# Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia

## a systematic review and meta-analysis of randomised controlled trials

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**Standard versus reduced dose of antipsychotics for relapse prevention in multi-episode schizophrenia: a systematic review and meta-analysis of randomized controlled trials**

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## RESEARCH IN CONTEXT

### Evidence before this study

Maintenance antipsychotic treatment following successful antipsychotic management of an acute episode of schizophrenia is recommended to reduce the risk of relapse. However, current treatment guidelines for schizophrenia differ in their recommendations regarding the length of maintenance treatment and the issue of whether the acute treatment dose should be maintained or can be reduced during the maintenance phase. Some randomized controlled trials and observational studies have shown that dose-reduction below a standard antipsychotic dose may be feasible without an increased risk of relapse and, in some cases, with improved cognitive performance. In contrast, other clinical trials have demonstrated an increased risk of relapse with reduced antipsychotic doses during maintenance treatment.

We searched PubMed for meta-analyses on the effect of dose-reduction during antipsychotic maintenance treatment in schizophrenia published from database inception until Jun 17, 2020, using the search terms “schizophrenia” AND “antipsychotic*” AND (“reduction” OR “low”) AND “relapse” AND “meta-analysis” Only three meta-analyses focused on the specific question of dose-reduction during maintenance treatment in individuals with multi-episode schizophrenia.

A meta-analysis of double blind randomized controlled trials (RCTs) published up to and including 2009 found an increased risk of relapse and all cause discontinuation with very low doses, defined as below 50% of World Health Organization Defined Daily Doses (DDD) versus standard doses. In contrast there was insufficient information to draw firm conclusions about the relative effectiveness of low doses (50% to 99% of DDD) versus standard doses. Limitations of this meta-analysis include the relatively small sample (13 trials and 1395 subjects) and the analysis being largely based on studies of first-generation antipsychotics, both oral and long-acting injectable formulations. Since then, treatment practices have changed significantly towards the use of second-generation antipsychotics and their long-acting injectable formulations. Two more recent meta-analyses have focused on predictors of successful antipsychotic dose reduction. Both found that lower antipsychotic doses increased relapse rates but both had methodological weakness; both assessed a single category of dose reduction, study size was limited and several short-term studies were included, which may underestimate the impact of dose reduction on relapse.

### Added value of this study

This is the largest systematic review and meta-analysis to compare standard doses with reduced maintenance doses of antipsychotics; we included 24 randomized controlled trials, and results from 3282 individuals. Additional strengths are that we restricted our analysis to randomized trials (thereby reducing the impact of confounders), required a minimum duration of 24 weeks (shorter studies may not allow the full impact of dose reduction to manifest), considered two dose reduction groups in comparison to standard dose, and conducted an extensive series of supplementary and sensitivity analyses. We defined our dose groups according to recommendations from The International Consensus Study of Antipsychotic Dosing (ICS). However, our supplementary analyses included an alternative definition of the three dose groups based on World Health Organization Defined Daily Doses. In our main analyses, we found a clear association of reduced efficacy in terms of higher rates of relapse and all cause discontinuation for two categories of dose reduction (low dose and very low dose) compared to

standard doses. With low dose (i.e. doses ranging from 50-99% of the lower limit (LL) of the standard dose range recommended for acute treatment), we found 44% increased risk of relapse versus standard dose. This risk increased to 72% with very low dose (i.e., doses below 50% of the LL of the recommended acute dose range) versus standard dose. Global psychopathology scores followed this same pattern though not all group differences reached statistical significance. Intolerability-related discontinuations did not differ between dose groups. Using the DDDs for dose classification yielded results that were comparable with the main analysis for all outcomes.

**Implications of all the available evidence**

To reduce the risk of relapse, all-cause discontinuation and worsening of psychopathology, the dose of antipsychotic maintenance treatment in schizophrenia should likely not be reduced below the recommended dose ranges that are effective for acute stabilization. These results are relevant for clinicians, patients, families, researchers, payers and guideline developers alike.

**SUMMARY**

**Background:** Dose reduction of antipsychotic maintenance treatment in individuals with schizophrenia may be desirable to minimize adverse effects, but evidence for this strategy is unclear. We compared risks and benefits of reduced versus standard doses (SD) of antipsychotics.

**Methods:** We searched Embase/Medline/PsycINFO/Cochrane Library from database inception until 17.06.2020 for randomized trials in adults comparing ≥2 doses of the same antipsychotic, excluding trials in first-episode psychosis or treatment-resistant schizophrenia. We compared low-dose (LD=99-50%SD) and very-low dose (VLD≥50%SD) with SD, defined as the lower limit of the treatment dose recommended by the International Consensus Study. Co-primary outcomes were relapse and all-cause discontinuation. Study-level data were meta-analyzed using random-effects models, calculating risk ratios (RRs) for dichotomous data, and Hedges'g for continuous data. The protocol was registered with OSF, doi:10.17605/OSF.IO/VA7X2.

**Findings:** Of 7854 references, we meta-analyzed 24 trials (n=3282; median [IQR] age = 38[36-40] years; 66%males; 34%females). Compared with SD, LD increased the risk of relapse by 44% (n=1920; RR=1·44; 95%CI:1·10-1·87; p=0·0076; $I^2$=46%) and the risk of all-cause discontinuation by 12% (n=1932; RR=1·12; 95%CI:1·03-1·22; p=0·0085; $I^2$=0%) and VLD increased the risk of relapse by 72% (n=2058; RR=1·72; 95%CI: 1·29-2·29; p=0·0002; $I^2$=70%) and all-cause discontinuation by 31% (n=1866; RR=1·31; 95%CI:1·11-1·54; p=0·0011; $I^2$=63%). Compared to LD, VLD did not significantly increase the risk of relapse (RR=1·31; p=0·092) or all-cause discontinuation (RR=1·11; p=0·18). Subgroup analyses comparing double-blind vs. open-label studies, first- vs. second-generation antipsychotics, and oral vs. long-acting injectable antipsychotics were consistent with the overall results. Psychopathology was significantly worse in LD vs SD (Hedges'g=0·17; p=0·016) and VLD vs LD (Hedges'g=0·23; p=0·0087), but not statistically significant for VLD vs SD (Hedges'g=0·25; p=0·064). Intolerability related discontinuations did not differ between dose groups.

**Interpretation:** During maintenance treatment in multi-episode schizophrenia, antipsychotic doses should likely not be reduced below the standard dose range recommended for acute stabilization, as reducing the dose further is associated with an increased risk of both relapse and all-cause discontinuation.

**Funding:** None

## Introduction

Meta-analyses of long-term RCTs show that continuing antipsychotics following successful antipsychotic treatment of an acute episode of schizophrenia, versus switching to placebo, reduces the risk of relapse.[1,2] Schizophrenia Clinical Practice Guidelines (CPG) recommend continuous maintenance therapy in schizophrenia treatment. However, there is a lack of consensus among CPGs regarding the optimal antipsychotic dose for maintenance therapy, as some recommend maintaining the antipsychotic dose that led to remission during acute treatment, whereas others recommend the lowest effective maintenance dose.[3] This debate has received more attention since the publication of a 7-year follow-up study of patients with first-episode psychosis, which reported a higher rate of recovery and functional remission in patients randomized to dose reduction/discontinuation compared to continued maintenance doses.[4] However the study had methodological weaknesses, including lack of long-term fidelity to the randomized treatment and that a baseline diagnosis of schizophrenia was not required for inclusion.[5,6]

Antipsychotic treatment can cause a wide range of side effects,[7–10] that can reduce quality of life and lead to poor adherence and discontinuation of treatment.[11] Weight gain and metabolic side effects are particularly relevant to maintenance treatment as they may worsen physical health. Nevertheless, overall antipsychotic treatment, versus no treatment, is associated with increased life expectancy.[12] Some antipsychotic side effects, e.g., extrapyramidal symptoms, hyperprolactinemia, and sedation, are dose related[13]. Maintenance treatment with the minimum effective dose may minimize such side effects and their consequences. Conversely, some side effects, e.g., weight gain and metabolic dysregulation, show little relationship with dose.[13–15]

Uchida and colleagues[16] conducted a meta-analysis of RCTs and compared the effectiveness of standard dose [(World Health Organization daily defined dose (DDD)] versus low dose (50-100% DDD) or very low dose (<50% DDD) for relapse prevention in schizophrenia. The DDD for antipsychotics is defined as the assumed average maintenance dose per day for the treatment of psychosis in adults[17]. Low-dose treatment, compared to standard-dose treatment, did not differ significantly in terms of hospitalization or overall treatment failure (i.e. all-cause discontinuation) but just missed (p=0·06) being inferior in preventing relapse. All three outcomes were inferior for VLD versus SD. The authors concluded that '*there are insufficient clinical trial data to draw firm conclusions on standard- vs low-dose maintenance antipsychotic therapy for schizophrenia'.* Uchida and colleagues' meta-analysis was primarily based on studies of first-generation antipsychotics (FGA) and their long-acting injectable formulations (LAIs), and used data published up to August 2009. Since then, new relevant trials have been published relating to second-generation antipsychotics (SGA) both oral and as LAI. As a growing number of patients are treated with SGAs and LAIs, we aimed to conduct a systematic review and meta-analysis of RCTs comparing SD with reduced antipsychotic doses as maintenance treatment in schizophrenia, estimating the risk of relapse, all-cause discontinuation and other clinically relevant outcomes associated with dose-reduction.

## Methods

### Search strategy and selection criteria

We searched Medline, Embase, PsycINFO, and Cochrane Library from database inception and without language restriction (last search: 17.06.2020) using the search strings provided in appendix (pp.5-6). We also manually searched reference lists from the included RCTs for additional studies. For further details on study review and selection see the appendix (p.7).

Antipsychotic dose in eligible trials was classified as either "SD", "LD", or "VLD". All three dose groups were defined relative to the lower limit (LL) of the recommended target dose range for the acute treatment in schizophrenia proposed in the International Consensus Study of Antipsychotic Dosing (ICS)[18], which developed dose ranges for 61 antipsychotics via consensus from a large, systematic, international survey using Delphi methods. The ICS target dose was derived after respondents were asked to indicate their usual target dosing range for a moderately symptomatic adult man with schizophrenia, with ≥2 years of antipsychotic treatment, and not considered treatment-refractory. The target dose range was the median lower and upper doses of the ranges recommended. Doses were classified as 1) "SD" if they were above or equal to the LL of the recommended target dose range for acute treatment, 2) "LD" if they were within 50-99% of the LL, and 3) "VLD" if they were <50% of LL. For antipsychotics not covered by the ICS (e.g., newer antipsychotics such as asenapine or formulations such as olanzapine pamoate), the LL of the standard dose range was determined as proposed by Leucht et al.[19], or Rothe et al..[20] The LL of the SD range for individual antipsychotics that we used is presented in table 1.

### Outcomes

Co-primary outcomes were relapse and all-cause discontinuation. Secondary outcomes were 1)psychiatric hospitalization, 2)intolerability-related discontinuation, change in 3)total psychopathology (assessed using the Positive and Negative Symptoms Scale for Schizophrenia (PANSS)[21] or the Brief Psychiatric Rating Scale (BRPS)[22]), 4)body weight, 5)prolactin levels 6)extrapyramidal symptom (EPS) scale scores, 7)other treatment-emergent adverse events relevant to antipsychotic treatment (e.g., somnolence, anxiety, agitation, and insomnia), and 8)anticholinergic use (a proxy of clinically relevant EPS). Outcomes were assessed as change from baseline to end of study. For details on data extraction see the appendix (p.7).

### Data analysis

We conducted a random-effects meta-analysis using DerSimonian and Laird's method, calculating risk ratios (RR) for dichotomous data and standardized mean differences (Hedges'g) for continuous outcomes, each with 95% confidence intervals (95%CIs). Heterogeneity was assessed using the $I^2$-statistic. For significant effect sizes, we calculated the number-needed-to-harm (NNH) with 95%CIs as the inverse of the risk difference. Studies were a priori stratified on 1) antipsychotic class (FGA vs SGA) to assess the potential mediating effect of tolerability differences in relation to relapse and hospitalization, 2) on antipsychotic formulation (oral antipsychotic (OAP) vs LAI) to assess the potentially mediating effect of non-adherence in relation to all-cause discontinuation, and 3) on blinding to assess its potential impact on effect sizes. For details on subgroup and meta-regression analyses see the appendix (pp.7-8). Publication bias was examined using funnel plots and the Duvall and Tweedie's trim and fill procedure, comparing calculated effect sizes with the potential change in effect size from imputed studies.

All analyses were conducted using R (version 4.0.2). No corrections were made for multiple comparisons. Search protocol and analysis plan were deposited at OSF Registries before data extraction (https://doi.org/10.17605/OSF.IO/VA7X2,appendix pp.9-11).

**Role of the funding source**
This study was unfunded.

## Results

Our database search captured 7853 references, plus one additional reference from manual review of relevant studies (figure 1). After excluding 2110 duplicates, we screened 5744 abstracts for eligibility, excluding 5643 references, leaving 101 references for full-text review. Of these 79 were excluded, leaving 22 studies for meta-analysis, reporting on 24 individual trials and 3282 individuals. Altogether, 18 RCTs were double-blind (n=2838),[23–41] while six were open-label or single-blind (n=444).[42–46] Altogether 1777 individuals were in the SD group, 726 in the LD group, and 779 in the VLD group.

Study participants had a median age of 38 years (interquartile range [IQR]: 36-40 years), 2166 (66%) were men, and the median trial duration was 52 weeks (IQR: 46-53 weeks). Details on design and definitions of stability and relapse are described in appendix (pp.15-19). The number of studies with low, some concerns, and high risk of bias was 2 (8%), 19 (79%), and 3 (13%), respectively (appendix p.20). The primary reason for the high proportion of trials with "some concerns" was the potential risk of bias in relation to reporting of results, as especially older studies did not have publicly available study registrations. Focusing on other domains (randomization, deviations, missing data, and measurement), the number of studies with low, some concerns, and high risk of bias was 17 (74%), 3 (13%), and 3 (13%), respectively.

Compared to SD, LD was associated with a 44% increased risk of relapse (RR=1·44; 95%CI:1·10-1·87; $I^2$=46%; NNH=15; figure2a), and 12% increased risk of all-cause discontinuation (RR=1·12; 95%CI: 1·03-1·22; $I^2$=0%; NNH=24;figure3a). Compared to SD, relapse risk was significantly larger with LD FGAs than with LD SGAs (RR=2·08 vs.1·23; p=0·026; table 2) and with LD LAIs vs LD OAPs (RR=2·13 vs.1·29; p=0·043; table 2). Likewise, all-cause discontinuation was significantly larger with LD FGAs than with LD SGAs (RR=1·34 vs. 1·07; p=0·036; table 2), however not significant for LD LAIs vs LD OAPs (RR=1·35 vs. 1·08 ;p=0·058; table 2).

Compared to SD, VLD was associated with a 72% increased risk of relapse (RR=1·72; 95%CI:1·29-2·29; $I^2$=70%; NNH=6; figure2b), and 31% increased risk of all-cause discontinuation (RR=1·31; 95%CI: 1·11-1·54; $I^2$=63%; NNH=8; figure3b). Compared to SD, the relapse risk did not differ significantly between VLD FGAs and VLD SGAs (RR=1·55 vs. 1·88; p=0·51; table 2) and with VLD LAIs and VLD OAPs (RR=1·94 vs. 1·35; p=0·15; Table 2). Likewise, compared to SD, all-cause discontinuation did not differ significantly with VLD FGAs and VLD SGAs (RR=1·14 vs. 1·38; p=0·20; table 2) and with VLD LAIs vs VLD OAPs (RR=1·39 vs. 1·20; p=0·35; table 2).

Compared to LD, VLD was not associated with a statistically significant difference in relapse risk (RR=1·31; 95%CI: 0·96-1·79; $I^2$=51%; figure2c) nor all-cause discontinuation (RR=1·11; 95%CI: 0·95-1·30; $I^2$=43%; figure3c). Subgroup analyses of VLD versus LD were limited to few studies, without significantly increased relapse or all-cause discontinuation risk, except for a higher relapse risk with VLD LAIs vs LD LAIs(p=0·003; table2) and when comparing VLD LAIs vs. VLD OAPs (RR=1·99 vs. RR=1·08; p=0·017; table2).

Among the secondary outcomes, only intolerability-related discontinuations, total psychopathology and weight change had ≥1 dose group with >1000 participants (appendix pp.21-22), and sample sizes within each dose group for most other secondary outcomes were small. Compared to SD, LD was associated with increased levels of total psychopathology (SMD=0·17; 95%CI: 0·03-0·31; $I^2$=14%; figure 4a). For VLD versus SD, the difference in levels of total psychopathology was not statistically significant (SMD=0·25; 95%CI: -0·01-0·52; $I^2$=80%; figure 4b). However, compared to LD, VLD was associated with increased levels of total psychopathology (SMD=0·23; 95%CI: 0·06-0·40; $I^2$=0%; figure 4c). Results for the remaining secondary outcomes are shown in appendix pp.21-22,33-39. There were no significant differences between the dose groups regarding hospitalization, intolerability-related discontinuations, anticholinergic use, and rating scale-based assessments of extrapyramidal symptoms (akathisia, dyskinesia and parkinsonism; appendix pp.21-22). Change in body weight was significantly lower for VLD versus SD (SMD=-0·46; p<0·0001) and VLD versus LD (SMD=-0·38; p<0·0001), but not for LD versus SD (SMD=-0·05; p=0·52). Serum prolactin was significantly lower for VLD versus SD (SMD=-0·26; p=0·0064) but not for LD versus SD (SMD=-0·14; p=0·093) or VLD versus LD (SMD=-0·16; p=0·14; appendix p.22). Subgroup analyses of secondary outcomes yielded similar results (appendix pp.23-27). Further, LD versus SD was associated with reduced akathisia and dyskinesia (rating scale-assessed) in the oral antipsychotic subgroup analysis (SMD=-0·72; p=0·072 and SMD=-0·70; p=0·045; appendix pp.25-27). Several miscellaneous side effects were also meta-analyzed post-hoc, and the only difference was reduced akathisia (clinical impression only) for LD versus SD (RR=0·59; p=0·037; appendix p.28).

In a pre-planned sensitivity analysis, restricted to double-blind trials, the higher relapse and all-cause discontinuation risk remained significant in the LD versus SD comparison (RR=1·38; p=0·025 and RR=1·12; p=0·024; figure2a+3a). The LD versus SD comparison was the only comparison including open-label/single-blind trials, and a similar lack of impact of blinding was observed for all secondary outcomes in the LD-SD comparison (appendix pp.33-36).

In meta-regression analyses, decreasing antipsychotic dose was significantly associated with increased risk of all-cause discontinuation (p=0·032), but not with increased relapse risk(p=0·051; appendix pp.29,40-41). A higher number of prior hospitalizations was significantly related to the risk of relapse (p=0·034), but not to all-cause discontinuation (p=0·14). Total drop-out rate was neither significantly correlated with relapse (p=0·086) nor all-cause discontinuation (p=0·10). Additionally, relapse and all-cause discontinuation risk varied substantially between studies in the three treatment groups (appendix pp.42-44).

A post-hoc sensitivity analysis classifying doses with the WHO DDD method confirmed the effects sizes from the primary results, without significant differences in effects sizes between the

two dose definitions in any outcome (appendix pp.45-48). Three post-hoc supplementary analyses investigated the effect of trial duration, trial design, and overall risk of bias: for LD versus SD, trials lasting ≥52 weeks had a higher, but not significantly different risk of relapse than those lasting <52 weeks (RR=1·64 vs. RR=1·05; p=0·13; appendix p.49). For VLD versus SD and VLD versus LD, the highest risk was observed in trials lasting <52 weeks (RR=2·94 vs. RR=1·42; p=0·0007 and RR=2·01 vs. RR=1·05; p=0·0072, respectively). Stratifying on trial design (switch, dose reduction, or extension phase studies), we found higher relapse risk with dose-reduction designs (LD vs. SD: RR=1·91; VLD vs. SD: RR=1·96; appendix p.49), while VLD and LD did not differ significantly from each other. In trials with low risk of bias, the differences favoring SD increased for both co-primary outcomes (appendix p.49).

Post-hoc analysis based on Kaplan-Meier analyses indicated that relapse was higher within 3-6 months after randomization than at 12-24 months (8studies; LDvs.SD: 3months RR=1 79/6months RR=1·92/9months RR=1·56; VLDvs.SD: 3months RR=2·04/6months RR=1·93/12months RR=1·56/24months RR=1·77; appendix p.30). Overall, imputation of missing events (post-hoc) did not suggest that missing data would change the observed effect sizes for the co-primary outcomes, except for all-cause discontinuation in LD vs. SD comparison using the Gamble and Hollis' method (p=0·073; appendix pp.31-32).

The trim and fill adjusted risk ratios (aRR) did not negate the statistically significant risk of relapse (LD vs. SD: aRR=1·55; p=0·0017; VLD vs SD: aRR=1·72; p=0·0002) or all-cause discontinuation (LD vs SD: aRR=1·12; p:0·007; VLDvsSD: aRR=1·34; p=0·00016; appendix pp.50-51). For the comparison of VLD versus LD, the aES did not suggest that small unpublished studies would have changed the non-significant difference in risk for relapse (aRR=1·02; p=0·91) or all-cause discontinuation (aRR=1·05; p=0·53; appendix p.52). Adjusted effect sizes (aES) for change in total psychopathology continued to remain significant for LD vs. SD (aES:0·25; p=0·00094) and VLD vs. LD (aES:0·20; p=0·017) and non-significant for VLD vs. SD (aES:0·25; p=0·064). For other secondary outcomes, the aES did not suggest that small unpublished studies would have changed the results from non-significant to significant (appendix pp.53-58).

**Discussion**

In this meta-analysis of RCTs, two categories of dose-reduction below the LL of the SD range significantly increased the risk of relapse and all-cause discontinuation (the two co-primary outcomes) in multi-episode schizophrenia. An increase in relative risk of relapse of 44% was observed with doses equal to 50-99% of recommended doses (LD), and the relapse risk increased to 72% with doses <50% of recommended maintenance doses (VLD). The overall effect size for both co-primary outcomes was higher in trials with a low overall risk of bias. Moreover, an increase in total psychopathology score was seen for the LD versus SD and VLD vs LD comparison, with a trend-level result for VLD vs SD. In summary, across 3 efficacy outcomes (relapse, all-cause discontinuation, total psychopathology) there was a consistent pattern of both LD and VLD being clinically inferior to SD with all comparisons, except one, being statistically significant. Conversely, intolerability-related discontinuations did not differ between dose groups. Most other analyzable secondary outcomes did not differ across dose groups, but data were limited to fewer studies/smaller samples.

The earlier meta-analysis by Uchida et al.[16] found a significantly increased risk of relapse (175%), hospitalization and all-cause discontinuation with VLD versus SD. However, in contrast to our study, the results for the more clinically applied LD versus SD comparison showed no significant difference for all-cause discontinuation, hospitalization and relapse rate. The limited sample size may explain why Uchida et al.[16] found no significant difference in the LD vs SD comparison. It appears that our meta-analysis benefited from an increased number of included studies and patients, which increased the precision of the findings and also allowed us to explore additional secondary outcomes, especially change in general psychopathology scores, which largely supported results for our co-primary outcomes.

Differences between antipsychotic dose groups in the co-primary outcomes were greater in the FGA versus SGA subgroups. The finding that LD LAIs had significantly worse relapse and all-cause discontinuation risk vs SD LAI dose compared to LD OAP versus SD OAP may seem counter-intuitive given that with LAIs therapeutic blood levels would be expected to last longer after dose reduction.[47] However, this finding is likely not due to a weaker effect of LD LAI vs LD OAP, but rather due to a superior relapse preventive effect of SD LAI than SD OAP, as with OAP treatment non-adherence that occurs in both dose arms will reduce dose group differences, biasing towards the null finding, while with LAIs the respective dose group assignment is adequately maintained. When examining the potential effect of trial design and duration, superiority of SD over both LD and VLD remained significant for the two co-primary outcomes (for additional discussion, see appendix p.14).

Two recent meta-analyses.[48,49] found that dose reduction below specific thresholds was associated with an increased relapse risk, supporting our results. Tani et al.[48] found an overall increase in relapse risk by 96% with dose reduction analyzing RCTs. However, their results were based on a smaller sample than our study (n=1385vs.n=3282), and they used a different classification of doses comparing the effectiveness of ≤vs.>200mg chlorpromazine equivalents. These authors found that reduction to antipsychotic doses below ≤200mg chlorpromazine equivalents was associated with a 2-3-fold increased risk of relapse compared to doses >200mg chlorpromazine equivalents. Our meta-regression analysis, found a similar pattern, with an increased risk of both relapse and all-cause discontinuation, with doses <200mg chlorpromazine equivalents. Furthermore, Bogers et al.[49] investigated predictors of relapse in both clinical trials and observational studies (n=1677), finding that a reduction below 5 mg haloperidol equivalents (corresponding to 10mg olanzapine, i.e., the lower limit of SD that we adopted for olanzapine) was associated with a 2·5-fold increase in relapse-risk versus 5-15mg haloperidol equivalents per day (0·67 versus 0·27 relapse per person-year). A notable difference between these two studies[48,49] and the present analysis is that they were not confined to studies lasting ≥24 weeks, but included a number of short-term studies potentially overestimating the risk of relapse with dose-reduction.

A major rationale to reduce antipsychotic dose is to reduce side effects. However, we found that most side effect outcomes, including intolerability-related discontinuations, did not differ between dose groups. Furthermore, where differences occurred, they were largely in the VLD versus SD comparison (i.e. reduced weight gain and prolactin elevation) and not in the more clinically relevant LD versus SD comparison.

Our findings on side effects need to be interpreted with caution. First, only a limited number of trials reported these outcomes (13 trials for intolerability-related discontinuation, six for weight gain, five for anticholinergic use and less for the other side effect outcomes). Second, anticholinergic use and intolerability-related discontinuation are crude proxies for extrapyramidal symptoms and overall adverse effect burden respectively. Accurate assessment of adverse effects requires standardized rating instruments, ideally clinician-administered, complemented by measurement of body weight and metabolic indices. Consequently, in most cases, our data cannot reliably answer the question of whether antipsychotic dose reduction reduces adverse effect burden and related discontinuations. Additionally, some RCTs in the meta-analysis randomized participants to different doses of the pre-trial antipsychotic which would reduce side effects differences between doses, as participants were chosen on the basis of having already tolerated the antipsychotic. Our side effect findings appear most reliable in terms of weight change and serum prolactin; both are single objective measures with data from six and four trials respectively. In each case, there was no difference between SD and LD.

We did not find any significant difference between the 3 dose groups in terms of hospitalization. This may initially seem counterintuitive. However, RCTs require close monitoring of participants and once relapse criteria are met subjects are withdrawn from a trial, minimizing the risk of subsequent hospitalization. In clinical practice, dose reduction in stable patients is likely to be accompanied by less stringent longitudinal assessments, and as such the risk of hospitalization may be higher.

The strengths of our study have already been considered under 'Added value of this study'. Several limitations need to be considered. First, although we included almost twice as many RCTs and 2-3-fold more patients than the prior meta-analyses using a similar design[16], the total number of trials lasting ≥ 24 weeks, randomizing patients to ≥2 doses of the same antipsychotic within ≥2 of our three dose ranges imposed a limit to the number of trials eligible for inclusion and meta-analysis. Second, several included RCTs had small sample sizes, increasing the risk of small study effects, potentially inflating the results in subgroup analyses. Third, analyses of all secondary outcomes beyond total psychopathology were inadequately powered and can, thus, only be regarded as exploratory. This pertains particularly to the stratified analyses. However, results remained generally consistent. Fourth, studies providing data for the meta-analysis included 6 different oral SGAs and 3 oral FGAs, as well as 2 FGA-LAIs and 2 SGA-LAIs . Thus, although the results likely generalize to other antipsychotics, which all share the same basic mechanism of action of dopamine D2-receptor blockade, future RCTs with antipsychotics not included in the analyses are needed to substantiate this general assumption. Fifth, the definitions of clinical stability at baseline and of relapse varied considerably between the studies. Lastly, our results only apply to patients with multi-episode schizophrenia, and cannot be generalized to first-episode or treatment-resistant schizophrenia where different doses (generally lower in first-episode schizophrenia) and antipsychotics (clozapine for treatment-resistant schizophrenia) are used/recommended.[52] Particularly, the pharmacological treatment of first-episode schizophrenia differs from multi-episode schizophrenia with regards to higher antipsychotic response rates[50], response occurring at lower doses but with a greater adverse effect risk[18] and in that a minority of patients experience only one episode and do not require long-term antipsychotic treatment.[51]

In conclusion, this meta-analysis indicates that the dose of antipsychotic maintenance treatment should likely not be reduced below the recommended dose ranges for acute treatment because of the associated significantly increased risk of relapse and all-cause discontinuation with their known adverse impact on overall outcome.[5] Our findings should inform future CPG, which currently vary significantly on their recommendations on this area. However, our findings are restricted to multi-episode schizophrenia patients.

Additional high-quality RCTs are required to examine the effect of dose reduction during maintenance treatment. This applies particularly to dopamine partial agonists as only one study of such a drug was included in our review. Studies should report key outcomes in a time-based fashion and examine ≥2 different dose-groups. Future studies should adopt a 'dose reduction' design, rather than switch designs. Side effects should be assessed using validated tools. The criteria used to define stability at trial entry and relapse should be clearly stated, and more uniform criteria be adopted.

**Contributors**
CUC, PMH and JCN formulated the research question. MH and AFK did the literature search. MH, AFK and PMH selected the articles and extracted outcome data. MH did the statistical analyses. MH, AFK, PMH and CUC drafted the report. All authors critically reviewed/revised the report and approved the final version.

**Declaration of interests**
In the last 3 years, PMH has received honoraria for lecturing and/or consultancy from Janssen, Lundbeck, NewBridge Pharmaceuticals, Otsuka and Sunovion.
In the last 3 years, JCN has received honoraria for consultancy from Janssen and Lundbeck.
In the last 3 years, CUC reports personal fees from Acadia, Alkermes, Allergan, Angelini, Axsome, Gedeon Richter-Recordati, Gerson Lehrman Group, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Neurocrine, Noven, Otsuka, Pfizer, Rovi, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. , personal fees from Bristol-Myers Squibb, Janssen, and Otsuka, other from UpToDate, other from LB Pharma, outside the submitted work.
MH and AFK have no conflicts of interest to declare

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**Data sharing statement**
The collected study-level data and statistical code for analyses are available upon request to the authors. The study protocol is available at: https://doi.org/10.17605/OSF.IO/VA7X2

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**Figure 1: Flow diagram of study review and selection**

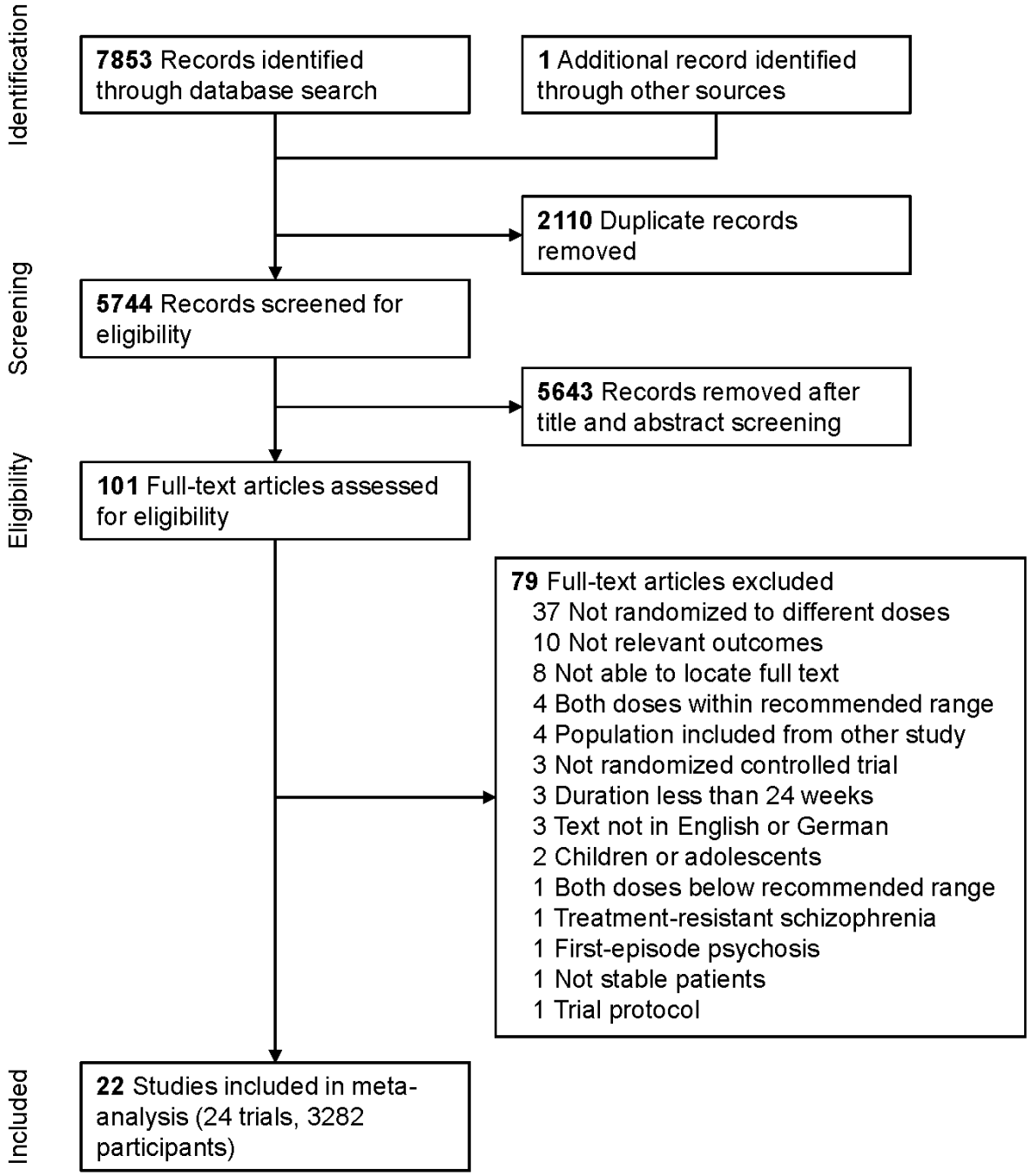
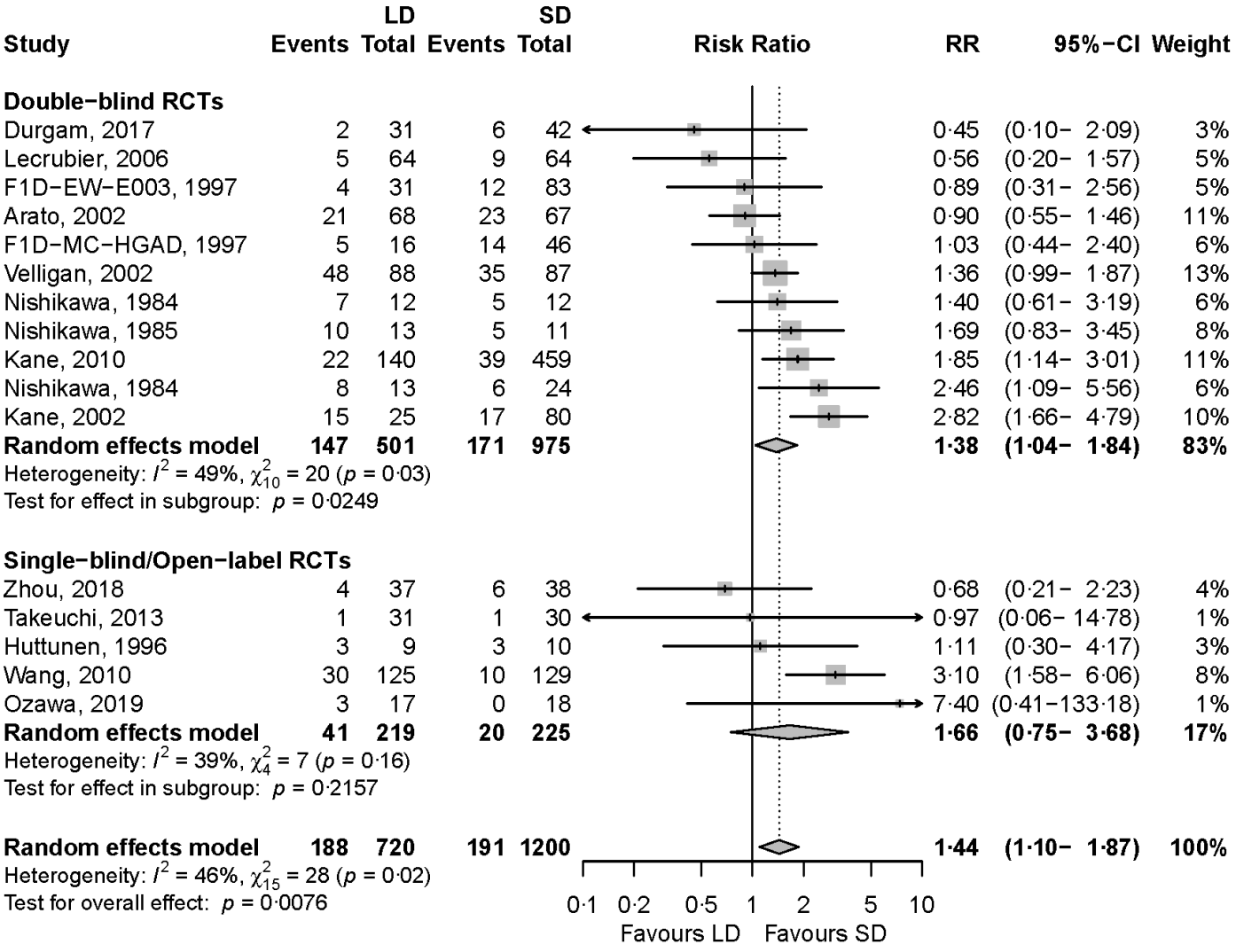
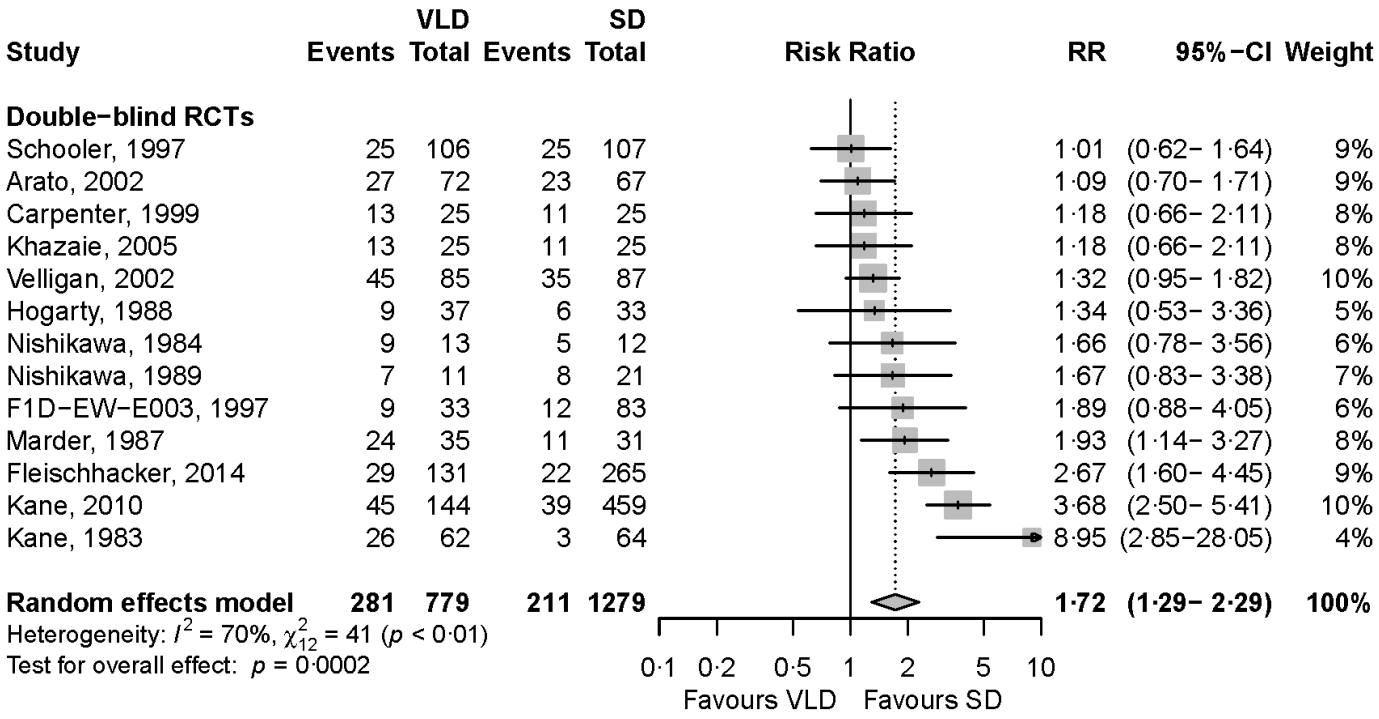


**Figure 2: Forest plots for risk of relapse.**
**A: Low versus standard doses**



**B: Very low versus standard doses**



**C: Very low versus low doses**

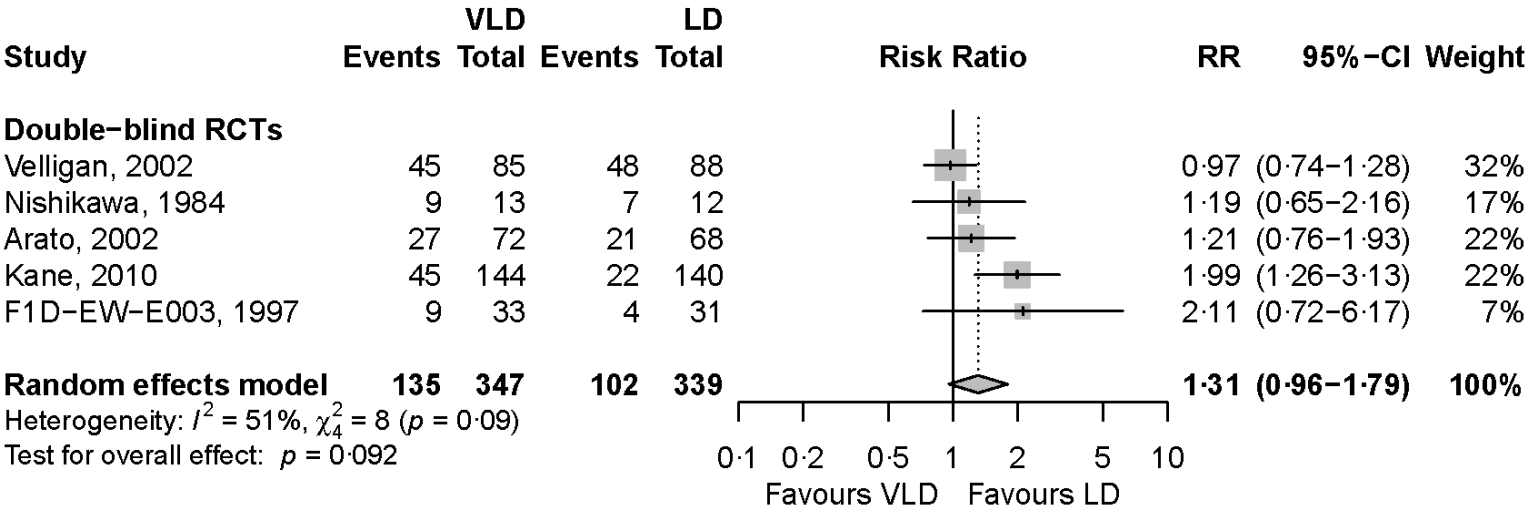
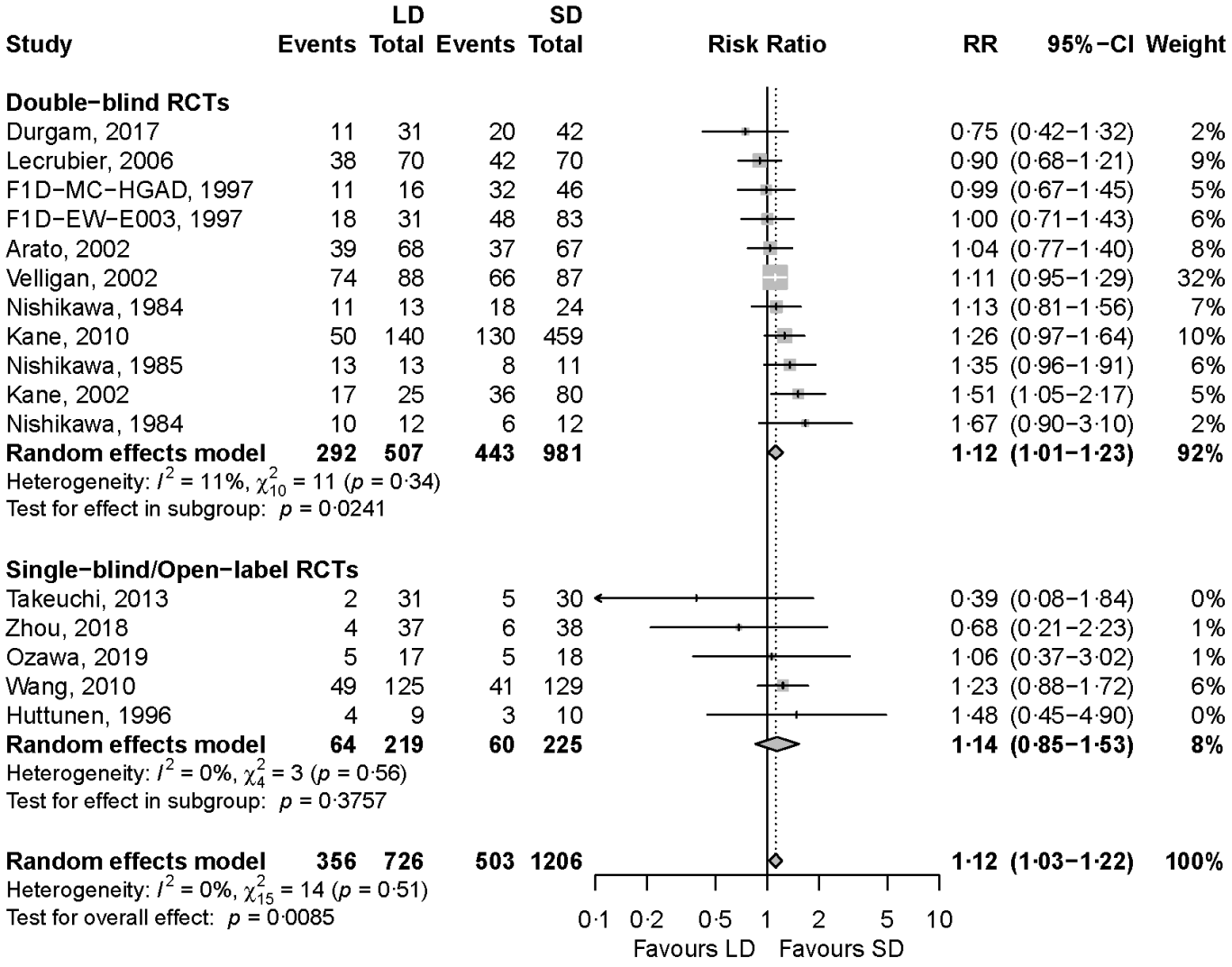
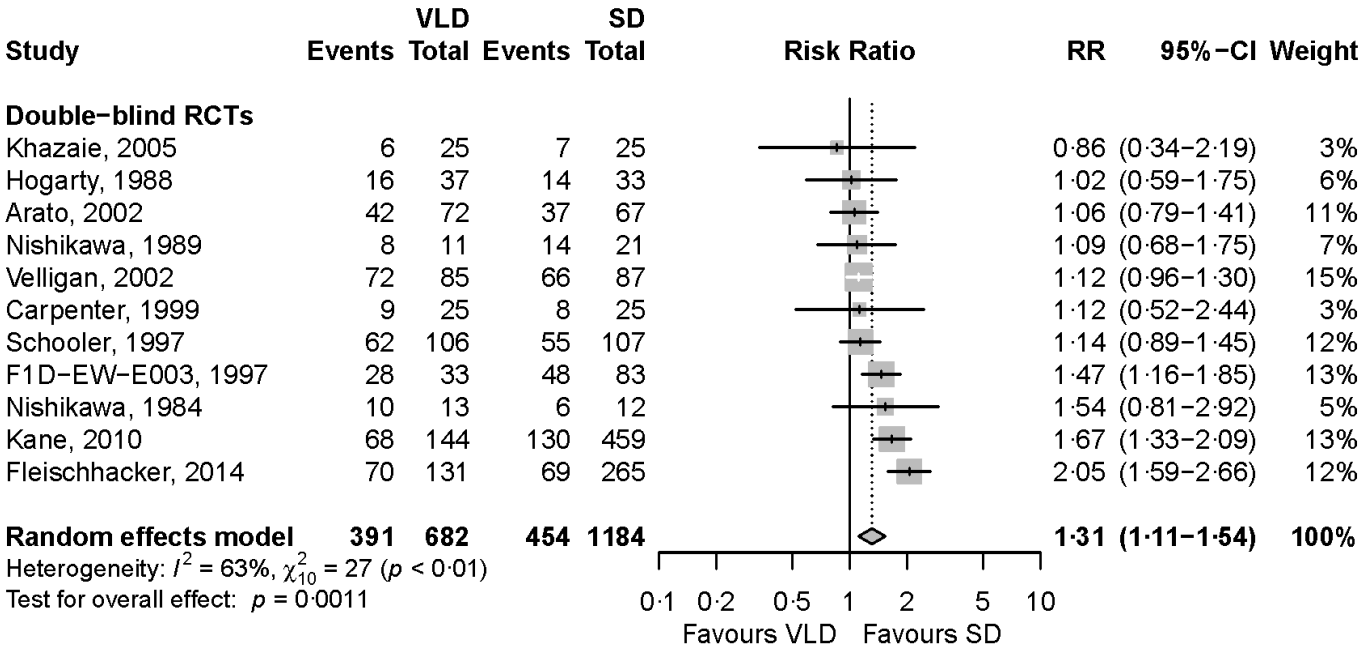


**Figure 3: Forest plots for risk of all-cause discontinuation.**
**A: Low versus standard doses**



**B: Very low versus standard doses**



**C: Very low versus low doses.**

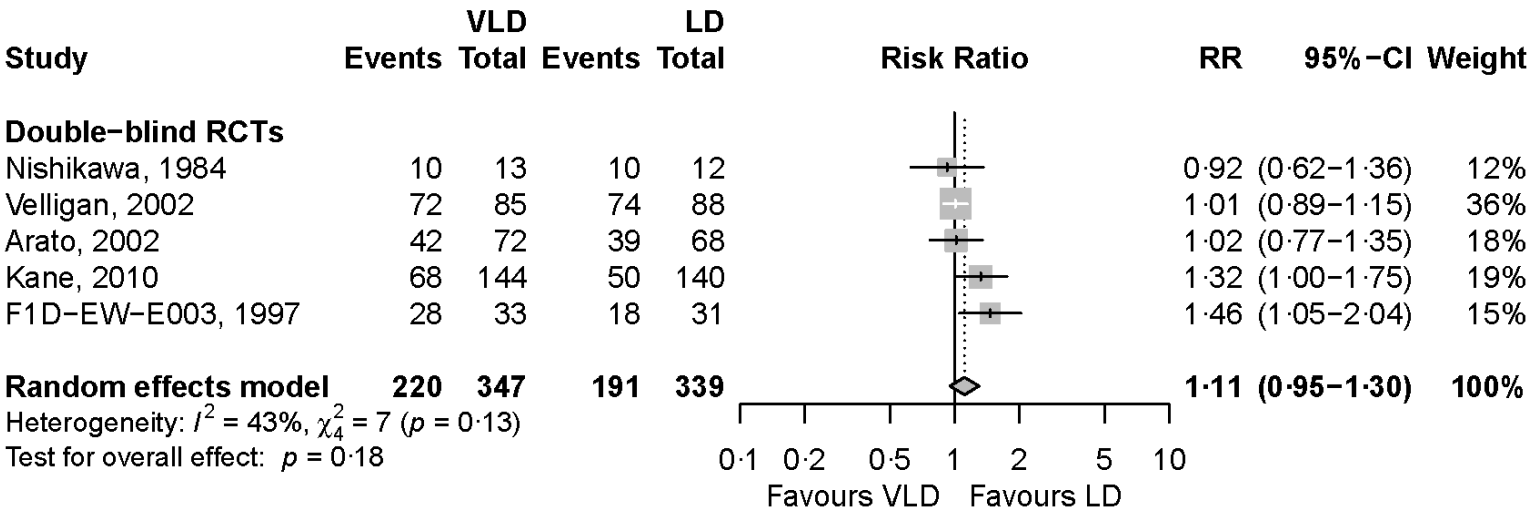
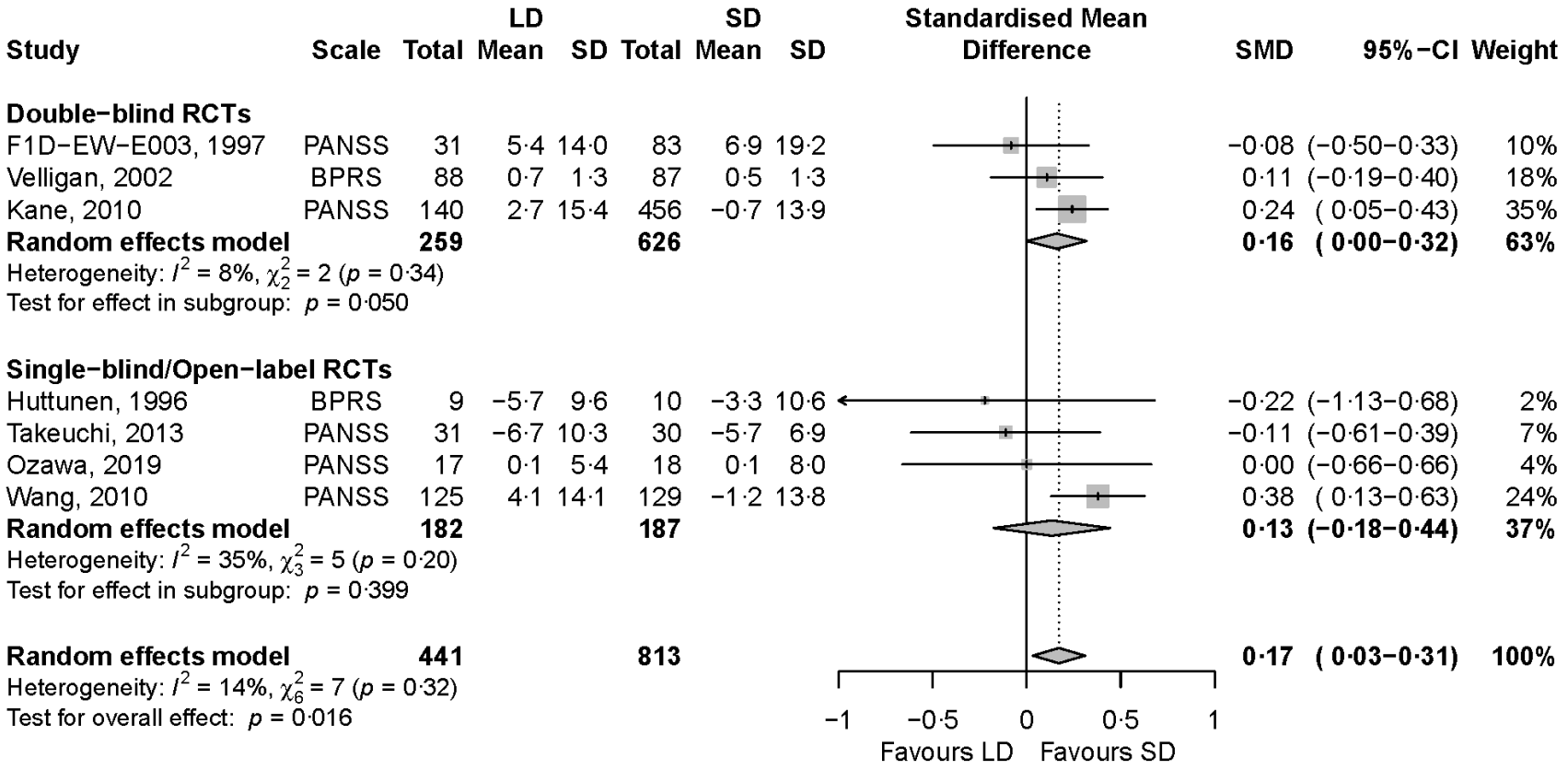
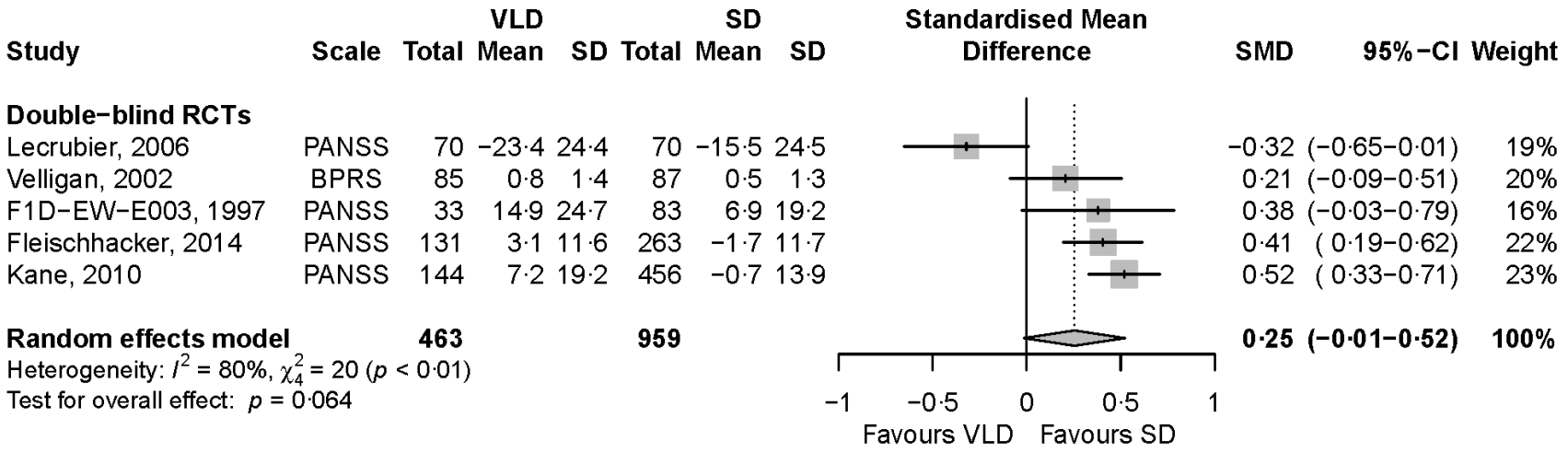


**Figure 4: Forest plots for change in total psychopathology. PANSS: The Positive and Negative Syndrome Scale for schizophrenia; BPRS: The Brief Psychiatric Rating Scale.**
**A: Low versus standard doses**



**B: Very low versus standard doses**




**C: Very low versus low doses.**

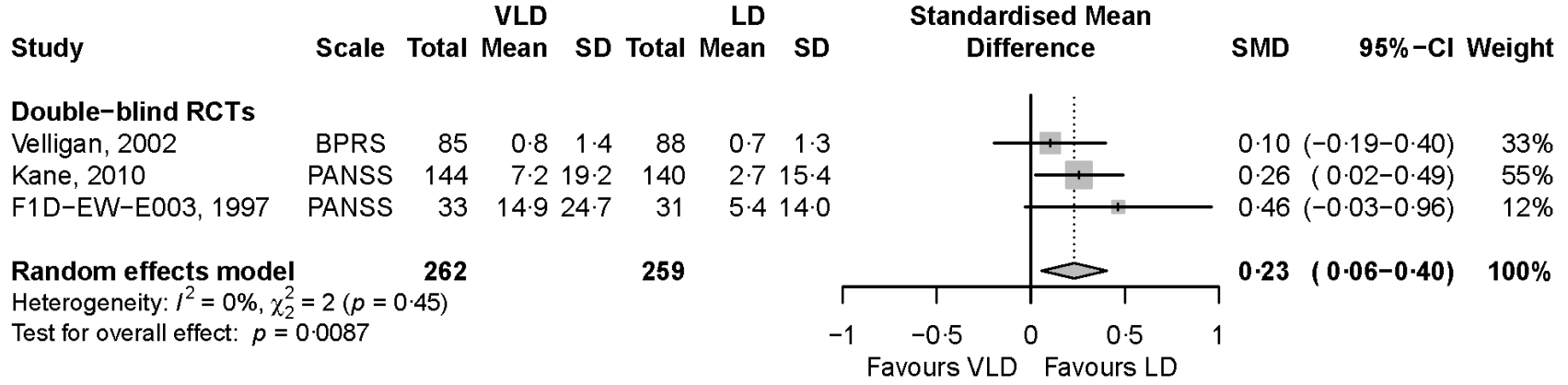


**Table 1: Characteristics of included randomized controlled trials (3282 patients in total)**

| Study (year), ref, total number of participants in included arms | Design/Blinding | Antipsychotic (LL, DDD, OLA) | LL dose groups (participants, % of LL) | DDD dose groups (participants, % of DDD (only shown if DDD ≠ LL)) | Duration (weeks) | Overall risk of bias assessment | Mean age (years)/Male (%)/Female (%) | Mean illness duration (years)/No. hospitalisations | Overall drop-out rate (%)/Patients lost to follow-up (%). |
|---|---|---|---|---|---|---|---|---|---|
| **Oral FGAs (N=98)** | | | | | | | | | |
| Nishikawa et al (1984)[23], N=37 | SW/DB | Periciazine (20mg/d, 50mg/d, 2·5mg) | SD: 30-60mg/d (N=24, 150-300%) | SD: 60mg/d (N=12, 120%) | 52 | Some concerns | 39 years 51%/49% | 8·9/4·1 | 78/12 |
| | | | LD: 10mg/d (N=13, 50%) | LD: 30mg/d (N=12, 60%) | | | | | |
| | | | VLD: - | VLD: 10mg/d (N=13, 20%) | | | | | |
| Nishikawa et al (1984)[23], N=37 | SW/DB | Haloperidol (5mg/d, 8mg/d, 0·5mg) | SD: 6mg/d (N=12, 120%) | SD: - | 52 | Some concerns | 40 years 68%/32% | 8·7/3·5 | 70/11 |
| | | | LD: 3mg/d (N=12, 60%) | LD: 6mg/d (N=12, 75%) | | | | | |
| | | | VLD: 1mg/d (N=13, 20%) | VLD: 1-3mg/d (N=25, 12·5-37·5%) | | | | | |
| Nishikawa et al (1985)[24], N=24 | SW/DB | Pimozide (4mg/d, 4mg/d, 0·4mg) | SD: 6mg/d (N=11, 150%) | | 52 | Some concerns | 39 years 79%/21% | 13·0/3·3 | 88/17 |
| | | | LD: 2mg/d (N=13, 50%) | | | | | | |
| | | | VLD: - | | | | | | |
| **Oral SGAs (N=1346)** | | | | | | | | | |
| Arato et al (2002)[25], N=207 | SW/DB | Ziprasidone (120mg/d, 80mg/d, 8mg) | SD: 160mg/d (N=67, 133%) | SD: 80-160mg/d (N=135, 100-200%) | 52 | Some concerns | 50 years 70%/30% | 21·9/9·4 | 57/12 |
| | | | LD: 80mg/d (N=68, 67%) | LD: 40mg/d (N=72, 50%) | | | | | |
| | | | VLD: 40mg/d (N=72, 33%) | VLD: - | | | | | |
| Durgam et al (2017)[26], N=73 | EX/DB | Asenapine (10mg/d, 20mg/, 0·99mg) | SD: 10mg/d (N=42, 100%) | SD: - | 26 | Some concerns | 40 years 59%/41% | 12·0/NA | 42/29 |
| | | | LD: 5mg/d (N=31, 50%) | LD: 10mg/d (N=42, 50%) | | | | | |
| | | | VLD: - | VLD: 5mg/d (N=31, 25%) | | | | | |
| Eli-Lilly Ltd. F1D-EW-E003 (1997)[28]*, N=147 | EX/DB | Olanzapine (10mg/d, 10mg, 1mg) | SD: 10-15mg/d (N=83, 100-150%) | | 46 | Some concerns | 36 years 66%/34% | NA/NA | 64/24 |
| | | | LD: 5mg/d (N=31, 50%) | | | | | | |
| | | | VLD: 1mg/d (N=33, 10%) | | | | | | |
| Eli-Lilly Ltd. F1D-MC-HGAD (1997)[29]*, N=62 | EX/DB | Olanzapine (10mg/d, 10mg, 1mg) | SD: 10-15mg/d (N=46, 100-150%) | | 46 | Some concerns | 36 years 82%/18% | NA/NA | 69/NA |
| | | | LD: 5mg/d (N=16, 50%) | | | | | | |
| | | | VLD: - | | | | | | |
| Lecrubier et al (2006)[30], N=140 | SW/DB | Olanzapine (10mg/d, 10mg, 1mg) | SD: 20mg/d (N=70, 200%) | | 26 | Some concerns | 37 years 67%/33% | 10·6/NA | 57/17 |
| | | | LD: 5mg/d (N=70, 50%) | | | | | | |
| | | | VLD: - | | | | | | |

**Table 1: Characteristics of included randomized controlled trials (Total N=3282 pts.) (continued)**

| Study (year), ref, total number of participants | Design/Blinding | Antipsychotic (LL, DDD, OLA) | LL dose groups (participants, % of LL) | DDD dose groups (participants, % of DDD (only shown if DDD ≠ LL)) | Duration (weeks) | Overall risk of bias assessment | Mean age/Male (%)/Female(%) | Mean illness duration (years)/No. hospitalisations | Overall drop-out rate (%)/Patients lost to follow-up (%). |
|---|---|---|---|---|---|---|---|---|---|
| Nishikawa et al (1989)[31], N=32 | SW/DB | Sulpiride (300mg/d, 800mg/d, 40mg) | SD: 300-600mg/d (N=21, 100-200%) | | 52 | Some concerns | 40 years 69%/31% | 15·3/3·1 | 69/13 |
| | | | LD: - | LD: 600mg/d (N=11, 75%) | | | | | |
| | | | VLD: 100mg/d (N=11, 33%) | VLD: 100-300mg/d (N=21, 12·5-37·5%) | | | | | |
| Velligan et al (2002)[32], N=260 | SW/DB | Quetiapine (400mg/d, 400mg/d, 37mg) | SD: 600mg/d (N=87, 150%) | | 52 | Some concerns | 38 years 78%/22% | NA/NA | 82/15 |
| | | | LD: 300mg/d (N=88, 67%) | | | | | | |
| | | | VLD: 75mg/d (N=85, 19%) | | | | | | |
| Ozawa et al (2019)[42], N=35 | DR/OL | Olanzapine (10mg/d, 10mg/d, 1mg) / Risperidone (4mg/d, 5mg, 0·3mg) | SD: 15·8mg/d† (N=9, 158%) / 4·3mg/d†‡ (N=9, 108%) | ‡ | 52 | Low | 64 years 66%/34% | 35·8/4·8 | 29/14 |
| | | | LD: 6·7mg/d† (N=7, 67%) / 1.4mg/d†‡ (N=10, 35%) | ‡ | | | | | |
| | | | VLD: - | ‡ | | | | | |
| Takeuchi et al (2013)[43], N=61 | DR/OL | Olanzapine (10mg/d, 10mg/d, 1mg) / Risperidone (4mg/d, 5mg/d, 0·3mg) | SD: 14·1mg/d† (N=19, 141%) / 4·5mg/d†‡ (N=11, 113%) | ‡ | 28 | Some concerns | 40 years 61%/39% | 14·2/1·5 | 11/5 |
| | | | LD: 7·1mg/d† (N=19, 71%) / 2·1mg/d†‡ (N=12, 53%) | ‡ | | | | | |
| | | | VLD: - | ‡ | | | | | |
| Wang et al (2010)[44], N=254 | DR/OL | Risperidone (4mg/d, 5mg/d, 0·3mg) | SD: 4·3mg/d† (N=129, 108%) | | 52 | Some concerns | 33 years 44%/56% | 6·7/NA | 35/14 |
| | | | LD: 2·2mg/d† (N=125, 55%) | LD: 4·3mg/d† (N=129, 86%) | | | | | |
| | | | VLD: - | VLD: 2·2mg/d† (N=125, 44%) | | | | | |
| Zhou et al (2018)[45], N=75 | DR/OL | Olanzapine (10mg/d, 10mg/d, 1mg) / Risperidone (4mg/d, 5mg/d, 0·5mg) | SD: 17·2 mg/d† (N=9, 172%) / 4·9 mg/d† (N=29, 123%) | ‡ | 52 | Some concerns | 45 years 60%/40% | NA/NA | 13/0 |
| | | | LD: 7·8mg/d† (N=10, 78%) / 3·3mg/d† (N=27, 83%) | ‡ | | | | | |
| | | | VLD: - | ‡ | | | | | |

**Table 1: Characteristics of included randomized controlled trials (Total N=3282 pts.) (continued)**

| Study (year), ref, total number of participants | Design/Blinding | Antipsychotic (LL, DDD, OLA) | LL dose groups (participants, % of LL) | DDD dose groups (participants, % of DDD (only shown if DDD ≠ LL)) | Duration (weeks) | Overall risk of bias assessment | Mean age/Male (%)/Female(%) | Mean illness duration (years)/No. hospitalisations | Overall drop-out rate (%)/Patients lost to follow-up (%). |
|---|---|---|---|---|---|---|---|---|---|
| **FGA LAIs (N=699)** | | | | | | | | | |
| Carpenter et al (1999)[41], N=50 | DR/DB | Fluphenazine decanoate (25mg/2wk, 14mg/2wk, 0·09mg) | SD: 25mg/2wk (N=25, 100%)<br>LD: -<br>VLD: 25mg/6wk (N=25, 33%) | SD: 25mg/2wk (N=25, 179%)<br>LD: 25mg/6wk (N=25, 60%)<br>VLD: - | 54 | Some concerns | 36 years 72%/28% | 13·0/NA | 34/8 |
| Hogarty et al (1988)[33], N=70 | DR/DB | Fluphenazine decanoate (25mg/2wk, 14mg/2wk, 0·09mg) | SD: 25mg/2wk† (N=33, 100%)<br>LD: -<br>VLD: 3·8mg/2wk† (N=37, 15%) | SD: 25mg/2wk† (N=33, 179%)<br>LD: -<br>VLD: 3·8mg/2wk† (N=37, 27%) | 104 | High | 28 years 57%/43% | 7·0/NA | 43/4 |
| Kane et al (1983)[34], N=126 | DR/DB | Fluphenazine decanoate (25mg/2wk, 14mg/2wk, 0·09mg) | SD: 12·5-50mg/2wk† (N=64, 50-200%)<br>LD: -<br>VLD: 1·25-5mg/2wk† (N=62, 5-20%) | SD: 12·5-50mg/2wk† (N=64, 89-357%)<br>LD: -<br>VLD: 1·25-5mg/2wk† (N=62, 9-36%) | 52 | Some concerns | 29 years 49%/51% | NA/3·2 | 23/NA |
| Kane et al (2002)[35], N=105 | SW/DB | Haloperidol decanoate (50mg/4wk, 92mg/4wk, 0·27mg) | SD: 50-200mg/4wk (N=80, 100-400%)<br>LD: 25mg/4wk (N=25, 50%)<br>VLD: - | SD: 100-200mg/4wk (N=52, 109-217%)<br>LD: 50mg/4wk (N=28, 54%)<br>VLD: 25mg/4wk (N=25, 27%) | 52 | Some concerns | 39 years 83%/17% | 14·5/5·5 | 50/10 |
| Khazaie and Shakeri (2005)[36], N=50 | DR/DB | Fluphenazine decanoate (25mg/2wk, 14mg/2wk, 0·09mg) | SD: 25mg/2wk (N=25, 100%)<br>LD: -<br>VLD: 25mg/6wk (N=25, 33%) | SD: 25mg/2wk (N=25, 179%)<br>LD: 25mg/6wk (N=25, 60%)<br>VLD: - | 54 | Some concerns | 34 years 72%/28% | 12·0/NA | 26/4 |
| Marder et al (1987)[37], N=66 | SW/DB | Fluphenazine decanoate (25mg/2wk, 14mg/2wk, 0·09mg) | SD: 25mg/2wk (N=31, 100%)<br>LD: -<br>VLD: 5mg/2wk (N=35, 20%) | SD: 25mg/2wk (N=31, 179%)<br>LD: -<br>VLD: 5mg/2wk (N=35, 36%) | 104 | Some concerns | 37 years 100%/0% | 12·7/NA | 53/NA |

**Table 1: Characteristics of included randomized controlled trials (Total N=3282 pts.) (continued)**

| Study (year), ref, total number of participants | Design/Blinding | Antipsychotic (LL, DDD, OLA) | LL dose groups (participants, % of LL) | DDD dose groups (participants, % of DDD (only shown if DDD ≠ LL)) | Duration (weeks) | Overall risk of bias assessment | Mean age/Male (%)/Female(%) | Mean illness duration (years)/No. hospitalisations | Overall drop-out rate (%)/Patients lost to follow-up (%). |
|---|---|---|---|---|---|---|---|---|---|
| Schooler et al (1997)[38], N=213 | DR/DB | Fluphenazine decanoate (25mg/2wk, 14mg/2wk, 0·09mg) | SD: 12·5-50mg/2wk† (N=107, 50-200%) | SD: 12·5-50mg/2wk† (N=107, 89-357%) | 104 | Some concerns | 30 years 66%/33% | NA/NA | 55/NA |
| | | | LD: - | LD: - | | | | | |
| | | | VLD: 2·5-10mg/2wk† (N=106, 10-40%) | VLD: 2·5-10mg/2wk† (N=106, 18-71%) | | | | | |
| Huttunen et al (1996)[46], N=19 | SW/OL | Haloperidol decanoate (50mg/4wk, 92mg/4wk, 0·27mg) | SD: 150mg/4wk (N=10, 300%) | SD: 150mg/4wk (N=10, 163%) | 104 | High | NA 53%/47% | NA/NA | 37/0 |
| | | | LD: 25mg/4wk (N=9, 50%) | LD: - | | | | | |
| | | | VLD: - | VLD: 25mg/4wk (N=9, 27%) | | | | | |
| **SGA LAIs (N=1139)** | | | | | | | | | |
| Fleischhacker et al (2014)[39], N=396 | DR/DB | Aripiprazole monohydrate (400mg/4wk, 372mg/4wk, 1·33mg) | SD: 400mg/4wk (N=265, 100%) | SD: 400mg/4wk (N=265, 108%) | 38 | High | 41 years 60%/40% | NA/NA | 35/18 |
| | | | LD: - | LD: - | | | | | |
| | | | VLD: 50mg/4wk (N=131, 13%) | VLD: 50mg/4wk (N=131, 13%) | | | | | |
| Kane et al (2010)[40], N=743 | DR/DB | Olanzapine pamoate (210mg/2wk, 140mg/2wk, 1mg) | SD: 405mg/4wk or 300mg/2wk (N=459, 96-143%) | SD: 405mg/4wk or 300mg/2wk or 150mg/2wk (N=599, 107-214%) | 24 | Low | 39 years 66%/34% | NA/NA | 33/14 |
| | | | LD: 150mg/2wk (N=140, 71%) | LD: - | | | | | |
| | | | VLD: 45mg/4wk (N=144, 11%) | VLD: 45mg/4wk (N=144, 16%) | | | | | |

Notes: *Reported in Dellva et al (1997)[27], †Dose reported as mean dose of group, ‡Results did not allow separation of outcome for risperidone users and they were classified as "low dose" together with olanzapine users even though mean dose is <50% of LL. We classified trials as having one of three designs: 1) Switch studies, i.e., patients were randomized from an existing antipsychotic to a new antipsychotic at two or more doses or different doses of the same antipsychotic, 2) Dose reduction studies, i.e., patients were randomized to continue an existing dose of an antipsychotic or to a lower dose of that same antipsychotic, or 3) Extension studies, i.e., patients continued doses that they had been randomized to in an acute phase study. Overall drop-out rate refers to the proportion of those randomized who discontinued the trial for any reason (including those lost to follow-up). Patients lost to follow-up refers to the proportion of those randomized who left the trial early and were classified as either "lost to follow-up", "moved", "excluded for protocol variance", or "withdrew consent".

Abbreviations: d: day, DB: Double-Blind, DDD: Defined Daily Dose (according to the WHO Collaborating Centre for Drug Statistics Methodology ATC/DDD-index), DR: Dose-reduction, EX: Extension (of acute phase study), FGA: First-generation antipsychotic, LAI: Long-acting injectable antipsychotic, LD: Low dose group (50-99% of LL/DDD), LL: Lower limit of recommended maintenance dose from Gardner et al.[18], Leucht et al.[19], or Rothe et al.[20], NA: Not available, OL: Open label, OLA: Olanzapine equivalents (daily dose equivalent to 1mg of oral olanzapine from Gardner et al.[18], Leucht et al.[19], or Rothe et al.[20]), SD: Standard dose group (≥100% of LL/DDD), SGA: Second-generation antipsychotic, SW: Switching (from other antipsychotic at randomization), VLD: Very low dose group (>50% of LL/DDD), wk: Week.

## Table 2: Subgroup analysis of co-primary outcomes by antipsychotic type and formulation

| | | | Effect size | | Subgroup comparison | Heterogeneity | | Effect size |
|---|---|---|---|---|---|---|---|---|
| | **Trials (N)** | **Participants (N)** | **RR (95%CI)** | **p-value** | **p-value** | **I2 (%)** | **p-value** | **NNH (95%CI)** |
| **Low vs Standard Antipsychotic Maintenance Dose** | | | | | | | | |
| Relapse | | | | | | | | |
| FGA | 5 | 209 | 2·08 (1·49-2·90) | **<0·0001** | **0·026** | 0 | 0·48 | 3 (2-6) |
| SGA | 11 | 1711 | 1·23 (0·88-1·70) | 0·22 | | 46 | 0·048 | NA |
| OAP | 13 | 1197 | 1·29 (0·96-1·72) | 0·09 | **0·043** | 38 | 0·08 | NA |
| LAI | 3 | 723 | 2·13 (1·44-3·14) | **0·00015** | | 15 | 0·31 | 6 (2-16) |
| All-cause discontinuation | | | | | | | | |
| FGA | 5 | 209 | 1·34 (1·11-1·63) | **0·0025** | **0·036** | 0 | 0·74 | 5 (3-11) |
| SGA | 11 | 1723 | 1·07 (0·97-1·18) | 0·17 | | 0 | 0·65 | NA |
| OAP | 13 | 1209 | 1·08 (0·98-1·18) | 0·11 | 0·058 | 0 | 0·63 | NA |
| LAI | 3 | 723 | 1·35 (1·09-1·66) | **0·0055** | | 0 | 0·72 | 10 (6-56) |
| **Very low vs Standard Antipsychotic Maintenance Dose** | | | | | | | | |
| Relapse | | | | | | | | |
| FGA | 7 | 600 | 1·55 (1·06-2·28) | **0·024** | 0·51 | 58 | 0·028 | 6 (3-40) |
| SGA | 6 | 1458 | 1·88 (1·22-2·90) | **0·004** | | 79 | 0·00024 | 6 (5-10) |
| OAP | 5 | 484 | 1·35 (1·08-1·69) | **0·0081** | 0·15 | 0 | 0·69 | 9 (5-35) |
| LAI | 8 | 1574 | 1·94 (1·25-3·01) | **0·003** | | 78 | <0·0001 | 6 (4-13) |
| All-cause discontinuation | | | | | | | | |
| FGA | 5 | 408 | 1·14 (0·93-1·39) | 0·20 | 0·20 | 0 | 0·85 | NA |
| SGA | 6 | 1458 | 1·38 (1·11-1·72) | **0·0038** | | 79 | 0·00025 | 6 (4-11) |
| OAP | 5 | 484 | 1·20 (1·04-1·38) | **0·011** | 0·35 | 23 | 0·27 | 8 (4-32) |
| LAI | 6 | 1382 | 1·39 (1·06-1·81) | **0·018** | | 67 | 0·0093 | 8 (4-34) |
| **Very low vs Low Antipsychotic Maintenance Dose** | | | | | | | | |
| Relapse | | | | | | | | |
| FGA | 1 | 25 | 1·19 (0·65-2·16) | 0·58 | 0·71 | NA | NA | NA |
| SGA | 4 | 661 | 1·36 (0·92-2·01) | 0·13 | | 63 | 0·044 | NA |
| OAP | 4 | 402 | 1·08 (0·87-1·34) | 0·49 | **0·017** | 0 | 0·49 | NA |
| LAI | 1 | 284 | 1·99 (1·26-3·13) | **0·003** | | NA | NA | 6 (4-17) |
| All-cause discontinuation | | | | | | | | |
| FGA | 1 | 25 | 0·92 (0·62-1·36) | 0·69 | 0·32 | NA | NA | NA |
| SGA | 4 | 661 | 1·15 (0·96-1·37) | 0·14 | | 54 | 0·091 | NA |
| OAP | 4 | 402 | 1·06 (0·91-1·25) | 0·45 | 0·19 | 35 | 0·2 | NA |
| LAI | 1 | 284 | 1·32 (1·00-1·75) | 0·052 | | NA | NA | NA |

Bolded values: p<0.05; CI: Confidence interval, FGA: First-generation antipsychotic, LAI: Long-acting injectable antipsychotic, OAP: Oral antipsychotic, NA: Not applicable, NNH: Number needed to harm, RR: Risk ratio, SGA: Second-generation antipsychotic