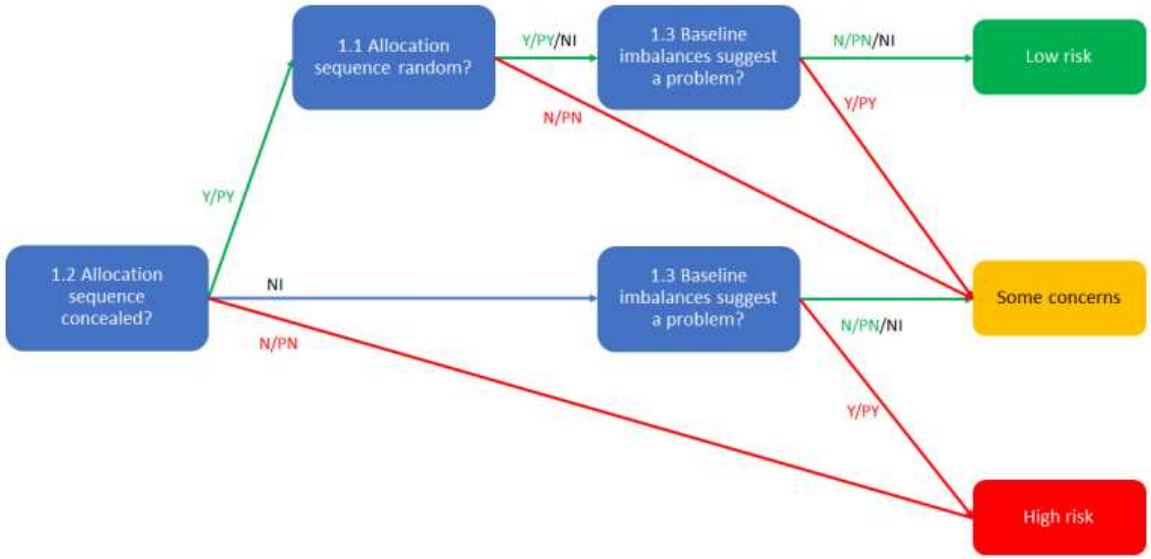


Explanations for our decisions concerning risk of bias judgements according to the risk of bias tool version 2

For judgement of risk of bias, we followed the concept of the Cochrane Risk of Bias tool 2.(Sterne et al. 2019 and Higgins et al. 2019)

This tool provides a framework for evaluating potential risks of bias in five different domains and provides guidance by signaling questions. However, there are not always clear rules and specific situations found in the analyzed trials may deviate from the ideal case. Thus, judgement is needed to make decisions and these specific judgements and decisions made by the authors of the review are made explicit below.

Domain 1: RANDOMIZATION PROCESS



Algorithm for suggested judgement of risk of bias arising from the randomization process

1.1 Was the allocation sequence random?

In principle, if there was no information about the exact methods (e.g. only stated “randomized”), we stated “not indicated”. For trials investigating second-generation-antipsychotic drugs that were sponsored by pharmaceutical companies, we assume that the sequence generation for randomization was appropriate, even when it is only stated “randomized”, and we stated “probably yes”. The reason is that we contacted many pharmaceutical companies in the past and all reported use of appropriate methods in these modern studies, even when it was not clearly stated in the primary publications.

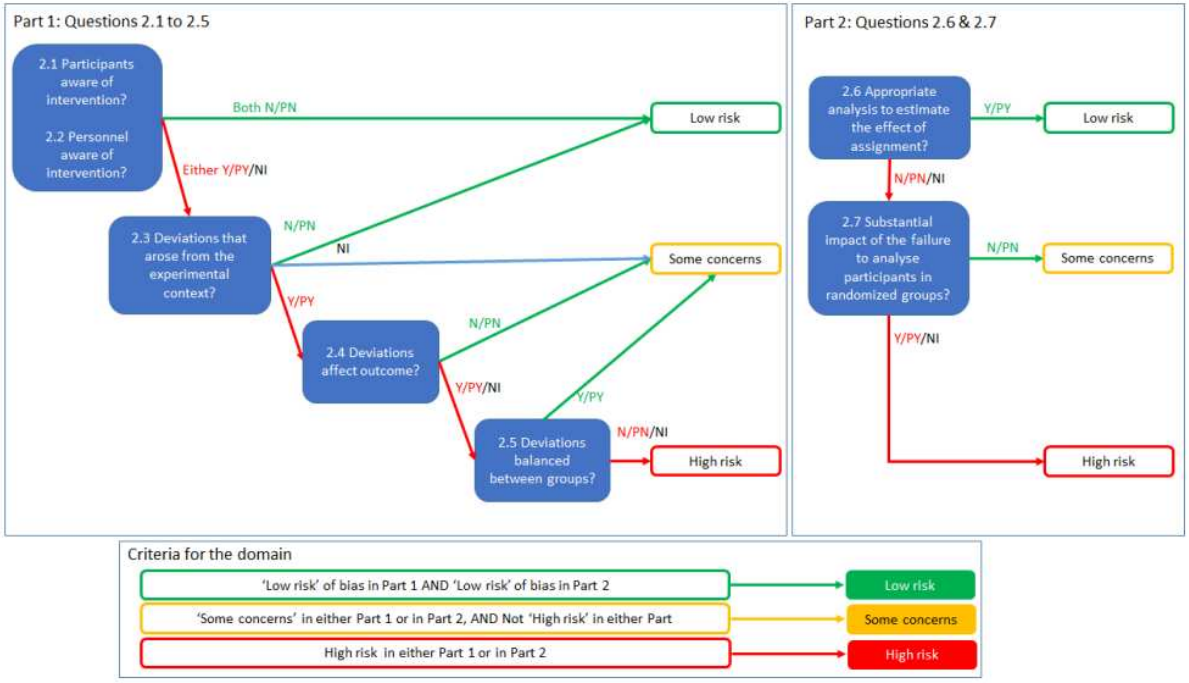
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?

Similar to 1.1.

1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?

No specific comments

Domain 2: DEVIATIONS FROM INTENDED INTERVENTIONS



Algorithm for suggested judgement of risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Part 1:

2.1 Were participants aware of their assigned intervention during the trial?

If only stated “double-blind” without further information about the methods, a judgement is needed. We decided to assume that the method of blinding was appropriate and to state “probably no”, as in studies of antipsychotic drugs blinding can be rather easily achieved by encapsulating drugs with identical capsules.

In placebo-controlled trials, following the suggestion of the RoB2-guidance document, (Sterne et al. 2019) we assumed unblinding due to side effects. In head-to-head trials of antipsychotics, we did not make this assumption, because the different antipsychotics still have some similarities (overlapping receptor-binding-profiles). Consequently, differences in side-effects are more difficult to evaluate for patients and personal which makes it more difficult to guess the assigned intervention.

2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?

Similar to 2.1.

2.3 If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?

This question is only relevant for unblinded studies (open, single-blind or placebo-controlled (unblinded due to side effects) trials).

Typically protocol deviations are not reported in detail, which leads to a judgement of “some concerns”.

Although protocol deviations due to the experimental context cannot be excluded, we do not deem that substantial protocol deviations (that potentially affect the outcome, see questions below), happen frequently. Thus, we do not expect important bias from deviations of the outcome and a judgement of “some concerns” seems fair or even too punitive.

2.4. Were these deviations likely to have affected the outcome?

No specific comments

2.5. Were these deviations from intended intervention balanced between groups?

No specific comments

Part 2:

2.6. Was an appropriate analysis used to estimate the effect of assignment to intervention?

We considered completer analyses as inappropriate because from such analyses patients are excluded post-randomization due to toxicity or lack of efficacy.

2.7. Was there potential for a substantial impact (on the results) of the failure to analyse participants in the group to which they were randomized?

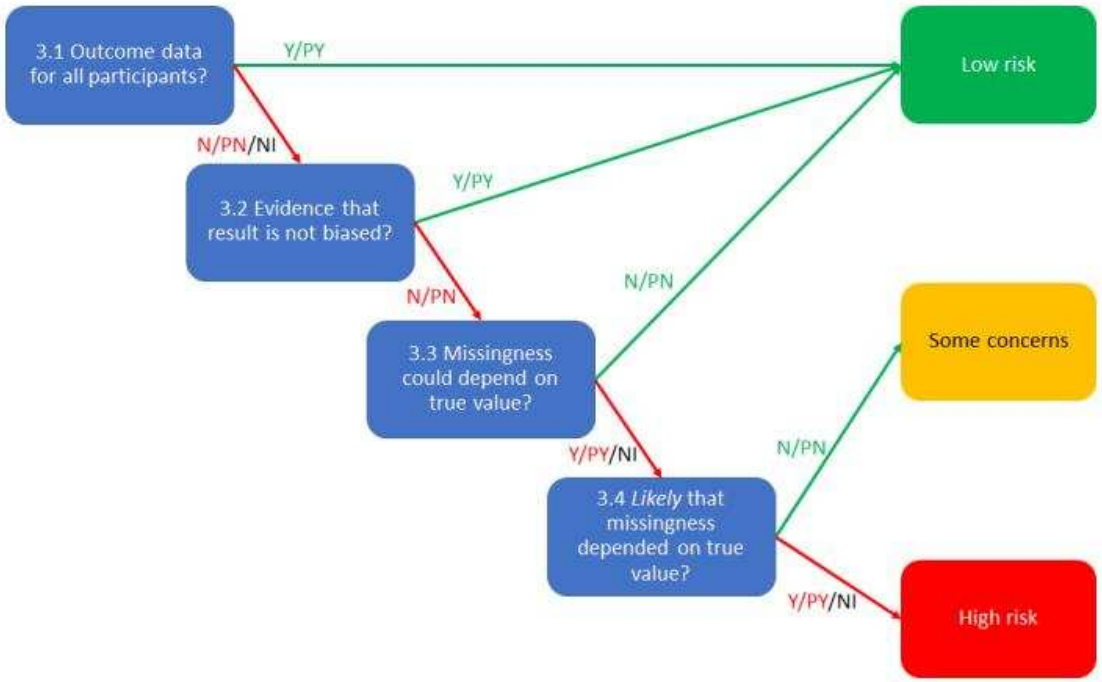
According to the guidance, authors need to decide about when exclusion of patients post-randomization could have a substantial impact on the results.

We considered completer analyses at “some concerns” when the total number of patients with premature study discontinuation was at maximum 20% of the number randomized.

We considered completer analyses at “high risk” when more than 20% of the patients randomized discontinued prematurely.

The decision for this threshold was informed by the work of Xia et al.(Xia et al. 2009)

Domain 3: MISSING OUTCOME DATA



Algorithm for suggested judgement of risk of bias due to missing outcome data

3.1 Were data for this outcome available for all, or nearly all, participants randomized?

We used the threshold of 5% (study discontinuation rate at maximum 5% of number of patients randomized) mentioned in the RoB2-guidance-document.

For the outcome “relapse” which we analyzed here, this threshold was applied to the number of participants who discontinued for reasons other than relapse.

3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?

We conducted a sensitivity analysis as suggested by the RoB2-guidance-document using plausible assumptions (i.e. patients who discontinued due to inefficacy were assumed to have a relapse; patients who discontinued for reasons other than inefficacy were assumed to have the same relapse rate as observed in the trial (after counting discontinuation due to inefficacy as relapse)). We considered a result as at low risk of bias, when the result of the sensitivity analyses did not differ more than by a factor of 0.8/1.25 from the observed result (i.e. as an example, it is considered acceptable, when in the sensitivity 23 instead of 20 relapses were assumed to happen in a study group of 100 patients (and the event-rate in the other group did not change)).

3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?

If no reasons for study discontinuation are reported, then “probably yes”, because in studies of antipsychotics in schizophrenia, discontinuation due to lack of efficacy (potentially related to relapse) are likely.

Also, for many reported reasons, doubts remain whether the reason is related to efficacy.

Moreover, it needs to be noted that in our aggregate data (where events are usually reported from all patients randomized) also patients that discontinued due to reasons unrelated to the outcome can affect the result. This is because patients who discontinued prematurely are not at risk for the event anymore.

Thus, all studies with rates of premature study discontinuation above the threshold mentioned in 3.1 need further evaluation.

3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?

As recommended in the RoB2-guidance-document, we investigated whether there were differences in the total number of participants with premature study discontinuation (dropouts) and in the number of participants with premature study discontinuation for reasons related to the outcome. Thereby, we judged whether it is likely that missingness depended on the outcome and that missingness influenced the outcome substantially (high risk) or to some extend (some concerns).

For the outcome “relapse” analyzed here, we make use of the sensitivity analysis described in 3.2 which includes information about the total number of dropouts and the number of dropouts for related reasons, i.e. due to inefficacy. When the result of the sensitivity analysis differed less than by a factor of 0.67/1.50, but more then 0.8/1.25, from the observed result, then we judged the result at “some concerns”. When the result of the sensitivity analysis differed more than by a factor of 0.67/1.50, we judged the result at “high risk” (i.e. as an example, when in a sensitivity analysis more than 27 instead of 20 relapses were assumed in a study group of 100 participants (and the result of the other group did not change)).

When sensitivity analyses investigating the potential impact of missing data on the results were not possible (because information on study discontinuations was not clear enough), we judged the mechanism of missingness and its potential impact on the result according to the following algorithm:

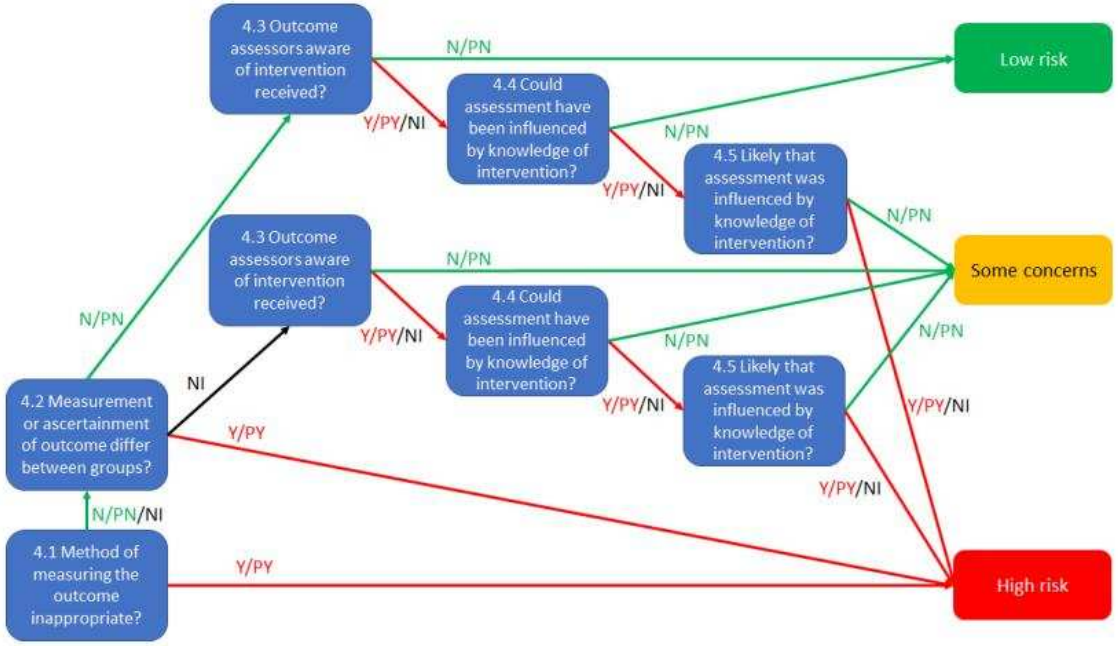
When the rate of study discontinuation for reasons other than relapse was ≤ 20% (in each arm of a comparison), we judged at some concerns. This threshold was informed by the work of Sacket et al.(Sackett 1998) and Xia et al.(Xia et al. 2009). Otherwise proceed.

When the rate ratio of study discontinuation for reasons other than relapse (between two groups compared in a trial) is <0.5/ >2 (half/double), we judged at high risk. Otherwise proceed.

When the rate of study discontinuation due to related reasons (i.e. due to inefficacy) was ≤ 20% (in each arm of a comparison), we judged at some concerns. Otherwise proceed.

When the rate of study discontinuation due to related reasons (between two groups compared in a trial) is <0.5/ >2 (half/double), we judged at high risk of bias, when ≥0.5/ ≤2, we judge at some concerns.)

Domain 4: MEASUREMENT OF THE OUTCOME



Algorithm for suggested judgement of risk of bias in measurement of the outcome

4.1. Was the method of measuring the outcome inappropriate?

No specific comments

4.2. Could measurement or ascertainment of the outcome have differed between intervention groups?

No specific comments

4.3. Were outcome assessors aware of the intervention received by study participants?

In head-to-head studies of antipsychotic drugs, when only reported that the study was double-blind, we assumed that blinding was appropriate and stated probably yes (similar to 2.1.).

In open trials or double-blind placebo-controlled trials (with potential unblinding of study personal, see 2.1.) we checked if there were particular methods to blind the outcome assessors. If such particular methods were not explicitly described, we assumed that the outcomes were assessed by study personal and answered “probably yes”.

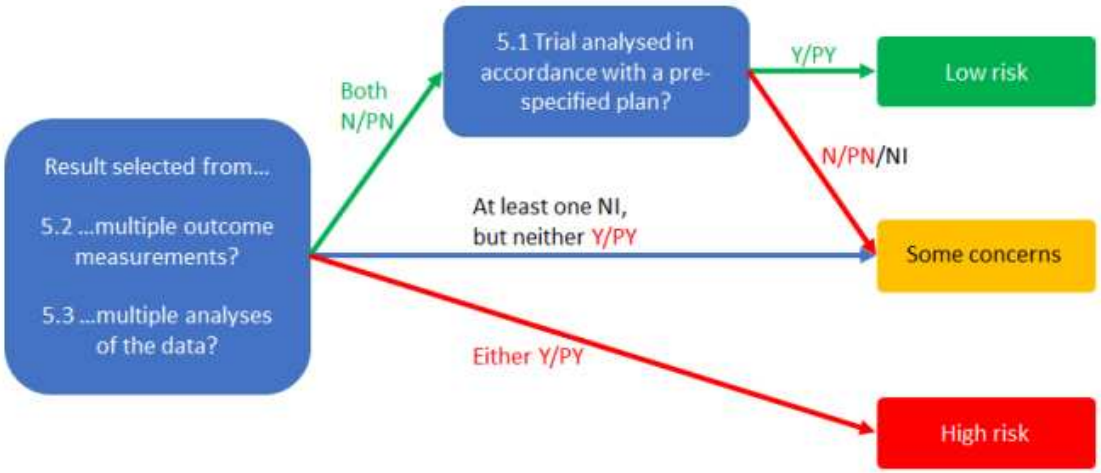
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?

We considered the outcome “relapse” as potentially influenced by knowledge of the intervention received.

4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?

In general, we considered the influence of knowledge of intervention received as minor, resulting in a judgement of some concerns.

Domain 5: SELECTION OF THE REPORTED RESULTS



Algorithm for suggested judgement of risk of bias in selection of the reported result

5.1. Were the data that produced this result analysed in accordance with a pre-specified analysis plan that as finalized before unblinded outcome data were available for analysis?

Typically, the analysis plan was not available. In this case, we followed the recommendations of the Cochrane handbook(Higgins 2020) and compared the reported results with the reported methods section and with the outcomes that are expected for such trials as informed by other trial.

Is the numerical result being assessed likely to have been selected, on the basis of the results, from...

5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?

No specific comments

5.3 ... multiple eligible analyses of the data?

No specific comments

Overall risk of bias:

Overall risk-of-bias judgement	Criteria
Low risk of bias	The study is judged to be at **low risk of bias for all domains** for this result.
Some concerns	The study is judged to raise **some concerns** in at least one domain for this result, but not to be at high risk of bias for any domain.
High risk of bias	The study is judged to be at **high risk of bias** in at least one domain for this result. Or The study is judged to have **some concerns** for **multiple domains** in a way that substantially lowers confidence in the result.

For multi-arm-studies (i.e. with several comparisons), for each domain, we used the average of the different comparisons, for the rating of the study. In case of intermediate averages between two categories (e.g. between “high risk” and “some concerns”), we conservatively used the more severe rating (here “high risk”).

We judged a study at overall high risk of bias when at least 1 domain was rated at “high risk” or when 4 or more domains were rated as “some concerns”.

References

1. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng HY, Corbett MS, Eldridge SM, Emberson JR, Hernán MA, Hopewell S, Hróbjartsson A, Junqueira DR, Jüni P, Kirkham JJ, Lasserson T, Li T, McAleenan A, Reeves BC, Shepperd S, Shrier I, Stewart LA, Tilling K, White IR, Whiting PF, Higgins JPT. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019 Aug 28;366:l4898. doi: 10.1136/bmj.l4898. PMID: 31462531.

2. Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, Welch VAe: Cochrane Handbook for Systematic Reviews of Interventions version 6.1 (updated September 2020). Cochrane; 2019

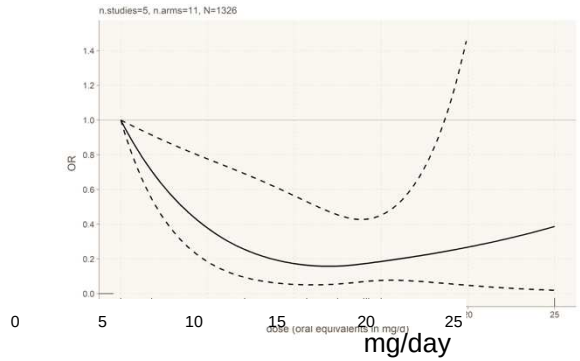
3. Jun Xia, Clive Adams, Nishant Bhagat, Vinaya Bhagat, Paranthaman Bhoopathi, Hany El-Sayeh, Vanessa Pinfold and Yahya Takriti. Losing participants before the trial ends erodes credibility of Findings Psychiatric Bulletin 2009, 33:254-257.

4. Sackett, David L. (1998): Evidence-based medicine. How to practice and teach EBM. 7. print. N.Y.: Churchill Livingstone.

eAppendix 4. Individual drugs and Additional sensitivity/subgroup analyses

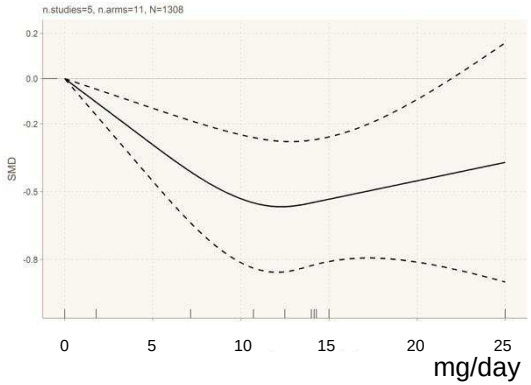
Aripiprazole oral and long-acting injectable pooled

Relapse
(5 studies, 11 dose arms)



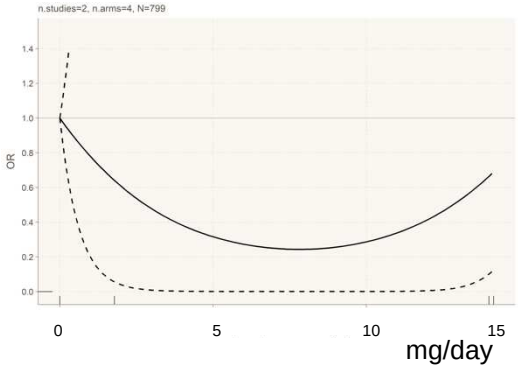
Available studies: Pigott 2003, McEvoy 2007b_extension, Kane 2012, Fleischhacker 2014, Mallikaarjun 2013)

Overall symptoms
(5 studies, 11 dose arms)



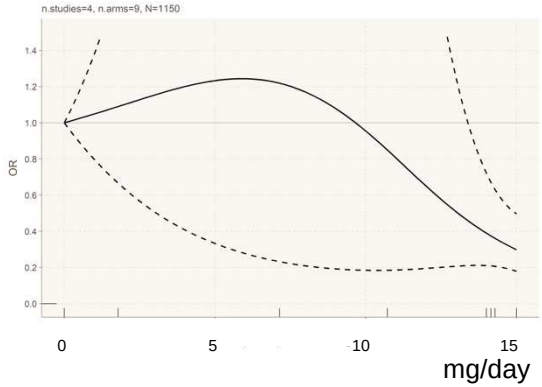
Available studies: Pigott 2003, McEvoy 2007b_extension, Kane 2012, Fleischhacker 2014, Mallikaarjun 2013

Rehospitalisation
(2 studies, 4 dose arms)



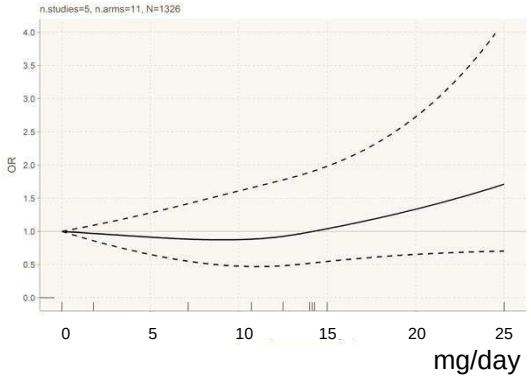
Available studies: Kane 2012, Fleischhacker 2014

All cause discontinuation (4 studies, 9 dose arms)



Available studies: Pigott 2003, Kane 2012, Fleischhacker 2014, Mallikaarjun 2013

Dropouts due to side-effects (5 studies, 11 dose arms)



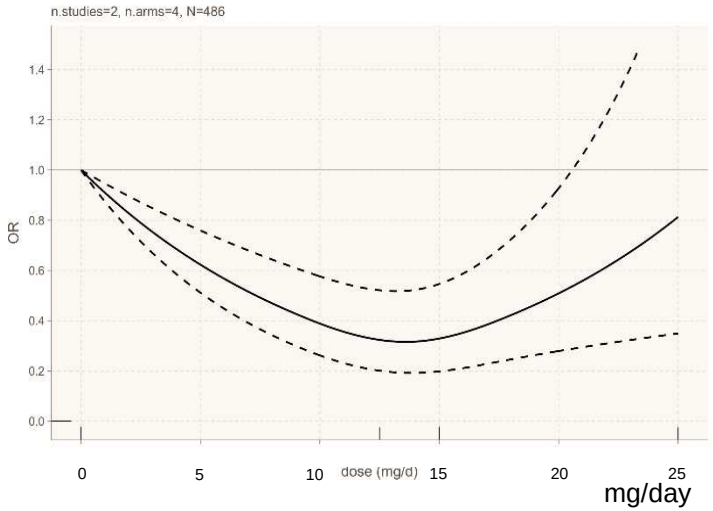
Available studies: Pigott 2003, McEvoy 2007b_extension, Kane 2012, Fleischhacker 2014, Mallikaarjun 2013)

Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference

Aripiprazole oral separately

2 studies, 4 dose arms

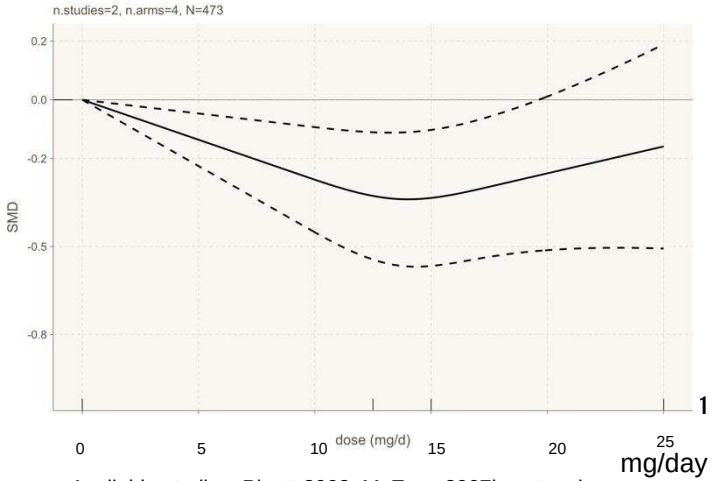
Relapse



Available studies: Pigott 2003, McEvoy 2007b_extension

2 studies, 4 dose arms

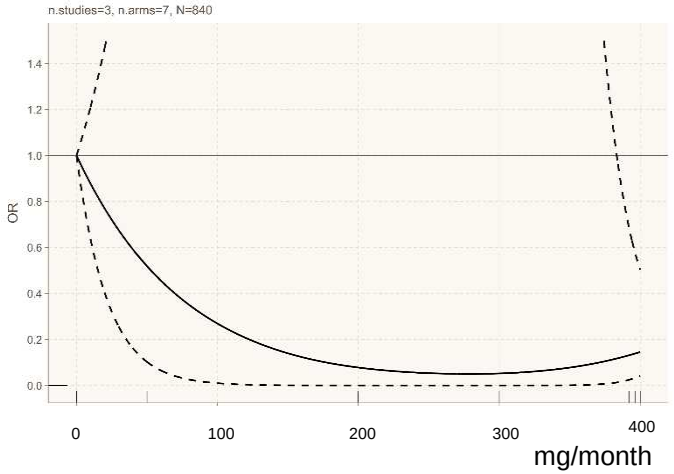
Overall symptoms



Available studies: Pigott 2003, McEvoy 2007b_extension

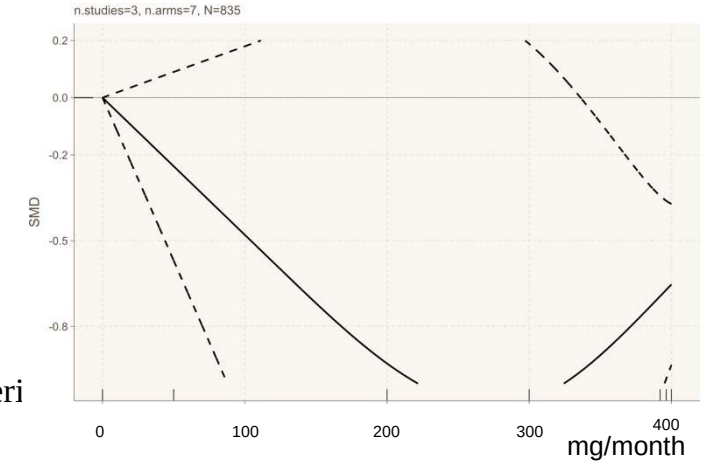
Aripiprazole LAI separately

3 studies, 7 dose arms



Available studies: Kane 2012, Fleischhacker 2014, Mallikaarjun 2013

3 studies, 7 dose arms



Available studies: Kane 2012, Fleischhacker 2014, Mallikaarjun 2013)

Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference, LAI = long-acting injectable

Description of the aripiprazole results

First slide, oral and long-acting injectable pooled

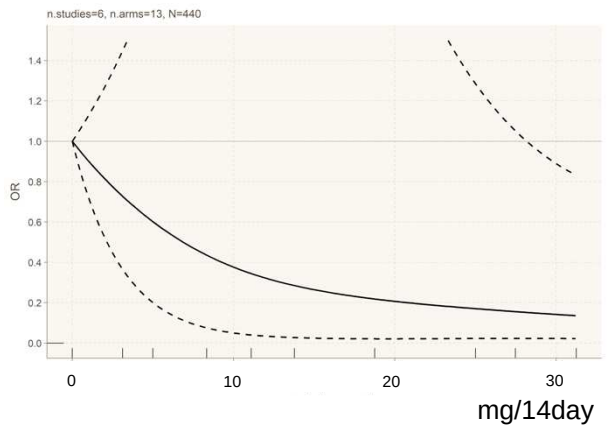
Five studies with 11 individual dose arms were available, two on oral aripiprazole (Pigott 2003, McEvoy 2007b_extension), three on aripiprazole long-acting injectable (LAI), all of which used the “maintena” formulation originally developed by Otsuka and BristolMyersSquibb (Kane 2012, Fleischhacker 2014, Mallikaarjun 2013). Long-acting injectable doses were converted to daily doses. The dose response curve was flat at approximately 12.5mg/day for relapse (5 studies) and overall symptoms (5 studies). For rehospitalisation it flattened earlier, but this result was based on only 2 studies. 12.5mg/day is similar to the near-to-maximum dose found for acute treatment (Leucht S, Crippa A, Siafis S, Patel MX, Orsini N, Davis JM. Dose-Response Meta-Analysis of Antipsychotic Drugs for Acute Schizophrenia. Am J Psychiatry. 2020 Apr 1;177(4):342-353). The all-cause discontinuation slope showed an initial increase (i.e. aripiprazole worse) and then a decrease (i.e. aripiprazole better). This is plausible in the sense that most dropouts are due to inefficacy.

Second slide, oral and long-acting injectable separately

The second aripiprazole slide shows that the results for were similar when aripiprazole oral (plateau ~12.5mg/day) and aripiprazole LAI (plateau ~ 270mg monthly ≙ 10mg/day were analysed separately. Only relapse and overall symptoms were analyzed, because data on other outcomes were scarce.

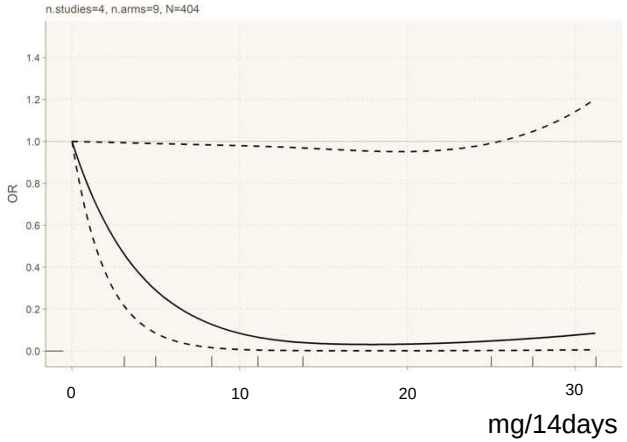
Fluphenazine long-acting injectable

Relapse
(6 studies, 13 dose arms)



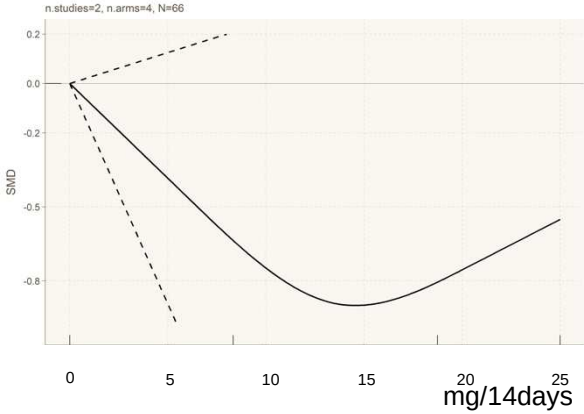
Available studies: Carpenter 1999, Dotti 1979, Kane 1979, Kane 1983, Marder 1984, Schooler 1993

Rehospitalisation
(4 studies, 9 dose arms)



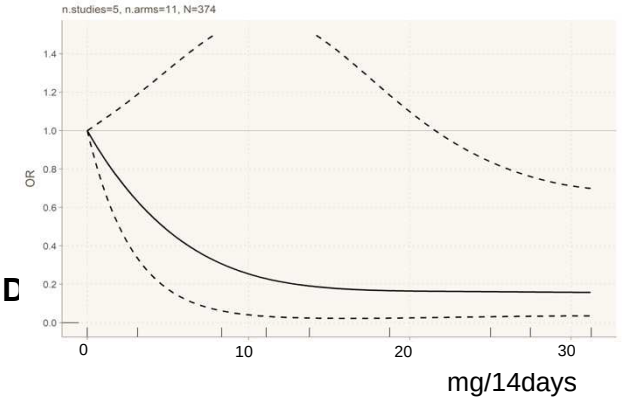
Available studies: Carpenter 1999, Kane 1983, Marder 1984, Schooler 1993

Overall symptoms
(2 studies, 4 dose arms)



Available studies: Carpenter 1999, Dotti 1979

All cause discontinuation (5 studies, 11 dose arms)



Available studies: Carpenter 1999, Dotti 1979, Kane 1979, Kane 1983, Schooler 1993

Dropouts due to side-effects
(no study)

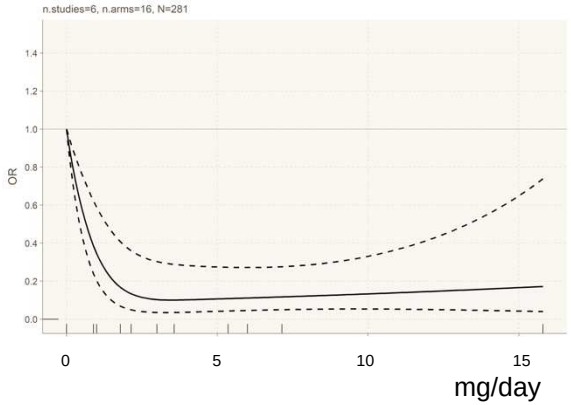
D ng injectable results

Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference

Six studies with 13 individual dose arms were available (Carpenter 1999, Dotti 1979, Kane 1979, Kane 1983, Marder 1984, Schooler 1993), all using long-acting injectable formulations which were converted to biweekly doses. The dose-response curve for relapse does not show a clear plateau. However, the dose-response curves for rehospitalization and all-cause discontinuation were essentially flat at 15mg biweekly. The curve for overall symptoms is difficult to interpret, because only 2 studies reported this outcome and confidence intervals were extremely wide, but it also suggests that 15mg/biweekly is the plateau dose. No study provided data on dropouts due to adverse events/side-effects.

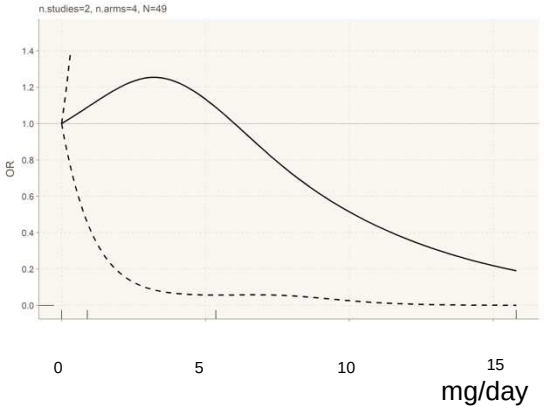
Haloperidol oral and long-acting injectable pooled

Relapse (6 studies, 16 arms)



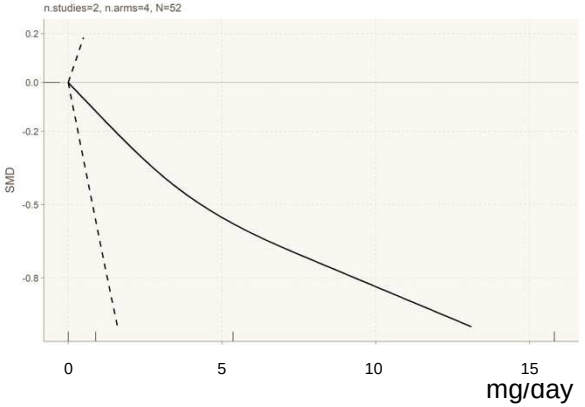
Available studies: Beasley 1996_extension, Eklund 1991, Huttunen 1996, Kane 2002, Nishikawa 1982, Nishikawa 1984

Rehospitalisation (2 studies, 4 arms)



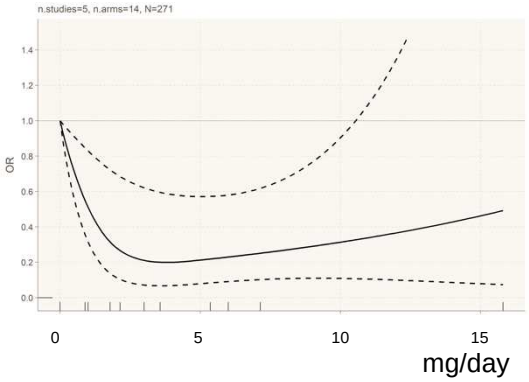
Available studies: Beasley 1996_extension, Huttunen 1996

Overall symptoms (2 studies, 4 arms)



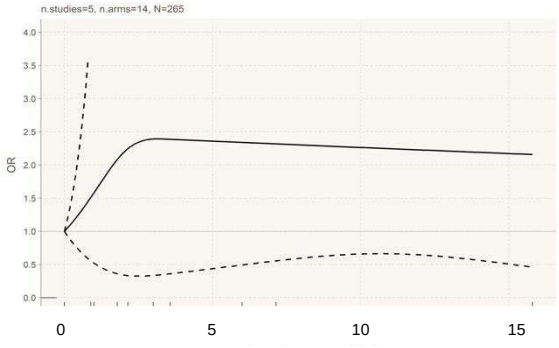
Available studies: Beasley 1996_extension, Huttunen 1996

All cause discontinuation (5 studies, 14 arms)



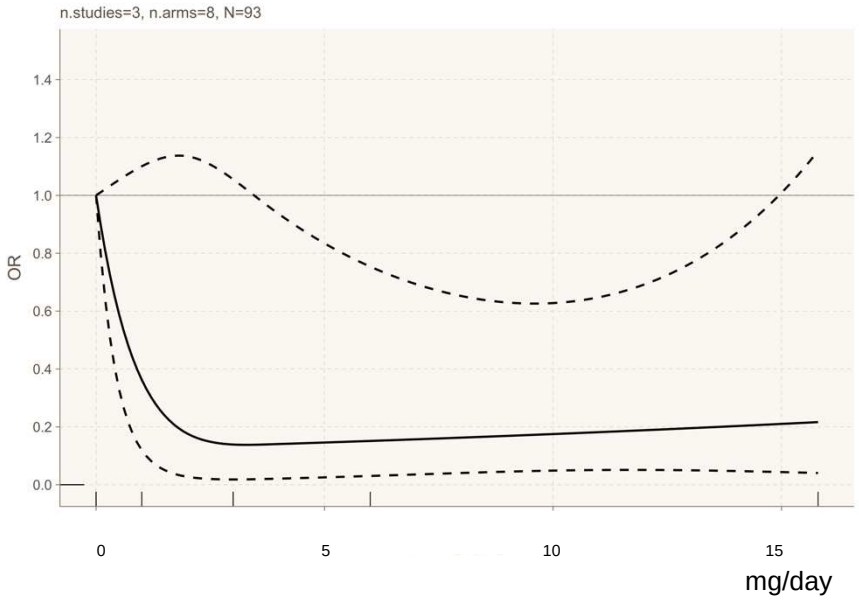
Available studies: Beasley 1996_extension, Eklund 1991, Huttunen 1996, Kane 2002, Nishikawa 1984

Dropouts due to side-effects (5 studies, 14 arms)



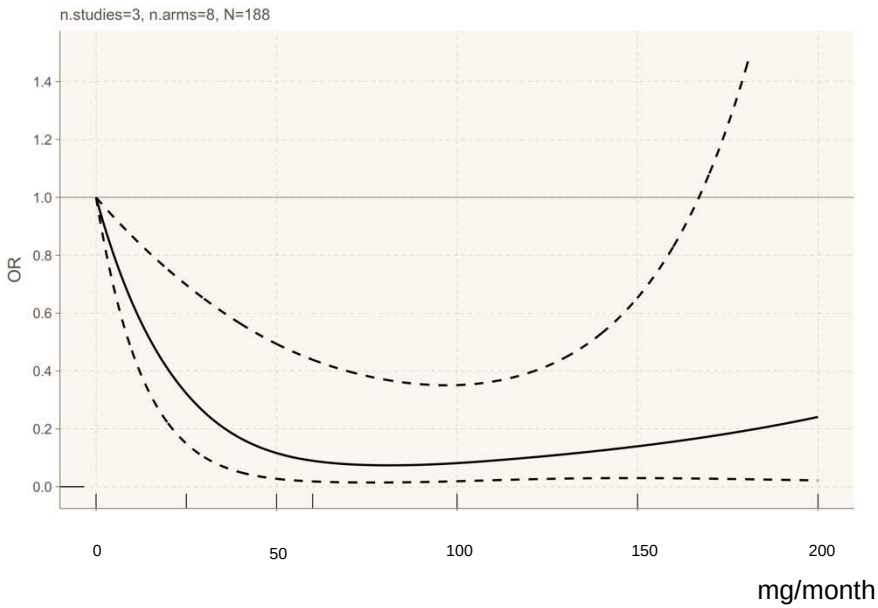
Available studies: Beasley 1996_extension, Eklund 1991, Kane 2002, Nishikawa 1982, Nishikawa 1984

Relapse - haloperidol oral (3 studies, 8 arms)



Available studies: Beasley 1996_extension, Nishikawa 1982, Nishikawa 1984

Relapse - haloperidol long-acting injectable (3 studies, 8 arms)



Available studies: Eklund 1991, Huttunen 1996, Kane 2002

Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference.

Description of the haloperidol results

First slide, oral and long-acting injectable pooled

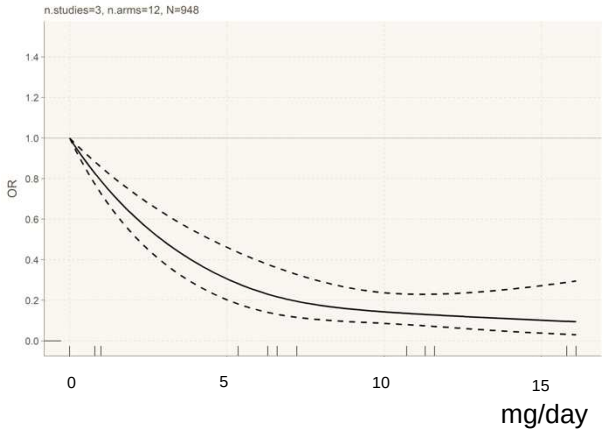
Six studies were available, three on long-acting injectable haloperidol (Kane 2002, Huttunen 1996, Eklund 1991) and three on oral haloperidol (Nishikawa 1982, Nishikawa 1984, Beasley 1996). Long-acting injectable doses were converted to daily doses. The dose-response curves for relapse and all-cause discontinuation plateauted at approximately 3mg/day for relapse, but slightly increased thereafter for all-cause discontinuation. For overall efficacy and rehospitalisation only 2 studies were available making the data uninterpretable. Dropouts due to adverse events were higher in the haloperidol groups than in the placebo groups already at low doses and plateatued at approximately 3mg/day. The large confidence intervals needs to be considered.

Second slide, oral and long-acting injectable separately

Separate analyses of oral (plateau ~ 3mg/day) and long-acting injectable formulations (plateau ~75mg monthly ≙ 2.7mg/day) on the second haloperidol slide showed consistent results. We only analysed relapse, because for the other efficacy outcomes overall symptoms and rehospitalisation only two studies were available

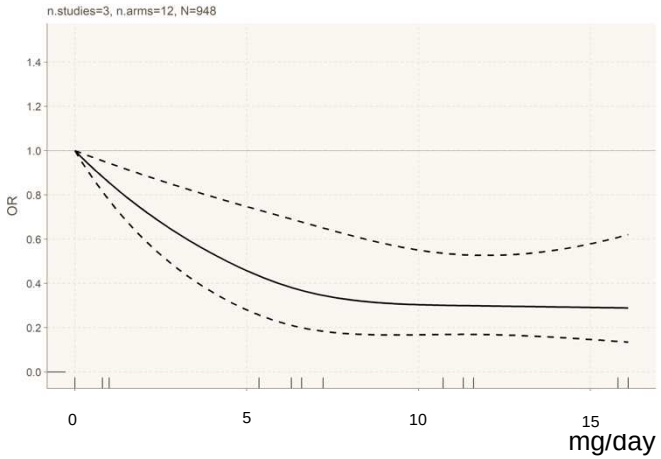
Olanzapine – oral and long-acting injectable pooled

Relapse (3 studies, 12 dose arms)



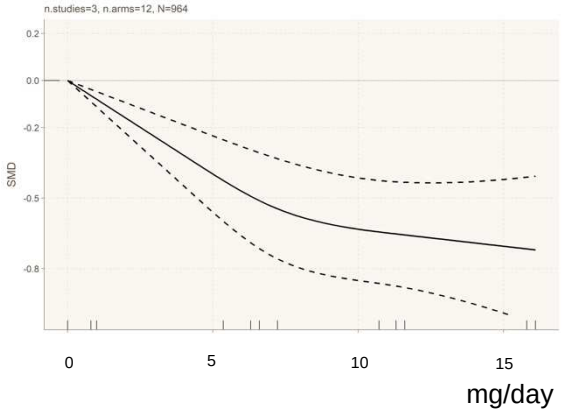
Available studies: Kane 2010, Beasley 1996, Beasley 1997

Rehospitalisation (3 studies, 12 dose arms)



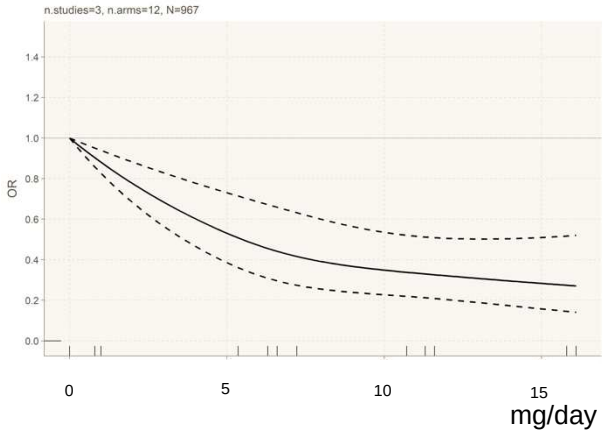
Available studies: Kane 2010, Beasley 1996, Beasley 1997

Overall symptoms (3 studies, 12 dose arms)

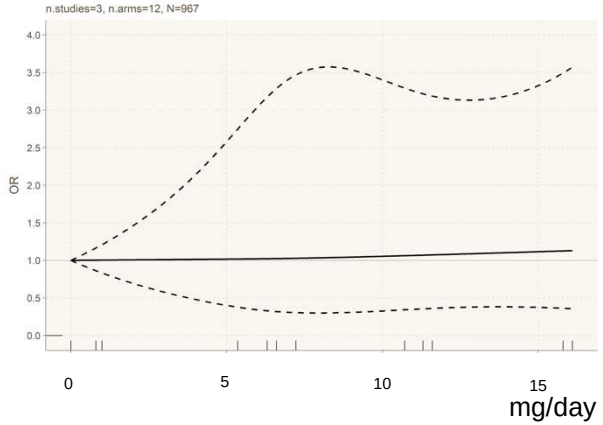


Available studies: Kane 2010, Beasley 1996, Beasley 1997

All cause discontinuation (3 studies, 12 dose arms)



Dropouts due to side-effects (3 studies, 12 dose arms)



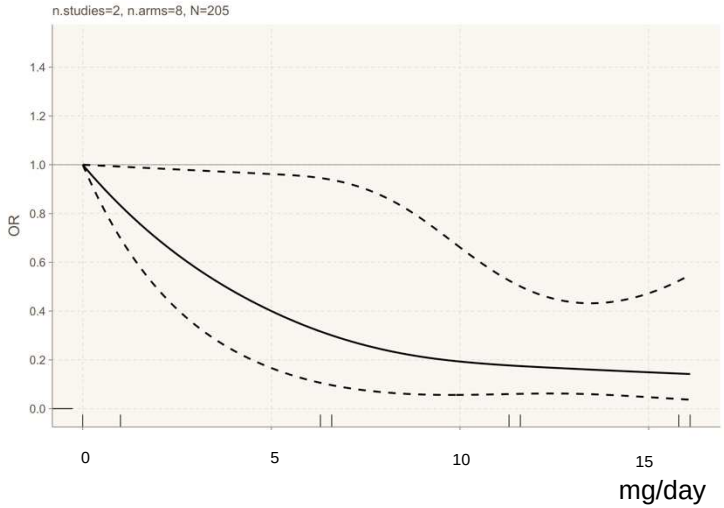
Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference

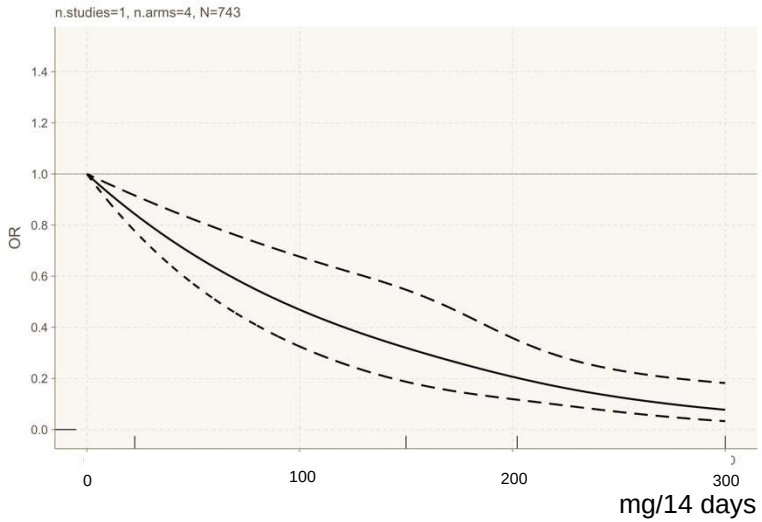
Olanzapine – oral and long-acting injectable studies separately

Oral (2 studies, Beasley 1996, 1997)

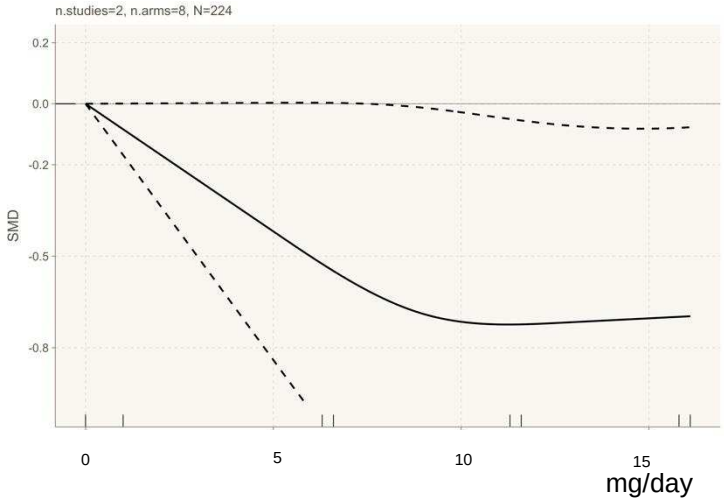
Long-acting injectable (1 study, Kane 2010)

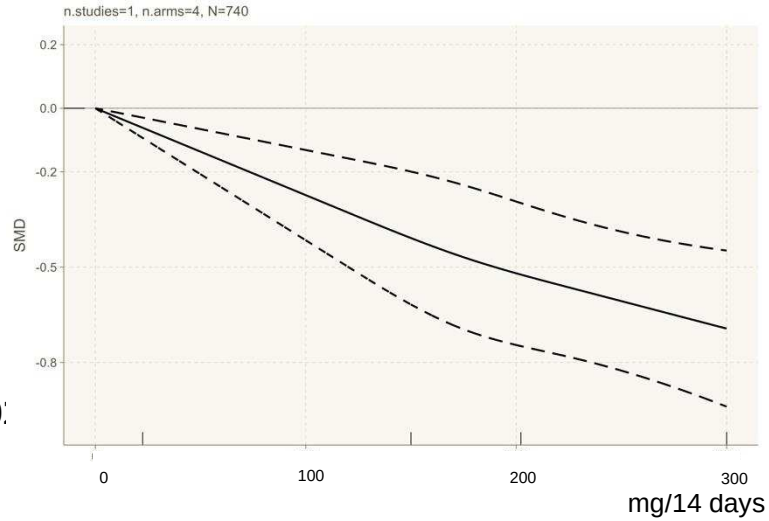
Relapse





Overall symptoms





Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference

Description of the olanzapine results: Three studies with 12 individual dose arms were available, one on olanzapine long-acting injectable (Kane 2010) and two on oral olanzapine (Beasley 1996 and Beasley 1997). The dose response curve for relapse, rehospitalisation and overall symptpoms and all-cause discontinuation seemed to be flat at around 10mg/day, although they still go slightly down up to the maximum examined dose of 20mg/day, in particular for overall symptoms.

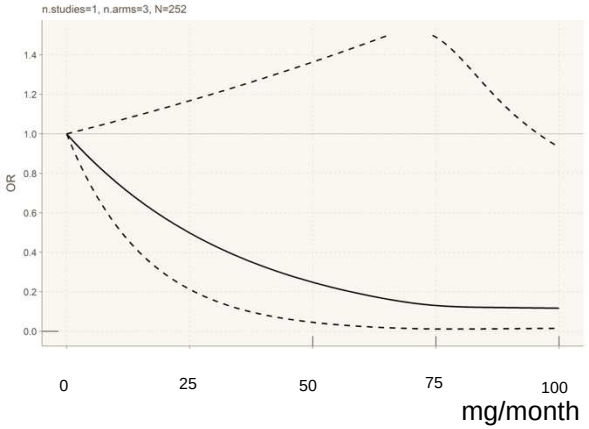
A possible explanation for this phenomenon is that **the two oral studies were "continuation"** studies. This means that acute phase responders (here defined as at least 40% PANSS/BPRS reduction from baseline and outpatient at week 6) were followed up without an additional randomisation. In these studies the efficacy curves flattened at approximately 10mg/day. However, this design has a potential bias in favour of placebo / 1mg/day olanzapine, because it may "corrupt" randomization. Probably only special patients may have shown such a strong response in the acute phase. Thus, the patients in the placebo / 1 mg olanzapine group may differ from those in the other groups.

In contrast, the study **on long-acting injectable olanzapine** by Kane et al. 2010 patients who were stabilized on oral olanzapine were randomized to the various long-acting injectable doses. This study showed no clear efficacy plateau at the highest dose of 300mg biweekly which approximately corresponds to 20mg per day.

The results for oral and long-acting injectable separately are shown on the next page (the results for rehospitalization were similar and can be sent upon request).

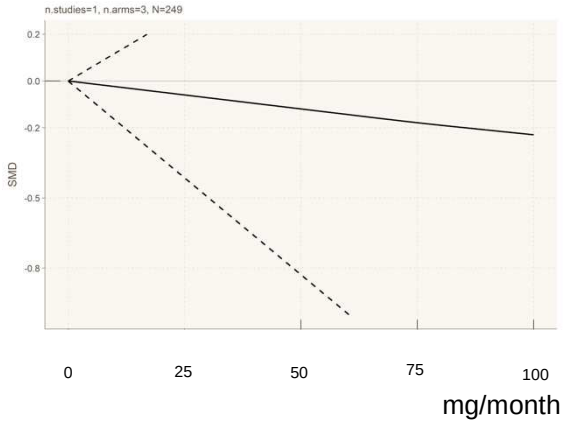
Paliperidone long-acting injectable

Relapse (1 study, 3 dose arms)



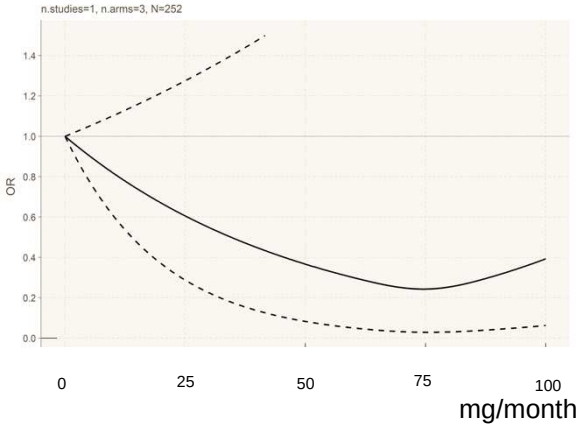
Available studies: Hough 2009

Overall symptoms (1 study, 3 dose arms)



Hough 2009

All cause discontinuation (1 study, 3 dose arms)



Hough 2009

Rehospitalisation (no study)

Dropouts due to adverse events (no study)

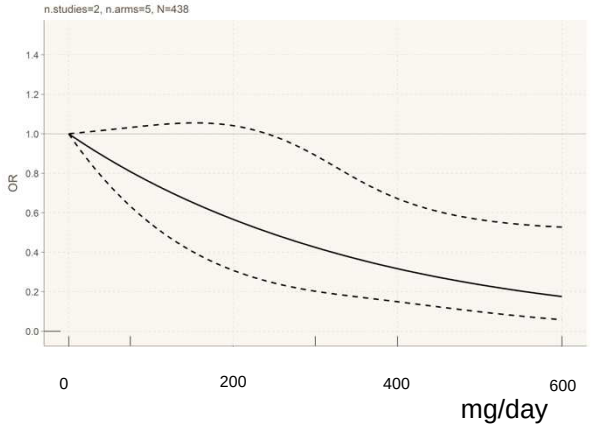
Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference

Description of the paliperidone long-acting injectable results

One study with three dose arms was available (Hough 2009). The curves for relapse, and all-cause discontinuation flattened at approximately 75mg/four weekly, while the overall symptom curves shows a gradually increasing efficacy up to the maximum examined dose of 100mg/month. **The data are uninterpretable for clinical practice, because the maximum licensed dose of 150mg/month was not included in the single study available.** Moreover, the enormous uncertainty due to the paucity of data expressed by very wide confidence intervals must be considered.

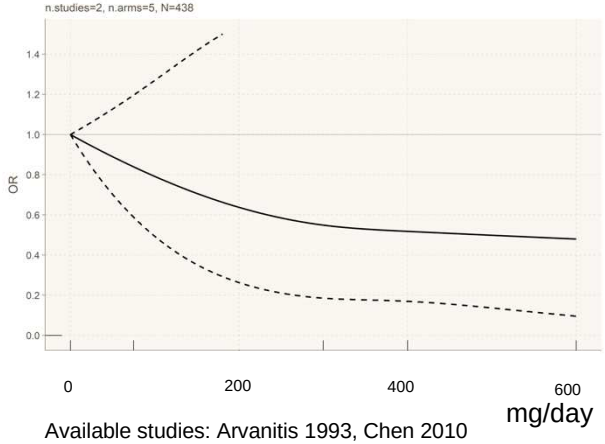
Quetiapine immediate release

Relapse
(2 studies, 5 dose arms)



Available studies: Arvanitis 1993, Chen 2010

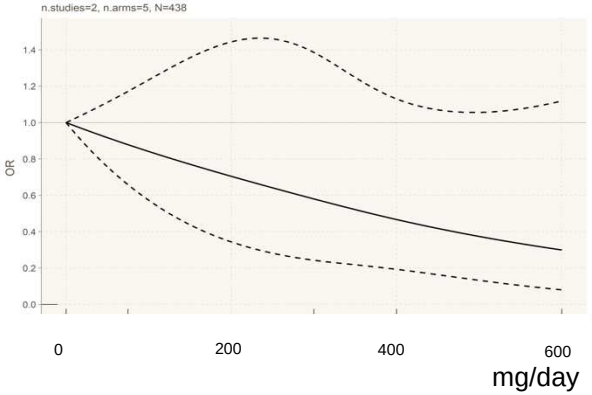
Rehospitalisation
(2 studies, 5 dose arms)



Available studies: Arvanitis 1993, Chen 2010

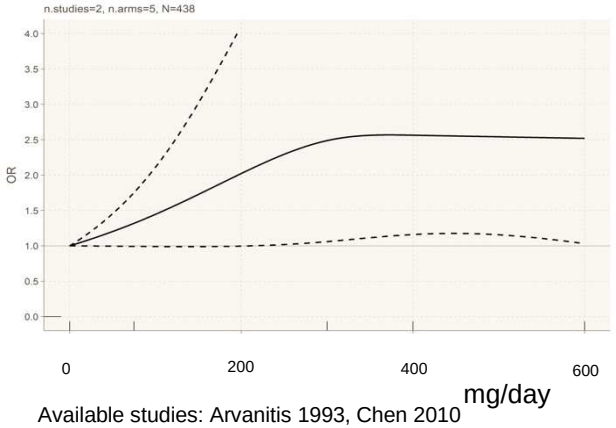
Overall symptoms
(0 studies)

All cause discontinuation (2 studies, 5 dose arms)



Available studies: Arvanitis 1993, Chen 2010

Dropouts due to side-effects (2 studies, 5 dose arms)



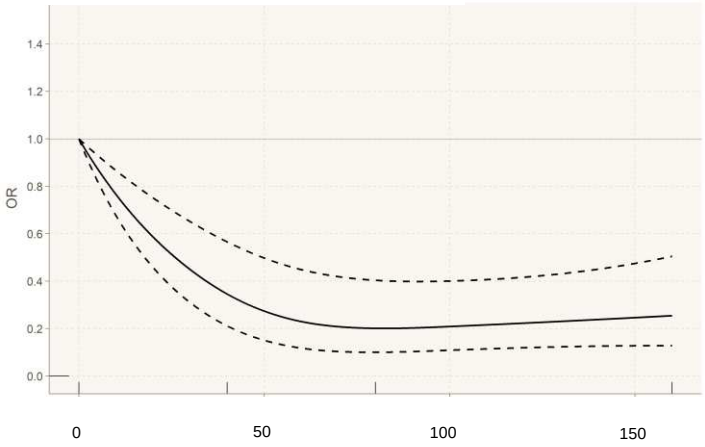
Available studies: Arvanitis 1993, Chen 2010

Description of the quetiapine results

Two quetiapine immediate release studies (Arvanitis 1993, an unpublished study for which we identified relapse data in a report sent to the FDA; and Chen 2010 which was a first-episode study) were included. They 75mg/day, 300mg/day, 400mg/day (Chen 2010), 600mg/day and placebo. They showed increasing effectiveness in terms of relapse prevention and all-cause discontinuation up to 600mg/day, the maximum dose tested. **It seems that a plateau was not yet reached**. The dose-response curve for rehospitalization remained stable from approximately 300mg/day upward. Data on overall efficacy were not available. Dropouts due to side-effects increased up to a dose of approximately 300mg/day. Data on quetiapine extended release were not available.

Ziprasidone

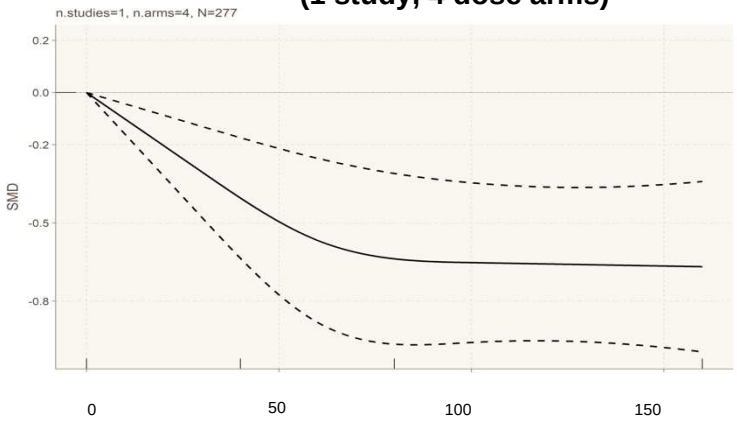
Relapse
(1 study, 4 dose arms)



Available studies: Arato 2002

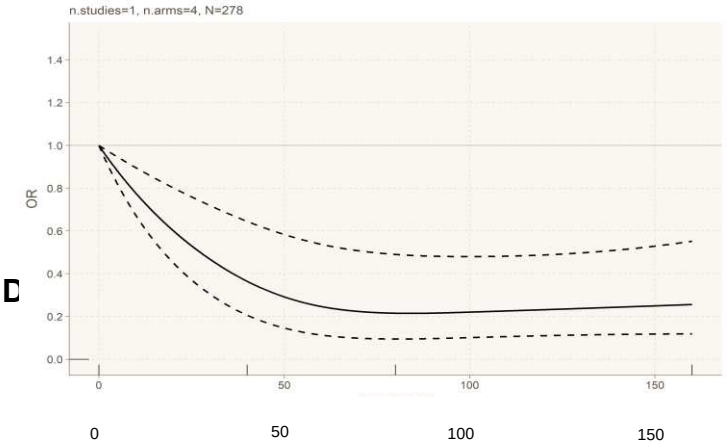
Rehospitalisation (no study)

Overall symptoms
(1 study, 4 dose arms)



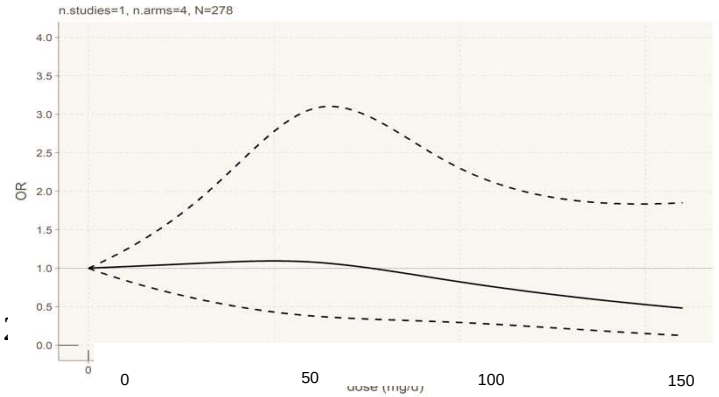
Available studies: Arato 2002

All cause discontinuation (1 study, 4 dose arms)



Available studies: Arato 2002

Dropouts due to side-effects
1 study, 4 dose arms



Available studies: Arato 2002

Footnote for all figures: The marks on the x-axis indicate the available dose arms. OR = odds ratio, SMD = standardized mean difference

One ziprasidone study with four individual dose arms (placebo, 40mg/day, 80mg/day and 160mg/day) was available (Arato 2002). A plateau was reached at approximately 75mg/day for relapse, overall symptoms and all-cause discontinuation. No data on rehospitalisation were available.

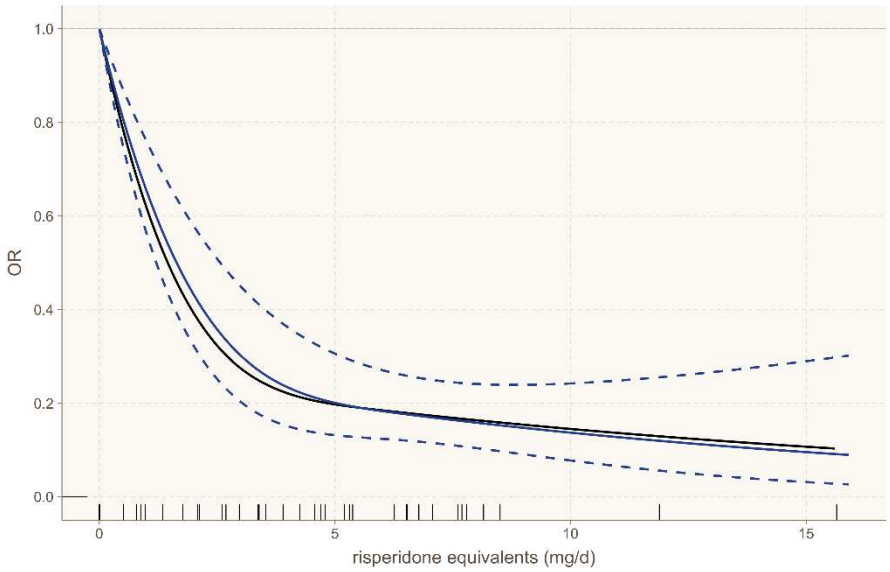
Risperidone long-acting injectable
Simpson 2006 compared two doses of risperidone consta, 50mg/14 days was somewhat more efficacious than 25mg/14 days. As dose-response meta-analysis requires at least 3 arms, such an analysis was not possible, but the study was included in the overall analyses across drugs.

Lurasidone
Tandon 2016 compared only a single lurasidone dose with placebo. Therefore, a separate dose-response meta-analysis was not possible for lurasidone. The study was, however, included in the overall analyses across drugs.

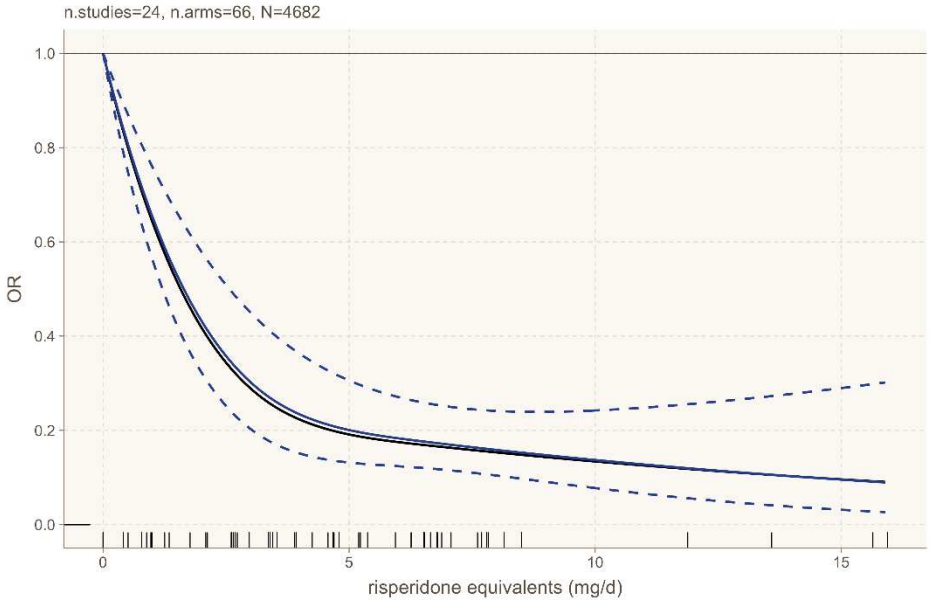
Zotepine
Cooper 2000 compared only a single zotepine dose with placebo. Therefore, a separate dose-response meta-analysis was not possible for zotepine. The study was, however, included in the overall analyses across drugs.

Additional sensitivity and subgroup analyses

Sensitivity analysis of the primary outcome relapse: Eight studies with high overall risk of bias excluded (Beasley 1997_Extension, Hough 2009, Kane 1983, Mallikaarjun 2013, Marder 1984, McEvoy 2007, Nishikawa 1984, Schooler 1993)



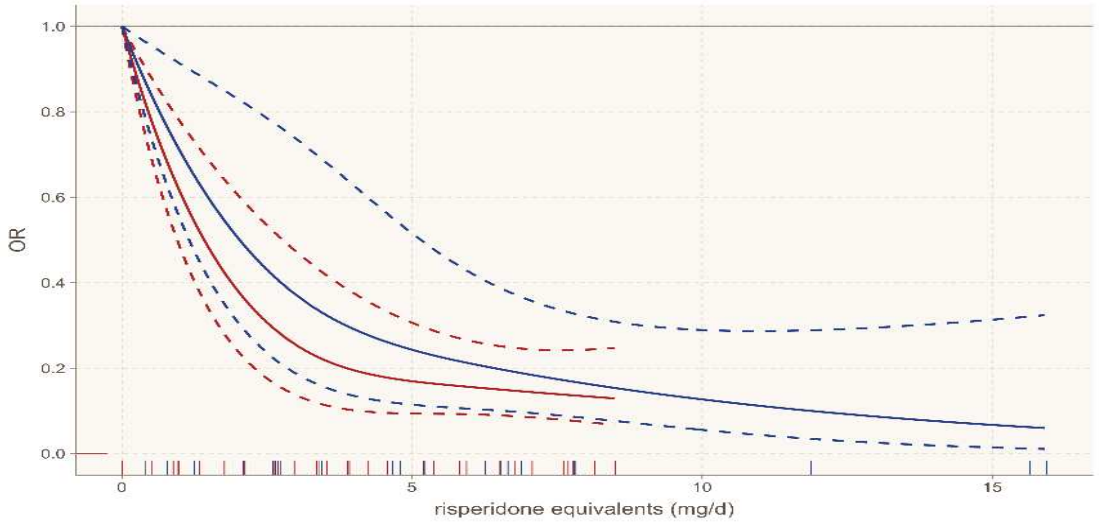
Sensitivity analysis of the primary outcome relapse: Two non double-blind studies excluded (Huttunen 1996, Mallikaarjun 2013)



The results of both sensitivity analyses were virtually identical with those of the primary analysis

Subgroup analysis of the outcome relapse: Median split of the mean age of the study population

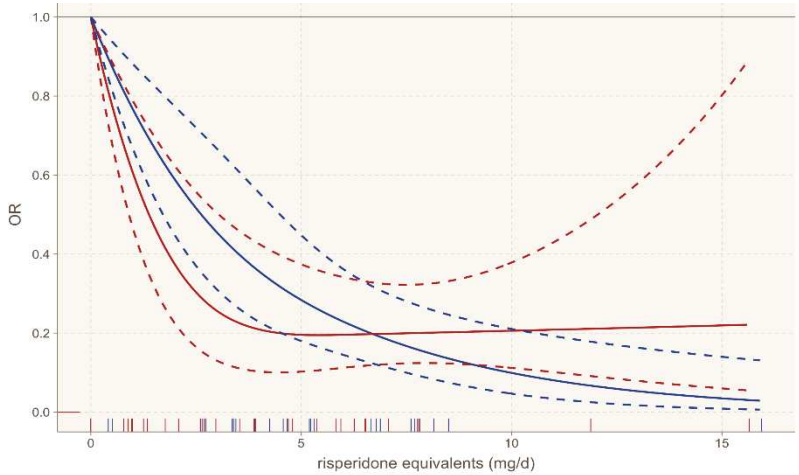
The post-hoc subgroup analysis dividing the studies in two groups according to the median mean age (38.5 years) is shown below. There was no clear difference between the groups. The older group (red) bulged only slightly earlier, the confidence intervals overlapped broadly and the shape of the curves was similar. One reason may be that the median age in both groups was not very different (≥ median age group: median 41.6 years, <median age group: 35.3 years)



Mean age: median 38.5 years interquartile range (35.5;42.0)
Red: mean age ≥ median: 13 studies,36 arms, 3365 particiants
Median mean age 41.6 IQR (39.5;43.6)
Studies: Arato 2002, Cooper 2000b, Eklund 1991, Fleischhacker 2014, Hough 2009, Kane 2002b, Kane 2010c, Kane 2012, Mallikaarjun 2013, Nishikawa 1984, Pigott 2003, Simpson 2006, Tandon 2016
Blue: mean age < median: 10 studies, 29 arms, 1162 participants
Median age 35.4 IQR (29.6;35.8)
Studies: Arvanitis 1993, Beasley 1996b_Extension, Beasley 1997_Extension, Carpenter 1999, Chen 2010, Kane 1979, Kane 1983, Marder 1984, Nishikawa 1982, Schooler 1993

Subgroup analysis of the outcome relapse: Median split of the percentage men in the studies

The subgroup analysis dividing the studies in two groups according to the median of percentage male (67%) is shown below. The group with more men (red) bulged earlier (~3mg risperidone equ. per day). The result does not seem to be driven by age which was similar in both subgroups (38.2years versus 39 years). It is unexpected in the sense that one analysis suggested that women respond better than men in the acute phase[1]. We would therefore have expected that a lower dose might be sufficient for them. Moreover, two reviews did not find sex to be a predictor of relapse[2,3]. Moreover, this is a post-hoc analysis, the sample size is small, subgroup analyses are hypothesis generating only, and there maybe hidden moderators explaining this result.



Percentage men: median 67% Interquartile range (60%;80%)
Red: Percentage male ≥ median: 12 studies,36 arms, 1150 participants
Median percentage male 80% IQR (71%;88%)
Age: Median 38.2 years IQR (35.4; 41.6)
Studies: Arato 2002, Arvanitis 1993, Beasley 1996b_Extension, Carpenter 1999, Cooper 2000b, Dotti 1979, Kane 1979, Kane 2002b, Mallikaarjun 2013, Marder 1984, Nishikawa 1982, Nishikawa 1984
Blue: Percentage male < median: 12 studies, 31 arms, 3380 participants[3,13-23]
Median percentage male 60% IQR (58%;66%)
Age: Median 39.0 years IQR (35.8; 41.2)
Studies: Beasley 1997_Extension, Chen 2010, Fleischhacker 2014, Hough 2009, Huttunen 1996, Kane 1983, Kane 2010c, Kane 2012, Pigott 2003, Schooler 1993, Simpson 2006, Tandon 2016

References:
1. Rabinowitz J, Werbeloff N, Caers I, Mandel FS, Stauffer V, Ménard F, Kinon BJ, Kapur S. Determinants of antipsychotic response in schizophrenia: implications for practice and future clinical trials. J Clin Psychiatry. 2014 Apr;75(4):e308-16
2. Lecomte T, Potvin S, Samson C, et al. Predicting and preventing symptom onset and relapse in schizophrenia-A metareview of current empirical evidence. J Abnorm Psychol. 2019;128(8):840-854.
3. Alvarez-Jimenez M, Priede A, Hetrick SE, et al. Risk factors for relapse following treatment for first episode psychosis: a systematic review and meta-analysis of longitudinal studies.

eAppendix 5. Conversion to absolute rates, relative risks and PANSS units

Conversion of ORs and SMDs

Formulas for the conversion

The conversions were conducted according to the formulas in the Cochrane Handbook:[1]

1. ORs to absolute rates and RRs

The conversion of ORs to absolute rates and RRs requires an assumed control risk (ACR). As ACR, we used the meta-analytic point estimate of event rates in the placebo group (for the outcomes relapse, re-hospitalization, dropouts due to any cause, dropouts due to any reason).

Then, we transformed ORs using the equations:

- From OR to RR: $RR = \frac{OR}{(1-ACR*(1-OR))}$
- From OR to absolute rates: $Absolute\ rate = ACR * \frac{OR}{(1-ACR*(1-OR))}$

The same formulas were used to transform the lower and upper boundaries of the 95% confidence intervals.

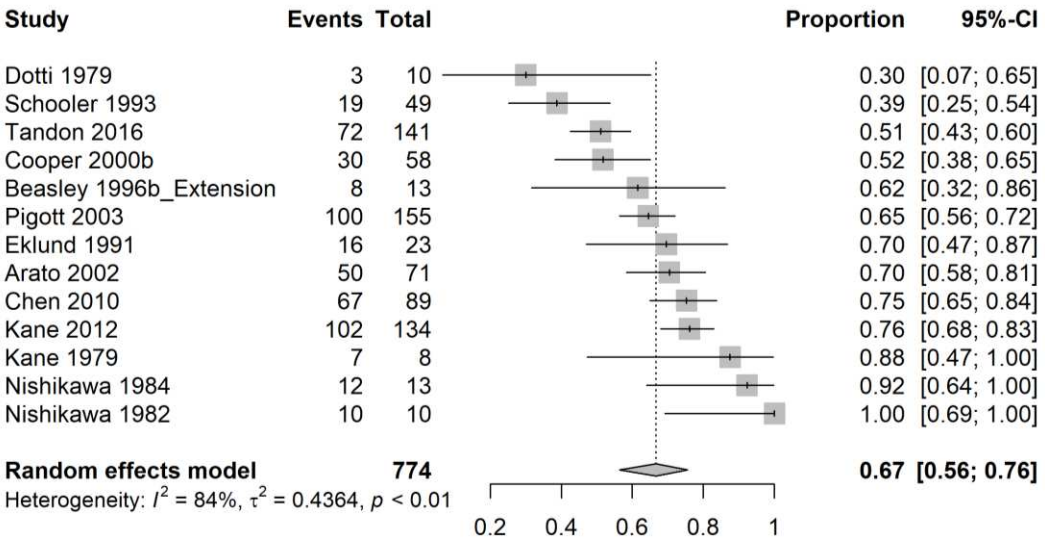
2. SMDs to absolute PANSS change scores

The conversion of SMD to absolute PANSS scores require a) a standard deviation of the scale, for which the weighted average of SD of PANSS change scores was used: 16.47 (median 19.47 IQR [11.56-30.46]); and b) the absolute PANSS change score in the placebo group (PANSS at 0 mg), for which we used the meta-analytic point estimate of change in the placebo group.

Then, we transformed SMDs using the equation: $PANSS\ change\ scores\ (dose) = PANSS\ change\ score\ (0\ mg) + SMD * SD$

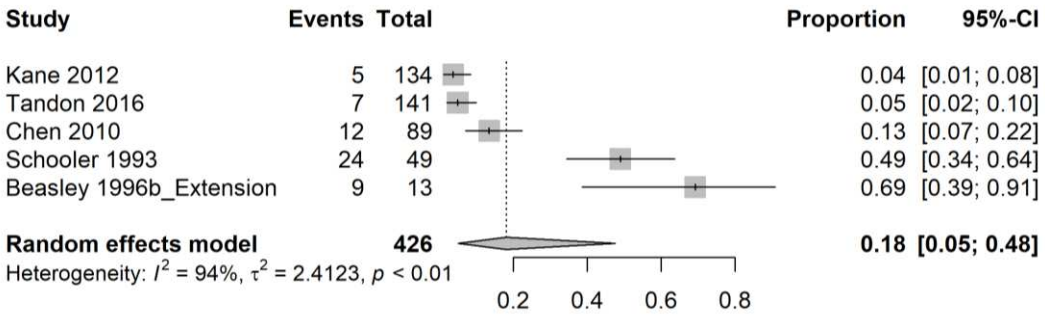
Estimating event rates and PANSS change scores in placebo groups

1. Relapse



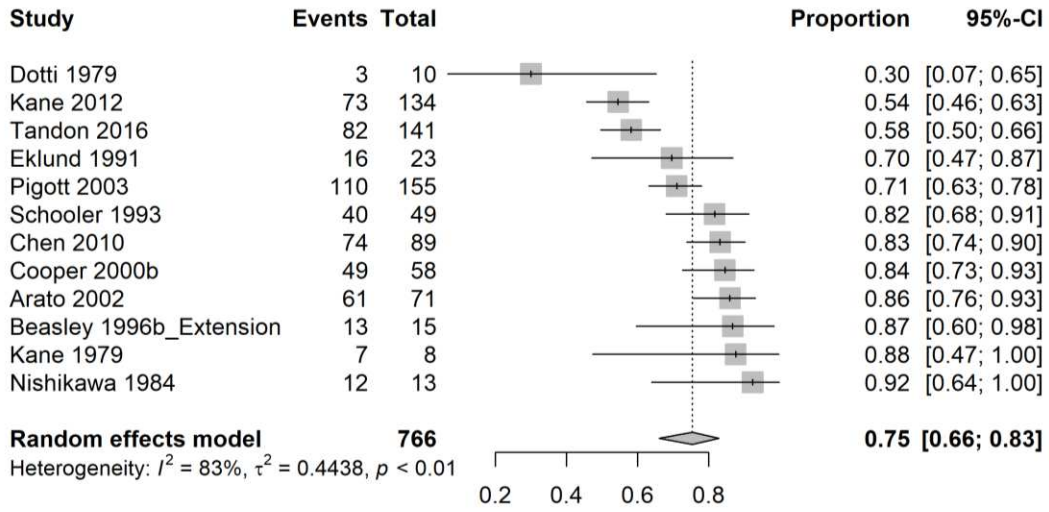
On average, about 67% of the participants in the placebo group relapsed, and ACR was set at 67%.

2. Re-hospitalization



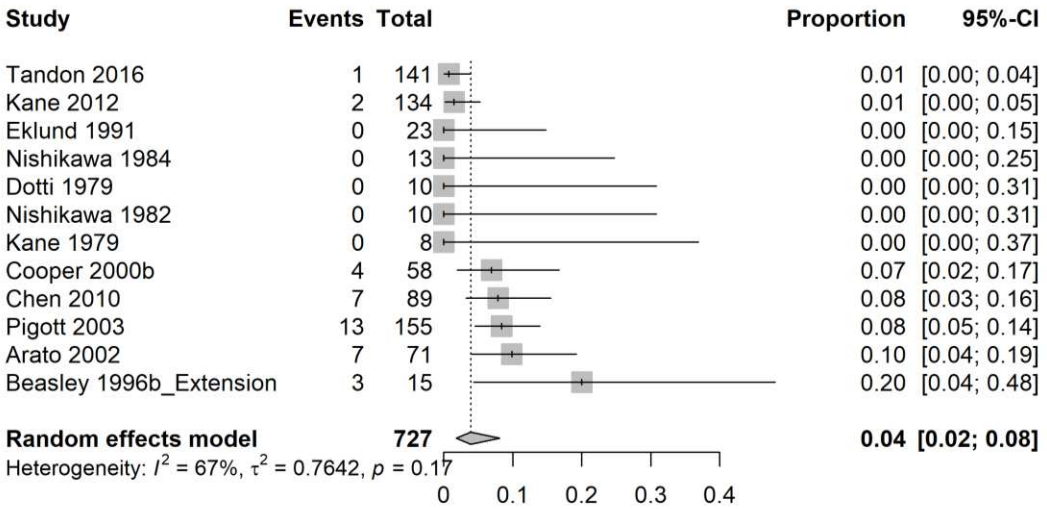
On average, about 18% of the participants in the placebo group had a re-hospitalization, and ACR was set at 18%.

3. Dropouts due to any reason



On average, about 75% of the participants in the placebo group dropped out due to any reason, and ACR was set at 75%.

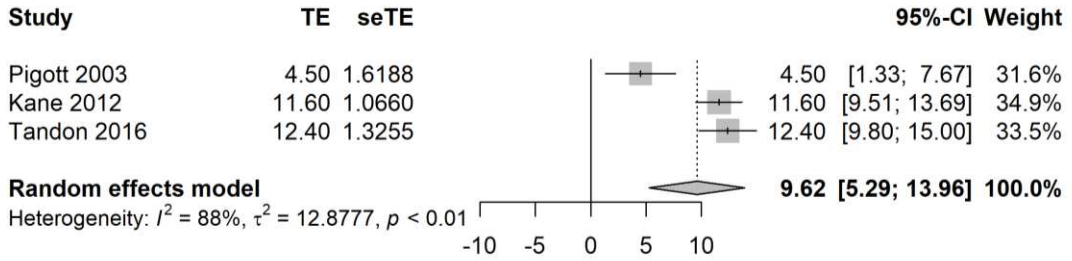
4. Dropouts due to side effects



On average, about 4% of the participants in the placebo group dropped out due to side effects, and ACR was set at 4%.

5. Overall symptoms

First, we pooled original PANSS change scores from baseline to endpoint in the placebo group:



Three out of the seven placebo-controlled studies with data for overall symptoms reported original PANSS change scores. On average, there was a 9.62 increase of PANSS scores from baseline to endpoint in placebo groups.

Since the other four studies reported PANSS endpoint scores or BPRS scores, we further evaluated the robustness of the above meta-analysis. First, we transformed other measures to PANSS mean change scores:

- PANSS mean endpoint to PANSS mean change scores (change score = endpoint – baseline scores). The same was applied when BPRS endpoint scores were reported.
- BPRS mean change scores to PANSS mean change scores according to an equipercentile linking method[2]

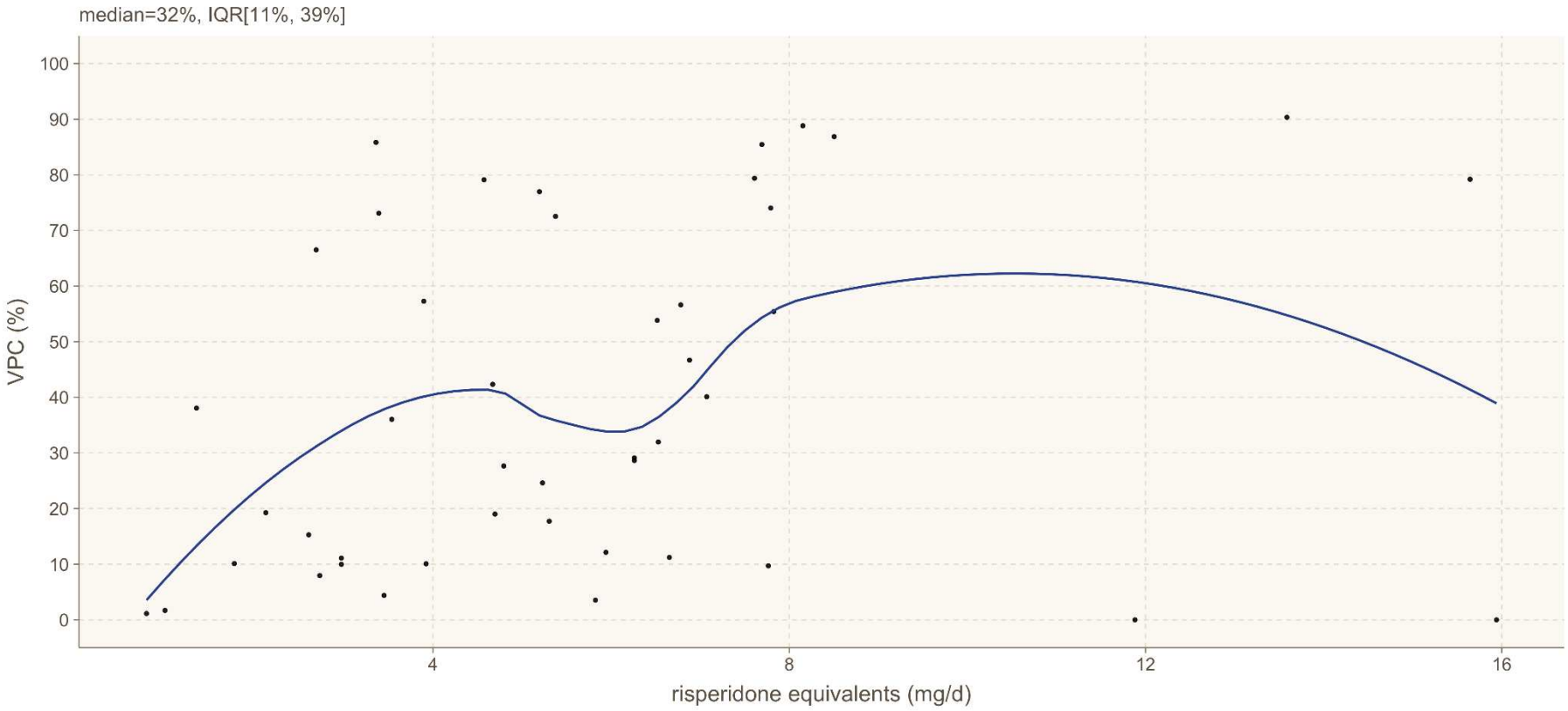
The weighted average of PANSS change scores (original or transformed) was 8.9 (median 4.5 IQR [1.75-15.6]), which is in line with the meta-analysis of original data. A meta-analysis of original or transformed data was avoided, since further assumptions for the calculation of their standard deviations were required.

References

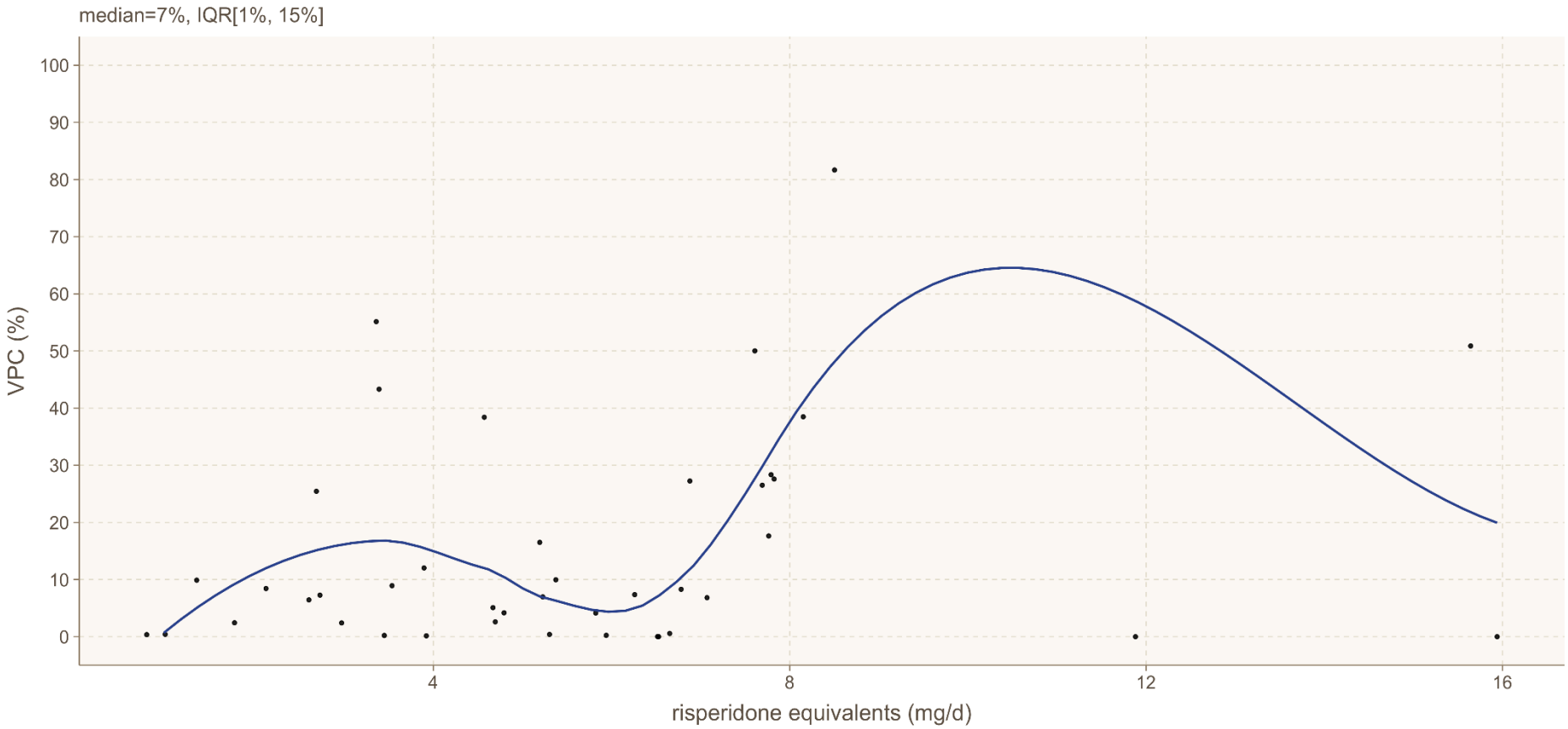
1. Higgins JP, Thomas J, Chandler J, Cumpston M, Page MJ, Welch VA. Cochrane Handbook for Systematic Reviews of Interventions version 6.0; 2019.
2. Leucht S, Rothe P, Davis JM, Engel RR. Equipercentile linking of the BPRS and the PANSS. Eur Neuropsychopharmacol 2013; **23**(8): 956-9.

eAppendix 6. Heterogeneity and small-trial / publication bias

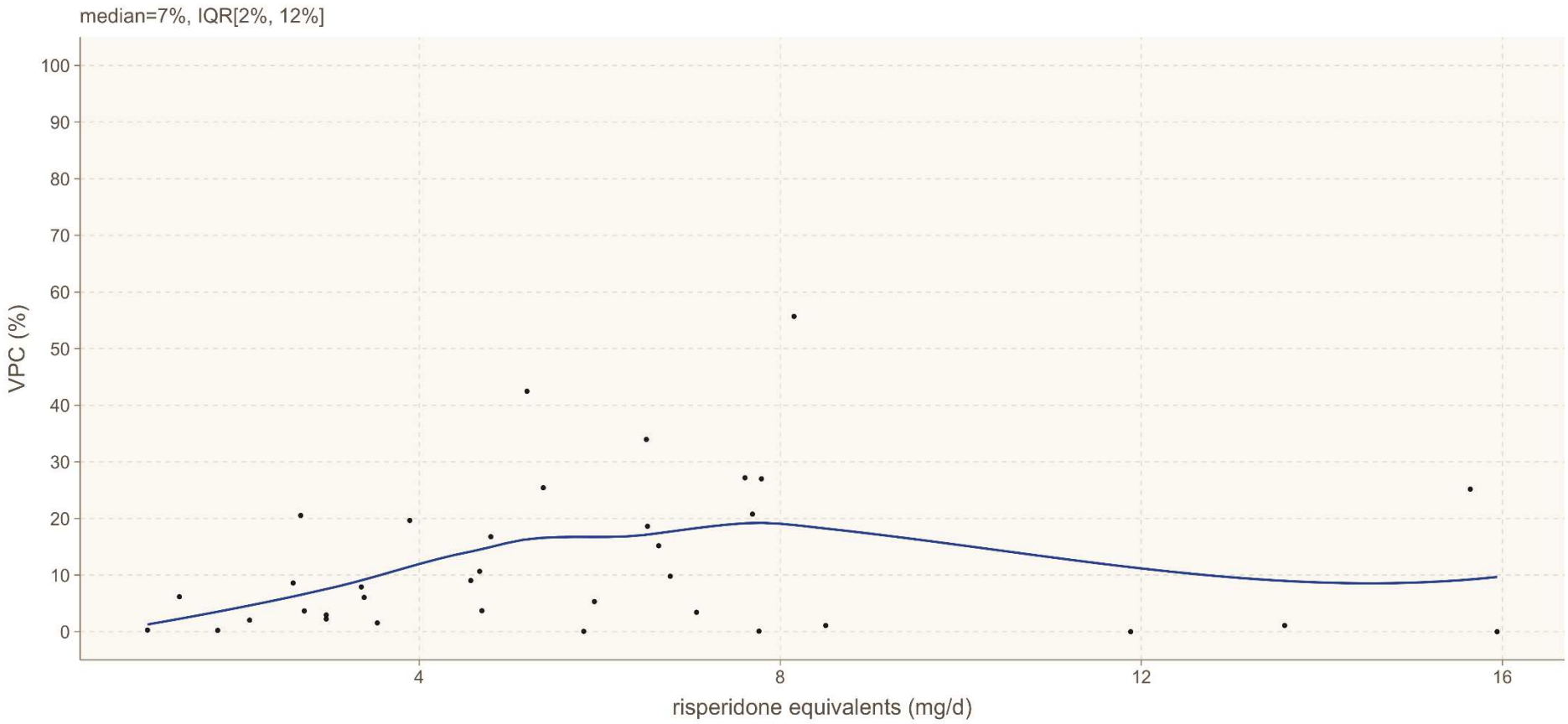
eAppendix 6_Variation-Partition-Coefficients – Relapse (primary outcome)



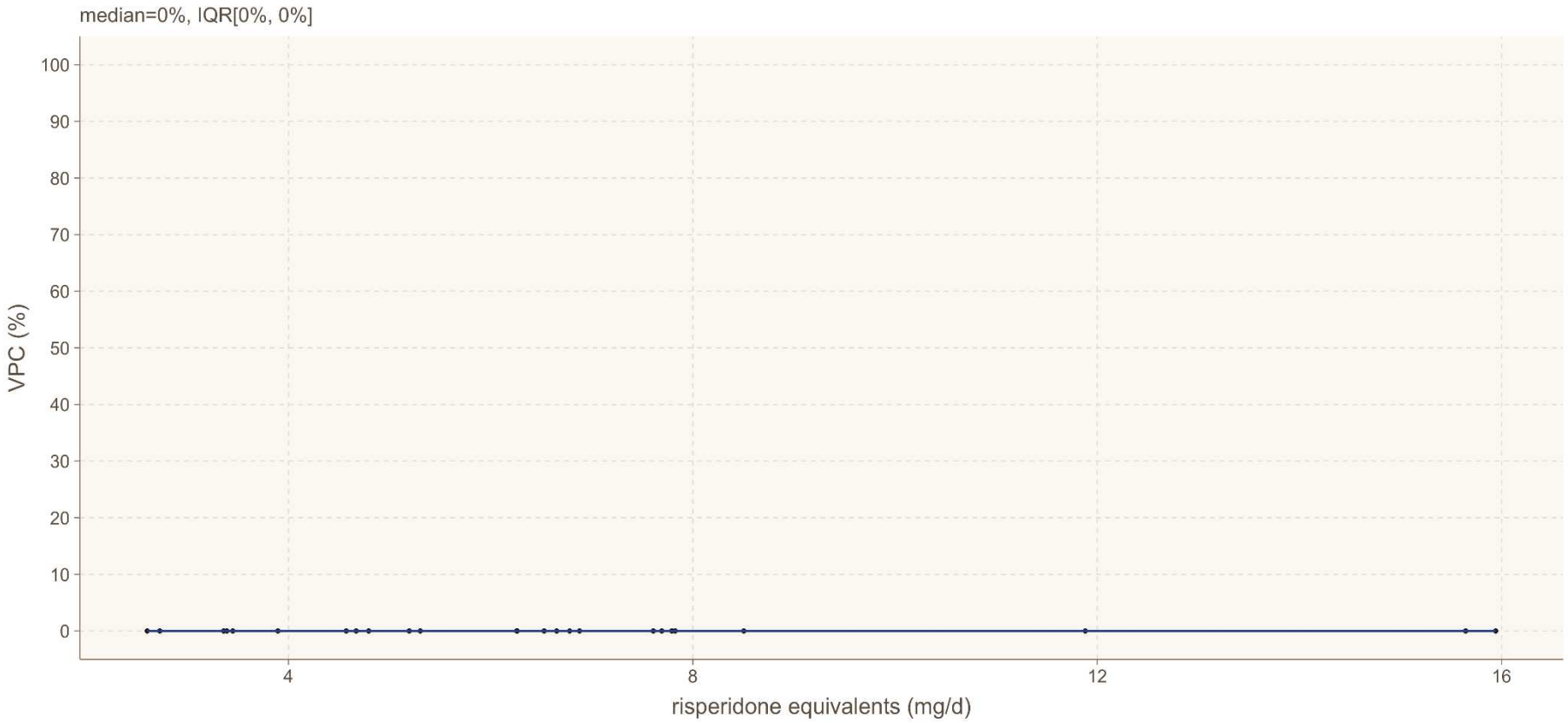
eAppendix 6_Variation-Partition-Coefficients – All-cause discontinuation



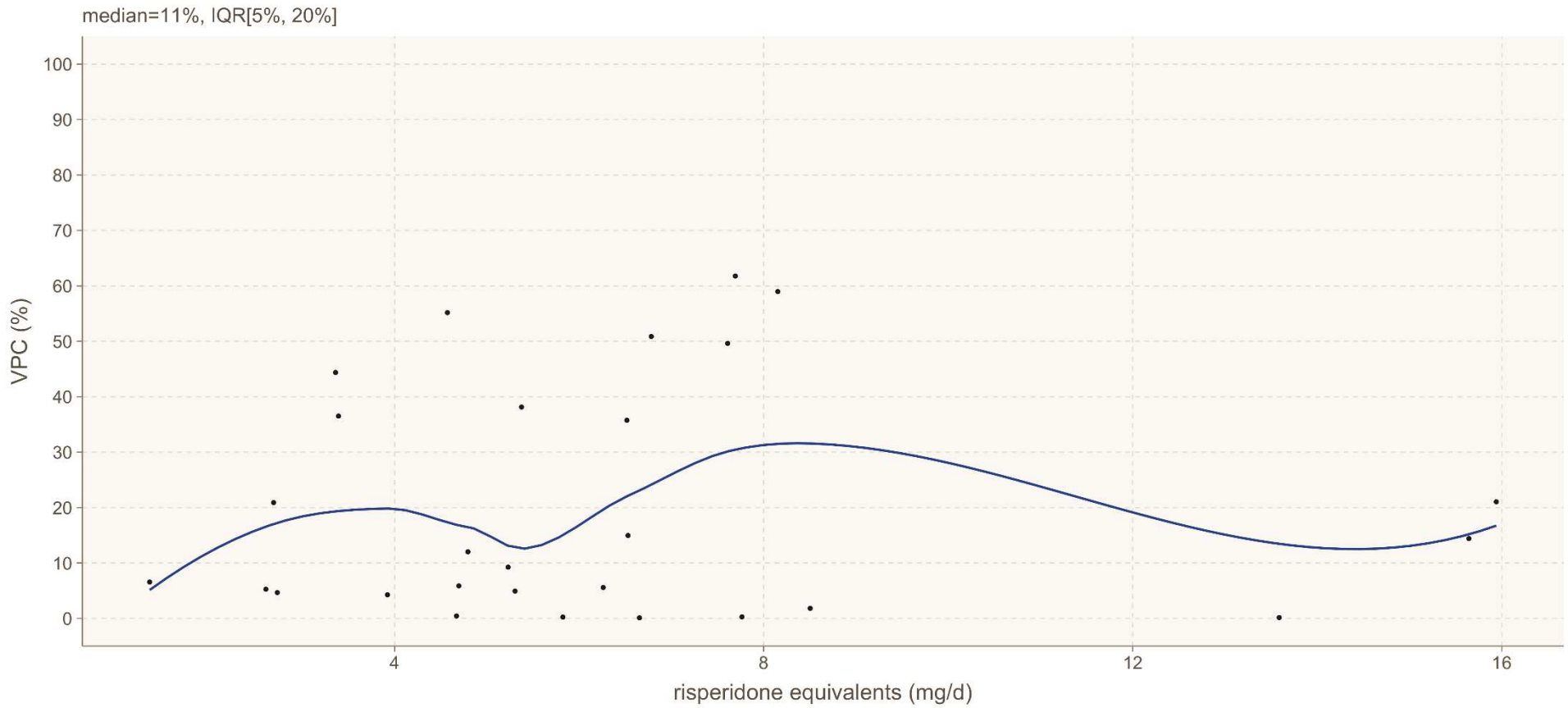
eAppendix 6_Variation-Partition-Coefficients – Dropouts due to adverse events



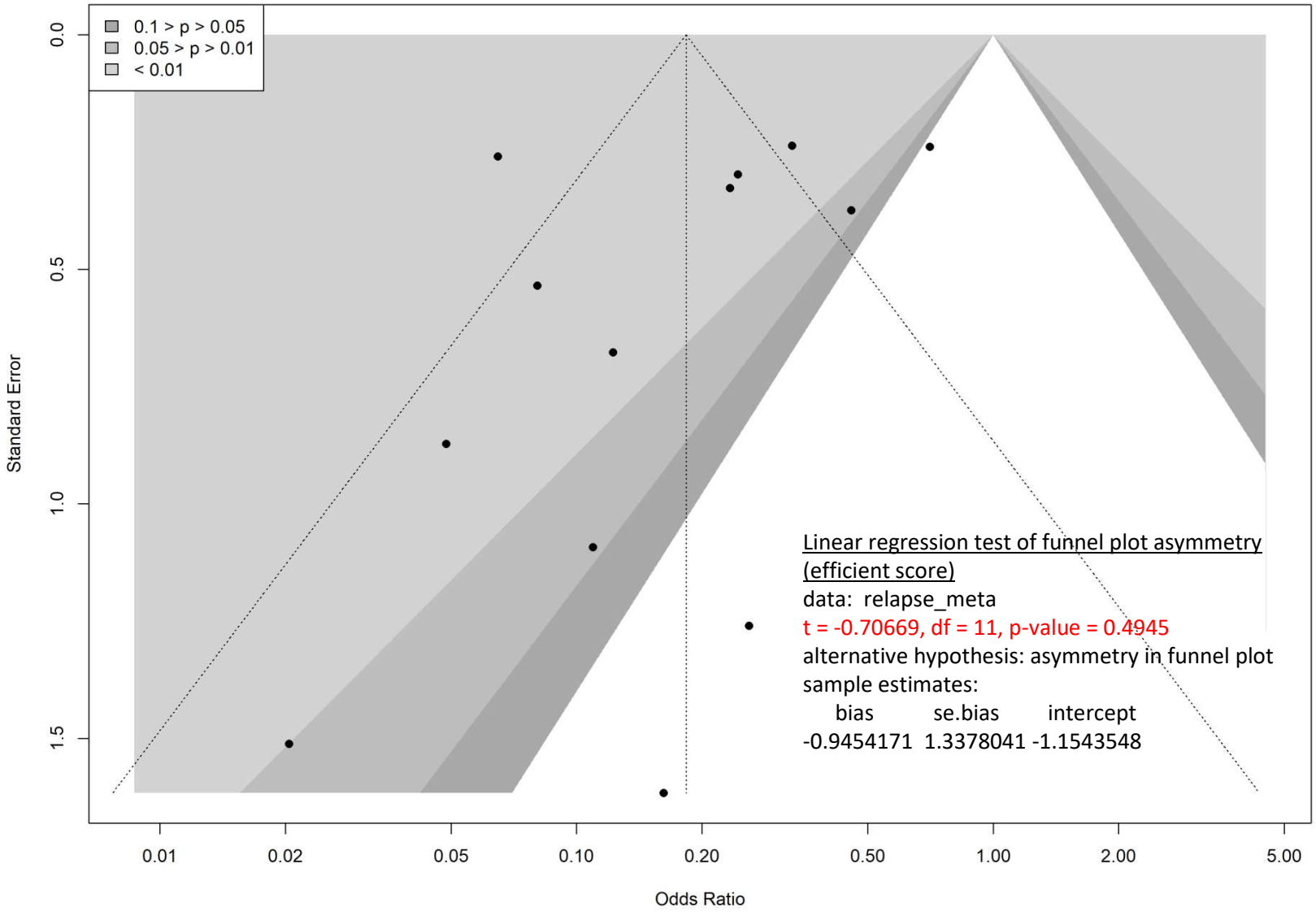
eAppendix 6_Variation-Partition-Coefficients – Rehospitalization



eAppendix 6_Variation-Partition-Coefficients – Overall symptoms



eAppendix 6_Contour enhanced funnel plot and Egger's test of the primary outcome (relapse)



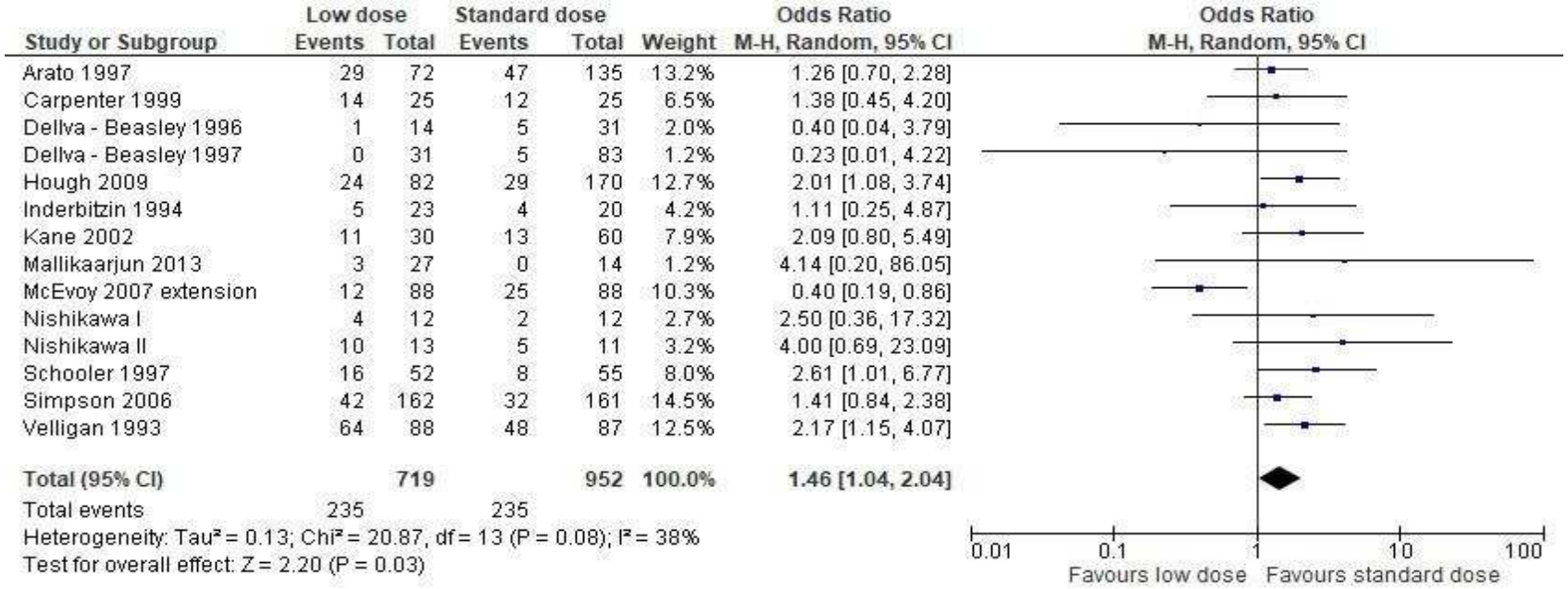
eReference

Crippa A, Discacciati A, Bottai M, Spiegelman D, Orsini N. One-stage dose-response meta-analysis for aggregated data. Stat Methods Med Res. 2019;28:1579-1596
Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997 Sep 13;315(7109):629-34.
Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Contour-enhanced meta-analysis funnel plots help distinguish publication bias from other causes of asymmetry. J Clin Epidemiol 2008;61:991-996

eAppendix 7. Update of the meta-analysis of Uchida et al. 2011 and additional analyses of doses higher than standard doses (≥5mg risperidoneequivalent per day)

eAppendix 7_A, Relapse - standard dose (= 1 Daily-Defined-Dose or higher) versus low-dose (≥50 % < 1 DDD)

Uchida et al. 2011[1] had reported in a pairwise meta-analysis that standard doses (= 1 Daily-Defined-Dose) were just not statistically significantly more effective



than low doses (≥50 % < 1 DDD) for relapse prevention with antipsychotics in schizophrenia (p=0.05). We updated their Figure 4a with new studies found by us. We also obtained additional data on studies which had already been included by them (Velligan 1993, Carpenter 1999, Beasley 1996, Beasley 1997, Hough 2009, Kane 2010, Mallikaarjun 2013, McEvoy 2007 extension). After this update standard doses outperformed low doses more clearly (p=0.03).

Comment

1. Minor differences in numbers between our and their analysis stem from the fact that Uchida et al. 2011[1] a) had several times dropout due to inefficacy/relapse for their analysis while we always used relapse if available; b) they did not always use the strict intention-to-treat (once-randomized – analyzed) population for the denominator. Moreover, in the Schooler 1997 study we used only the arms with 'supportive' family treatment, while they also used the arms with 'intensive' family treatment. Our decision was made a priori; and the rationale was that we were interested in the "pure" dose-effect which could have been confounded by additional intensive family treatment (or at least more than by just supportive family treatment).
2. It should be noted that the only three studies which showed an effect in favour of the low dose groups were the only continuation studies (Beasley 1996, Beasley 1997, McEvoy 2007). In this design the responders in the acute phase are followed up. Removing these studies, heterogeneity drops to an I^2 of 0% and the p-value for efficacy is < 0.0001).
3. Most importantly, it should be noted that p-values must not be overemphasized, and there is a strong movement of statisticians against them. The direction of effect in Uchida et al. 2011[1] was in favour of standard doses as well, just the p-value was somewhat higher (also see American Statistical Association 2016[2])

References

1. Uchida H, Suzuki T, Takeuchi H, Arenovich T, Mamo DC. Low dose vs standard dose of antipsychotics for relapse prevention in schizophrenia: meta-analysis. Schizophr Bull. 2011;37(4):788-799.
2. Americian Statistical Association. Statement on statistical significance and p-values. 2016; https://www.amstat.org/asa/files/pdfs/p-valuestatement.pdf

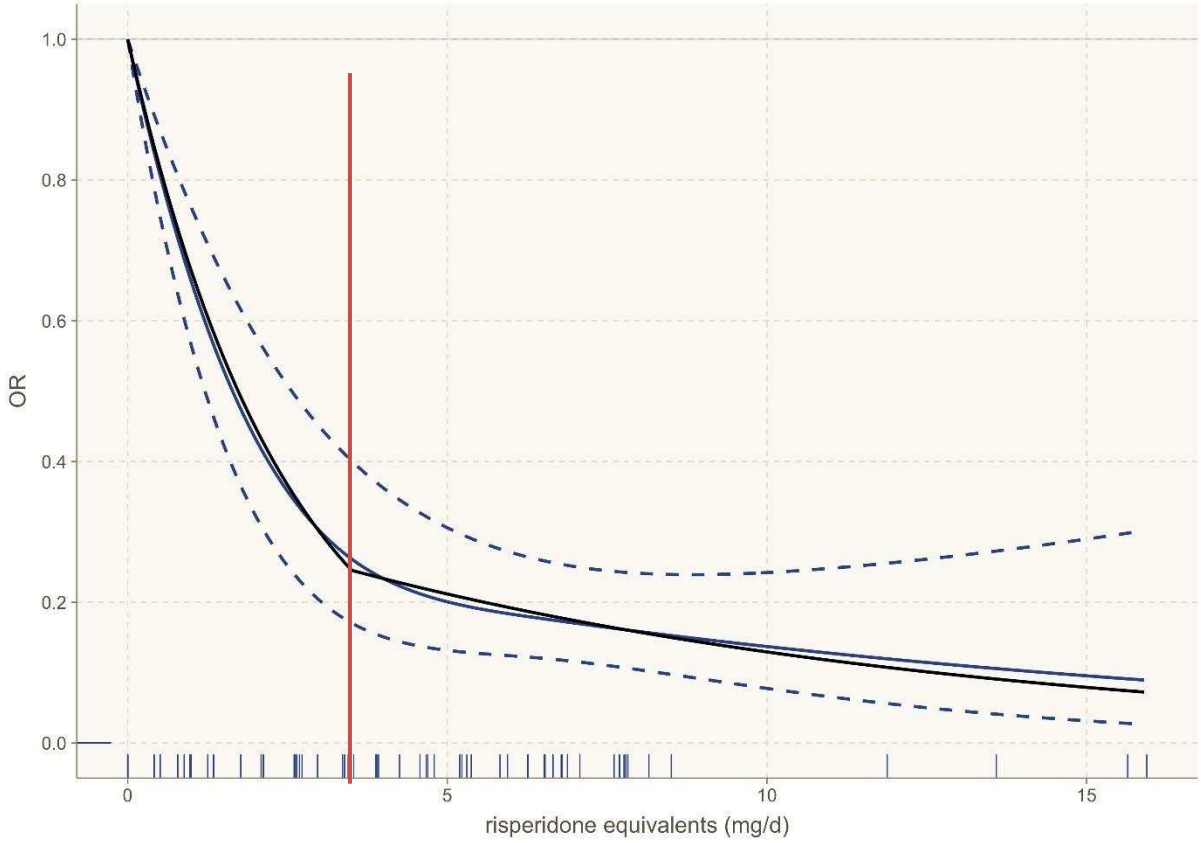
As the slope in Figure 1 of the manuscript – dose-response of the primary outcome relapse – is still slightly increasing above 5mg/day risperidone equivalent, we conducted two post-hoc analyses following reviewer comments:

1. An analysis using linear splines - as in our dose-response analysis of acute phase studies (Leucht et al. 2020) - to find out above which dose the slope of the curve does not longer increase (Figure 2 below)
2. A simple pairwise meta-analysis in which we compared doses between 3-7mg/day risperidone equivalent with higher doses (Figure 3 below)

Neither one suggested important efficacy gains at very high doses

There was no significant difference ($p=0.48$). It should noted that too few 5mg doses were available, therefore we had to use a range. We tested with linear splines up to which dose the dose-response curve still showed a significantly increasing slope (post-hoc, $p<0.1$)

eAppendix 7, B_ Relapse - above which dose does the slope of the dose-response curve no longer significantly increase?



The red line represents the linear spline at 3.5 mg/day risperidone equivalents, above which dose the slope did not show a significant decrease (p.0.1). The marks on the x-axis indicate for which doses study-arms were available and how many.

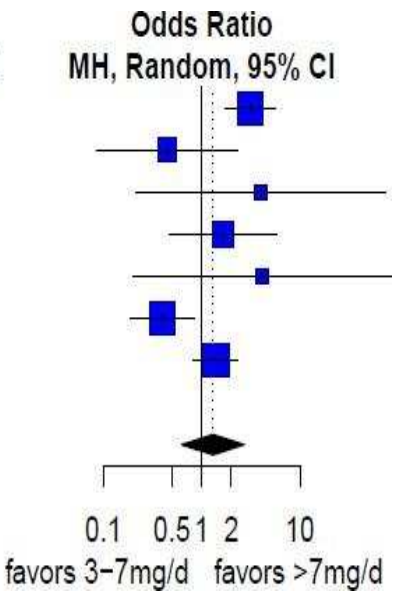
eAppendix 7_C Pairwise meta-analysis of OR for relapse of 3-7mg/day risperidone equivalent versus more than 7mg/day

1

Study	3−7mg/d Events	Total	>7mg/d Events	Total	Weight	Odds Ratio MH, Random, 95% CI
Arvanitis 1993	64	88	59	128	22.0%	3.12 [1.74; 5.59]
Beasley 1996b_Extension	5	31	3	10	11.1%	0.45 [0.09; 2.35]
Beasley 1997_Extension	5	83	0	28	5.0%	3.99 [0.21; 74.54]
Kane 2002b	8	31	5	29	14.6%	1.67 [0.48; 5.86]
Mallikaarjun 2013	3	27	0	14	4.8%	4.14 [0.20; 86.05]
McEvoy 2007b_Extension	12	88	25	88	20.0%	0.40 [0.19; 0.86]
Simpson 2006	42	163	32	161	22.6%	1.40 [0.83; 2.36]
Total (95% CI)		**511**		**458**	**100.0%**	**1.30 [0.63; 2.72]**

Heterogeneity: $Tau^2 = 0.5501$; $Chi^2 = 20.48$, df = 6 (P < 0.01); $I^2 = 71\%$

Test for overall effect: Z = 0.71 (P = 0.48)



We conducted a pairwise meta-analysis in which we compared doses between 3-7mg/day risperidone equivalent with higher doses. Therewas no significant difference (p=0.48). It should be noted that too few arms with exactly 5mg were available, therefore we had to use a range.

eTable 3. Average Dopamine Receptor Occupancies for Risperidone Doses

Dose, mg	Dopamine receptor occupancy, % (95%CI)[a]
Placebo	0 (0 to 0)
0.5	31 (15 to 39)
1.0	45 (31 to 56)
1.5	54 (40 to 64)
2.0	60 (47 to 69)
2.5	64 (54 to 72)
3.0	68 (59 to 75)
3.5	71 (62 to 77)
4.0	73 (65 to 78)
4.5	74 (67 to 80)
5.0	76 (69 to 82)
5.5	78 (71 to 83)
6.0	79 (72 to 84)
6.5	79 (73 to 84)
7.0	80 (73 to 85)
7.5	81 (74 to 86)
8.0	82 (74 to 86)
8.5	82 (75 to 87)
9.0	83 (75 to 88)
9.5	83 (76 to 88)
10.0	84 (76 to 89)
15.0	86 (77 to 92)

[a]Data on dopamine occupancy per risperidone dose were taken from the meta-analysis by Lako et al for use in the discussion section. The median and interquartile ranges for study durations for the various outcomes were as follows: relapse, 48.0 (interquartile range [IQR], 33.0-52.0) months; rehospitalization, 52.00 (IQR, 46.00-52.00) months; efficacy, 46.00 (IQR, 26.00-52.00) months; all-cause discontinuation, 48.00 (IQR, 28.00-52.00) months; and dropout due to adverse events, 46.00 (IQR, 38.00-52.00).

eReference

Lako IM, van den Heuvel ER, Knegtering H, Bruggeman R, Taxis K. Estimating dopamine D2 receptor occupancy for doses of 8 antipsychotics: a meta-analysis. J Clin Psychopharmacol. 2013;33(5):675-681.

