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Antipsychotic dose reduction compared to dose continuation for people with schizophrenia (Review)

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[Intervention Review]

Antipsychotic dose reduction compared to dose continuation for people with schizophrenia

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ABSTRACT

Background

Antipsychotic drugs are the mainstay treatment for schizophrenia, yet they are associated with diverse and potentially dose-related side effects which can reduce quality of life. For this reason, the lowest possible doses of antipsychotics are generally recommended, but higher doses are often used in clinical practice. It is still unclear if and how antipsychotic doses could be reduced safely in order to minimise the adverse-effect burden without increasing the risk of relapse.

Objectives

To assess the efficacy and safety of reducing antipsychotic dose compared to continuing the current dose for people with schizophrenia.

Search methods

We conducted a systematic search on 10 February 2021 at the Cochrane Schizophrenia Group's Study-Based Register of Trials, which is based on CENTRAL, MEDLINE, Embase, CINAHL, PsycINFO, PubMed, ClinicalTrials.gov, ISRCTN, and WHO ICTRP. We also inspected the reference lists of included studies and previous reviews.

Selection criteria

We included randomised controlled trials (RCTs) comparing any dose reduction against continuation in people with schizophrenia or related disorders who were stabilised on their current antipsychotic treatment.

Data collection and analysis

At least two review authors independently screened relevant records for inclusion, extracted data from eligible studies, and assessed the risk of bias using RoB 2. We contacted study authors for missing data and additional information. Our primary outcomes were clinically important change in quality of life, rehospitalisations and dropouts due to adverse effects; key secondary outcomes were clinically

important change in functioning, relapse, dropouts for any reason, and at least one adverse effect. We also examined scales measuring symptoms, quality of life, and functioning as well as a comprehensive list of specific adverse effects. We pooled outcomes at the endpoint preferably closest to one year. We evaluated the certainty of the evidence using the GRADE approach.

Main results

We included 25 RCTs, of which 22 studies provided data with 2635 participants (average age 38.4 years old). The median study sample size was 60 participants (ranging from 18 to 466 participants) and length was 37 weeks (ranging from 12 weeks to 2 years). There were variations in the dose reduction strategies in terms of speed of reduction (i.e. gradual in about half of the studies (within 2 to 16 weeks) and abrupt in the other half), and in terms of degree of reduction (i.e. median planned reduction of 66% of the dose up to complete withdrawal in three studies). We assessed risk of bias across outcomes predominantly as some concerns or high risk.

No study reported data on the number of participants with a clinically important change in quality of life or functioning, and only eight studies reported continuous data on scales measuring quality of life or functioning. There was no difference between dose reduction and continuation on scales measuring quality of life (standardised mean difference (SMD) −0.01, 95% confidence interval (CI) −0.17 to 0.15, 6 RCTs, n = 719, I^2 = 0%, moderate certainty evidence) and scales measuring functioning (SMD 0.03, 95% CI −0.10 to 0.17, 6 RCTs, n = 966, I^2 = 0%, high certainty evidence).

Dose reduction in comparison to continuation may increase the risk of rehospitalisation based on data from eight studies with estimable effect sizes; however, the 95% CI does not exclude the possibility of no difference (risk ratio (RR) 1.53, 95% CI 0.84 to 2.81, 8 RCTs, n = 1413, I^2 = 59% (moderate heterogeneity), very low certainty evidence). Similarly, dose reduction increased the risk of relapse based on data from 20 studies (RR 2.16, 95% CI 1.52 to 3.06, 20 RCTs, n = 2481, I^2 = 70% (substantial heterogeneity), low certainty evidence).

More participants in the dose reduction group in comparison to the continuation group left the study early due to adverse effects (RR 2.20, 95% CI 1.39 to 3.49, 6 RCTs with estimable effect sizes, n = 1079, I^2 = 0%, moderate certainty evidence) and for any reason (RR 1.38, 95% CI 1.05 to 1.81, 12 RCTs, n = 1551, I^2 = 48% (moderate heterogeneity), moderate certainty evidence).

Lastly, there was no difference between the dose reduction and continuation groups in the number of participants with at least one adverse effect based on data from four studies with estimable effect sizes (RR 1.03, 95% CI 0.94 to 1.12, 5 RCTs, n = 998 (4 RCTs, n = 980 with estimable effect sizes), I^2 = 0%, moderate certainty evidence).

Authors' conclusions

This review synthesised the latest evidence on the reduction of antipsychotic doses for stable individuals with schizophrenia. There was no difference between dose reduction and continuation groups in quality of life, functioning, and number of participants with at least one adverse effect. However, there was a higher risk for relapse and dropouts, and potentially for rehospitalisations, with dose reduction. Of note, the majority of the trials focused on relapse prevention rather potential beneficial outcomes on quality of life, functioning, and adverse effects, and in some studies there was rapid and substantial reduction of doses. Further well-designed RCTs are therefore needed to provide more definitive answers.

PLAIN LANGUAGE SUMMARY

Reduction in the dose of antipsychotics for people with schizophrenia

Key messages

Reducing the dose of antipsychotics may be associated with a higher number of study participants relapsing and leaving the study early.

Very little information was available on quality of life, functioning, and side effects.

Introduction to the review topic

Schizophrenia is a severe disease that needs treatment with medication (antipsychotics). Use of antipsychotics is connected with side effects, and it appears that these side effects may be worse with higher doses. On the other hand, the dose needs to be high enough to have an effect on the symptoms.

What did we want to find out?

We wanted to know if reducing the dose of antipsychotics is better than keeping the same dose, in order to improve:

- quality of life;
- number of participants readmitted to hospital;
- number of participants leaving the study early because of side effects;
- functioning;
- relapse;

- number of participants leaving the study early for any reason;
- number of participants with at least one side effect.

What did we do?

We searched for studies that examined reducing the dose of antipsychotics compared with keeping the same dose in people with schizophrenia.

We compared and summarised the results of the studies and rated our confidence in the evidence, based on factors such as study methods and sizes.

What did we find?

We found 25 studies involving a total of 2721 participants with schizophrenia. Twenty-two studies (2635 participants) provided data for the analyses. The studies lasted between 12 weeks and 2 years. They were conducted all over the world, including in the USA, the UK, Europe, and Asia. Fourteen studies were sponsored by public institutions, five by pharmaceutical companies, two by public institutions and pharmaceutical companies jointly, and four studies did not provide clear information on funding.

We found that dose reduction:

- probably has little to no effect on quality of life;
- makes no difference in readmission to hospital, but we are very uncertain about the results;
- probably increases the number of participants leaving the study early due to side effects;
- has little to no effect on functioning;
- may increase the number of participants with a relapse;
- probably increases the number of participants leaving the study early for any reason;
- probably has little to no effect on the number of participants with at least one side effect.

What are the limitations of the evidence?

We are mainly confident or moderately confident in our results.

Regarding readmission to hospital, we are not confident in the evidence because it is possible that study participants were aware of which treatment they were getting. Moreover, the studies were done in different types of people or used different ways of reducing the dose.

Regarding relapse, we have little confidence in the evidence because it is possible that study participants were aware of which treatment they were getting. Moreover, the studies were done in different types of people or used different ways of reducing the dose.

How up-to-date is the evidence?

The evidence is current to February 2021.

SUMMARY OF FINDINGS

Summary of findings 1. Summary of findings table - Antipsychotic dose reduction compared to dose continuation for people with schizophrenia

Antipsychotic dose reduction compared to dose continuation for people with schizophrenia

Patient or population: people with schizophrenia
Setting: inpatients and outpatients
Intervention: Dose reduction
Comparison: Dose continuation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with Dose continuation	Risk with Dose reduction				
Quality of life - mean change/endpoint all available scales (combined scales and time points)	-	SMD **0.01 lower** (0.17 lower to 0.15 higher)	-	719 (6 RCTs)	⊕⊕⊕⊖ Moderate[a,b]	
Service use - readmission to hospital (combined time points)	82 per 1000	**125 per 1000** (69 to 230)	**RR 1.53** (0.84 to 2.81)	1433 (9 RCTs)	⊕⊖⊖⊖ Very low[c,d,e]	
Adverse effect - leaving the study early due to adverse effects - overall tolerability (combined time points)	38 per 1000	**83 per 1000** (52 to 131)	**RR 2.20** (1.39 to 3.49)	1340 (10 RCTs)	⊕⊕⊕⊖ Moderate[c]	
Functioning - mean endpoint/change all available scales (combined scales and time points)	-	SMD **0.03 higher** (0.1 lower to 0.17 higher)	-	966 (6 RCTs)	⊕⊕⊕⊕ High[b]	
Global state - number of participants with relapse/exacerbations of psychosis (combined time points)	109 per 1000	**236 per 1000** (166 to 334)	**RR 2.16** (1.52 to 3.06)	2481 (20 RCTs)	⊕⊕⊖⊖ Low[c,f]	
Leaving the study early - for any reason - overall acceptability (combined time points)	239 per 1000	**330 per 1000** (251 to 433)	**RR 1.38** (1.05 to 1.81)	1551 (12 RCTs)	⊕⊕⊕⊖ Moderate[g,h]	
Adverse effects - number of participants with at least 1 adverse effect (combined time points)	598 per 1000	**616 per 1000** (562 to 670)	**RR 1.03** (0.94 to 1.12)	998 (5 RCTs)	⊕⊕⊕⊖ Moderate[c]	

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **SMD:** standardised mean difference

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_431868494444062467.

[a] Downgraded by one level for risk of bias: half of the studies had high risk of bias in one or more domains.
[b] No serious imprecision. Adequate information size (> 400 participants for a continuous outcome), and CI lower and upper extremes do not exceed the boundaries of 0.2 SMD. Precise results showing no difference between dose reduction and dose continuation.
[c] Downgraded by one level for risk of bias: some of the studies had high risk of bias in one domain, whilst the remaining studies had low or unclear risk of bias.
[d] Downgraded by one level for inconsistency: visual inspection of the forest plot suggests inconsistency, and I^2 = 59% (may represent substantial heterogeneity).
[e] Downgraded by one level for imprecision: adequate information size (> 1000 participants for a dichotomous outcome), but CI includes both no difference and better outcome for dose continuation.
[f] Downgraded by one level for inconsistency: visual inspection of the forest plot suggests inconsistency, and I^2 = 70% (may represent substantial heterogeneity).
[g] One out of 13 studies was at high risk of bias for only one domain; this study contributes only 4.2% of weight, therefore no serious risk of bias.
[h] Downgraded by one level for publication bias: visual inspection of the funnel plot shows marked asymmetry, even if not confirmed by statistical test (P = 0.14).

BACKGROUND

Antipsychotic drugs are effective for the acute treatment and relapse prevention of schizophrenia (Leucht 2012; Leucht 2013), but they have important adverse effects such as movement disorders and weight gain including associated metabolic problems, which are likely to contribute to a well-documented excess mortality (Hjorthoj 2017). Controversial data suggest that antipsychotics, particularly in people treated with higher doses, are likely to be associated with brain tissue and volume loss (Ho 2011). However, in clinical practice, acutely ill patients are frequently treated with high doses or combinations of antipsychotics; this is due to various pressures, such as risk for suicide or aggressive behaviour, lack of hospital beds and cost issues leading to shorter durations of hospitalisation, and high rates of non-response (Samara 2016; Samara 2019). For example, one systematic review of 147 studies showed that 20% of people with schizophrenia received several antipsychotics (Gallego 2012), and 10% received doses above the officially approved labels (Patel 2014). Consequently, the critical question the clinician must address is whether high-dose antipsychotics can be carefully reduced whilst continuing to maintain the relapse prevention benefit once the acute phase of the illness has been treated and the patient is in a maintenance phase. This could include a complete withdrawal of antipsychotics in up to 20% of patients who do not experience a second episode of schizophrenia within five years (Robinson 1999). In matter of fact, there will always be a difficult trade-off, because if the dose is too low or if the antipsychotic is stopped, there may be a high risk for relapse that can have adverse consequences for patients (Leucht 2013). In the current review, we summarised all randomised controlled trials that compared reducing antipsychotic doses with continuing the same dose. A companion review will address the related question of reducing antipsychotic polypharmacy.

Description of the condition

Schizophrenia is a chronic and disabling psychiatric disorder with a lifetime prevalence of approximately 1% of the population worldwide (McGrath 2008; Moreno-Küstner 2018). Onset is usually in early adulthood, and the symptoms can be severe (Carpenter 1994). Its typical manifestations are 'positive' symptoms such as fixed, false beliefs (delusions) and perceptions without a stimulus (hallucinations); 'negative' symptoms such as apathy and lack of drive, disorganisation of behaviour and thought; and catatonic symptoms such as mannerisms and bizarre posturing (Carpenter 1994).

It is one of the leading causes of long-term disability worldwide, with a devastating impact on patients and their families (GBD 2018). The degree of distress and impairment is considerable; employment rates vary between 4.5% and 50% (Bouwmans 2015), and lifetime suicide prevalence is estimated around 4% to 10%, with the highest rates amongst males in the early course of the disorder (Palmer 2005; Popovic 2014; Tanskanen 2018). Quality of life for people with schizophrenia can be poor, and it is likely to deteriorate during the course of the disease; overall lifespan is thought to be about 15 years shorter than average (Hjorthoj 2017).

The course of the illness can be divided into three stages. In the onset, or prodromal phase, initial changes such as subtle modifications in the person's behaviour, feelings, and cognition can occur, which then develop into clear psychotic symptoms during the acute phase. The acute episode, frequently treated with high doses of antipsychotics, is followed by a remission phase, in which the florid symptoms recede (Andreasen 2005); however, in this phase most individuals will still require maintenance treatment to prevent relapses (Leucht 2012). Remission is a necessary, but not sufficient, step towards recovery that is intended as "the ability to function in the community, socially and vocationally, as well as being relatively free of disease-related psychopathology" (Andreasen 2005).

Description of the intervention

Antipsychotic medication is the current mainstay of treatment in schizophrenia. Due to the chronic nature of the disease, long-term treatment with antipsychotics is usually needed to prevent the risk of relapse (Leucht 2012). Unfortunately, these medications have many adverse effects that make their use complicated (Leucht 2013), including movement disorders, weight gain, metabolic problems, and sexual dysfunction (Leucht 2013); possible brain volume loss (Ho 2011); and increased risk of mortality (McGrath 2008). These adverse effects are usually dose related (Kaar 2020; Schneider-Thoma 2019). Consequently, if gradual dose reduction was possible, this would have an immediate impact on patients' well-being (Kaar 2020). Nevertheless, there will be a difficult trade-off, because if the dose gets too low, there is a high risk for relapse, which can have dramatic consequences for patients.

The intervention was reduction of the antipsychotic dose. Dose reduction may be described as a reduction of the initial dose of antipsychotics by any amount; however, the precise strategies regarding how to reduce antipsychotics and to what extent vary (Takeuchi 2012). Sometimes dose may only be reduced by a certain percentage (Caroff 2018). Another option is a gradual, slow decrease of the initial dose with the aim of complete withdrawal of the antipsychotic (Wunderink 2013). In that case, it should be possible to recommence the antipsychotic and titrate the dose if psychotic symptoms re-emerge, because it has been clearly documented that in most patients withdrawing antipsychotics completely often leads to relapse (Leucht 2012). Where patients receive several antipsychotics, withdrawing one or more of their antipsychotics is also considered a reduction of the dose (Suzuki 2003). How much the dose can be reduced a priori is unclear, as studies on plasma levels of antipsychotics show interindividual variability due to factors such as liver enzyme induction and pharmacogenomic factors. This may explain why some patients need much higher antipsychotic doses than other patients (Hiemke 2018). It is also unclear how quickly antipsychotic dose reductions can be performed for people with schizophrenia (Takeuchi 2012).

How the intervention might work

The concept behind reducing antipsychotic dose is that most adverse effects are dose related (Takeuchi 2015), including somatic serious adverse events (Schneider-Thoma 2019), weight gain (Spertus 2018), QT prolongation (Barbui 2016), and tardive dyskinesia (Bergman 2018).

The main mechanism of action of most antipsychotic drugs includes blocking dopamine D2 receptors, and around 60% to 80% of blockade is required to achieve efficacy. The occupancy of the receptor is dose related (Lako 2013). However, with higher doses and, therefore, higher receptor occupancy, the risk for extrapyramidal adverse effects increases. A similar mechanism can be speculated for the other receptors responsible for adverse

effects, such as histamine H_1 receptors for sedation or muscarinic receptors for anticholinergic effects such as dry mouth (Kaar 2020).

Reducing the antipsychotic dose should therefore reduce the adverse-effect burden (Citrome 2009; Hill 2011; Knox 2004; Simon 2009). Higher adverse-effect rates can reduce quality of life and prevent the afflicted individuals from functioning well in the community (Achtyes 2018; Sağlam Aykut 2019). One study reported that the functional outcome of people with a first episode of schizophrenia in whom a dose reduction had been attempted was better than that of people in whom antipsychotics were continued (Wunderink 2013). High doses of antipsychotics have also been associated with brain volume loss (Ho 2011). This finding is debated (Andreasen 2013), but if true, dose reduction could also counteract this problem. The risk of dose reduction is that doses become so low that psychotic symptoms re-emerge, requiring rehospitalisations and jeopardising personal relationships and vocational functioning (Leucht 2012).

Why it is important to do this review

Debate exists as to whether people with schizophrenia receive higher doses of antipsychotics than necessary. This has been fuelled by analyses suggesting that long-term treatment with antipsychotics is associated with a dose-related brain volume loss (Ho 2011), although these data are controversial (Andreasen 2013), and the clinical relevance is unclear (Lesh 2015). However, it is difficult to differentiate this volume change from the one deriving from the illness (Van Haren 2013). It is also understood from long-term studies that up to 20% of individuals with a first episode of schizophrenia will not experience a second episode (Robinson 1999; Shepherd 1989). Some epidemiological data suggest that untreated people with schizophrenia do better overall (Harrow 2012), whilst another epidemiological study from rural China showed that mortality of untreated people with schizophrenia was higher than that of treated individuals (Ran 2015). Unfortunately, these patients cannot be identified in advance. In the seven-year follow-up of one non-randomised study, the long-term outcome of gradual dose reduction was better than that of maintaining patients on the same dose (Wunderink 2013). Given the complexity of the matter, a systematic review of the data is important. The results are also potentially important for guidelines and policymakers given the high rates of disability and thus costs of schizophrenia for society (Vos 2012).

A companion review will address the related question of reducing antipsychotic polypharmacy (Bighelli 2022).

OBJECTIVES

To assess the effects and safety of reducing antipsychotic dose compared to continuing the current dose for people with schizophrenia.

To examine factors of dose reduction such as its degree and rapidity.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all relevant randomised controlled trials (RCTs) for inclusion. If a trial was described as 'double-blind', but randomisation was implied, we would include such trials and examine the effect of their inclusion by excluding them in a sensitivity analysis (see Sensitivity analysis). If their inclusion did not result in a substantive difference, they would remain in the analyses. If their inclusion resulted in important clinically significant but not necessarily statistically significant differences, we would not add the data from these lower-quality studies to the results of the high-quality trials, but would present such data within a subcategory. We excluded quasi-RCTs, such as those allocating by alternate days of the week.

Where studies had multiple publications, we collated the reports of the same study so that each study, rather than each report, was the unit of interest for the review; such studies have a single identifier with multiple references.

Types of participants

Adults, however defined, with schizophrenia or related disorders, including schizophreniform disorder, schizoaffective disorder, and delusional disorder, by any means of diagnosis (irrespective of the diagnostic criteria used), who were stabilised on their current antipsychotic treatment, irrespective of age, gender, race, or country. We accepted any definition of stability that was used in the individual studies. We excluded studies that addressed the question of the minimum effective *acute phase dose* for acutely ill people with schizophrenia.

We were interested in ensuring that information is relevant to the current care of people with schizophrenia, therefore we have highlighted the current clinical state clearly (early postacute, partial remission, remission), as well as the stage (first episode, early illness, persistent), and whether the studies focused primarily on people with particular problems (e.g. negative symptoms, treatment-resistant illnesses).

See Subgroup analysis and investigation of heterogeneity.

Types of interventions

1. Dose reduction

Any reduction in dose of the current antipsychotic drug licensed in at least one country, irrespective of how it was defined and how fast it was undertaken.

We included studies that allowed a gradual dose reduction up to complete withdrawal as long as it was possible to increase the dose if symptoms re-emerged. We excluded studies where antipsychotics were fully withdrawn in all participants without the possibility to increase doses if necessary. The reason for this is that the aim of this review was to investigate the effect of dose reduction, not of antipsychotic withdrawal. We excluded studies on so-called 'intermittent treatment', where medication is more or less abruptly withdrawn from all patients and only restarted if early warning signs of psychosis re-emerge. We planned to examine the degree of dose reduction in a subgroup analysis.

2. Dose continuation

Continuation of the current antipsychotic dose.

Types of outcome measures

We divided all outcomes into very short term (up to three months), short term (up to six months), medium term (up to one year, i.e. seven to 12 months), and long term (more than 12 months). The primary time point of interest was up to one year.

We reported data for separate time points when available, and calculated subtotals without calculating totals in order to avoid double counting when one study contributed for multiple time points. When we combined the time points, if multiple time points were reported for the same study, we selected the one closest to 12 months for the primary analysis.

Primary outcomes

1. Quality of life

1.1. Clinically important change in quality of life

Number of participants with a clinically important change in quality of life, as defined in each study.

2. Service use

2.1. Readmission to hospital

Number of participants that were readmitted to hospital.

3. Adverse effect

3.1. Leaving the study early due to adverse effects – overall tolerability

Number of participants that discontinued participation in the study due to adverse effects.

Secondary outcomes

1. Quality of life

1.1. Mean endpoint or change score on quality of life scale

We accepted any published quality of life scales (e.g. Heinrich-Carpenter Quality of Life Scale or Subjective Well-Being Under Neuroleptic Treatment Scale (SWUN)).

2. Service use

3. Functioning

3.1. Clinically important change in functioning

Number of participants with a clinically important change in functioning, as defined in each study.

3.2. Mean endpoint or change score on functioning scale

We accepted any published rating scales, such as the Global Assessment of Functioning or the Psychosocial Performance Scale.

4. Global state

4.1. Relapse/exacerbations of psychosis

We accepted any definitions from the original authors of each study.

4.2. Mean endpoint or change score on global state scale

We accepted any published rating scale.

5. Leaving the study early

5.1. Due to any reason – overall acceptability

Number of participants that prematurely discontinued for any reason.

5.2. Due to inefficacy – overall efficacy

Number of participants that prematurely discontinued due to inefficacy.

6. Mental state

6.1. General

6.1.1. Clinically important change in general mental state

Number of participants with a clinically important change, as defined by the individual studies (e.g. mental state much improved, or less than 50% reduction on a specified rating scale).

6.1.2. Mean endpoint or change score on general mental state scale

6.2. Specific

6.2.1. Clinically important change in positive symptoms

6.2.2. Mean endpoint or change score on positive symptom scale

We examined the positive symptoms of schizophrenia according to the positive subscale of the Positive and Negative Syndrome Scale (PANSS), the Scale for Assessment of Positive Symptoms (SAPS), or any other validated positive symptom scale.

6.2.3. Clinically important change in negative symptoms

6.2.4. Mean endpoint or change score on negative symptom scale

We investigated the negative symptoms of schizophrenia according to the negative subscale of the PANSS, the Scale for the Assessment of Negative Symptoms (SANS), or any other validated negative symptom scale.

6.2.5. Clinically important change in depressive symptoms

6.2.6. Mean endpoint or change score on depressive symptom scale

We investigated depressive symptoms according to the Calgary Depression Scale, the Hamilton Depression Scale, the Montgomery Asberg Depression scale, or or any other published depression scales.

7. Behaviour

7.2. Mean endpoint or change score on behaviour scale

We accepted any published rating scale.

8. Satisfaction with care

8.2. Mean endpoint or change score on satisfaction with care scale

We accepted any published rating scale.

9. Adverse effects/events

9.1. Effects

9.1.1. At least one adverse effect

9.1.2. Weight gain: clinically important change

9.1.3. Incidence of various specific adverse effects

9.2. Event: mortality

9.2.1. Overall mortality

9.2.2. Mortality due to natural causes

9.2.3. Mortality due to suicide

11. Medication – mean antipsychotic dose at endpoint

We converted antipsychotic doses to olanzapine equivalents for this outcome (Gardner 2010). If the drug was not available in the Gardner conversion method, we used the defined daily doses (DDDs) instead (Leucht 2016).

Search methods for identification of studies

Electronic searches

Cochrane Schizophrenia Group's Study-Based Register of Trials

On 10 February 2021, the Information Specialist searched the register using the following search strategy:

Dosage Reduction in Intervention of STUDY

In such study-based register, searching the major concept retrieves all the synonyms and relevant studies because all the studies have already been organised based on their interventions and linked to the relevant topics (Roberts 2021; Shokraneh 2017; Shokraneh 2021). This allows rapid and accurate searches that reduce waste in the next steps of systematic reviewing (Shokraneh 2019).

Following Cochrane methods (Lefebvre 2019), this register is compiled by systematic searches of major resources (the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), PsycINFO, PubMed, ClinicalTrials.gov, ISRCTN registry, and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP)) and their monthly updates, ProQuest Dissertations and Theses A&I and its quarterly update, handsearches, grey literature, and conference proceedings (Shokraneh 2020; see Group's website). There are no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We inspected the references of all included studies, previous relevant systematic and narrative reviews, and guidelines for further relevant studies.

2. Personal contact

We contacted the first author of each included study to request further studies and for missing information on their studies. We noted the outcome of this contact in the Characteristics of included studies or Characteristics of studies awaiting classification tables. We contacted pharmaceutical companies of second-generation antipsychotics for further studies, if we found in our literature search that the pharmaceutical company had conducted at least one such study.

Data collection and analysis

Selection of studies

After removal of duplicates, at least two review authors (of IBi, AR, LB, IBa, SS, PC) independently inspected citations from the searches and identified potentially relevant abstracts using Covidence (Covidence). Where disputes arose, we acquired the full report for more detailed scrutiny. At least two review authors (of IBi, AR, LB, IBa, SS, PC) independently obtained and inspected full reports of the abstracts meeting the review criteria. Any disagreements were resolved by discussion with another review author (SL). Where it was not possible to resolve disagreements by discussion, we attempted to contact the authors of the study for clarification. We listed studies excluded at this stage in the Characteristics of excluded studies table.

Data extraction and management

1. Data extraction

Two review authors (of IBi, AR, LB, IBa, SS, PC) independently extracted data from the included studies. We discussed any disagreements (eventually with SL), and, if necessary, contacted authors of studies with an open-ended request to obtain missing information or for clarification. We documented information obtained from study authors in Characteristics of included studies.

We extracted data presented only in graphs and figures, but included these data only if two review authors had independently obtained the same result.

For each included study we also extracted the following study characteristics (see Characteristics of included studies).

- Methods (study design, study grouping, additional medication allowed, compliance measured, study phases, duration in weeks, number of study arms, number of drugs used, randomisation assumed from double-blind, type of blinding, type of data analysis for overall efficacy, use of prophylactic medication, number of sites).
- Participants (diagnosis, current clinical state, definition of stability, inclusion criteria, exclusion criteria, setting, N, gender, age, history of illness, severity of disease, duration of illness, weight, height, body mass index, average time in study in days).
- Interventions (drug, dose, application, dose scheme, rescue medication, degree and speed of dose reduction).
- Outcomes.
- Sponsorship source.
- Country.
- Trial registration ID.

2. Management

2.1. Forms

We extracted data using Covidence software after piloting the form with a sample of five studies (Covidence; accessed 07 October 2022).

2.2. Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument have been described in a peer-reviewed journal (Marshall 2000);

- the measuring instrument has not been written or modified by one of the trialists for that particular trial; and
- the instrument is a global assessment of an area of functioning, and not a subscore that has not been validated or shown to be reliable as a stand-alone instrument. However, there were exceptions: we included subscores from mental state scales that measure positive and negative symptoms of schizophrenia.

2.3. Endpoint versus change data

There are advantages of both endpoint and change data: change data can remove a component of between-person variability from the analysis; however, calculation of change needs two assessments (baseline and endpoint), which can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We have decided primarily to use endpoint data, and only use change data if endpoint data are not available. In the presence of substantial baseline imbalance, which could have influenced the results if endpoint scores were used, we used change scores, and noted this decision in the footnotes of the forest plots.

2.4. Skewed data

Continuous data on clinical and social outcomes are often not normally distributed. To avoid the pitfall of applying parametric tests to non-parametric data, we planned to apply the following standards to relevant continuous data before inclusion.

For endpoint data from studies including fewer than 200 participants, we planned to calculate the observed mean minus the lowest possible value of the scale and divide this by the standard deviation (SD) (Higgins 2021a).

For example, in a scale that has possible lowest values higher than 0 (such as the PANSS, which can have values from 30 to 210) (Kay 1986), we planned to subtract the minimum score (in this case 30) from the observed mean, and then divide by the SD. In a scale that has 0 as minimum possible score, we planned to divide the observed mean by the SD.

For this calculation, we planned to check the original publication of the scales referenced in the studies to understand if they can have a lowest possible score different from 0, and whether the adjustment described above is needed or not.

If the ratio obtained is lower than one, it strongly suggests that the data are skewed. If it is higher than one but less than two, there is suggestion that the data are skewed; if the ratio is larger than two, it is less likely that the data are skewed (Altman 1996).

Where there is suggestion of skewness (ratio < 2), we would exclude the relevant studies in a sensitivity analysis to determine whether they impact the results (see Sensitivity analysis).

We planned that if skewed results were found, we would report them in Additional tables.

We planned to enter all relevant data from studies of more than 200 participants in the analysis irrespective of the above rules, because skewed data pose less of a problem in large studies. We also planned to enter all relevant change data, as when continuous data are presented on a scale that includes the possibility of negative values (such as change data), it is difficult to determine whether data are skewed.

2.5. Common measurement

To facilitate comparison between trials, we planned to convert variables that can be reported in different metrics, such as days in hospital (mean days per year, per week, or per month) to a common metric (e.g. mean days per month).

2.6. Conversion of continuous to binary

Where possible, we attempted to convert outcome measures to dichotomous data. This can be done by identifying cut-off points on rating scales and dividing participants accordingly into 'clinically improved' or 'not clinically improved'. It is generally assumed that if there is a 50% reduction in a scale-derived score such as the Brief Psychiatric Rating Scale (BPRS), Overall 1962, or the PANSS, Kay 1986, this could be considered to be a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds were not available, we used the primary cut-off presented by the authors of the original studies.

2.7. Direction of graphs

Where possible, we entered data so that the area to the left of the line of no effect indicates a favourable outcome for the intervention under investigation (reduction of antipsychotic dose). Where keeping to this makes it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not un-improved'), we would report data where the left of the line indicates an unfavourable outcome and note this in the graphs.

Assessment of risk of bias in included studies

Two review authors (of IBi, AR, LB, IBa, SS, PC) independently assessed risk of bias using the RoB 2 tool, Sterne 2019, and referring to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2021a). This set of criteria is based on judgement of the following domains:

- 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; and
- bias in selection of the reported result.

For each domain, we rated the available 'signalling questions' to reach a judgement (high risk of bias, some concerns, low risk of bias) following the tool algorithms implemented in the RoB 2 Excel tool (available on the riskofbiasinfo.org website).

The effect of interest in performing ratings with the tool was to be the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended (the intention-to-treat (ITT) effect), as described in Chapter 8 and Section 8.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021b).

We performed an evaluation using the RoB 2 tool for the following outcomes.

- Quality of life: clinically important change
- Service use: readmission to hospital
- Adverse effect: leaving the study early due to adverse events – overall tolerability
- Functioning: clinically important change

- Global state: relapse/exacerbations of psychosis
- Leaving the study early: for any reason – overall acceptability
- Adverse effects/events: at least one adverse effect

For cluster-randomised trials, we planned to use the additional domain specific for cluster-RCTs from the archived version of the tool (Domain 1b: Bias arising from the timing of identification and recruitment of participants) and the signalling questions from the archived version.

For cross-over trials, we planned to only use data from the first phase (see Measures of treatment effect) and the standard version of the RoB 2.

If the raters disagreed, the final rating was made by consensus with another review author (SL). Where studies provided inadequate details on randomisation and other characteristics, we attempted to contact the study authors to request further information. We reported non-concurrence in quality assessment, but if disputes arose regarding the category to which a trial was to be allocated, we resolved this by discussion.

We noted the level of risk of bias in the text of the review, in the risk of bias tables in the 'Characteristics of included studies' section, and next to the forest plots of the analyses of outcomes contributing to the summary of findings table.

In addition, if one of the predefined outcomes was not available, but data were available for a similar one, we rated the risk of bias of this as a proxy of the predefined.

Measures of treatment effect

1. Binary data

For binary outcomes, we calculated a standard estimation of the risk ratio (RR) and its 95% confidence interval (CI), as it has been shown that RR is more intuitive than odds ratios (Boissel 1999), and that odds ratios tend to be interpreted as RR by clinicians (Deeks 2000).

Although the number needed to treat for an additional beneficial outcome (NNTB) and the number needed to treat for an additional harmful outcome (NNTH), with their CIs, are intuitively attractive to clinicians, they are problematic to calculate and interpret in meta-analyses (Hutton 2009). For binary data presented in the summary of findings table, we calculated illustrative comparative risks, where possible.

2. Continuous data

Where studies used scales of reasonable similarity for a given outcome, we calculated mean differences (MDs) with 95% CIs as the effect size measure, and transformed the effect back to the units of one or more of the specific instruments. If the scales were not sufficiently similar, we estimated the standardised mean differences (SMDs) between groups.

Unit of analysis issues

1. Cluster trials

Studies increasingly employ 'cluster randomisation' (such as randomisation by clinician or practice); however, the analysis and pooling of clustered data pose problems. Firstly, authors often fail to account for intraclass correlation in clustered studies, leading to a unit of analysis error whereby P values are spuriously low, CIs unduly narrow, and statistical significance overestimated (Divine 1992). This causes type I errors (Bland 1997; Gulliford 1999).

Where clustering was incorporated into the analysis of primary studies, we would present these data as if from a non-cluster randomised study, but adjusting for the clustering effect.

Where clustering was not accounted for in primary studies, we would present data in a table with a (*) symbol to indicate the presence of a probable unit of analysis error. We planned to attempt to contact first authors of studies to obtain intraclass correlation coefficients (ICCs) for their clustered data and to adjust for this by using accepted methods (Gulliford 1999).

We have sought statistical advice and have been advised that the binary data from cluster trials presented in a report should be divided by a 'design effect'. This is calculated using the mean number of participants per cluster (m) and the ICC: thus design effect = 1 + (m − 1) × ICC (Donner 2002). If the ICC was not reported, we would assume it to be 0.1 (Ukoumunne 1999).

If cluster studies were appropriately analysed and had taken ICCs and relevant data documented in the report into account, synthesis with other studies would be possible using the generic inverse-variance technique.

2. Cross-over trials

A major concern of cross-over trials is the carry-over effect. This occurs if an effect (e.g. pharmacological, physiological, or psychological) of the treatment in the first phase is carried over to the second phase. As a consequence, participants can differ significantly from their initial state at entry to the second phase, despite a wash-out phase. For the same reason, cross-over trials are not appropriate if the condition of interest is unstable (Elbourne 2002). As both carry-over and unstable conditions are very likely in severe mental illness, we only used data from the first phase of cross-over studies.

3. Studies with multiple treatment groups

Where a study involved more than two treatment arms, if relevant, we would present the additional treatment arms in comparisons. If data were binary, we would simply add these and combine within the 2 x 2 table.

If data were continuous, we would combine data using the formula in Section 7.7.3.8 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). Where additional treatment arms were not relevant, we did not reproduce these data. However, we listed all treatment arms in the Characteristics of included studies table.

Dealing with missing data

1. Overall loss of credibility

We share the concern that at some degree of loss to follow-up, data lose credibility (Xia 2009). However, it is unclear at which point this becomes a problem, therefore we did not exclude studies based on degree of attrition, accounting for attrition in the risk of bias assessment.

2. Binary

We presented data in an ITT analysis. We post hoc assumed that participants leaving the study early did not have the outcome. We believe that another assumption would have overestimated the risk, and this assumption is frequently used in meta-analysis of antipsychotics for schizophrenia (Leucht 2021).

3. Continuous

3.1. Assumptions about participants who leave the trials early or are lost to follow-up

Various methods exist to account for participants who leave the trial early or who are lost to follow-up. Some trials simply present the results of study completers, whilst other trials use the method of last observation carried forward (LOCF); however, methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While MMRMs seem to be somewhat better than LOCF (Leon 2006), we consider that the high percentage of participants leaving the studies early and differences between groups in their reasons for doing so is often the core problem in RCTs of people with schizophrenia, therefore we did not exclude studies based on the statistical approach used. However, we preferentially used the more sophisticated approaches (i.e. we preferred MMRM or multiple imputation to LOCF), and only presented completer analyses if some type of ITT data were not available. We excluded studies presenting only completer data in a sensitivity analysis.

3.2. Standard deviations

If SDs were not reported, we attempted to obtain the missing values from the authors. If these were not available, where there were missing measures of variance for continuous data, but an exact standard error (SE) and CIs available for group means, and either P value or t value available for differences in mean, we calculated SDs following the rules in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021a). When only the SE is reported, SDs are calculated using the formula $SD = SE \times \sqrt{(n)}$. Sections 7.7.3 and 16.1.3 of the *Cochrane Handbook* present detailed formulae for estimating SDs from P, t, or F values; CIs; ranges; or other statistics (Higgins 2021a). If these formulae did not apply, we calculated the SDs according to a validated imputation method based on the SDs of the other included studies (Furukawa 2006). Although some of these imputation strategies can introduce error, the alternative would be to exclude a given study's outcome data and thus lose information. Nevertheless, we examined the validity of the imputations in a sensitivity analysis that excluded imputed values.

Assessment of heterogeneity

1. Clinical heterogeneity

We considered all included studies initially, without seeing comparison data, to judge clinical heterogeneity. We inspected all studies for participants who were clearly outliers or situations that we had not predicted would arise and, where found, discussed such situations or participant groups.

2. Methodological heterogeneity

We considered all included studies initially, without seeing comparison data, to judge methodological heterogeneity. We inspected all studies for clearly outlying methods that we had not predicted would arise and discussed any such methodological outliers.

3. Statistical heterogeneity

3.1. Visual inspection

We inspected graphs visually to investigate the possibility of statistical heterogeneity.

3.2. Employing the I^2 statistic

We investigated heterogeneity between studies by considering the I^2 statistic alongside the Chi^2 P value. The I^2 statistic provides an estimate of the percentage of inconsistency thought to be due to chance (Higgins 2003). The importance of the observed value of the I^2 statistic depends on the magnitude and direction of effects as well as the strength of evidence for heterogeneity (e.g. P value from Chi^2 test, or a CI for the I^2 statistic). We interpreted an I^2 statistic estimate of 50% or greater and accompanied by a statistically significant Chi^2 statistic as evidence of substantial heterogeneity, per Section 9.5.2 of the *Cochrane Handbook* (Higgins 2021a). When there were substantial levels of heterogeneity for the primary outcomes, we explored the reasons for the heterogeneity (Subgroup analysis and investigation of heterogeneity).

Assessment of reporting biases

Reporting biases arise when the dissemination of research findings is influenced by the nature and direction of results (Egger 1997). These are described in Chapter 10 of the *Cochrane Handbook* (Higgins 2021a). We are aware that funnel plots may be useful in investigating reporting biases, but are of limited power to detect small-study effects. We did not use funnel plots for outcomes where there are 10 or fewer studies, or where studies were of a similar size. In other cases, where funnel plots were possible, we sought statistical advice in their interpretation and produced a contour-enhanced funnel plot (Peters 2008). We conducted funnel plot analyses if there were sufficient studies for the outcomes in the summary of findings table.

Data synthesis

We understand that there is no closed argument for preference of use of fixed-effect or random-effects models. The random-effects method incorporates an assumption that the different studies are estimating different, yet related, intervention effects. This seems often to be true to us, and the random-effects model takes into account differences between studies, even if there is no statistically significant heterogeneity. However, there is a disadvantage to the random-effects model in that it puts added weight onto small studies, which are often the most biased type of study. Depending on the direction of effect, these studies can either inflate or deflate the effect size. We used a random-effects model for all analyses.

Subgroup analysis and investigation of heterogeneity

1. Subgroup analyses

We only conducted subgroup analyses on our primary outcomes. We are aware that subgroup analyses are observational by nature, and the results are therefore considered to be exploratory, not explanatory. If the moderators in question were continuous, we either dichotomised them by a median split or we conducted meta-regression analyses in R (R 2017). We conducted subgroup analyses

only for comparisons with at least 10 studies, as described in Section 10.11.5.1 of the *Cochrane Handbook* (Higgins 2021a).

1.1. Degree of dose reduction

We planned to perform subgroup/meta-regression analyses based on the degree of dose reduction in the selected studies. The effects on the primary outcomes depend on by how much doses are reduced. We presented the degree of dose reduction as a percentage reduction of the baseline dose. We converted doses to olanzapine equivalents for this purpose (Gardner 2010).

1.2. Speed of dose reduction

Too fast a reduction of doses may increase the risk for major relapses in terms of rehospitalisation, therefore we categorised the studies into abrupt and gradual reduction. In order to further explore the impact of the speed of dose reduction, we also post hoc conducted this subgroup analysis for the outcome of relapse.

1.3. Initial antipsychotic dose

Results may differ based upon whether participants were originally on a high or a low dose of antipsychotic. We converted doses to olanzapine equivalents for this purpose (Gardner 2010).

1.4. Severity of illness

It may be easier to reduce doses in people with less severe schizophrenia than in people with more severe schizophrenia.

1.5. Clinical state, stage, or problem

We provided an overview of the effects of dose reduction versus dose maintenance for people with schizophrenia in general. In addition, we reported data on subgroups of people in the same clinical state, stage, and with similar problems. The following groups appeared to be especially pertinent.

1.5.1. Participants with first episode versus participants with multiple episodes

Up to 20% of first-episode patients may not have a second episode (Robinson 1999), therefore reducing antipsychotic doses may be particularly useful in this subgroup.

1.5.2. Participants in remission versus other participants

Reductions of doses of antipsychotics may be more meaningful in people in remission (if available according to Andreasen 2005) than in those who are stable but not symptom-free.

1.6. Endpoint antipsychotic dose in the dose reduction group (post hoc)

A previous meta-analysis found that dose reductions at an endpoint dose dose < 200 mg/d in chlorpromazine equivalents are associated with a higher risk of relapse (Tani 2020), therefore we conducted post hoc a meta-regression analysis between the secondary outcome of relapse and the endpoint mean of the antipsychotic dose in the dose reduction group. We converted doses into oral olanzapine equivalents (mg/d) (Gardner 2010). Since studies could report mean doses after an increase of the dose due to relapses, we estimated the mean endpoint dose before relapse using descriptions provided in the publications or dose ranges.

2. Investigation of heterogeneity

We reported if inconsistency was high. Firstly, we investigated whether data had been entered correctly. Secondly, if data were correct, we inspected the graph visually and removed outlying studies successively to see if homogeneity was restored. Decisions as to whether single studies should be excluded from the analysis, or whether a formal meta-analysis should not be undertaken depended on issues such as whether the heterogeneity was due to differences in direction of effect or only to the degree of difference between the intervention and control (Higgins 2021a). When unanticipated clinical or methodological heterogeneity was obvious, we simply stated hypotheses regarding this for future reviews or updates of this review. We did not anticipate undertaking analyses relating to this.

Sensitivity analysis

We planned to carry out sensitivity analyses for primary outcomes only to explore the influence of the factors listed below. We excluded the studies identified in each sensitivity analysis, and discussed the difference with the main analysis.

1. Risk of bias

We analysed the effects of excluding trials judged to be at overall high risk of bias for the primary outcomes (see Assessment of risk of bias in included studies).

2. Imputed values

We analysed the effects of excluding data from trials where we had used imputed values for ICC to calculate the design effect in cluster-RCTs (see Unit of analysis issues), or where SDs were imputed.

3. Operationalised criteria to diagnose schizophrenia

We analysed the effects of excluding data from trials that did not use operational criteria to diagnose schizophrenia.

4. Fixed-effect and random-effects models

In the main analyses, we synthesised data using a random-effects model; however, in this sensitivity analysis we also synthesised data for the primary outcomes using a fixed-effect model to evaluate whether this altered the significance of the results.

5. Suggestion of skewed data

We analysed the effects of excluding data from trials where it was suggested that data were skewed (mean/SD ratio < 2; see Data extraction and management). If this changed the results in comparison with the main analysis (from significantly favouring the intervention to significantly favouring the control, or vice-versa), we excluded these studies also from the main analysis, and presented their data in Additional tables in the review.

6. Chinese studies

Studies from mainland China often use other randomisation methods than the internationally approved ones; the reports are very short; and methods are often not described in detail (Woodhead 2016). To account for these potential differences, we planned to exclude these studies in a sensitivity analysis.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to interpret findings (Schünemann 2011), and employed GRADEpro GDT to import data from Review Manager Web to create a summary of findings table for the comparison of dose reduction compared to dose continuation (GRADEpro GDT; RevMan Web 2022). This table provides outcome-specific information concerning the overall certainty of evidence from each included study in the comparison, the magnitude of effect of the interventions examined, and the sum of available data on all outcomes rated as important to patient care and decision-making. The overall RoB 2 judgements were used to feed into the GRADE assessment. We aimed to include the following main outcomes in the summary of findings table.

- Quality of life: clinically important change
- Service use: readmission to hospital
- Adverse effect: leaving the study early due to adverse events – overall tolerability
- Functioning: clinically important change
- Global state: relapse/exacerbations of psychosis
- Leaving the study early: for any reason – overall acceptability
- Adverse effects/events: at least one adverse effect

We justified all decisions to downgrade the certainty of evidence using footnotes and made comments to aid the reader's understanding of the review where necessary.

If one of the predefined outcomes was not available, but data were available for a similar outcome, we rated this as a proxy of the predefined.

RESULTS

Description of studies

For details, see Characteristics of included studies and Characteristics of excluded studies.

Results of the search

Our search of the Cochrane Schizophrenia Group's Study-Based Register of Trials identified 57 eligible studies (in 123 reports) for full-text screening (Figure 1). We identified a further 30 studies (in 49 reports) through handsearching. We included a total of 25 studies in the review and 22 studies in the quantitative synthesis.

Figure 1.

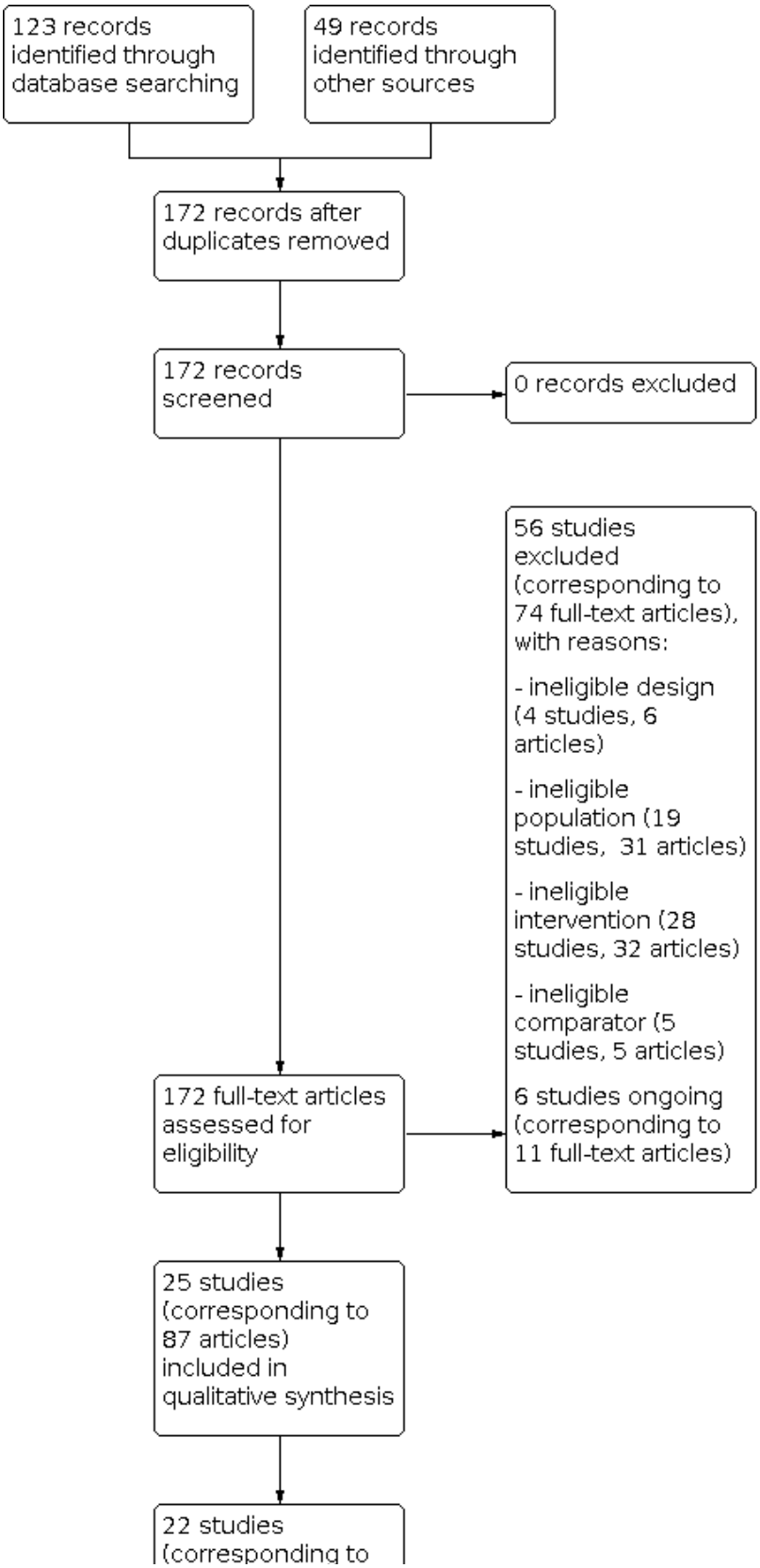
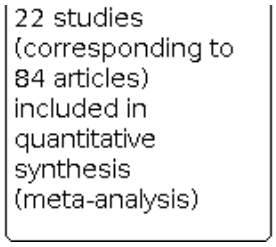


Figure 1. (Continued)



Included studies

We included 25 studies (2721 participants) in the review, of which 22 studies (2635 participants) contributed to the meta-analyses.

1. Design and duration

All included studies were RCTs. Of the studies contributing data to the meta-analyses, eight studies had a duration of between 12 and 26 weeks (Caffey 1964; Faraone 1989; Hogarty 1995; Huhn 2020; Kane 2010; Lonowski 1978; Remington 2011; Rouillon 2008); 10 studies lasted between 27 and 52 weeks (Branchey 1981; Cookson 1987; Fleischhacker 2014; Johnson 1987; Kane 1983; Ozawa 2019; Takeuchi 2014; Volavka 2000; Wang 2010; Zhou 2018); and four studies lasted more than 52 weeks (Carpenter 1999; Hogarty 1988; Schooler 1997; Wunderink 2007). The length of the longest studies was two years (Hogarty 1995; Schooler 1997).

2. Participants

Of the studies contributing data to the meta-analyses, the diagnosis was clinically based in three studies (Caffey 1964; Lonowski 1978; Volavka 2000). In one study, participants could be diagnosed according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) or the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (Ozawa 2019). In eight studies, the researchers used DSM-IV or Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) diagnostic criteria (Fleischhacker 2014; Kane 2010; Remington 2011; Rouillon 2008; Takeuchi 2014; Wang 2010; Wunderink 2007; Zhou 2018). In three studies, the authors used Diagnostic and Statistical Manual of Mental Disorders, Third Edition (DSM-III) or Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria (Faraone 1989; Schooler 1997; Carpenter 1999 (in combination with Research Diagnostic Criteria)). In two studies, the researchers applied the Feighner criteria (Johnson 1987; Cookson 1987 (in combination with the International Classification of Diseases, Ninth Revision (ICD-9))). In one study, the authors used the ICD-10 (Huhn 2020), and in the remaining four studies researchers used the Research Diagnostic Criteria (Branchey 1981; Hogarty 1988; Hogarty 1995; Kane 1983). Fourteen studies involved individuals in remission or partial remission state (Carpenter 1999; Fleischhacker 2014; Hogarty 1988; Huhn 2020; Johnson 1987; Kane 1983; Kane 2010; Ozawa 2019; Rouillon 2008; Schooler 1997; Takeuchi 2014; Wang 2010; Wunderink 2007; Zhou 2018), whilst seven studies were focused on chronically ill patients (Branchey 1981; Caffey 1964; Cookson 1987; Faraone 1989; Hogarty 1995; Lonowski 1978; Volavka 2000). One study did not provide information on the clinical state of participants (Remington 2011). The average age of participants in the studies contributing to meta-analyses was about 38.4 years old.

3. Size

The median number of participants was 60. The smallest study included only 18 participants (Cookson 1987), and the largest study randomised 466 participants (Kane 2010).

4. Setting

Participants were recruited in an inpatient setting in three studies (Caffey 1964; Lonowski 1978; Volavka 2000), an outpatient setting in 13 studies (Carpenter 1999; Faraone 1989; Fleischhacker 2014; Hogarty 1988; Hogarty 1995; Huhn 2020; Johnson 1987; Kane 1983; Kane 2010; Remington 2011; Rouillon 2008; Wunderink 2007; Zhou 2018), and both in- and outpatient settings in four studies (Ozawa 2019; Schooler 1997; Takeuchi 2014; Wang 2010). This information was not available for two studies (Branchey 1981; Cookson 1987). Twelve studies were conducted partly or entirely in the USA (Branchey 1981; Caffey 1964; Carpenter 1999; Faraone 1989; Fleischhacker 2014; Hogarty 1988; Hogarty 1995; Kane 1983; Kane 2010; Lonowski 1978; Schooler 1997; Volavka 2000), one in Canada (Remington 2011), and two in the UK (Cookson 1987; Johnson 1987). The other studies were conducted in Europe, Huhn 2020; Rouillon 2008; Wunderink 2007, and Asia (Ozawa 2019; Takeuchi 2014; Wang 2010; Zhou 2018). Two multicentre studies involved participants in various countries (Fleischhacker 2014; Kane 2010)

5. Interventions

All included studies compared the continuation of treatment with the dose prescribed at the beginning of the trial with reduction of the dose of the antipsychotic. In half of the studies, the antipsychotic dose reduction was gradual (Branchey 1981; Faraone 1989; Hogarty 1995; Huhn 2020; Ozawa 2019; Rouillon 2008; Takeuchi 2014; Volavka 2000; Wang 2010; Wunderink 2007; Zhou 2018), and was done in an interval ranging between 2 and 16 weeks; in the other half the dose reduction was done abruptly (Caffey 1964; Carpenter 1999; Cookson 1987; Fleischhacker 2014; Hogarty 1988; Johnson 1987; Kane 1983; Kane 2010; Lonowski 1978; Remington 2011; Schooler 1997). In some studies the goal of the dose reduction was to achieve complete withdrawal of the antipsychotic drug (Branchey 1981; Huhn 2020; Wunderink 2007). The median planned antipsychotic reduction was equal to 66%.

6. Outcomes

The scales used to assess symptoms and adverse events were diverse. Study reporting was often incomplete, and authors were contacted for missing outcome data and clarifications via e-mail (and a reminder e-mail in case of no response). Some study authors provided additional data and clarifications (see Notes in Characteristics of included studies).

6.1. Outcome scales

6.1.1 Quality of life

EuroQol-5 Dimensions three-level version (EQ-5D-3L) (The EuroQol Group 1990)

EQ-5D-3L is a self-rated scale that can be used as a valid and reliable measure of the health-related quality of life across a wide range of health conditions as well as in clinical trials. It consists of two parts: 1) a descriptive system that consists of five questions about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, each rated from 1 "no problem" to 3 "extreme problems"; and 2) a visual analogue scale that can be rated from 0 "worst imaginable" to 100 "best imaginable" health. The scores of the descriptive system can be converted to a single summary index of health-related quality of life (EQ-5D-HRQOL) according to the preferences of the general population of a region/country, and can range from less than 0 (worse than death) to 1 (perfect health). One study used EQ-5D (Takeuchi 2014), and the EQ-5D-HRQOL was used in the meta-analysis.

Heinrich-Carpenter Quality of Life Scale (QLS) (Heinrichs 1984)

QLS is a clinician-rated scale administered as a semi-structured interview to measure the quality of life in people with schizophrenia. It consists of 21 items regarding four domains: 1) interpersonal relations, 2) instrumental role, 3) intrapsychic foundations, and 4) common objects and activities. Each item can be rated on a 7-point Likert scale from 0 to 6, with a higher score indicating less impairment within the last four weeks. A total score can be calculated by summing the scores of all items with higher scores indicating less impairment. Two studies used QLS (Carpenter 1999; Kane 2010).

Schizophrenia Quality of Life (S-QoL) (Auquier 2003)

S-QoL is a self-rated scale to measure the health-related quality of life of people with schizophrenia and can be sensitive to change. It consists of 41 questions about eight dimensions of psychological well-being, self-esteem, family relationships, relationships with friends, resilience, physical well-being, autonomy, and sentimental life. Each item can be scored on a 5-point Likert scale, from 1 "less than expected" to 5 "more than expected", and the score of negatively worded items is reversed. A score for each domain can be calculated by computing the mean score of all items within a domain, and scores are linearly transformed on a scale of 0 "least favorable quality of life" to 100 "most favorable quality of life". Similarly, a global quality of life index can be computed by calculating the mean score of the eight domains ranging from 0 to 100 (with a higher score indicating better quality of life). One study used S-QoL (Rouillon 2008).

Subjective Well-Being Under Neuroleptic Treatment Scale (SWNS) (Naber 1995)

SWNS is a self-rated scale assessing the quality of life of people receiving antipsychotic drugs, referring to the last seven days. It originally consisted of 38 items, but a more recent, shorter version (SWN-K) consists of 20 items (10 positive and 10 negative) concerning five domains: 1) mental functioning, 2) self-control, 3) emotional regulation, 4) physical functioning, and 5) social integration. Each question is scored on a 6-point Likert scale, ranging for the positive items from 1 to 6, and for the negative items from −6 to −1. A total score can be calculated by subtracting the sum of the positive items minus the sum of the negative items (ranging from 20 to 120, with a higher score indicating better quality of life). Two studies used SWN-K (Huhn 2020; Takeuchi 2014).

World Health Organization Quality of Life abbreviated form (WHOQOL-BREF) (O'Carroll 2000)

WHOQOL-BREF is a self-rated scale measuring quality of life. It consists of 26 questions regarding satisfaction with health, psychological functioning, social relationships, and environmental opportunities within the last 2 weeks. Each question can be rated on a 5-point Likert scale from 1 to 5. A total score can be calculated by summing the scores of all items ranging from 26 to 130, with a higher score indicating better quality of life. One study used WHOQOL-BREF (Wunderink 2007).

6.1.2 Functioning

Global Assessment of Functioning (GAF) (APA 1987)

GAF is a clinician-rated scale of the impact of a patient's severity of illness on their daily life. It is a brief and easily administered scale measuring impact on functioning on a numeric scale from 0 to 100, broken into 10 intervals, with a higher score indicating better functioning. One study used GAF (Ozawa 2019).

Groningen Social Disabilities Schedule (GSDS) (Wiersma 1988)

GSDS is a clinician-administered semi-structured interview to measure social functioning within the last four weeks. It consists of eight domains: 1) vocational functioning, 2) community integration, 3) peer relationships, 4) relationship with family members, 5) parental functioning, 6) partner relationship, 7) housekeeping, and 8) self-care. Each domain can be rated on a 4-point Likert scale, from 0 "no disability" to 4 "serious disability". A total score can be calculated by summing the scores from all domains except for parental functioning (due to limited applicability), ranging from 0 to 21, with a higher score indicating worse social functioning. One study used GSDS (Wunderink 2007).

Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) (Ware 1992)

SF-36 is a self-rated scale measuring functioning and well-being. It consists of 36 questions about eight domains: 1) physical function, 2) bodily pain, 3) role limitations due to physical problems, 4) vitality, 5) general health perceptions, 6) role limitations due to emotional problems, 7) mental health, and 8) social functioning. The score of each domain is linearly transformed to a scale ranging from 0 to 100, with a higher score indicating better health or functioning. Two summary scores can be calculated, the physical and mental health component summaries, constructed from the eight domains and transformed in order to have a mean of 50 and an SD of 10. The mental health summary component was used in the meta-analysis as a measure of functioning (Schennach-Wolff 2009). One study used SF-36 (Kane 2010).

Personal and Social Performance Scale (PSP) (Morosini 2000)

PSP is a clinician-rated scale validated to measure personal and social functioning in psychiatric disorders. It is a single-item scale ranging from 1 to 100 and subdivided into 10 equal intervals, with a higher score corresponding to better functioning. The total score is

derived by considering four domains rated on a 6-point scale from 1 "absent" to 6 "very severe" difficulties: 1) socially useful activities, including work and study, (2) personal and social relationships, 3) self-care, and 4) disturbing and aggressive behaviours. Two studies used PSP (Fleischhacker 2014; Huhn 2020).

Strauss and Carpenter Level of Functioning Scale (SCLoF) (Hawk 1975; Strauss 1974; Strauss 1977)

SCLoF is a clinician-rated scale administered as a semi-structured interview to measure functioning in people with schizophrenia. It consists of 14 items regarding four domains: 1) social contacts, 2) work, 3) symptomatology, and 4) function. Each item can be scored on a 5-point Likert scale from 0 to 4, with a higher score indicating better functioning. A subscale score can be calculated by computing the mean score of all items within the subscale. A total score can be calculated by summing the scores of the four subscales. One study used SCLoF (Carpenter 1999).

6.1.3 Global state

Clinical Global Impression (CGI) (Guy 1976)

CGI scales are 7-point clinician-rated scales, comprised of two scales measuring global severity of illness (CGI-Severity, or CGI-S) and global clinical improvement (CGI-Improvement, or CGI-I). A lower score corresponds to lower severity of illness or more improvement (or less deterioration), respectively. A CGI-I score of 1 "very much improved" or 2 "much improved" corresponds to a clinically important improvement (Busner 2007/07). If data based on this cut-off were not available, other cut-offs or study definitions were used. Six studies used CGI-S (Fleischhacker 2014; Huhn 2020; Kane 2010; Remington 2011; Takeuchi 2014), and three studies used CGI-I (Fleischhacker 2014; Huhn 2020; Kane 2010).

There are also variations of CGI scales. The CGI scales for schizophrenia (CGI-SCH) could be considered valid measures of severity and treatment response (Haro 2003). Similar to the original CGI scales, CGI-SCH consists of 7-point scales measuring severity or improvement in the domains of 1) positive, 2) negative, 3) depressive, and 4) cognitive symptoms, as well as 5) overall symptoms. One study used the overall domain of CGI-SCH (Ozawa 2019).

Investigator's Assessment Questionnaire (IAQ) (Tandon 2005)

IAQ is a 10-item clinician-rated scale validated to measure the relative effectiveness of the current antipsychotic medications in comparison to previous medications in people with schizophrenia. It includes 10 items for efficacy, safety, and tolerability: positive and negative symptoms, cognition, energy, mood, somnolence, weight gain, prolactin elevation, akathisia, and extrapyramidal symptoms. Each item can be rated on a 5-point Likert scale from 1 "much better" to 5 "much worse". A total score can be calculated by summing all items as a measure of overall effectiveness, with a higher score corresponding to less improvement or worsening. One study used IAQ (Fleischhacker 2014).

Symptom Checklist 90 (SCL-90) (Deragotis 1973)

SCL-90 is a self-rated scale that measures a broad range of psychiatric symptomatology. It consists of 90 questions about nine domains of symptoms: 1) somatisation, 2) obsessive/compulsive, 3) depression, 4) anxiety, 5) hostility, 6) phobic anxiety, 7) paranoid ideation, 8) psychoticism, and 9) additional items (e.g. sleep and appetite patterns). Each item is scored on a 5-point Likert scale ranging from 0 "no symptom" to 4. There are three global measures: 1) Global Severity Index (GSI), which is the average of the 90 item scores and is proposed to be the best index of the current level of the disorder; 2) Positive Symptom Distress Index (PSDI), which is the average of the items with a score above 0; and 3) Positive Symptoms Total (PST), which is the number of items with a score above 0. One study used SCL-90 GSI (Kane 1983).

6.1.4 Mental state

Brief Psychiatric Rating Scale (BPRS) (Overall 1962)

BPRS is a clinician-rated scale used to measure the severity of psychiatric symptoms, including psychotic symptoms. The most frequently used version of the scale consists of 18 items encompassing positive, negative, and affective symptoms. Each item is scored on a 7-point Likert scale from 1 "not present" to 7 "extremely severe". A total score can be calculated by summing the score of all items as a measure of overall symptoms of schizophrenia (ranging from 18 to 126, with a higher score corresponding to higher severity of symptoms). Three studies used BPRS (Carpenter 1999; Kane 2010; Remington 2011).

Positive and Negative Symptom Scale (PANSS) (Kay 1986)

PANSS was developed based on the BPRS (see above). It is a 30-item clinician-rated scale that covers positive, negative, and general psychopathology symptoms of schizophrenia. Each item is scored on a 7-point Likert scale ranging from 1 "absent" to 7 "extreme". A total score can be calculated by summing the score of all items as a measure of overall symptoms of schizophrenia (ranging from 30 to 210, with a higher score corresponding to higher severity of symptoms).

There are three original subscales: 1) positive symptoms, 2) negative symptoms, and 3) general psychopathology. The former two are validated and often used as measures of positive and negative symptoms, respectively. A different structure is suggested by a more recent factor analysis, such as the five Marder factors: 1) positive symptoms, 2) negative symptoms, 3) anxiety/depression, 4) uncontrolled hostility/excitement, and 5) disorganised thought (cognitive) (Marder 1997). These factors were also used as valid measures of positive and negative symptoms (when the original factors were not presented), as well as depressive symptoms, El Yazaji 2002, and aggressive behaviour. However, we did not use the subscale of general psychopathology, as it covers a wide range of symptoms, and the cognitive factor, because it does not well reflect cognitive deficits in schizophrenia (Nielsen 2014).

Ten studies used PANSS (Fleischhacker 2014; Huhn 2020; Kane 2010; Ozawa 2019; Rouillon 2008; Takeuchi 2014; Volavka 2000; Wang 2010; Wunderink 2007; Zhou 2018). There are also different versions of PANSS, but none of the included studies used them.

Negative Symptom Assessment 16 (NSA-16) (Alphs 1989)

NSA-16 is a 16-item clinician-administered semi-structured interview to assess negative symptoms in schizophrenia (i.e. communication, emotion/affection, social involvement, motivation, and retardation). Each of the items is scored on a 7-point scale ranging from 0 to 6 (from lower to higher severity). A total score is calculated by summing the scores of all items (ranging

from 0 to 96, with a higher score corresponding to higher severity of symptoms). One study used NSA-16 (Zhou 2018).

Calgary Depression Scale for Schizophrenia (CDSS) (Addington 1993)

CDSS is a clinician-rated scale that measures depressive symptoms in people with schizophrenia. It consists of 9 items considering depressive symptoms that can be scored on a 4-point Likert scale from 0 "absent" to 3 "severe". A total score can be calculated by summing the score of all items (ranging from 0 to 27, with a higher score corresponding to higher severity of symptoms). One study used CDSS (Takeuchi 2014).

Profile of Mood States Short Form (POMS-SF) (Shacham 1983)

POMS-SF is a self-rated scale measuring psychological distress at the time of evaluation. Due to the large number of questions of the original scale (i.e. 65), a shorter form was developed with 37 items about six domains: 1) fatigue, 2) vigour, 3) tension, 4) depression, 5) anger, and 6) confusion. Each item can be rated on a 5-point Likert scale from 0 "not at all" to 5 "extremely". A total score is calculated by summing the scores of the items of the negative subscales (fatigue, tension, confusion, anger) and subtracting the scores of the items of the positive subscale (vigour). The total score can be used as a measure of mood disturbance, and a higher score indicates a higher severity of mood disturbance. One study used POMS-SF (Takeuchi 2014). There are other variations of the scale, but none of the included studies used them.

Schedule for Assessment of Insight (SAI) (David 1990)

SAI is a clinician-rated scale measuring the insight of the person with psychosis. It consists of seven items on three components of insight: 1) treatment compliance, 2) awareness of the illness, and 3) relabelling of psychotic experiences. Each item can be scored from 0 to 2 (from a lower to a higher insight), and a total score can be calculated by summing the score of all items ranging from 0 to 14, with a higher score indicating more insight. One study used SAI (Takeuchi 2014).

6.1.5 Satisfaction with care

Medication Adherence Questionnaire (MAQ) (Morisky 1986)

MAQ is a self-rated scale that measures non-adherence. It consists of four questions about forgetting or being careless about taking the medication as well as stopping the medication when feeling worse or better. Each question can be answered with a no or a yes. A total score can be calculated ranging from 0 to 4, with a higher score indicating worse adherence. One study used MAQ (Fleischhacker 2014).

Drug Attitude Inventory (DAI) (Hogan 1983)

DAI is a self-rated scale that assesses the attitudes of the patient towards the medication, and can be used as a measure of adherence. The original version consists of 30 questions that can be answered with a yes or a no about seven domains: 1) subjective positive feelings, 2) subjective negative feelings, 3) health, 4) confidence in the physician, 5) control, 6) prevention, and 7) harm. A total score can be calculated ranging from −30 to 30, with a higher positive score indicating a higher positive attitude towards the medication. There is also a short version (DAI-10) that consists of 10 questions, and a total score can be calculated ranging from −10 to 10 (Awad 1993). One study used the original version of the scale (Fleischhacker 2014), and one study used the short version (Takeuchi 2014).

Medication Adherence Rating Scale (MARS) (Thompson 2000)

MARS is a self-rated scale that measures medication compliance in psychiatric patients. It was developed based on a principal component analysis using the questions of DAI and MAQ (see above). It consists of 10 questions about attitudes or behaviour towards the medication in the past week. Each question could be answered with a no or a yes. A total score can be calculated ranging from 0 to 10, with a higher score indicating better medication adherence. One study used MARS (Huhn 2020).

Patient Satisfaction with Medication Questionnaire (PSMQ) (Kalali 1999)

PSMQ is a self-rated scale that assesses satisfaction with medication as well as frequency of side effects in patients receiving antipsychotic medication. It consists of three questions about the comparison between the current and previous medication: 1) satisfaction with the treatment scored on a 6-point scale from "extremely satisfied" to "extremely unsatisfied"; 2) frequency of side effects scored on a 6-point scale from "no side effects" to "much more side effects"; and 3) preference to treatment scored with "current treatment" or "previous treatment". There are additional questions about differences noted by the caregiver or additional comments from the patient. The number of participants preferring the current medication was analysed in this meta-analysis. The categorical responses of other domains were not analysed. One study used PSMQ (Fleischhacker 2014).

6.1.6 Adverse effects

Udvalg for Kliniske UndersoBgelser (UKU) (Lingjaerde 1987)

UKU is a clinician-administered semi-structured interview for assessing side effects related to psychotropic medications. It consists of a catalogue of 48 psychological, neurological, autonomic, and other side effects, scored on a 4-point Likert scale from 0 "not or doubtfully present" to 3 "present to a severe degree". A total score can be calculated by summing the score of all items, with a higher score corresponding to higher severity of side effects. The score of individual items is used to identify patients with an adverse event (a score of at least 1 for a side effect), and the total score as a measure of the overall severity of side effects.

Additionally, it is possible to score the potential relationship of the side effect with the treatment ("improbable", "possible", "probable"). There are also two global ratings according to the judgement of the patient and physician about the influence of the side effects on daily functioning (0 "no side effects" to 3 "side effects that interfere markedly with the patient's performance"), as well as the consequences of the side effects (0 "no action" to 3 "discontinuation of drug or change to another preparation"). These domains of UKU were not considered in the systematic review.

One study used UKU (Huhn 2020). There is also a self-rated version of the scale (Lindström 2001), but none of the included studies used it.

Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS) (Day 1995)

LUNSERS is a self-rated scale consisting of 41 items regarding antipsychotic-related side effects (i.e. extrapyramidal, autonomic, psychic, anticholinergic, allergic reactions, prolactin, and others). There are also 10 additional items concerning symptoms that are not directly related to antipsychotic side effects and are used as red herrings to indicate the accuracy of self-assessment. Each item can be scored on a 5-point Likert scale from 0 "not at all" to 4 "very much". A total score can be calculated by summing the scores of the 41 items, with a higher score corresponding to higher severity of side effects. One study used LUNSERS (Wunderink 2007).

Simpson and Angus Scale (SAS) (Simpson 1970)

SAS is a clinician-rated scale that measures extrapyramidal side effects focusing on parkinsonism. It consists of 10 symptoms, each scored on a 4-point Likert scale from 0 to 4 (from lower to higher severity). A total score is calculated by summing the scores of all items (ranging from 0 to 40, or from 0 to 4 when divided by 10; a higher score corresponds to higher severity of extrapyramidal symptoms). Seven studies used SAS (Fleischhacker 2014; Kane 2010; Ozawa 2019; Rouillon 2008; Volavka 2000; Wang 2010; Zhou 2018).

Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS) (Inada 2009)

DIEPSS is a clinician-rated scale assessing extrapyramidal side effects. It consists of eight items concerning individual extrapyramidal symptoms, scored on a 5-point Likert scale from 0 "normal" to 4 "severe". Similarly, a ninth item measures the global severity and frequency of extrapyramidal symptoms as well their impact on daily living. A total score can be calculated by summing the score of the eight individual items (ranging from 0 to 32, with a higher score indicating greater severity of extrapyramidal symptoms), as well as subscores that can be used to measure parkinsonism, akathisia, and dyskinesia. One study used DIEPSS (Takeuchi 2014)

Maryland Psychiatric Research Center Involuntary Movement Scale (MPRC) (Cassady 1997)

MPRC is a clinician-rated scale measuring drug-induced dyskinesia and parkinsonism. The dyskinesia rating consists of 13 items, each of which is scored on an 8-point Likert scale ranging from 0 to 7 (from lower to higher severity). A total score can be calculated by summing the score of all relevant items, with a higher score indicating a higher severity of dyskinesia. Similarly, the parkinsonism rating consists of 15 items that can be scored from 0 to 7, and a total score can be calculated by summing the score of all relevant items, with a higher score indicating a higher severity of parkinsonism. One study used MPRC (Carpenter 1999).

Barnes Akathisia Rating Scale (BARS) (Barnes 1989)

BARS is a clinician-rated scale measuring drug-induced akathisia. It consists of three items corresponding to two domains: 1) objective scored from 0 to 3 (from normal to a higher severity); and 2) subjective awareness of restlessness scored from 0 to 3 (from absence to a higher severity) and distress related to restlessness from 0 to 3 (from no distress to severe). A total score is calculated by summing the scores of these items (from 0 to 9, with a higher score indicating a higher severity of akathisia). In addition, there is a global assessment of akathisia scored from 0 "absent" to 5 "severe akathisia". Three studies reported BARS global scores (Fleischhacker 2014; Kane 2010; Ozawa 2019); it was unclear in another study if total or global scores were reported (Rouillon 2008).

Abnormal Involuntary Movement Scale (AIMS) (Guy 1976)

AIMS is a 12-item clinician-rated scale measuring antipsychotic-related dyskinesia, usually as a long-term complication of antipsychotic treatment (i.e. tardive dyskinesia). It consists of seven items concerning facial/oral, extremities, and trunk movements, with each item scoring from 0 "none" to 4 "severe". A total score can be calculated by summing the score of the seven items as an overall measure of the severity of abnormal movements (from 0 to 28; a higher score indicates a higher severity of dyskinesia). As supplementary assessments, the scale also has three items that measure the global severity of abnormal movements, awareness of abnormal movements, and their impact, with each item scoring from 0 to 4. Lastly, the scale also has two items assessing dental status. Seven studies used AIMS to assess abnormal movements (Fleischhacker 2014; Huhn 2020; Johnson 1987; Kane 2010; Ozawa 2019; Remington 2011; Rouillon 2008).

Rockland Tardive Dyskinesia Rating Scale (RTDRS) (Simpson 1979).

RTDRS is a clinician-rated scale measuring tardive dyskinesia; it also includes other movement disorders such as restless legs and akathisia. The scale consists of 34 items that can be rated on a 6-point Likert scale from 1 "absent" to 6 "very severe" (or from 0 to 5). A total score can be calculated by summing the scores of all items (with a higher score indicating a higher severity of tardive dyskinesia). There is also an abbreviated version with 13 items. One study used the abbreviated version of RTDRS (Branchey 1981). The standard deviation of this scale was not reported in the manuscript, therefore it was imputed from a study evaluating the prevalence of tardive dyskinesia in 148 people with schizophrenia (Altamura 1990).

Columbia Suicide Severity Rating Scale (C-SSRS) (Posner 2008)

C-SSRS is a clinician-rated scale that can be used for the screening and measurement of suicidal ideation and behaviour. There are five questions about suicidal ideation and five about suicidal behaviour for screening for suicidality. Each question can be answered with 0 "no" or 1 "yes" indicating the absence or presence of ideation or behaviour. There are also two additional questions about the actual medical damage and the potential lethality of suicidal behaviours. The most severe suicidal ideation identified from the previous five questions can be rated using five items about the intensity of the suicidal ideation (frequency, duration, controllability, deterrents, and reasons for the suicidal ideation), with each item scored from 0 to 5 (from a lower to a higher severity). A total score can be calculated by summing the score of these five items, and it can be used as a measure of change for the severity of suicidal ideation (ranging from 0 to 25, with a higher score indicating a higher severity of intensity of the suicidal ideation). One study used C-SSRS (Fleischhacker 2014).

Clinical Global Impression - Severity of Suicidality (CGI-SS) (Lindenmayer 2003)

CGI-SS can be a valid measure for suicidality risk, and in contrast to other CGI scales is rated on a 5-point Likert scale, from 1 "not at all suicidal" to 5 "attempted suicide". One study used CGI-SS (Fleischhacker 2014).

6.1.7 Cognition

Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) (Kern 2008; Nuechterlein 2008)

MCCB is a cognitive battery consisting of neurocognitive tests on seven domains: 1) speed of processing, 2) attention/vigilance, 3) working memory, 4) verbal learning, 5) visual learning, 6) reasoning and problem-solving, and 7) social cognition. There can be more than one test for a given domain. Raw scores of tests are transformed into standardised T-scores (mean 50 and SD 10, with a higher score corresponding to a higher cognitive function). When there is more than one test for a domain, T-scores of the different tests are summed, and the sum is again standardised to a T-score. Similarly, an overall composite score is calculated as a measure of overall cognitive functions. One study used MCCB (Zhou 2018)

Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) (Randolph 1998)

RBANS is a cognitive battery consisting of 12 neurocognitive tests on seven domains: 1) immediate memory, 2) visuospatial/constructional, 3) language, 4) attention, and 5) delayed memory. Based on the results of the tests, an index score is calculated for each domain, as well as a total score as a measure of overall cognitive functions, with a higher score corresponding to a higher cognitive function. One study used RBANS (Takeuchi 2014)

7. Funding sources

Five studies were industry sponsored; 14 studies reported public funding; two studies were jointly funded by public institutions and pharmaceutical companies; and four studies did not provide clear information on funding.

Excluded studies

We excluded 56 studies based on full-text assessment. The reasons for exclusion were:

- ineligible design: not randomised, Inderbitzin 1994; Soria 1994; Sukegawa 2013, or limited confidence in data (Khazaie 2005);
- ineligible population: no schizophrenia, Kalachnik 1984; Marken 1994, or not stable patients (AstraZeneca 2007; Baker 2002; Bogers 2018; Dellva 1997; Durgam 2017; Eli-Lilly F1D-EW-E003 1997; Eli-Lilly F1D-MC-HGAD 1997; Kinon 2004; NCT00254787; NCT00254813; NCT00304473; NCT00457899; NCT00486798; Pae 2007; Schultz 2007; Townsend 2004; Uchida 2006);
- ineligible intervention: no dose reduction (Arato 2002; Caffey 1971; European Medicines Agency 2007; Faber 2012; Goldstein 1978; Harris 1997; Hsiao 2011; Huttunen 1996; Kane 1979; Kane 2002; Lecrubier 2006; Lee 2002; Lublin 1991; Marder 1984; Matkovits Gupta 1999; Matkovits Gupta 2001; Miller 1965; NCT00919607; Nishikawa 1984; Nishikawa 1985; Nishikawa 1989; Simpson 2007; Smith 2002; Sramek 1997; Sramek 1998; Sukegawa 2008; Velligan 2002; Yamanouchi 2015);
- ineligible comparator: no dose maintenance (Hirschowitz 1997; Koshikawa 1991; Mallikaarjun 2013; Suzuki 1992; Yoon 2016).

Ongoing studies

We identified six ongoing studies that matched our inclusion criteria (EUCTR2017 002406 12; JPRN UMIN000037282; Liu 2018; NCT03559426; NCT03593213; Weller 2018).

Studies awaiting classification

There were no studies awaiting classification.

Risk of bias in included studies

The risk of bias assessment for each of the predefined outcomes is located in the risk of bias section (see Characteristics of included studies), including all domain judgments and support for judgements, and at the side of the relevant forest plots. Detailed risk of bias assessments are available upon request.

The risk of bias in outcomes across all studies was predominantly assessed as some concerns. In most studies, the allocation of participants was described as randomised, but without providing details on how the random sequence was generated. However, there were baseline differences in only two studies (Branchey 1981; Hogarty 1988), suggesting potential problems with the randomisation process.

Seven out of 22 studies included in the meta-analyses were not double-blind, resulting in an assessment of some concerns or high risk of bias for the domain 'deviations from intended interventions'.

We assessed risk of bias as some concerns or high risk of bias across outcomes. We assessed only two studies as at low risk of bias for most of the outcomes analysed (Fleischhacker 2014; Kane 2010).

On the one hand, we judged risk of bias for readmission to hospital to be some concerns for most studies. On the other hand, we judged the outcome of relapse/exacerbations of psychosis as at high risk of bias for almost half of the included studies. The tolerability and acceptability outcomes, namely leaving the study early due to side effects or for any reason, generated a judgement of some concerns in most cases.

We judged functioning and quality of life, measured with various rating scales, to be at overall some concerns or low risk of bias.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Antipsychotic dose reduction compared to dose continuation for people with schizophrenia

See Summary of findings 1 and forest plots for detailed results.

Comparison 1: Dose continuation versus dose reduction

Primary outcomes

1. Quality of life

1.1. Clinically important change in quality of life

No study reported this outcome.

2. Service use

2.1. Readmission to hospital

Nine studies reported data for readmission to hospital, and the effect size was calculated on eight studies (one study had 0 events

in both arms (Huhn 2020)). Results showed a trend in the direction of fewer participants being readmitted to hospital in the dose maintenance group in comparison with the dose reduction group, but the 95% confidence interval (CI) did not exclude the possibility of no difference (risk ratio (RR) 1.53, 95% CI 0.84 to 2.81, 9 RCTs, n = 1433 (8 studies and n = 1413 with estimable effect sizes), I^2 = 59% (moderate heterogeneity), very low certainty evidence) (Analysis 1.1). When looking at the different time points, no clear differences emerge (test for subgroup differences = 0.07) (Analysis 1.2)

We performed sensitivity analysis by removing two studies with an overall high risk of bias (Remington 2011; Rouillon 2008), and the results did not materially change (RR 1.66, 95% CI 0.81 to 3.39, 7 RCTs, n = 1301, I^2 = 64% (moderate heterogeneity)) (Analysis 2.1). We have also reported the results of the fixed-effect model (RR 1.46, 95% CI 1.08 to 1.98, 9 RCTs, n = 1433, I^2 = 59% (moderate heterogeneity)) (Analysis 2.2), which were in general similar, although more precise, and the 95% CIs excluded the possibility of no difference. All studies used operationalised criteria to diagnose schizophrenia.

3. Adverse effect

3.1. Leaving the study early due to adverse effects – overall tolerability

Ten studies reported data for this outcome, six of which provided estimable effect sizes. Fewer participants in the dose maintenance group left the study early due to adverse effects compared to the dose reduction group (RR 2.20, 95% CI 1.39 to 3.49, 10 RCTs, n = 1340 (6 studies and n = 1079 with estimable effect sizes), I^2 = 0%, moderate certainty evidence) (Analysis 1.3). When looking at the different time points, no differences emerge (test for subgroup differences P = 0.72) (Analysis 1.4).

We performed sensitivity analysis by removing one study with an overall high risk of bias (RR 2.21, 95% CI 1.38 to 3.53, 5 RCTs, n = 1243, I^2 = 0%) (Analysis 3.1) (Rouillon 2008); one study that did not use operationalised criteria to diagnose schizophrenia (RR 2.20, 95% CI 1.37 to 3.52, 5 RCTs, n = 1317, I^2 = 0%) (Analysis 3.2) (Volavka 2000); and one study conducted in mainland China (RR 2.20, 95% CI 1.39 to 3.49, 5 RCTs, n = 1265, I^2 = 0%) (Analysis 3.3) (Zhou 2018), and the results did not materially change. We have also reported the results of a fixed-effect model (RR 2.20, 95% CI 1.39 to 3.49, 6 RCTs, n = 1340, I^2 = 0%) (Analysis 3.4), which were identical due to a lack of statistical heterogeneity.

Secondary outcomes

1. Quality of life

1.1. Mean endpoint or change score on quality of life scale

Based on six studies, results did not show a difference between maintaining and reducing the dose on quality of life measured with different rating scales (standardised mean difference (SMD) −0.01, 95% CI −0.17 to 0.15, 6 RCTs, n = 719, I^2 = 0%, moderate certainty evidence) (Analysis 1.13). No difference emerged between separate time points (test for subgroup differences P = 0.63) (Analysis 1.14).

2. Service use

2.1. Days in hospital

No study reported this outcome.

3. Functioning

3.1. Clinically important change in functioning

No study reported this outcome.

3.2. Mean endpoint or change score on functioning scale

Based on six studies, results did not show a difference between maintaining and reducing the dose on functioning measured with different rating scales (SMD 0.03, 95% CI −0.10 to 0.17, 6 RCTs, n = 966, I^2 = 0%, high certainty evidence) (Analysis 1.22). No differences emerged when looking at different time points (test for subgroup differences P = 0.62) (Analysis 1.23).

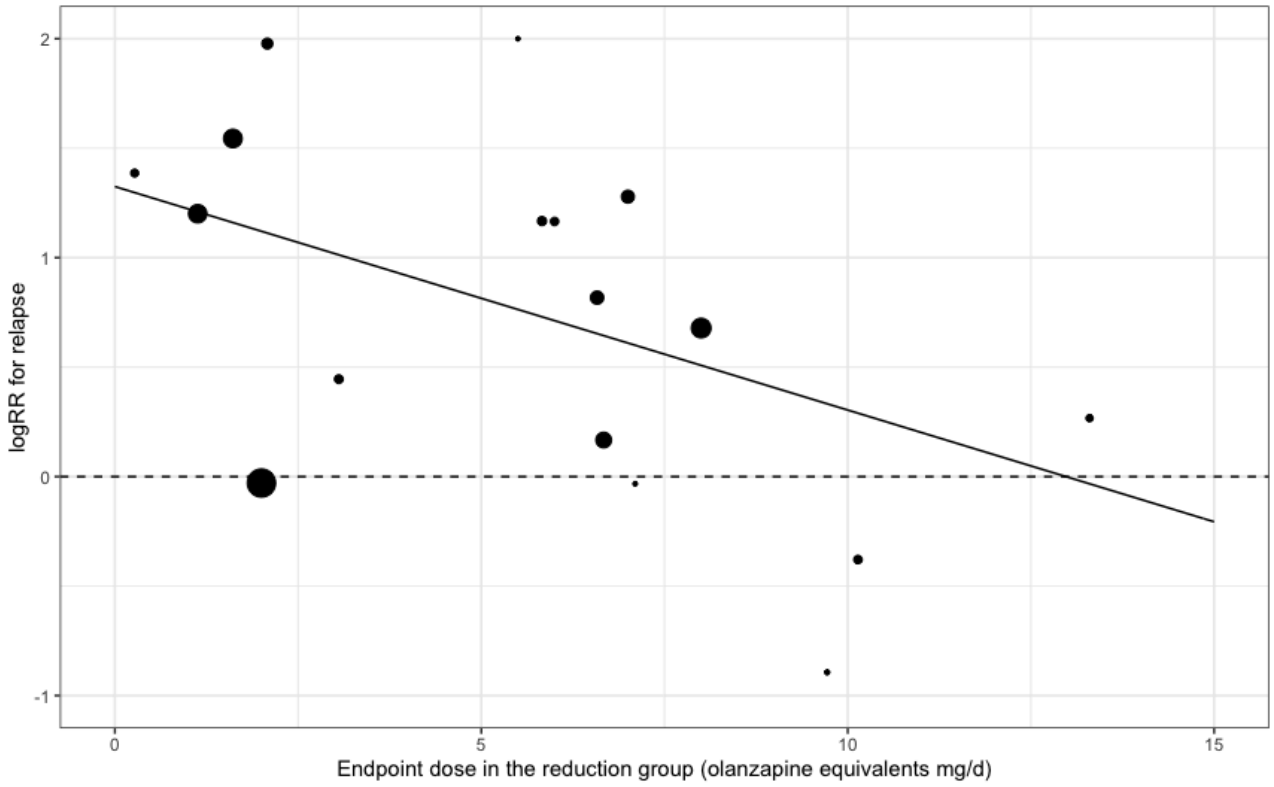
4. Global state

4.1. Relapse/exacerbations of psychosis

Twenty studies reported data on this outcome. Participants in the dose reduction group had a higher risk of relapsing compared to those in the dose continuation group (RR 2.16, 95% CI 1.52 to 3.06, 20 RCTs, n = 2481, I^2 = 70% (substantial heterogeneity), low certainty evidence) (Analysis 1.24). No differences emerged between time points (test for subgroup differences P = 0.33) (Analysis 1.25).

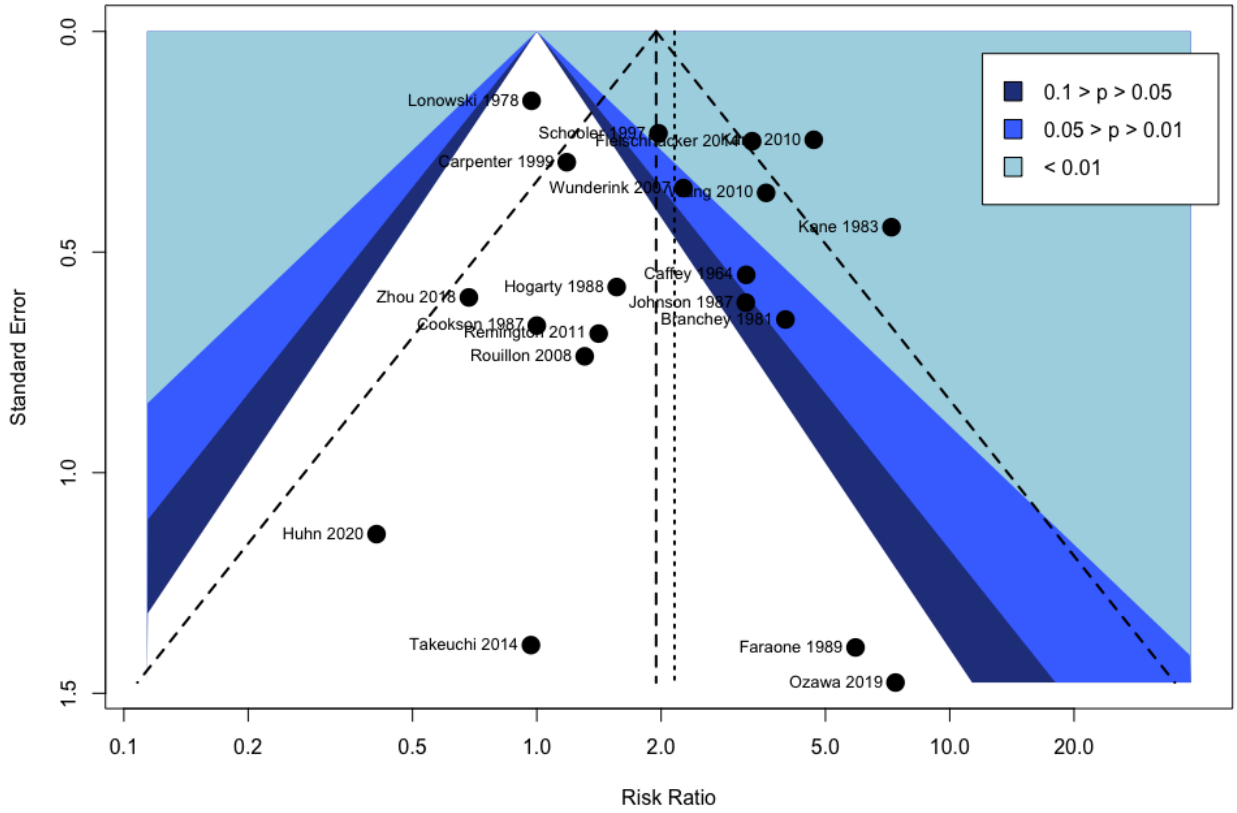
The results of a post hoc meta-regression investigating the effects of endpoint antipsychotic dose in the dose reduction group were unclear (Figure 2). There was an indication that lower endpoint doses are associated with a higher relative risk for relapse, yet the results were not formally statistically significant at 0.05 (beta = 0.102 increase in log relative risk per mg/d increase, standard error = 0.060, P = 0.087). The results were influenced by an outlier study, which was very old and with unclear information about the doses and high relapse rates in both groups (74% in the dose reduction group and 80% in the dose continuation group) (Lonowski 1978). Excluding this study, there was a clearer indication that lower endpoint doses are associated with a higher risk for relapse (beta = 0.129, standard error = 0.036, P < 0.001). There was no difference in the post hoc subgroup analysis investigating the speed of dose reduction (abrupt versus gradual) (Chi^2 = 0.03, df = 1, P = 0.87) (Analysis 4.1).

Figure 2. Meta-regression between log risk ratio (logRR) for relapse and endpoint mean dose in olanzapine equivalents (mg/d) in the dose reduction group. The results of the analysis were unclear, and there was an indication that a lower the endpoint dose was associated with higher relative risk for relapse (beta = −0.102, standard error = 0.060, P = 0.087 and intercept = 1.325, standard error = 0.365, P < 0.001). The results were influenced by a very old outlier study, Lonowski 1978, with unclear dose information and high relapse rates in both groups (74% in the dose reduction and 80% in the dose continuation).



There was no indication of small-study effects by funnel plot analysis, since no asymmetry was detected by visual inspection of the funnel plot and a linear regression test (t = 0.75, df = 18, P = 0.465) (Figure 3).

Figure 3. Funnel plot for the outcome global state - relapse/acute exacerbation of psychosis. No clear asymmetry can be observed by visual inspection of the funnel plot. There was no evidence of asymmetry according to a linear regression test of funnel plot assymetry (bias = 0.57, t = 0.75, df = 18, P = 0.465).



4.2 Remission

Based on one study, results showed no difference in the number of participants in remission between groups (RR 0.82, 95% CI 0.61 to 1.09, 1 RCT, n = 397) (Analysis 1.26).

4.3 Number of participants with clinically important change in global state

One study reported data on this outcome at two separate time points. No difference emerged between the dose reduction and dose continuation group either at less than three months (RR 4.17, 95% CI 0.23 to 77.11, 1 RCT, n = 20) or at less than six months (RR 4.17, 95% CI 0.23 to 77.11, 1 RCT, n = 20) (Analysis 1.27).

4.4. Mean endpoint or change score on global state scale

Six studies reported data on CGI-S. Results showed no difference between dose reduction and dose continuation (mean difference (MD) 0.05, 95% CI −0.18 to 0.28, 6 RCTs, n = 999, I^2 = 66% (substantial heterogeneity)) (Analysis 1.30). No differences emerged between the separate time points (test for subgroup differences P = 0.91) (Analysis 1.31).

Three studies reported data on CGI-I. Results showed no difference between dose reduction and dose continuation (MD 0.19, 95% CI −0.47 to 0.85, 3 RCTs, n = 881, I^2 = 89% (substantial heterogeneity)) (Analysis 1.32). No differences emerged between the separate time points (test for subgroup differences P = 0.81) (Analysis 1.33).

One study reported data using IAQ-12 (MD 1.69, 95% CI 0.47 to 2.91, 1 RCT, n = 397) (Analysis 1.34).

One study with 39 participants reported results using SCL-90, at three different time points. At all time points, dose reduction was associated with better global state (less than three months: MD −0.38, 95% CI −0.61 to −0.15; less than six months: MD −0.52, 95% CI −0.80 to −0.24; less than one year: MD −0.59, 95% CI −0.91 to −0.27) (Analysis 1.35).

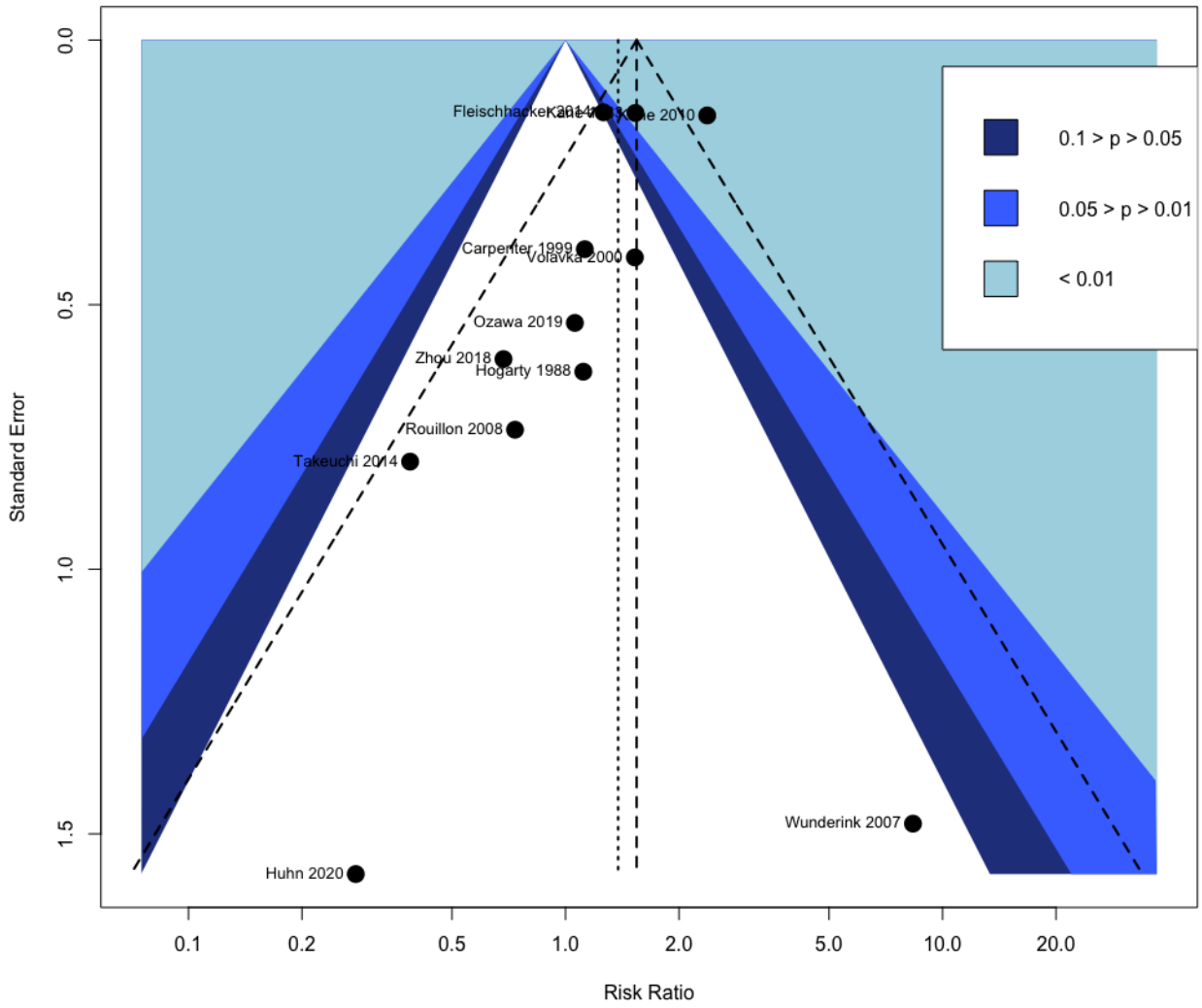
5. Leaving the study early

5.1. For any reason – overall acceptability

Twelve studies provided data on this outcome. The number of participants leaving the study early for any reason was lower in the dose continuation group (RR 1.38, 95% CI 1.05 to 1.81, 12 RCTs, n = 1551, I^2 = 48% (moderate heterogeneity), moderate certainty evidence) (Analysis 1.36). No differences emerged between separate time points (test for subgroup differences P = 0.83) (Analysis 1.37).

There was an indication of small-study effects by funnel plot analysis, since asymmetry could be detected by visual inspection of the funnel plot; however, the linear regression test was not formally statistically significant (t = −1.59, df = 10, P = 0.143) (Figure 4).

Figure 4. Funnel plot for the outcome leaving the study early for any reason - overall acceptability. We could detect asymmetry by visual inspection of the funnel plot, yet the results of the regression test analysis were not formally statistically significant (bias = −0.93, t = −1.59, df = 10, P = 0.143).



5.2. Due to inefficacy – overall efficacy

Ten studies provided data on this outcome. The number of participants leaving the study early due to inefficacy was higher in the dose reduction group (RR 2.06, 95% CI 1.21 to 3.50, 10 RCTs, n = 1322, I^2 = 38% (not important heterogeneity)) (Analysis 1.38). The test for subgroup differences indicated a possible difference between the separate time points (P = 0.08) (Analysis 1.39).

6. Mental state

6.1. General

6.1.1. Clinically important change in general mental state

Two studies provided data on this outcome. The number of participants with a clinically important change in general mental state was higher in the dose continuation group (RR 0.84, 95% CI 0.75 to 0.94, 2 RCTs, n = 417, I^2 = 0%) (Analysis 1.40). No differences emerged between separate time points (P = 0.62) (Analysis 1.41).

6.1.2. Mean endpoint or change score on general mental state scale

Twelve studies provided data on this outcome. Results did not show a difference between maintaining and reducing the dose on mental state measured with PANSS and BPRS (SMD 0.02, 95% CI −0.24 to 0.27, 12 RCTs, n = 1718, I^2 = 80% (substantial heterogeneity)) (Analysis 1.46). No differences emerged between separate time points (test for subgroup differences P = 0.60) (Analysis 1.47).

6.2. Specific

6.2.1. Clinically important change in positive symptoms

No study reported this outcome.

6.2.2. Mean endpoint or change score on positive symptom scale

Ten studies provided data on this outcome. Results did not show a difference between maintaining and reducing the dose on positive symptoms (SMD 0.07, 95% CI −0.22 to 0.35, 10 RCTs, n = 1337, I^2 = 79% (substantial heterogeneity)) (Analysis 1.50). No differences emerged between the time points considered separately (test for subgroup differences P = 0.91) (Analysis 1.51).

6.2.3. Clinically important change in negative symptoms

No study reported this outcome.

6.2.4. Mean endpoint or change score on negative symptom scale

Nine studies provided data on this outcome. Results did not show a difference between maintaining and reducing the dose on negative symptoms measured with the PANSS (SMD −0.19, 95% CI −0.49 to 0.12, 9 RCTs, n = 1302, I^2 = 81% (substantial heterogeneity)) (Analysis 1.54). No differences emerged between separate time points (test for subgroup differences P = 0.96) (Analysis 1.55).

6.2.5. Clinically important change in depressive symptoms

No study reported this outcome.

6.2.6. Mean endpoint or change score on depressive symptom scale

Five studies provided data on this outcome. Results did not show a difference between maintaining and reducing the dose on depressive and anxiety symptoms measured with the PANSS and CDSS (SMD 0.11, 95% CI −0.02 to 0.25, 5 RCTs, n = 915, I^2 = 0%) (Analysis 1.60). No differences emerged between separate time points (test for subgroup differences P = 0.72) (Analysis 1.61).

7. Behaviour

7.1. Clinically important change in behaviour (including aggression)

No study reported this outcome.

7.2. Mean endpoint or change score on behaviour scale

Three studies provided data on this outcome. Results did not show a difference between maintaining and reducing the dose on aggressive behaviours measured with the PANSS excitement/hostility subscale (MD 0.25, 95% CI −0.32 to 0.82, 3 RCTs, n = 757, I^2 = 53% (moderate heterogeneity)) (Analysis 1.66). The test for subgroup differences indicated a possible difference between the separate time points (test for subgroup differences P = 0.009) (Analysis 1.67).

8. Satisfaction with care

8.1. Clinically important change in satisfaction with care

One study with 397 participants reported results using PSMQ, in particular referring to the number of participants preferring the current antipsychotic medication over the previous one. Data are provided for the 12-month time point; dose continuation is associated with a clinically important change in satisfaction with care (RR 0.86, 95% CI 0.77 to 0.96) (Analysis 1.68).

8.2. Mean endpoint or change score on satisfaction with care scale

Three studies provided data on this outcome. Results did not show a difference between maintaining and reducing the dose on satisfaction with care measured with different rating scales (SMD −0.06, 95% CI −0.26 to 0.14, 3 RCTs, n = 440, I^2 = 0%) (Analysis 1.75). Test for subgroup differences excluded a possible difference between the separate time points (test for subgroup differences P = 0.18) (Analysis 1.76).

9. Adverse effects/events

9.1. Effects

9.1.1. At least one adverse effect

Based on data from five studies (four with estimable effect sizes), results did not show a difference between dose reduction and dose continuation in the number of participants with at least one adverse effect (RR 1.03, 95% CI 0.94 to 1.12, 5 RCTs, n = 998 (4 RCTs, n = 980 with estimable effect sizes), I^2 = 0%, moderate certainty evidence) (Analysis 1.77). No differences emerged between separate time points (test for subgroup differences P = 0.62) (Analysis 1.78).

9.1.2. Serious adverse events

Based on one study, no differences emerged between groups in the number of participants with at least one serious adverse event (RR 1.49, 95% CI 0.70 to 3.15, 1 RCT, n = 417) (Analysis 1.79). Another study reported this outcome, but no events were registered for both groups, so the calculation of effect size was not possible (Analysis 1.80).

9.1.3. Adverse effects evaluated with scales

Based on two studies, no differences emerged between dose reduction and dose continuation in terms of adverse effects evaluated with LUNSERS and UKU (SMD −0.01, 95% CI −0.34 to 0.31, 2 RCTs, n = 147, I^2 = 0%) (Analysis 1.81). No differences emerged between separate time points (test for subgroup differences P = 0.95) (Analysis 1.82), or when looking at the two scales separately (Analysis 1.83; Analysis 1.84).

9.1.4. Weight gain

Based on three studies, the number of participants with clinically important weight gain was lower in participants with dose reduction (RR 0.39, 95% CI 0.25 to 0.61, 3 RCT, n = 883) (Analysis 1.85). No differences emerged between separate time points (test for subgroup differences P = 0.93) (Analysis 1.86).

Considering the different measures of weight together, results showed a trend in favour of dose reduction, but the CI did not exclude the possibility of no difference (SMD −0.22, 95% CI −0.50 to 0.06, 8 RCTs, n = 1175) (Analysis 1.87).

Six studies provided data about changes in weight (kg). No difference emerged between dose reduction and dose continuation (MD −0.80, 95% CI −2.14 to 0.53, 6 RCTs, n = 1074, I^2 = 81% (substantial heterogeneity)) (Analysis 1.88). No clear difference emerged between separate time points (test for subgroup differences P = 0.14) (Analysis 1.89), or when considering change and endpoint scores separately (Analysis 1.90; Analysis 1.91).

One study reported information on weight change in %. No difference emerged between dose reduction and dose continuation (MD 1.00, 95% CI −0.60 to 2.60, 1 RCT, n = 26) (Analysis 1.92).

One study with 75 participants reported information on body mass index at different time points. Results tended to favour dose reduction (less than three months: MD −2.30, 95% CI −4.66 to 0.06; less than six months: MD −2.20, 95% CI −4.49 to 0.09; less than one year: MD −3.20, 95% CI −5.29 to −1.11). There was no difference between separate time points (test for subgroup differences P = 0.78) (Analysis 1.93).

9.1.5. Incidence and scale-based change of various specific adverse effects

9.1.5.1 Number of participants needing antiparkinsonian medication

Two studies reported the number of participants needing antiparkinsonian medication. Only one study reported data at the 12-month time point. No difference emerged between dose reduction and dose continuation (RR 0.79, 95% CI 0.48 to 1.31, n = 397) (Analysis 1.94).

9.1.5.2 Number of participants with at least one extrapyramidal symptom

Two studies reported the number of participants with at least one extrapyramidal symptom. No difference emerged between dose reduction and dose continuation (RR 1.06, 95% CI 0.63 to 1.76, 2 RCTs, n = 417, I^2 = 0%) (Analysis 1.95). There was no difference between separate time points (test for subgroup differences P = 0.88) (Analysis 1.96).

9.1.5.3 Number of participants with parkinsonism

Two studies reported the number of participants with parkinsonism. No difference emerged between dose reduction and dose continuation at any time point (RR 1.19, 95% CI 0.51 to 2.81, 2 RCTs, n = 863, I^2 = 0%). There was no difference between separate time points (test for subgroup differences P = 0.66) (Analysis 1.97).

9.1.5.4 Numbers of participants with other movement disorders symptoms

Two studies reported the number of participants with rigidity. No difference emerged between dose reduction and dose continuation at any time point (less than six months: RR 2.50, 95% CI 0.11 to 54.87, 1 RCT, n = 20; less than one year: RR 2.50, 95% CI 0.11 to 54.87, 2 RCTs, n = 486). There was no difference between separate time points (test for subgroup differences P = 1.00) (Analysis 1.98).

Two studies reported the number of participants with tremors. No difference emerged between dose reduction and dose continuation at any time point (less than six months: RR 0.82, 95% CI 0.22 to 3.11, 1 RCT, n = 20; less than one year: RR 0.57, 95% CI 0.14 to 2.24, 2 RCTs, n = 486, I^2 = 11% (not relevant heterogeneity)). There was no difference between separate time points (test for subgroup differences P = 0.71) (Analysis 1.99).

Only one study reported the number of participants with dystonia. No difference emerged between dose reduction and dose continuation at any time point (less than six months: RR 2.50, 95% CI 0.11 to 54.87, 1 RCT, n = 20; less than one year: RR 0.82, 95% CI 0.06 to 11.33, 1 RCT, n = 20). There was no difference between separate time points (test for subgroup differences P = 0.59) (Analysis 1.0).

9.1.5.5 Mean endpoint or change score of extrapyramidal symptoms scales

Nine studies provided data on this outcome. Results showed a difference between maintaining and reducing the dose on extrapyramidal symptoms measured with multiple scales (SMD −0.17, 95% CI −0.32 to −0.03, 9 RCTs, n = 1532, I^2 = 35% (not important heterogeneity)) (Analysis 1.5). Test for subgroup differences excluded a possible difference between the separate time points (test for subgroup differences P = 0.48) (Analysis 1.6).

9.1.5.6 Number of participants with akathisia

Three studies reported the number of participants with akathisia. No difference emerged between dose reduction and dose continuation (RR 1.07, 95% CI 0.55 to 2.09, 3 RCTs, n = 883) (Analysis 1.7). There was no difference between separate time points (test for subgroup differences P = 0.54) (Analysis 1.8).

9.1.5.7 Mean endpoint/change BARS

Four studies provided data on this outcome. Results showed no difference between maintaining and reducing the dose on the akathisia scale measured with BARS (SMD −0.08, 95% CI −0.26 to 0.11, 4 RCTs, n = 986, I^2 = 36% (not important heterogeneity)). Test for subgroup differences excluded a possible difference between separate time points (test for subgroup differences P = 0.41) (Analysis 1.11).

9.1.5.8 Number of participants with dyskinesia (including tardive dyskinesia)

Four studies reported the number of participants with dyskinesia (including tardive dyskinesia). No difference emerged between dose reduction and dose continuation (RR 0.83, 95% CI 0.02 to 38.90, 4 RCTs, n = 630, I^2 = 72% (substantial heterogeneity)) (Analysis 1.12). There was no difference between separate time points (test for subgroup differences P = 0.17) (Analysis 1.13).

9.1.5.9 Mean endpoint/change dyskinesia scales

Nine studies provided data on this outcome. Results excluded a difference between maintaining and reducing the dose on dyskinesia measured with multiple scales (SMD −0.01, 95% CI −0.16 to 0.14, 9 RCTs, n = 1162, I^2 = 17% (not important heterogeneity)) (Analysis 1.18). Test for subgroup differences excluded a possible difference between separate time points (test for subgroup differences P = 0.51) (Analysis 1.19).

9.1.5.10 Number of participants with QTc prolongation and mean change QTc interval

Two studies reported the number of participants with QTc prolongation. No difference emerged between dose reduction and dose continuation at the six-month time point (RR 2.24, 95% CI 0.14 to 35.50, 1 RCT, n = 863) (Analysis 1.20). The difference between the two time points was not estimable because the study reporting data at the one-year time point had no events.

Three studies provided data on mean change QTc interval in milliseconds. Results excluded a difference between maintaining

and reducing the dose (MD 0.70, 95% CI −1.82 to 3.21, 3 RCTs, n = 544, I^2 = 0%). Test for subgroup differences excluded a possible difference between separate time points (test for subgroup differences P = 0.22) (Analysis 1.21).

9.1.5.11 Number of participants with arrhythmia, tachycardia, bradycardia, hypotension, or dizziness

The same unique study provided data on arrhythmia and hypotension at the six-month time point. No difference was found between dose reduction and dose maintenance groups in the two analyses (arrhythmia: RR 0.74, 95% CI 0.03 to 18.12, n = 466 (Analysis 1.22); hypotension: RR 4.47, 95% CI 0.41 to 48.92, n = 466 (Analysis 1.23)). In one study, data were collected on bradycardia, but no events were reported, thereby preventing comparison between the interventions (Analysis 1.24).

Two studies provided data on tachycardia and dizziness. No difference was found between dose reduction and dose maintenance groups in the two analyses (tachycardia: RR 1.09, 95% CI 0.25 to 4.79, n = 486, I^2 = 0% (Analysis 1.25); dizziness: RR 0.94, 95% CI 0.36 to 2.46, n = 486, I^2 = 0% (Analysis 1.26)). Test for subgroup differences excluded a possible difference between separate time points in both analyses (tachycardia: P = 0.85; dizziness: P = 0.65).

9.1.5.12 Number of participants with increased prolactin and mean change prolactin levels (ng/mL)

Two studies reported data on participants with increased prolactin levels. No difference emerged between dose reduction and dose continuation (RR 0.94, 95% CI 0.49 to 1.80, 2 RCTs, n = 645, I^2 = 0%). There was no difference between separate time points (test for subgroup differences P = 0.35) (Analysis 1.27).

Four studies reported data on mean change prolactin levels. No difference emerged between dose reduction and dose continuation (MD −2.27, 95% CI −6.07 to 1.53, 4 RCTs, n = 778, I^2 = 72% (substantial heterogeneity)). The test for subgroup differences suggested a possible difference between separate time points (P = 0.002) (Analysis 1.28).

9.1.5.13 Number of participants (women) with amenorrhoea

Only one study reported the number of women with amenorrhoea. No difference emerged between dose reduction and dose continuation at the six-month time point (RR 2.00, 95% CI 0.11 to 37.83, n = 8) (Analysis 1.29).

9.1.5.14 Number of participants (men) with erectile dysfunction

Two studies reported the number of men with erectile dysfunction. No difference emerged between dose reduction and dose continuation at the six-month time point (RR 4.32, 95% CI 0.48 to 38.83, n = 317, I^2 = 0%) (Analysis 1.30).

9.1.5.15 Number of participants with libido decreased or increased

Two studies report the number of participants with libido decreased. No difference emerged between dose reduction and dose continuation at the six-month time point (RR 0.37, 95% CI 0.06 to 2.11, n = 486, I^2 = 0%). There was no difference between separate time points (test for subgroup differences P = 0.74) (Analysis 1.31).

Only one study reported the number of participants with libido increased. No difference emerged between dose reduction and dose continuation at the six-month time point (RR 2.50, 95% CI 0.11 to 54.87, n = 20, I^2 = 0%). The difference between time points was not estimable because there were no events at the three-month time point (Analysis 1.32).

9.1.5.16 Number of participants with sedation

Two studies reported the number of participants with sedation. No difference emerged between dose reduction and dose continuation at the six-month time point (RR 2.34, 95% CI 0.56 to 9.70, n = 486, I^2 = 0%). There was no difference between separate time points (test for subgroup differences P = 0.36) (Analysis 1.33).

9.1.5.17 Number of participants with insomnia

Three studies reported the number of participants with insomnia. No difference emerged between dose reduction and dose continuation (RR 1.60, 95% CI 0.55 to 4.67, n = 883, I^2 = 81% (substantial heterogeneity)) (Analysis 1.34). There was no difference between separate time points (test for subgroup differences P = 0.27) (Analysis 1.35).

9.1.5.18 Number of participants with epileptic seizures

Only one study reported data on this outcome. The difference between dose reduction and dose continuation could not be estimated because there were no events in any study arm at any time point (Analysis 1.36).

9.1.5.19 Mean change CGI-SS and CSSRS

The same individual study provided data on suicidality scales. No difference emerged between dose reduction and dose continuation at the one-year time point (CGI-SS: MD 0.05, 95% CI −0.01 to 0.11, n = 397 (Analysis 1.37; per-protocol analysis); CSSRS: MD −0.10, 95% CI −0.39 to 0.19, n = 109 (Analysis 1.38; completers analysis)).

9.1.5.20 Number of participants with anticholinergic side effects

Two studies collected data on blurred vision. However, only one study reported events at both the three-month and six-month time points. Nevertheless, no difference emerged between dose reduction and dose continuation at any time point (three months: RR 2.50, 95% CI 0.11 to 54.87, n = 20; six months: RR 0.28, 95% CI 0.01 to 6.10, n = 20) (Analysis 1.39).

The same two studies provided data on constipation, dry mouth, and hypersalivation. No difference emerged between dose reduction and dose continuation for any outcome at the six-month time point (constipation: RR 0.35, 95% CI 0.04 to 3.07, 2 RCTs, n = 486, I^2 = 0% (Analysis 1.40); dry mouth: RR 1.75, 95% CI 0.36 to 8.42, 2 RCTs, n = 486, I^2 = 0% (Analysis 1.41); hypersalivation: RR 0.99, 95% CI 0.03 to 36.96, 2 RCTs, n = 486, I^2 = 0% (Analysis 1.42)). No differences emerged between the time points considered separately (constipation: P = 0.75 (Analysis 1.40); dry mouth: P = 0.61 (Analysis 1.41); hypersalivation: P = 0.45 (Analysis 1.42)).

Only one study provided data on the number of participants with urinary retention. No difference emerged between dose reduction and dose continuation at any time point (three months: RR 0.17, 95% CI 0.01 to 3.08, n = 20; six months: RR 0.17, 95% CI 0.01 to 3.08, n = 20) (Analysis 1.43).

9.1.5.21 Number of participants with haematological side effects

Only one study provided data on the number of participants with haematological side effects. No difference emerged between dose reduction and dose continuation for any outcome at the six-month time point (leukopenia: RR 6.68, 95% CI 0.27 to 163.06, n = 466 (Analysis 1.44); neutropenia: no events in any study arm (Analysis 1.45); thrombosis: RR 0.74, 95% CI 0.03 to 18.12, n = 466 (Analysis 1.46)).

9.2. Event: mortality

9.2.1. Overall mortality

Five studies provided data on deaths due to any reason. No difference emerged between dose reduction and dose continuation (RR 2.69, 95% CI 0.48 to 15.05, 5 RCTs, n = 941, I^2 = 0%) (Analysis 1.47). There were no differences between separate time points (test for subgroup differences P = 0.88) (Analysis 1.48).

9.2.2. Mortality due to natural causes

Four studies provided data on deaths due to natural causes. No difference emerged between dose reduction and dose continuation (RR 1.51, 95% CI 0.16 to 14.02, 3 RCTs, n = 906, I^2 = 0%) (Analysis 1.49). There were no differences between separate time points (test for subgroup differences P = 0.49) (Analysis 1.50).

9.2.3. Mortality due to suicide

Five studies reported data on mortality due to suicide. Only one study reported data at the 12-month time point. No difference emerged between dose reduction and dose continuation (RR 6.07, 95% CI 0.25 to 147.95, n = 397) (Analysis 1.51).

10. Cognition – mean endpoint or change score on cognition scale

Based on two studies, results showed a difference between maintaining and reducing the dose on cognition with different rating scales (SMD −0.74, 95% CI −1.08 to −0.39, 2 RCTs, n = 136, I^2 = 0% (Analysis 1.54). No difference emerged between separate time points (test for subgroup differences P = 0.08) (Analysis 1.55).

11. Medication – mean antipsychotic dose at endpoint

Based on the studies that provided data on antipsychotic dose, after converting the dose of the antipsychotics to olanzapine equivalents, the average baseline dose of the studies ranged from 17.7 mg to 23.4 mg in the reduction group and from 10.2 mg to 21.91 mg in the continuation group. The endpoint dose ranged from 1.13 mg to 13.3 mg in the reduction group and from 9 mg to 20.75 mg in the continuation group (Analysis 1.56; Analysis 1.57). In two studies that used haloperidol, Volavka 2000, and flupenthixol, Cookson 1987, oral olanzapine dose equivalents were very high at baseline and endpoint (baseline: 74.60 to 169.93; endpoint: 38.80 to 60.21). There were no differences between groups at baseline, with MDs ranging from −0.37 to 0.41.

DISCUSSION

Summary of main results

We identified 25 studies eligible for inclusion in the review, of which 22 studies (2635 participants) provided data for the meta-analyses.

Based on evidence ranging from very low or low certainty for the outcomes readmission to hospital and number of participants with relapse/exacerbations of psychosis, to moderate and high certainty for the remaining most relevant outcomes of interest (high certainty: functioning; moderate certainty: quality of life, number of participants with at least one adverse effect, leaving the study early due to adverse effects, and leaving the study early for any reason), our results show that reducing the dose of antipsychotic compared to continuing the treatment on the same dose has an effect in terms of a higher number of participants having a psychotic relapse, leaving the study earlier due to adverse effects, and leaving the study for any reason. These effects are not compensated by an improvement in quality of life or functioning, since no difference was found between groups for these outcomes. However, the number of admissions and relapse rates should be interpreted with caution, considering their respective 'very low' and 'low' levels of certainty according to GRADE.

The general mental state, intended as a clinically important change, improved for the continuation arm, but this result was not confirmed by the scale-measured outcome (using PANSS, BPRS, or CGI). We found similar results for the positive, negative, depressive, or anxiety symptoms and aggressive behaviours.

We found no difference between groups in adverse events, with some exceptions.

Dose reduction was associated with a clinically important change in weight gain, meaning that a weight gain was observed in fewer participants. However, this result was not consistent for other weight change measures (weight change in kg, weight change in percentage, and body mass index changes).

The dose reduction of the antipsychotic led to a small decrease in extrapyramidal symptoms measured with scales. However, the number of participants with movement disorders symptoms did not differ between groups.

Reduction of the antipsychotic dose did not impact cardiological, endocrinological, haematological, or other adverse effects. Nevertheless, results for these outcomes should be interpreted with caution, given that such events were reported primarily in only three studies (Fleischhacker 2014; Huhn 2020; Kane 2010), and their rare presentation.

We found no difference in mortality (for any reason, due to natural causes, or to suicide) between the intervention and the control arms.

Of note, the dose reduction group showed an improvement in cognitive functioning. Notwithstanding, these results were derived from two RCTs with few participants, and should therefore be further investigated.

Overall completeness and applicability of evidence

Even if antipsychotic dose reduction is a relevant topic, only a few systematic reviews and meta-analyses were available. In particular, the most recent and comprehensive review on RCTs on the subject, Tani 2020, presented data restricting the selection to studies maintaining the same administration route. The authors searched for studies only in two databases and did not address some relevant outcomes, such as functioning or the presence of specific side effects. The current review meta-analysed four more

studies and considered almost twice as many participants. Other reviews with many overlapping studies with our review focused on different research questions, namely the comparison between low and standard doses of antipsychotics for relapse prevention (Højlund 2021; Uchida 2011), or the dose-response of antipsychotic drugs for relapse prevention (Leucht 2021), thus they could not provide an answer to the question of dose reduction.

This review summarises the current evidence on antipsychotic dose reduction. The review follows methodologically robust Cochrane standards, providing an overall picture of the most relevant outcomes that should be considered when the option of reducing the dose is relevant for the patient. It also integrates the most up-to-date methods for estimating the certainty of the evidence, enabling clinicians, patients, and policymakers to decide on the best clinical option.

On the one hand, it should be noted that even if almost all included studies provided relapse data, functioning and quality of life data were available only in a subgroup of studies, reducing their generalisability. On the other hand, evidence for the latter outcomes has a higher certainty than for the former, making the overall picture harder to define.

Furthermore, caution is advised in the interpretation of the results of this review considering that the aim of many of the included studies was relapse prevention and not dose reduction, potentially generating a methodological inhomogeneity.

Finally, most of the evidence for our prespecified outcomes was burdened by high statistical heterogeneity, potentially due to the variability of the degree and speed of dose reduction (abrupt versus gradual), route of administration, participants, and range of drugs.

Quality of the evidence

Using the GRADE approach, we assessed the certainty of the evidence as ranging from very low for the outcome of service use - readmission to the hospital, to high for the outcome of functioning.

We evaluated the certainty of the evidence for quality of life as moderate, as half of the studies contributing to this outcome had a high risk of bias (downgraded one level for risk of bias).

We evaluated the certainty of the evidence as very low for service use - readmission to the hospital. Some studies contributing to the meta-analyses had a high risk of bias. There was substantial heterogeneity, and the confidence interval includes both no difference and appreciable harm with dose reduction. We downgraded the certainty of evidence by one level each for risk of bias, inconsistency, and imprecision.

We evaluated the certainty of the evidence as moderate for adverse effects - leaving the study early due to adverse effects, as some of the studies contributing to this outcome had a high risk of bias (downgraded one level for risk of bias).

We evaluated the certainty of the evidence for functioning as high. The studies contributing to this outcome did not have a high risk of bias; results were not inconsistent across studies; and results based on a high number of participants were precise in showing no difference between dose continuation and dose reduction.

We evaluated the certainty of the evidence for global state - number of participants with relapse as low. Some studies contributing to this outcome had a high risk of bias, and the meta-analyses presented substantial heterogeneity. We downgraded the certainty of evidence by one level each for risk of bias and inconsistency.

We evaluated the certainty of the evidence for leaving the study early - for any reason as moderate, as visual inspection of the funnel plot suggested marked asymmetry (downgraded one level for publication bias).

We evaluated the certainty of the evidence for adverse effects - number of participants with at least one adverse effect as moderate, as some studies contributing to this outcome had a high risk of bias (downgraded one level for risk of bias).

Potential biases in the review process

We have documented and justified modifications to our published protocol in the Differences between protocol and review section.

The current review has some limitations.

Regarding the search, there were three relevant limitations. Firstly, the date of the search is over a year old; however, considering that there are plans to convert this review into a Living Systematic Review, this issue will be addressed soon. Secondly, the search strategy was focused on studies on dose reduction, meaning there was a risk of skipping some relapse prevention studies in which a dose reduction was implemented. Consequently, we screened other available reviews on the topic, Højlund 2021; Leucht 2021; Tani 2020; Uchida 2011, to include all relevant trials. Finally, the search excluded Chinese manuscripts.

Another limitation of the current review is the deviation from protocol in analysing the outcomes. Originally, we planned to analyse the data for up to 12 months. However, in the final review, we merged all the studies' time points in the meta-analyses, choosing the data of the time point closest to 12 months when multiple time points were available. Indeed, study duration may be a potential effect modifier. In particular, a previous meta-analysis found that the efficacy of antipsychotics in reducing relapses was smaller in longer trials (Ceraso 2020). Nonetheless, this approach permitted us to collect more data in individual analyses, preventing a scattered evidence picture.

Moreover, we decided to exclude two studies because of a complex dose reduction approach (Sukegawa 2008; Yamanouchi 2015); these studies implemented dose reduction and polypharmacy reduction together. Additionally, we excluded another study where the reduction of the dose was obtained by blocking drug activity instead of reducing the drug dose, as occurs in common clinical practice (Hirschowitz 1997).

Furthermore, on the one hand, the reader should consider that some standard deviations of continuous outcomes and the average baseline or endpoint doses of antipsychotics were imputed. On the other hand, it should be noted that for binary outcomes, the denominator we used in the analyses was the number of randomised participants. This would imply that all missing participants are considered not to have the outcomes.

Finally, we found three studies as not informative for the outcomes investigated in the current review (Hirschowitz 1995; Kinion 2000;

Newcomer 1992). However, these studies are quite old, with a small sample size, and therefore would not likely have impacted our conclusions much.

Agreements and disagreements with other studies or reviews

The most similar review to the current one is Tani 2020. The included studies differ slightly between the reviews because of different inclusion criteria. Nonetheless, most of the analyses are similar. Indeed, the relapse rate is lower in the dose continuation arm in both reviews, whilst readmissions do not differ between the intervention and control arms in both reviews.

In Tani 2020, study discontinuations for any reason, due to inefficacy, and to intolerability do not differ between dose reduction and maintenance arms. However, in contrast, all of those are less frequent in the reduction arm in the current review. This discrepancy derives from not perfectly overlapping included studies in the two reviews.

Similarly to this review, in Tani 2020, psychopathology, measured in terms of general mental state and negative and positive symptoms, does not differ between dose maintenance and reduction groups. In addition, quality of life did not differ between the intervention and control groups in both reviews.

Dose reduction resulted in an improvement in neurocognition, showing similar results in both the current review and Tani 2020.

Different from other reviews, we found that extrapyramidal scale scores were slightly lower in the dose reduction arm.

Tani 2020 did not find bodyweight differences, similar to our review. However, our review found that the number of clinically important weight gain participants was lower in the dose reduction arm than in the dose maintenance arm.

Højlund 2021 and Uchida 2011 differ from our review in comparing 'low' and 'very low' antipsychotic doses with standard antipsychotic doses. Consequently, although our review shares some studies with Højlund 2021 and Uchida 2011, other studies are missing, making the comparison only partially applicable.

Finally, even though the included studies are quite similar, the objective of Leucht 2021 was to identify the optimum doses for relapse prevention in people with stable schizophrenia, therefore the two reviews cannot be compared.

AUTHORS' CONCLUSIONS

Implications for practice

The evidence identified by this review suggests that dose reduction is connected with a higher relapse risk. The impact of adverse effects improving after dose reduction was negligible in most cases, with a few relevant exceptions (extrapyramidal symptoms and weight gain). However, sparse data precluded any definitive conclusions on specific adverse effects.

Most of the available studies were quite old and not well designed, and the dose reduction scheme was not always detailed enough to replicate.

Amongst the available schizophrenia treatment guidelines, the topic was adequately described only in Japanese guidelines (Japanese Society of Neuropsychopharmacology 2021). The reason for this is likely that these guidelines are amongst the most recent, and because Japanese authors have an active interest in the topic (Ozawa 2019; Sukegawa 2008; Takeuchi 2014; Uchida 2011; Yamanouchi 2015). The final consideration of this guideline is non-conclusive.

Other guidelines generally suggest that the dose reduction process should be done in a shared decision-making framework (DGPPN 2019; Keepers 2020).

Our detailed set of analyses offers the basis for future development of this relevant aspect of the treatment of people with a schizophrenia spectrum disorder. In particular, these data could help patients and clinicians in a shared decision-making context to weigh the advantages and disadvantages of reducing the antipsychotic dose once clinical stability has been reached. In particular, the paternalistic approach could generate distortions in the clinician's expectation of patients' desires. Indeed, some patients prefer to maintain a higher dose to avoid symptoms.

We expect that this review will improve the available guidelines, which lack indications on antipsychotic dosing in stable patients.

Implications for research

Before including relapse prevention trials, the original search suggested the need for new dose reduction studies on second-generation antipsychotics.

Future studies should also consider focusing more on patient-reported outcomes, such as changes in quality of life or functioning, to enrich the overall picture, enabling patients and clinicians to make decisions based not only on relapse risk but also on the patient expectation of subjective improvement in well-being.

Moreover, more details are expected on the rationale and strategies of the dose reduction approach. In particular, recent studies suggest different approaches that could be effectively implemented (Horowitz 2021; Liu 2020).

Finally, more studies should focus on dose reduction from off-label doses to standard doses, given that this is a relevant clinical problem that has not been sufficiently addressed.

The topic of dose reduction is still well active, and it is expected that new studies will be available soon. This provides a robust rationale for developing a Cochrane living systematic review, which is currently planned by the same team of authors.

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The Cochrane Schizophrenia Group Editorial Base, situated across the University of Melbourne, Australia, the Technical University of Munich, Germany, and the University of Nottingham, UK, produces

and maintains standard text for use in the Methods section of their reviews. We have used this text as the basis of what appears here and adapted it as required.

Editorial and peer-reviewer contributions:

Cochrane Schizophrenia supported the authors in the development of this review.

The following people conducted the editorial process for this article.

- Sign-off Editor (final editorial decision): Mahesh Jayaram, University of Melbourne
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Hui Wu, Technical University of Munich
- Contact Editor (provided editorial guidance to authors): Lone Baandrup, Mental Health Services Capital Region in Denmark
- Copy Editor (copy-editing and production): Lisa Winer, Cochrane Copy Edit Support
- Information Specialist (search strategy and search results): Farhad Shokraneh, Systematic Review Consultants, Anne Parkhill, University of Melbourne
- Peer reviewers* (provided comments and recommended an editorial decision): Puti Retasya Novira, University of Melbourne, Budi Gittanaya Anindyanari, University of Melbourne (clinical/content review)

*Peer reviewers are members of Cochrane Schizophrenia, and provided peer-review comments on this article, but they were not otherwise involved in the editorial process or decision-making for this article.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Branchey 1981

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: this study was conducted in 3 phases Prior to study commencement, the neuroleptics administered to patients were replaced by equivalent doses of loxapine hydrochloride in liquid form using the formula loxapine 10 mg = chlorpromazine 100 mg.

Branchey 1981 *(Continued)*

	Subsequently, Phase 1: 6-week period of initial observation Phase 2: randomisation to 2 study groups: the continuation arm stayed on the same dose of loxapine, and the reduction arm had gradual reduction of loxapine. This phase lasted 18 weeks. Phase 3: The intervention group received placebo after cessation of loxapine for 24 weeks. Duration: 36 weeks (only the duration from phase 2 onwards was taken into account) Number of study arms: 2 Number of drugs used: 1 (loxapine) Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, investigator); "Following a relapse, the code was broken and the drug dose increased until symptoms disappeared. All treating personnel were informed of changes in the dose schedule. Patients were not informed and continued to receive the same volume of liquid medication." Type of data analysis for overall efficacy: main scale (BPRS) data not available Use of prophylactic antiparkinson medication: no Number of sites: no information
Participants	Diagnosis: chronic schozophrenia; diagnostic criteria: Research Diagnostic Criteria Current clinical state: chronically ill Definition of stability: treatment with neuroleptics for more than 5 years and the same drug dose for at least 3 months before the beginning of the study Inclusion criteria: male and female inpatients, all younger than 65 years of age, who met Research Diagnostic Criteria for schizophrenia, chronic type, were the subjects of this investigation. All patients were in good physical health and had no neurological symptoms except for those resulting from neuroleptic use. They all met the definition of stability criteria. Written informed consent was obtained from participating patients or from a responsible relative. Exclusion criteria: no information Setting: no information N = 33, the distribution between sexes is not reported correctly Age: mean 51.7 years Continuation arm: participants total: 11, age: mean 52.2 years (SD = 8.9), PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 22, age: mean 51.4 years (SD = 9.6), PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 11 Antipsychotic used: loxapine. Mean dose: 66.4 mg/d (SD = 44.3 mg/d; range 20 to 160 mg/d), application: oral Description dose scheme: fixed (if the participant relapsed, the dose was increased by one-eighth of the initial dose; if the participant still showed signs of deterioration, further adjustments were left to the discretion of the ward physician)

Branchey 1981 *(Continued)*

	2. Reduction arm. N = 22 Antipsychotic used: loxapine. Mean dose: 70.9 mg/d (SD = 44.7 mg/d), application: oral Description dose scheme: dose was decreased, according to a predetermined schedule, in successive steps of 4 weeks' duration, to one-half, one-fourth, and finally one-eighth of its initial value. This was followed by the administration of a placebo for 24 weeks. If the participant relapsed, the dose reduction regimen was ceased and the dose was doubled. If the participant still showed signs of deterioration, further adjustments were left to the discretion of the ward physician. Degree of antipsychotic dose reduction: 100% Speed of antipsychotic dose reduction: gradual, over 4 weeks
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 1 year) Adverse effects - specific: mean endpoint abbreviated RTDRS (< 3 months, < 6 months)
Identification	Sponsorship source: no information Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1981
Notes	A valid e-mail not be found. Author not contactable.

Caffey 1964

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: urinary drug levels in a subsample (Caffey 1963) Study phases: no information Duration in weeks: 16 Number of study arms: 4 (dose maintenance, dose reduction, and 2 placebo groups not considered for the analyses) Number of drugs used: 2 (chlorpromazine or thioridazine) Randomisation assumed from double-blind: no Type of blinding: double-blind (it is not reported who is blind, although it is likely that participants and investigators were blind given that the placebo pills were identical to the drug ones; however, the blinding was broken when a participant relapsed) Type of data analysis for overall efficacy: no information Use of prophylactic antiparkinson medication: no information Number of sites: 14 academic sites (Veterans Affairs hospitals)

Caffey 1964 *(Continued)*

Participants	Diagnosis: chronic schizophrenics; diagnostic criteria: clinical diagnosis Current clinical state: chronically ill Definition of stability: participants had been treated with fairly stable doses of at least 100 mg and not more than 800 mg daily of either chlorpromazine or thioridazine for at least 3 months immediately prior to the beginning of the study Inclusion criteria: participants were chronic schizophrenics, men, and under 56 years who had been hospitalised for 2 or more years. They had been treated with fairly stable doses of at least 100 mg and not more than 800 mg daily of either chlorpromazine or thioridazine for at least 3 months immediately prior to the beginning of the study Exclusion criteria: patients were excluded if they had CNS disease or a history of seizures, or had had a prefrontal lobotomy Setting: inpatient N: 177 (348 considering the whole sample, with placebo groups) Gender: 177 men, 0 women Age: no information Continuation arm: participants total: 88, participants male: 88, participants female: 0, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 89, participants male: 89, participants female: 0, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 266 Antipsychotics used: chlorpromazine or thioridazine. Mean dose: chlorpromazine 400 mg, thioridazine 350 mg, application: oral Description dose scheme: continued to receive either chlorpromazine or thioridazine daily at their established dosage; fixed ("until [participants] showed a definite change for the worse and in the judgment of the treatment physician should be returned to known medication") 2. Reduction arm. N = 131 Antipsychotics used: chlorpromazine or thioridazine. Mean dose: NA, application: oral Description dose scheme: group received a reduced total dosage on an intermittent schedule; specifically, they received their usual daily dose on Monday, Wednesday, and Friday only. This resulted in a reduction of dosage to 3/7 of what it had been previously; fixed ("until [participants] showed a definite change for the worse and in the judgment of the treatment physician should be returned to known medication") Degree of antipsychotic dose reduction: 57.1% Speed of antipsychotic dose reduction: abrupt
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months)
Identification	Sponsorship source: public (Project 9 of the VA Cooperative Studies in Psychiatry) Country: USA Trial registration ID: no information Number of countries: 1

Caffey 1964 *(Continued)*

	Publication year: 1964
Notes	A valid e-mail cannot be found. Author not contactable.

Carpenter 1999

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: at the beginning of the stabilisation phase, participants received 25 mg of intramuscular fluphenazine decanoate every 2 weeks. The minimum duration of the stabilisation phase was 6 weeks, or 3 fluphenazine decanoate injections, and participants were required to meet criteria for clinical stability before entry into the double-blind phase. Duration: 54 weeks Number of study arms: 2 Number of drugs used: no information Randomisation assumed from double-blind: no Type of blinding: double-blind Type of data analysis for overall efficacy: ITT Use of prophylactic medication: no information Number of sites: 2 (no information on number of academic sites)
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: DSM-III-R or Research Diagnostic Criteria Current clinical state: remission Definition of stability: at the beginning of the stabilisation phase, participants received 25 mg of intramuscular fluphenazine decanoate every 2 weeks. The minimum duration of the stabilisation phase was 6 weeks, or 3 fluphenazine decanoate injections, and participants were required to meet criteria for clinical stability before entry into the double-blind phase. Clinical stability was defined as 3 consecutive identical CGI scores. Inclusion criteria: patients meeting DSM-III-R criteria or Research Diagnostic Criteria for either schizophrenia or schizoaffective disorder Exclusion criteria: severe head trauma, current drug abuse, mental retardation, or a medical condition that could interfere with the evaluation or treatment of schizophrenia Setting: outpatient N: 50 Gender: 36 men, 14 women Age: mean 35.5 years (SD = 7.7)

Carpenter 1999 *(Continued)*

	Continuation arm: participants total: 25, participants male: 21, participants female: 4, age: mean 34.7 years (SD = 7.4), BPRS total: 24.0 (SD = 6.3), duration of illness: mean 12.9 years, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 25, participants male: 15, participants female: 10, age: mean 36.2 years (SD = 8.1), BPRS total: 24.9 (SD = 5.1), duration of illness: mean 13.1 years, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 25 Antipsychotics used: fluphenazine. Mean dose: no information, application: depot and oral ("rescue" drug) Description dose scheme: fixed (25 mg of intramuscular fluphenazine decanoate every 2 weeks; if participant met exacerbation criteria, then open-labelled oral fluphenazine was added to the participant's treatment regimen) 2. Reduction arm. N = 25 Antipsychotics used: fluphenazine. Mean dose: no information, application: depot and oral ("rescue" drug) Description dose scheme: fixed (all participants received an injection every 2 weeks, with 2 placebo injections between each active fluphenazine injection administered every 6 weeks) Degree of antipsychotic dose reduction: 67% (one-third of the injections are with the active drug, two-thirds are with the placebo) Speed of antipsychotic dose reduction: abrupt
Outcomes	Service use - readmission to hospital (< 1 year) Quality of life - mean endpoint QLS (Heinrich) (< 1 year) Functioning - mean endpoint SCLoF (< 6 months, < 1 year) Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months, < 1 year) Leaving the study early - for any reason - overall acceptability (< 1 year) Mental state - general: mean endpoint BPRS total (< 6 months, < 1 year) Adverse effects - mean endpoint MPRC Parkinsonian scale (< 6 months, < 1 year) Adverse effects - mean endpoint MPRC Dyskinesia scale (< 6 months, < 1 year)
Identification	Sponsorship source: public (NIMH grants MH-40279 and MH-35996) Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1999
Notes	The author replied with clarifications on the data.

Cookson 1987

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (haloperidol (oral) and zuclopenthixol decanoate (depot) and amitriptyline) Compliance measured: yes (depot) Study phases: no information Duration: 44 weeks Number of study arms: 2 Number of drugs used: 1 (cis(Z)-flupentixol) Randomisation assumed from double-blind: no Type of blinding: double-blind (no details on blinding) Type of data analysis for overall efficacy: no information, data on main scale not available Use of prophylactic antiparkinson medication: no information Number of sites: 1 (assumed)
Participants	Diagnosis: hebephrenic or paranoid schizophrenia; diagnostic criteria: ICD-9, Feighner criteria Current clinical state: chronically ill Definition of stability: patients had improved with higher dosages of neuroleptics and had maintained this improvement for at least 3 months Inclusion criteria: patients who were receiving cis(Z)-flupentixol decanoate 100 mg depot injection or more fortnightly, and who represented the most difficult of our chronic schizophrenic patients to manage. All patients were suffering from hebephrenic or paranoid schizophrenia according to the ICD-9 (1978) and the criteria of Feighner and colleagues (1972). 18 such patients who had been resistant to low doses of neuroleptic but had improved with higher dosages and had maintained this improvement for at least 3 months were entered into the study. Exclusion criteria: no information Setting: no information N: 18 Gender: 12 men, 6 women Age: mean 44.5 years Continuation arm: participants total: 9, participants male: 6, participants female: 3, age: mean 43 years, BPRS total: 12 (SD = 6.61), duration of illness: mean 14 years, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 9, participants male: 6, participants female: 3, age: mean 46 years, BPRS total: mean 20.2 (SD = 9.5), duration of illness: mean 14 years, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 9 Antipsychotics used: cis(Z)-flupentixol. Mean dose: 333.3 mg/biweekly (lower dose: 100 mg/biweekly; upper dose: 800 mg/biweekly), application: injection

Cookson 1987 *(Continued)*

	Description dose scheme: fixed (but concomitant neuroleptic medication was allowed) 2. Reduction arm. N = 9 Antipsychotics used: cis(Z)-flupentixol. Mean dose: 118.1 mg/biweekly (lower dose: 50 mg/biweekly; upper dose: 400 mg/biweekly), application: injection Description dose scheme: 50% reduction of dose; fixed (but concomitant neuroleptic medication was allowed) Degree of antipsychotic dose reduction: 50% Speed of antipsychotic dose reduction: abrupt
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 1 year) Adverse effects - number of participants with at least one adverse effect (< 3 months, < 6 months, < 1 year) Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (< 3 months, < 6 months, < 1 year) Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: pharma (Lundbeck) Country: UK Trial registration ID: no information Number of countries: 1 Publication year: 1987
Notes	A valid e-mail could not be found. Author not contactable.

Faraone 1989

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: participants were randomly assigned to 1 of 3 double-blind schedules: 80% dosage reduction over 8 weeks, 80% dosage reduction over 2 weeks, or continued treatment at their usual neuroleptic dose. All participants were treated as outpatients throughout the course of the study. At the first study visit, all participants were given a full dose of their neuroleptic in its disguised form (opaque capsules). The following week the reduced dose was given to participants assigned to a reduction schedule. Subsequently, all participants were followed weekly for 14 weeks and then monthly for 3 months. Duration: 26 weeks Number of study arms: 3 (1 arm maintained the initial dose, whilst the other 2 arms decreased the dose by 80%, but with a different speed, 2 vs 8 weeks; data from these 2 reduction arms were aggregated in our analysis)

Faraone 1989 *(Continued)*

	Number of drugs used: no information Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, investigator) Type of data analysis for overall efficacy: no information (main scale missing) Use of prophylactic medication: no information Number of sites: 1 (1 veteran center)
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: DSM-III Current clinical state: chronically ill Definition of stability: persistently psychotic patients Inclusion criteria: persistently psychotic outpatients from the Brock-Weston-West Roxbury Veterans Medical Center. Participants were 29 males between the ages of 37 and 74 who had a DSM-III diagnosis of schizophrenia or schizoaffective disorder and who had manifested chronic hallucinations, delusions, or both for at least 2 years despite maintenance neuroleptic therapy. Exclusion criteria: no information Setting: outpatient N: 36 Gender: 36 men Age: no information Continuation arm: participants total: 7, participants male: 7, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 29, participants male: 29, age: no information, PANSS total: no information, duration of illness: no information, baseline weight baseline: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 7 Antipsychotics used: no information. Mean dose: no information, application: oral (assumed) Description dose scheme: fixed (continued treatment at their usual neuroleptic dose) 2. Reduction arm. N = 29 Antipsychotics used: no information. Mean dose: no information Description dose scheme: fixed (80% dosage reduction over 2 or 8 weeks) Degree of antipsychotic dose reduction: 80% (in 2 or 8 weeks) Speed of antipsychotic dose reduction: gradual
Outcomes	Service use - readmission to hospital (< 6 months) Global state - number of participants with relapse/exacerbations of psychosis (< 6 months)
Identification	Sponsorship source: public (Veterans Administration's health services research and development program and grant l-R01-H41879-01 from the NIMH) Country: USA

Faraone 1989 *(Continued)*

	Trial registration ID: no information Number of countries: 1 Publication year: 1989
Notes	The author replied to our e-mail with the information that data are no longer accessible.

Fleischhacker 2014

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (benzodiazepines, zolpidem, benzatropine, and propranolol; antipsychotic polypharmacy was not allowed) Compliance measured: yes (assumed since doses were measured throughout the trial) Study phases: in treatment phase 1 (oral conversion phase, 4 to 6 weeks), participants were cross-titrated during weekly visits from other antipsychotic(s) to oral aripiprazole monotherapy to achieve a target dose of 10 to 15 mg/day. In phase 2 (oral stabilisation phase, 8 to 28 weeks), participants were assessed fortnightly and stabilised on oral aripiprazole (10 to 30 mg/day). In phase 3 (double-blind maintenance phase for up to 38 weeks), eligible participants were randomised 2:2:1 to aripiprazole once-monthly 400 mg, oral aripiprazole (10 to 30 mg/day), or aripiprazole once-monthly 50 mg. Duration: 38 weeks Number of study arms: 3 (only 2 arms were considered: oral aripiprazole 10 to 30 mg/day and aripiprazole long-acting injectable 50 mg/4 weeks; the third arm with aripiprazole long-acting injectable 400 mg/4 weeks was not considered since it was not a continuation or a reduction arm) Number of drugs used: 1 (aripiprazole oral or long-acting injection) Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, investigator); double-dummy design (all participants received oral and injectable formulations of aripiprazole or placebo) Type of data analysis for overall efficacy: mITT (all participants who received at least 1 dose of treatment and had at least 1 efficacy outcome assessment in the double-blind, active-controlled phase, LOCF and observed cases data) Use of prophylactic medication: no (assumed since these medications were used for symptomatic treatment) Number of sites: 105 (no information on the number of academic sites)
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV-TR Current clinical state: partial remission (no patient subgroup) Definition of stability: participants were assessed fortnightly and stabilised on oral aripiprazole (10 to 30 mg/day) during phase 2 (stabilisation phase). Stability was defined as meeting the following criteria for 8 consecutive weeks: outpatient status; PANSS total score <= 80 and a score of <= 4 (moderate) on each of the following items (possible scores of 1 to 7 for each item): conceptual disorganisation, suspiciousness, hallucinatory behaviour, and unusual thought content; CGI-S score <= 4 (moderately ill); and CGI-SS score <= 2 (mildly suicidal) on Part 1 and <= 5 (minimally worsened) on Part 2.

Fleischhacker 2014 *(Continued)*

	Inclusion criteria: eligible patients were aged 18 to 60 years and had a diagnosis of schizophrenia according to DSM-IV-TR criteria for ≥ 3 years and a history of symptom exacerbation when not receiving antipsychotic treatment. Patients needed to have been responsive to antipsychotic treatment (other than clozapine) in the past year. Exclusion criteria: key exclusion criteria were a DSM-IV-TR diagnosis other than schizophrenia; uncontrolled thyroid function abnormalities; a history of seizures, neuroleptic malignant syndrome, clinically relevant tardive dyskinesia, or other medical condition that would expose the patient to undue risk or interfere with study assessments. Patients who had been admitted to hospital, including for psychosocial reasons, for > 30 days total of the 90 days preceding entry into phase 1 or 2 of the study after screening were excluded. Individuals were also excluded if they met DSM-IV-TR criteria for substance dependence, including alcohol and benzodiazepines, but excluding nicotine and caffeine. Other exclusion criteria included patients who were considered to be treatment resistant/refractory to antipsychotic treatment by history. Patients were also excluded if they failed to respond to clozapine treatment or were responsive to clozapine treatment only. The use of CYP2D6 or CYP3A4 inhibitors or CYP3A4 inducers was also prohibited at screening and during the study. Adjunctive antipsychotics, antidepressants (including monoamine oxidase inhibitors), and mood stabilisers were not permitted during the study. Patients requiring more than 1 benzodiazepine beyond screening (e.g. lorazepam and oxazepam) were excluded. Setting: outpatient N: 397 (the total sample size was 662 when all 3 study arms were considered) Gender: 246 men, 151 women Age: mean 40.9 years (SD = 10.4) Continuation arm: participants total: 266, participants male: 168, participants female: 98, age: mean 41.2 years (SD = 10.8), PANSS total: 56.6 (SD = 12.7), duration of illness: mean 14.3 years, baseline weight: mean 83.7 kg (SD = 19.2), height: no information, BMI: mean 28.7 (SD = 5.9), average time in study: no information Reduction arm: participants total: 131, participants male: 78, participants female: 53, age: mean 40.2 years (SD = 9.6), PANSS total: mean 56.1 (SD = 12.6), duration of illness: mean 13.9 years, baseline weight: mean 82.9 kg (SD = 24.4), height: no information, BMI: mean 28.7 (SD = 7.9), average time in study: no information
Interventions	1. Continuation arm. N = 266 Antipsychotics used: aripiprazole. Mean dose: 20.0 mg (SD = 6.9 mg/day; range 10 to 30 mg/day), application: oral (aripiprazole) and injection (placebo) Description dose scheme: flexible (one-time option to decrease the dose within the range of 10 to 30 mg/day, as well as one-time option to return) 2. Reduction arm. N = 131 Antipsychotics used: aripiprazole. Mean dose: 49.8 mg/4 weeks (SD = 2.2 mg/4 weeks), application: oral (placebo) and injection (aripiprazole long-acting) Description dose scheme: participants stabilised to oral aripiprazole (10 to 30 mg/day) were randomised to aripiprazole 50 mg/4 weeks (about 1.8 mg/day oral equivalents); flexible (one-time option to decrease the dose from 50 to 25 mg/4 weeks, as well as one-time option to return) Degree of antipsychotic dose reduction: 94% (the degree of dose reduction was 10 to 30 mg/day to 50 mg/4 weeks, i.e. ranging from 82% to 94%) Speed of antipsychotic dose reduction: abrupt
Outcomes	Service use - readmission to hospital (< 1 year) Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 1 year)

Fleischhacker 2014 *(Continued)*

Functioning - mean change PSP (< 1 year) Functioning - mean endpoint PSP (< 1 year)

Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months, < 1 year)

Global state - remission (< 1 year)

Global state - mean change CGI-S (< 1 year)

Global state - mean endpoint CGI-I (< 1 year)

Global state - mean change IAQ-12 (< 1 year)

Leaving the study early - for any reason - overall acceptability (< 3 months, < 1 year)

Leaving the study early - due to inefficacy - overall efficacy (< 1 year)

Mental state - general: number of participants with clinically important change in general mental state (< 1 year)

Mental state - general: mean endpoint PANSS total (< 1 year)

Mental state - general: mean change PANSS total (< 3 months, < 6 months, < 1 year)

Mental state - specific: mean endpoint PANSS positive (< 1 year)

Mental state - specific: mean change PANSS positive (< 1 year)

Mental state - specific: mean endpoint PANSS negative (< 1 year)

Mental state - specific: mean change PANSS negative (< 1 year)

Mental state - specific: mean change PANSS depression/anxiety (< 1 year)

Behaviour - mean change PANSS excitment/hostility (< 1 year)

Satisfaction with care - number of participants with clinically important change in satisfaction with care (PSMQ-Modified preference to current medication) (< 1 year)

Satisfaction with care - mean endpoint DAI-30 (< 1 year)

Satisfaction with care - mean change MAQ (< 1 year)

Satisfaction with care - mean endpoint MAQ (< 1 year)

Adverse effects - number of participants with at least 1 adverse effect (< 1 year)

Adverse effects - number of participants with at least 1 serious adverse event (< 1 year)

Adverse effects - number of participants with clinically important weight gain (< 1 year)

Adverse effects - mean change weight (< 1 year)

Adverse effects - specific: number of participants that needed antiparkinsonian medication (< 1 year)

Adverse effects - specific: number of participants with at least 1 extrapyramidal symptom (< 1 year)

Adverse effects - specific: number of participants with parkinsonism (< 1 year)

Adverse effects - mean change SAS (< 1 year)

Adverse effects - specific: number of participants with akathisia (< 1 year)

Adverse effects - mean change BARS (< 1 year)

Adverse effects - mean change AIMS (< 1 year)

Adverse effects - specific: number of participants with QTc prolongation (< 1 year)

Fleischhacker 2014 *(Continued)*

	Adverse effects - specific: number of participants with increased prolactin (< 1 year)
	Adverse effects - mean change prolactin levels (ng/mL) (< 1 year)
	Adverse effects - specific: number of participants with insomnia (subtotals) (< 1 year)
	Adverse effects - mean change CGI-SS (< 1 year)
	Adverse effects - mean change C-SSRS (< 1 year)
	Adverse effect - mortality: overall mortality (< 1 year)
	Adverse effect - mortality: mortality due to natural causes (< 1 year)
	Adverse effect - mortality: mortality due to suicide (< 1 year)
	Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: Otsuka Pharmaceuticals Commercialisation Inc (Tokyo, Japan)
	Country: Austria, Belgium, Bulgaria, Chile, Croatia, Estonia, France, Hungary, Italy, South Korea, Poland, South Africa, Thailand, and the USA
	Trial registration ID: NCT00706654, ASPIRE EU (31-07-247)
	Number of countries: 14
	Publication year: 2014
Notes	We received no reply to our e-mail with data request.

Hirschowitz 1995

Study characteristics	
Methods	Study design: randomised controlled trial
	Study grouping: parallel group
	Additional medication allowed: no information
	Compliance measured: no information
	Study phases: participants were all on high doses of antipsychotic drug (more than 20 mg of haloperidol or equivalent) on entry. At baseline all participants were stabilised on 20 mg/day of haloperidol.
	Duration: 5 weeks
	Number of study arms: 3 (dose maintenance, dose reduction, and dose increase by 2:1:1)
	Number of drugs used: 1 (haloperidol)
	Randomisation assumed from double-blind: yes
	Type of blinding: double-blind (participant, investigator)
	Type of data analysis for overall efficacy: no information (main scale missing)
	Use of prophylactic medication: no information
	Number of sites: 1 (assumed)
Participants	Diagnosis: schizophrenia; diagnostic criteria: no information

Hirschowitz 1995 *(Continued)*

	Current clinical state: chronically ill Definition of stability: at baseline all participants were stabilised on 20 mg/day of haloperidol Inclusion criteria: schizophrenic patients who were all on high doses of antipsychotic drug (>= 20 mg of haloperidol or equivalent) on entry Exclusion criteria: no information Setting: no information N: 32 Gender: no information Age: no information Continuation arm: participants total: no information, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: no information, participants male: no information, participants female: no information, age in years: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N (no information) Antipsychotics used: haloperidol. Mean dose: 20 mg/day, application: no information Description dose scheme: fixed (kept at 20 mg/day) 2. Reduction arm. N (no information) Antipsychotics used: haloperidol. Mean dose: no information, application: no information Description dose scheme: fixed (half of the participants had their dose reduced) Degree of antipsychotic dose reduction: no information Speed of antipsychotic dose reduction: no information
Outcomes	Included without usable data
Identification	Sponsorship source: I Feinberg (unclear) Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 2014
Notes	We received no reply to our e-mail with data request.

Hogarty 1988

Study characteristics	
Methods	Study design: randomised controlled trial

Hogarty 1988 *(Continued)*

	Study grouping: parallel group Additional medication allowed: no information Compliance measured: yes (depot) Study phases: although patients were designated as potentially eligible for the outpatient study at hospital admission, they were entered into protocol only if they met explicit criteria for stabilisation after discharge Duration: 104 weeks Number of study arms: 2 Number of drugs used: 1 (fluphenazine decanoate) Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, investigator) Type of data analysis for overall efficacy: completer analysis Use of prophylactic medication: no information Number of sites: 1 (1 academic site)
Participants	Diagnosis: schizophrenia or schizoaffective disorder, the latter requiring 2 rather the 1 schizophrenic symptom traditionally required; diagnostic criteria: Research Diagnostic Criteria Current clinical state: remission or partial remission Definition of stability: behaviour not markedly influenced by hallucinations or delusions; clinical course not markedly fluctuating; no evidence of moderate or severe deterioration; at least a partial remission of symptoms; patient's living arrangements secure. Level of stabilisation deemed "optimal" for them and the best achieved in recent years Inclusion criteria: participants were required to meet Research Diagnostic Criteria for schizophrenia or schizoaffective disorder, the latter requiring 2 rather than the 1 schizophrenic symptom required. Participants were between the ages of 17 and 55 years and were free of medical contraindications for maintenance antipsychotic drug treatment (e.g. renal or hepatic disease). Participants were required to have been living within a family for at least 1 of the 3 months before admission and judged likely to return to this household on discharge. Although patients were designated as potentially eligible for the outpatient study at hospital admission, they were entered into protocol only if they met explicit criteria for stabilisation after discharge. Exclusion criteria: organic brain syndromes and alcohol or other drug abuse histories that might have compromised diagnosis were reasons for exclusion. Patients who either relapsed (a severe increase in persistent symptoms) during stabilisation or who failed to stabilise were excluded from the dosage study. Setting: outpatient N: 70 Gender: 40 men, 30 women Age: mean 28.3 years Continuation arm: participants total: 33, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 37, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline

Hogarty 1988 *(Continued)*

	weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 33 Antipsychotics used: fluphenazine decanoate. Mean dose: 21.5 mg/14 days, application: depot and oral ("rescue" medication) Description dose scheme: flexible (participants were stabilised to an average of 21.5 mg in both groups, and then maintained on an average of 25 mg in this group; dose could be decreased or increased by judgement of clinician) 2. Reduction arm. N = 37 Antipsychotics used: fluphenazine decanoate. Mean dose: 3.82 mg/14 days, application: depot and oral ("rescue" medication) Description dose scheme: flexible (participants were stabilised to an average of 21.5 mg/14 days in both groups, and then maintained on an average of 3.82 mg/14 days in this group; dose could be decreased or increased by judgement of clinician, with an initial fixed 80% reduction at randomisation) Degree of antipsychotic dose reduction: 80% at randomisation (the real degree of dose reduction was 10 to 30 mg/day to 50 mg/4 weeks, i.e. ranging from 82% to 94%) Speed of antipsychotic dose reduction: abrupt
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 1 year, > 1 year) Leaving the study early - for any reason - overall acceptability (< 1 year, > 1 year) Leaving the study early - due to inefficacy - overall efficacy (< 3 months)
Identification	Sponsorship source: Schizophrenia Research Branch, National Institute of Mental Health, Rockville, MD, USA Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1988
Notes	A valid e-mail could not be found. Author not contactable.

Hogarty 1995

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (antiparkinsonians: benztropine or equivalent) Compliance measured: yes (depot) Study phases: the study consisted of 3 phases; the second phase is the one considered (dose reduction vs dose maintenance trial). Trial 1: intramuscular challenge that compared centrally acting benztropine mesylaze with peripherally acting glycopyrrolate. Trial 2: neuroleptic medication dose-reduc-

Hogarty 1995 *(Continued)*

	tion group. Trial 3: patients who were maintained on a low dose of fluphenazine decanoate and randomly assigned to a supplemental desipramine hydrochloride, lithium carbonate, or placebo group Duration: 12 weeks Number of study arms: 2 Number of drugs used: 1 (fluphenazine decanoate) Randomisation assumed from double-blind: no Type of blinding: double-blind (treatment team was blind; likely that participants were also blind; injection nurses were not blind) Type of data analysis for overall efficacy: no information (data on main scale not available) Use of prophylactic antiparkinson medication: no Number of sites: 1 (academic)
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: Research Diagnostic Criteria Current clinical state: chronically ill Definition of stability: positive symptoms of schizophrenia were either absent, or, if present, did not interfere with adjustment Inclusion criteria: participants were 18 to 55 years old, met Research Diagnostic Criteria for either schizophrenia or schizoaffective disorder at the time of their last psychotic episode, and had shown persistent distress or defect features for at least 3 months prior to the study. Most commonly the features had been present for many years. Positive symptoms of schizophrenia were either absent, or, if present, did not interfere with adjustment. AII participants were maintained on fluphenazine decanoate only and if necessary were administered an anticholinergic antiparkinsonian drug. Patients were first screened and selected for inclusion into a distressed (anxiety or depression, or both) group based on a rating of 4 (moderate) or greater on a 7-point global judgement of personal distress. In addition, this subsample required a Raskin Depression Scale score of 7 or greater (i.e. an admission criterion identical to that used for depressed patients who qualify for trials of a tricyclic antidepressant) and/or a score of 7 or greater on the Covi Anxiety Scale, an instrument that uses the same format as the Raskin Depression Scale. Both scales include 3 ratings (subjective report, objective appearance, and secondary neurovegetative features), each of which was scored on a scale of 1 to 5. This subsample is referred to as distressed, even though 47% also met the criteria for the defect-state sample as described below. Patients who did not meet the distressed sample criteria required a score of 4 (moderate) or greater on a 7-point global judgement of defect state to be included, as well as a rating of severe or very severe impairment on at least 2 of the 6 negative features first scaled by Wing, 1 of which had to be flat affect, poverty of speech, or amotivation. This subsample is referred to as the defect-state sample. By definition, no patient in the defect-state sample met Raskin Depression Scale or Covi Anxiety Scale criteria at the point of study intake, although some did have mild anxiety. Exclusion criteria: no information Setting: outpatient N: 79 Gender: no information Age: no information Continuation arm: participants total: 41, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information

Hogarty 1995 *(Continued)*

	Reduction arm: participants total: 38, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness in years: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 41 Antipsychotics used: fluphenazine decanoate. Mean dose: 19.7 mg (SD = 13.8 mg)/2 weeks, application: injection Description dose scheme: maintained pre-study dose; fixed 2. Reduction arm. N = 38 Antipsychotics used: fluphenazine decanoate. Mean dose: 18 mg (SD = 11.2 mg)/2 weeks, application: injection Description dose scheme: participants were assigned to lower their maintenance dose of fluphenazine decanoate to the minimum effective dose, which was operationally defined as the dose below which prodromal signs of psychosis appeared and, above which more than minimal EPS developed; flexible Degree of antipsychotic dose reduction: NA Speed of antipsychotic dose reduction: gradual (timing not reported)
Outcomes	Medication – mean antipsychotic dose at endpoint < 3 months
Identification	Sponsorship source: public (NIMH) Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1995
Notes	A valid e-mail could not be found. Author not contactable.

Huhn 2020

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (lorazepam as rescue medication; antipsychotic polypharmacy was allowed) Compliance measured: yes (assumed, pill count and plasma levels) Study phases: 1 phase of reduction vs continuation Duration: 26 weeks Number of study arms: 2 Number of drugs used: 5 (aripiprazole, olanzapine, perazine, quetiapine, risperidone) Randomisation assumed from double-blind: no

Huhn 2020 *(Continued)*

	Type of blinding: single-blind (outcome assessor) Type of data analysis for overall efficacy: ITT (all participants randomised, LOCF) Number of sites: 1 academic
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: ICD-10 Current clinical state: remission (symptomatic remission of positive symptoms, e.g. PANSS P1, P2, P3, G5, G9 < 4 and a CGI-S < 4; no patient subgroup) Definition of stability: participants had to have been stable for at least 3 years, defined by no psychiatric hospitalisation, and they had to have been continuously treated with antipsychotic medication with no changes in the last 4 weeks. Participants had to be in symptomatic remission of positive symptoms as defined by the following criteria: 1) PANSS items (positive items of the Andreasen criteria) < 4: delusions (P1), conceptual disorganisation (P2), hallucinations (P3), mannerisms and posturing (G5), and unusual thought content (G9); 2) CGI < 4. Inclusion criteria: eligible participants were between 18 and 65 years old meeting ICD-10 criteria for schizophrenia or schizoaffective disorder. Participants had to have been stable for at least 3 years, defined by no psychiatric hospitalisation, and they had to have been continuously treated with antipsychotic medication with no changes in the last 4 weeks. There was no restriction in terms of the initially used antipsychotics and their doses, except for the exclusion of clozapine. This antipsychotic is reserved for treatment-resistant patients and is assumed to be associated with a high risk for rebound psychoses. Moreover, participants had to be in symptomatic remission of positive symptoms as defined by the following criteria: 1) PANSS items (positive items of the Andreasen criteria) < 4: delusions (P1), conceptual disorganisation (P2), hallucinations (P3), mannerisms and posturing (G5), and unusual thought content (G9); 2) CGI < 4. Exclusion criteria: further exclusion criteria were substance dependence other than tobacco dependency, suicidality, and initiation or dose change of antidepressants or mood stabilisers during the last 6 weeks before enrolment. Moreover, participants had to be in symptomatic remission of positive symptoms as defined by the following criteria: 1) PANSS items (positive items of the Andreasen criteria) < 4: delusions (P1), conceptual disorganisation (P2), hallucinations (P3), mannerisms and posturing (G5), and unusual thought content (G9); 2) CGI < 4. Setting: outpatient N: 20 Gender: 12 men, 8 women Age: mean 45.3 years (SD = 11.1) Continuation arm: participants total: 9, participants male: 6, participants female: 3, age: mean 46.1 years (SD = 12.1), PANSS total: 47.7 (SD = 8.1), duration of illness: mean 17.9 years (SD = 8.8), baseline weight: mean 76.9 kg (SD = 15.3), height: 174.1 cm (SD = 7.7), BMI: no information, average time in study: no information Reduction arm: participants total: 11, participants male: 6, participants female: 5, age: mean 44.7 years (SD = 10.3), PANSS total: mean 50.1 (SD = 10.4), duration of illness: mean 16.8 years (SD = 8.4), baseline weight: mean 88.7 kg (SD = 11.0), height: 175.1 cm (SD = 5.5), BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 9 Antipsychotics used: aripiprazole, olanzapine, perazine, quetiapine. Mean dose: 9.6 mg/day in olanzapine equivalents (range 3 to 22 mg/day in olanzapine equivalents), application: oral Description dose scheme: fixed 2. Reduction arm. N = 11

Huhn 2020 *(Continued)*

	Antipsychotics used: aripiprazole, olanzapine, risperidone, quetiapine. Mean dose: 14.6 mg/day in olanzapine equivalents (range 3 to 23 mg/day in olanzapine equivalents), application: oral Description dose scheme: the initial antipsychotic dose should be reduced by one-sixth every other week for the first 3 months, but this was adapted for each participant individually according to his or her needs and psychopathological status. So antipsychotic doses were reduced to the greatest degree possible for the first 3 months, and then participants were followed up with stable medication for 3 months; flexible (according to the psychological status of the individual). Degree of antipsychotic dose reduction: up to 100% (mean 42.3%, range 0% to 100%) Speed of antipsychotic dose reduction: gradual (by one-sixth every other week over a period of 3 months, as adapted by individual's psychological status)
Outcomes	Service use - readmission to hospital (< 3 months, < 6 months) Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 3 months, < 6 months) Quality of life - mean endpoint SWNS (< 3 months, < 6 months) Quality of life - mean change SWNS (< 3 months, < 6 months) Functioning - mean change PSP (< 3 months, < 6 months) Functioning - mean endpoint PSP (< 3 months, < 6 months) Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months) Global state: number of participants with clinically important change in global state (< 3 months, < 6 months) Global state - mean endpoint CGI-S (< 3 months, < 6 months) Global state - mean change CGI-S (< 3 months, < 6 months) Global state - mean endpoint CGI-I (< 3 months, < 6 months) Leaving the study early - for any reason - overall acceptability (< 3 months, < 6 months) Leaving the study early - due to inefficacy - overall efficacy (< 3 months, < 6 months) Mental state - general: number of participants with clinically important change in general mental state (< 3 months, < 6 months) Mental state - general: mean endpoint PANSS total (< 3 months, < 6 months) Mental state - general: mean change PANSS total (< 3 months, < 6 months) Mental state - specific: mean endpoint PANSS positive (< 3 months, < 6 months) Mental state - specific: mean change PANSS positive (< 3 months, < 6 months) Mental state - specific: mean endpoint PANSS negative (< 3 months, < 6 months) Mental state - specific: mean change PANSS negative (< 3 months, < 6 months) Mental state - specific: mean endpoint PANSS depression/anxiety (< 3 months, < 6 months) Mental state - specific: mean change PANSS depression/anxiety (< 3 months, < 6 months) Behaviour - mean endpoint PANSS excitement/hostility (< 3 months, < 6 months) Behaviour - mean change PANSS excitement/hostility (< 3 months, < 6 months) Satisfaction with care - mean endpoint MARS (< 3 months, < 6 months)

Huhn 2020 *(Continued)*

Satisfaction with care - mean change MARS (< 3 months, < 6 months)

Adverse effects - number of participants with at least 1 adverse effect (< 3 months, < 6 months)

Adverse effects - number of participants with at least 1 serious adverse event (< 3 months, < 6 months)

Adverse effects - mean endpoint UKU (< 3 months, < 6 months)

Adverse effects - number of participants with clinically important weight gain (< 3 months, < 6 months)

Adverse effects - mean change weight (< 3 months, < 6 months)

Adverse effects - mean weight endpoint (< 3 months, < 6 months)

Adverse effects - specific: number of participants that needed antiparkinsonian medication (< 3 months, < 6 months)

Adverse effects - specific: number of participants with at least 1 extrapyramidal symptom (< 3 months, < 6 months)

Adverse effects - specific: number of participants with rigidity (< 3 months, < 6 months)

Adverse effects - specific: number of participants with tremor (< 3 months, < 6 months)

Adverse effects - specific: number of participants with dystonia (< 3 months, < 6 months)

Adverse effects - specific: number of participants with akathisia (< 3 months, < 6 months)

Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (< 3 months, < 6 months)

Adverse effects - mean endpoint AIMS (< 3 months, < 6 months)

Adverse effects - mean change AIMS (< 3 months, < 6 months)

Adverse effects - specific: number of participants with tachycardia (< 3 months, < 6 months)

Adverse effects - specific: number of participants with dizziness (< 3 months, < 6 months)

Adverse effects - specific: number of participants (women) with amenorrhoea (< 3 months, < 6 months)

Adverse effects - specific: number of participants (men) with erectile dysfunction (< 3 months, < 6 months)

Adverse effects - specific: number of participants with libido decreased (< 3 months, < 6 months)

Adverse effects - specific: number of participants with libido increased (< 3 months, < 6 months)

Adverse effects - specific: number of participants with sedation (< 3 months, < 6 months)

Adverse effects - specific: number of participants with insomnia (subtotals) (< 3 months, < 6 months)

Adverse effects - specific: number of participants with epileptic seizures (< 3 months, < 6 months)

Adverse effects - specific: number of participants with blurred vision (< 3 months, < 6 months)

Adverse effects - specific: number of participants with constipation (< 3 months, < 6 months)

Adverse effects - specific: number of participants with dry mouth (< 3 months, < 6 months)

Adverse effects - specific: number of participants with hypersalivation (< 3 months, < 6 months)

Adverse effects - specific: number of participants with urinary retention (< 3 months, < 6 months)

Adverse effect - mortality: overall mortality (< 3 months, < 6 months)

Adverse effect - mortality: mortality due to natural causes (< 3 months, < 6 months)

Huhn 2020 *(Continued)*

	Adverse effect - mortality: mortality due to suicide (< 3 months, < 6 months)
	Medication – mean antipsychotic dose at endpoint (< 3 months, < 6 months)
Identification	Sponsorship source: German Research Association (Ministry of Education and Research (DO 1723/1–1))
	Country: Germany
	Number of countries: 1
	Trial registration ID: NCT02307396; EUCTR: 2013-000338-37
	Publication year: 2020
Notes	The authors provided unpublished data.

Johnson 1987

Study characteristics	
Methods	Study design: randomised controlled trial
	Study grouping: parallel group
	Additional medication allowed: yes (anticholinergics, benzodiazepines, and antidepressants)
	Compliance measured: yes (depot)
	Study phases: stable dose of no more than 40 mg every 2 weeks for the past 6 months (in practice all participants had been on this stable dose for 12 months or longer before commencement of the trial). Group A (maintenance group) continued on their pre-trial dosage for 12 months and then had their dose reduced to half. Group B (reduction group) had their pre-trial dosage reduced to half at the onset.
	Duration: 52 weeks
	Number of study arms: 2
	Number of drugs used: 1 (flupenthixol decanoate)
	Randomisation assumed from double-blind: no
	Type of blinding: double-blind (participant, investigator)
	Type of data analysis for overall efficacy: completer analysis
	Use of prophylactic medication: no
	Number of sites: 1 (assumed, no information on number of academic sites)
Participants	Diagnosis: schizophrenia; diagnostic criteria: Feighner criteria
	Current clinical state: remission
	Definition of stability: no more than 3 on the total score of the BPRS
	Inclusion criteria: the sample was of consecutive outpatients who had been diagnosed as suffering from schizophrenia by their psychiatrist and who met the Feighner criteria (Feighner et al, 1972). All participants were on the normal treatment regimens prescribed by their psychiatrist. In addition, they had to score no more than 3 on the total score of the BPRS (Overall & Gorham, 1962); to have been maintained on a relatively low dose of flupenthixol decanoate over the last 12 months; and to have been on a stable dose of no more than 40 mg every 2 weeks for the past 6 months (in practice all participants had been on this stable dose for 12 months or longer before commencement of the trial).

Johnson 1987 *(Continued)*

	Exclusion criteria: organic brain disease, physical illness, alcohol or substance abuse, below-normal IQ, or additional mental illness Setting: outpatient N: 60 Gender: 25 men, 34 women Age: mean 40.9 years (SD = 10.4) Continuation arm: participants total: 31, participants male: 12, participants female: 19, age: mean 42 years (SD = 7.7), PANSS total: no information, duration of ilness: mean 11.2 years (4.4), baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 29 (1 participant data lost, data available on 28), participants male: 78, participants female: 53, age: mean 40.2 years (SD = 9.6), PANSS total: no information, duration of illness: mean 13.9 years, baseline weight: mean 82.9 kg (SD = 24.4), height: no information, BMI: mean 28.7 (SD = 7.9), average time in study: no information
Interventions	1. Continuation arm. N = 31 Antipsychotics used: flupenthixol decanoate. Mean dose: 9 mg/week (range 4 to 20 mg/week), application: depot Description dose scheme: fixed (continued on their pre-trial dosage) 2. Reduction arm. N = 29 Antipsychotics used: flupenthixol decanoate. Mean dose: 6 mg/week (range 1.7 to 10 mg/week), application: depot Description dose scheme: fixed (pre-trial dosage reduced to half at the onset) Degree of antipsychotic dose reduction: 50% Speed of antipsychotic dose reduction: abrupt
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months, < 1 year, > 1 year) Adverse effects - mean endpoint AIMS (< 3 months, < 6 months, < 1 year) Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: Lundbeck Ltd Country: UK Trial registration ID: no information Number of countries: 1 Publication year: 1987
Notes	A valid e-mail could not be found. Author not contactable.

Kane 1983

Study characteristics	
Methods	Study design: randomised controlled trial

Kane 1983 *(Continued)*

	Study grouping: parallel group Additional medication allowed: yes (procyclidine, flurazepam, and diazepam; antipsychotic polypharmacy was not allowed) Study phase: participants were stabilised to a standard dose and then randomised to continuing the standard dose or to a low-dose group Compliance measured: yes (long-acting injectable) Duration: 52 weeks Number of study arms: 2 Number of drugs used: 1 (fluphenazine decanoate) Randomisation assumed from double-blind: no Type of blinding: double-blind (no information) Type of data analysis for overall efficacy: no information Number of sites: 3 academic sites
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: Research Diagnostic Criteria Current clinical state: remission or partial remission (no patient subgroup) Definition of stability: criteria for remission (or partial remission) were established using the GAS and the BPRS. To be considered eligible, patients had to score 35 or higher on the GAS and no more than 4 on the conceptual disorganisation and hallucinatory behaviour items, no more than 5 on suspiciousness, or no more than 3 on the unusual thought content item of the BPRS. Anchor points adapted from the Schedule for Affective Disorders and Schizophrenia were used in making these ratings. To be considered stable, a patient's ratings for the 4 weeks before study entry could not fluctuate in either direction more than 10 points on the GAS or 1 point on any of the BPRS items mentioned. Patients were required to maintain this stability whilst receiving a constant IM dose of fluphenazine decanoate within the range of 12.5 to 50 mg/2 weeks. Inclusion criteria: state of remission or at a stable clinical plateau, who had previously met Research Diagnostic Criteria for schizophrenia or schizoaffective disorder Exclusion criteria: patients with presumptive tardive dyskinesia, mental retardation, neurological disorder, serious drug abuse, alcoholism, or physical illness were excluded, as were those requiring adjunctive medication other than minor tranquilisers or antiparkinsonian agents Setting: outpatient N: 126 Gender: 79 men, 47 women Age: mean 28.9 years (SD = 7.1) Continuation arm: participants total: 64, participants male: no information, participants female: no information, age: no information, BPRS total: no information, duration of illness: no information, baseline weight baseline: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 62, participants male: no information, participants female: no information, age: no information, BPRS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 64

Kane 1983 *(Continued)*

	Antipsychotics used: fluphenazine decanoate. Mean dose: 25 mg/2 weeks (range 12.5 to 50 mg/2 weeks), application: long-acting injectable Description dose scheme: participants maintained on the standard dose range. Flexible (within the standard-dose range) 2. Reduction arm. N = 62 Antipsychotics used: fluphenazine decanoate. Mean dose: 2.5 mg/2 weeks (range 1.25 to 5 mg/2 weeks), application: long-acting injectable Description dose scheme: at entry into the study, participants were randomly assigned to either standard-dose (25 mg/mL) or low-dose (2.5 mg/mL) preparations of fluphenazine decanoate. Initial dose at study entry was equal in millilitres to the final dose at the end of the stabilisation period. (In other words, participants assigned to the standard-dose group received the same dose they had been receiving, whereas participants assigned to the low-dose group had their dosage reduced to one-tenth of what it had been). Flexible (dosage was flexible, at the treating research psychiatrist's discretion, within the range of 0.5 to 2 mL biweekly throughout the 1-year study unless the participant relapsed) Degree of antipsychotic dose reduction: up to 90% Speed of antipsychotic dose reduction: abrupt
Outcomes	Service use - readmission to hospital (< 1 year) Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months, < 1 year) Global state - mean endpoint SCL-90 (< 3 months, < 6 months, < 1 year) Leaving the study early - for any reason - overall acceptability (< 3 months, < 6 months, < 1 year) Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (< 1 year) Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: USPHS Grants MH-31776 and MH-33814 the NIMH Country: USA Number of countries: 1 Trial registration ID: no information Publication year: 1982
Notes	The author replied to our e-mail with the information that data are no longer accessible.

Kane 2010

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (anticholinergics and benzodiazepines) Compliance measured: yes (plasma concentration)

Kane 2010 *(Continued)*

	Study phases: phase 1 (conversion/stabilisation: open-label oral olanzapine monotherapy (10, 15, or 20 mg/day, per investigator's discretion) and required to demonstrate maintenance of clinical stability) and phase 2 (double-blind maintenance phase) Duration: 24 weeks Number of study arms: 5 (very low, 45 mg every 4 weeks; low, 150 mg every 2 weeks; medium, 405 mg every 4 weeks; high, 300 mg every 2 weeks; stabilised oral dose, 10, 15, or 20 mg/day). We considered only the very low arm as the dose reduction arm and the stabilised oral dose as the maintenance arm. Number of drugs used: 1 Randomisation assumed from double-blind: no Type of blinding: double-blind (participants and study personnel) Type of data analysis for overall efficacy: LOCF Use of prophylactic antiparkinson medication: no Number of sites: 112
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV or DSM-IV-TR Current clinical state: partial remission (no patient subgroup) Definition of stability: having outpatient status for at least 4 weeks before the first study visit, with a BPRS (8) positive symptom subscale score ≤ 4 (range 1 to 7) on each of the following items: conceptual disorganisation, suspiciousness, hallucinatory behaviour, and unusual thought content. Patients needed to maintain clinical stability after switching to olanzapine for at least 4 consecutive weeks. Inclusion criteria: participants were 18 to 75 years of age, with a DSM-IV or DSM-IV-TR diagnosis of schizophrenia. Participants were clinically stable, defined as having outpatient status for at least 4 weeks before the first study visit, with a BPRS (8) positive symptom subscale score ≤ 4 (range 1 to 7) on each of the following items: conceptual disorganisation, suspiciousness, hallucinatory behaviour, and unusual thought content. Patients treated previously with a depot antipsychotic were required to have received their last injection at least 2 weeks or 1 injection interval before entry (4 weeks for injectable risperidone). Exclusion criteria: significant suicidal or homicidal risk; pregnancy or breastfeeding; acute, serious, or unstable medical conditions; or substance dependence (except nicotine or caffeine) within the past month Setting: outpatient N: 466 (the total sample size was 1065 when the 5 arms of the trials were considered) Gender: 305 men, 161 women Age: mean 39.1 years (SD = 11.6) Continuation arm: participants total: 322, participants male: 209, participants female: 113, age: mean 39 years (SD = 11.6), PANSS total: 56.1 (SD = 16.1), duration of illness: mean 13.4, baseline weight: mean 77 kg (SD = 15.9), height: no information, BMI: mean 26.8 (SD = 5), average time in study: no information Reduction arm: participants total: 144, participants male: 96, participants female: 48, age: mean 39.5 years (SD = 11.6), PANSS total: mean 57.8 (SD = 15.6), duration of illness: mean 13.4 years, baseline weight baseline: mean 78.4 kg (SD = 17.3), height: no information, BMI: mean 27.1 (SD = 5.2), average time in study: no information
Interventions	1. Continuation arm. N = 322 Antipsychotics used: olanzapine. Mean dose: 14.3 mg (range 10 to 20 mg/day), application: oral (olanzapine) and injection (placebo)

Kane 2010 *(Continued)*

	Description dose scheme: participants remained on their stabilised dose of oral olanzapine; fixed
	2. Reduction arm. N = 144
	Antipsychotics used: olanzapine. Mean dose: 45 mg/4 weeks, application: oral (placebo) and injection (olanzapine)
	Description dose scheme: participants stabilised to oral olanzapine (10 to 20 mg/day) were randomised to olanzapine 45 mg/4 weeks (about 1.6 mg/day oral equivalents); fixed (no oral antipsychotic supplementation was allowed)
	Degree of antipsychotic dose reduction: up to 92%
	Speed of antipsychotic dose reduction: abrupt
Outcomes	Service use - readmission to hospital (< 3 months, < 6 months)
	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 6 months)
	Quality of life - mean change QLS Total (Heinrich) (< 6 months)
	Functioning - mean change SF-36 mental component summary (< 6 months)
	Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months)
	Global state - mean change CGI-S (< 3 months, < 6 months)
	Global state - mean endpoint CGI-I (< 3 months, < 6 months)
	Leaving the study early - for any reason - overall acceptability (< 3 months, < 6 months)
	Leaving the study early - due to inefficacy - overall efficacy (< 6 months)
	Mental state - general: mean change BPRS total (< 3 months, < 6 months)
	Mental state - general: mean endpoint PANSS total (< 3 months, < 6 months)
	Mental state - general: mean change PANSS total (< 3 months, < 6 months)
	Mental state - specific: mean change PANSS positive (< 3 months, < 6 months)
	Mental state - specific: mean change PANSS negative (< 3 months, < 6 months)
	Adverse effects - number of participants with at least 1 adverse effect (< 6 months)
	Adverse effects - number of participants with clinically important weight gain (< 6 months)
	Adverse effects - mean change weight (< 6 months)
	Adverse effects - specific: number of participants with parkinsonism (< 6 months)
	Adverse effects - specific: number of participants with rigidity (< 6 months)
	Adverse effects - specific: number of participants with tremor (< 6 months)
	Adverse effects - mean change SAS (< 6 months)
	Adverse effects - specific: number of participants with akathisia (< 6 months)
	Adverse effects - mean change BARS (< 6 months)
	Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (< 6 months)
	Adverse effects - mean change AIMS (< 6 months)
	Adverse effects - specific: number of participants with QTc prolongation (< 6 months)

Kane 2010 *(Continued)*

	Adverse effects - mean change QTc interval (milliseconds) (< 6 months)
	Adverse effects - specific: number of participants with arrhythmia (< 6 months)
	Adverse effects - specific: number of participants with tachycardia (< 6 months)
	Adverse effects - specific: number of participants with bradycardia (< 6 months)
	Adverse effects - specific: number of participants with hypotension (< 6 months)
	Adverse effects - specific: number of participants with dizziness (< 6 months)
	Adverse effects - specific: number of participants with increased prolactin (< 6 months)
	Adverse effects - mean change prolactin levels (ng/mL) (< 6 months)
	Adverse effects - specific: number of participants (men) with erectile dysfunction (< 6 months)
	Adverse effects - specific: number of participants with libido decreased (< 6 months)
	Adverse effects - specific: number of participants with sedation (< 6 months)
	Adverse effects - specific: number of participants with insomnia (subtotals) (< 6 months)
	Adverse effects - specific: number of participants with blurred vision (< 6 months)
	Adverse effects - specific: number of participants with constipation (< 6 months)
	Adverse effects - specific: number of participants with dry mouth (< 6 months)
	Adverse effects - specific: number of participants with hypersalivation (< 6 months)
	Adverse effects - specific: number of participants with leukopenia (< 6 months)
	Adverse effects - specific: number of participants with neutropenia (< 6 months)
	Adverse effects - specific: number of participants with thrombosis (< 6 months)
	Adverse effect - mortality: overall mortality (< 3 months, < 6 months)
	Adverse effect - mortality: mortality due to natural causes (< 3 months, < 6 months)
	Adverse effect - mortality: mortality due to suicide (< 3 months, < 6 months)
	Medication – mean antipsychotic dose at endpoint (< 6 months)
Identification	Sponsorship source: Eli Lilly
	Country: Argentina, Australia, Austria, Belgium, Brazil, Finland, France, Germany, Greece, Hungary, Israel, Italy, Mexico, the Netherlands, Norway, Poland, Portugal, Puerto Rico, Romania, Russian Federation, South Africa, Spain, Sweden, Taiwan, Turkey, the USA
	Trial registration ID: NCT00088491, F1D-MCHGKA
	Number of countries: 26
	Publication year: 2010
Notes	The corresponding author replied to our e-mail with the information that the data are in the hands of the sponsor.

Kinion 2000

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: no information Duration: 26 weeks Number of study arms: 2 Number of drugs used: no information Randomisation assumed from double-blind: no Type of blinding: single-blind (raters) Type of data analysis for overall efficacy: no information Use of prophylactic medication: no information Number of sites: 5 (no information on academic sites)
Participants	Diagnosis: schizophrenia; diagnostic criteria: no information Current clinical state: chronically ill Definition of stability: no information Inclusion criteria: residing in long-term care facilities, diagnosis of schizophrenia and received daily scheduled neuroleptic medications Exclusion criteria: no information Setting: outpatient N: 27 Gender: 18 men, 9 women Age: mean 73 years (SD = 5.2) Continuation arm: participants total: 11, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 16, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 11 Antipsychotics used: no information. Mean dose: no information, application: no information Description dose scheme: flexible (doses were reduced for 6 consecutive months or until the lowest effective dosage was reached) 2. Reduction arm. N = 16

Kinion 2000 *(Continued)*

	Antipsychotics used: no information. Mean dose: 370 mg (range 20 to 1500 mg chlorpromazine equivalent), application: no information Description dose scheme: no information Degree of antipsychotic dose reduction: no information Speed of antipsychotic dose reduction: gradual
Outcomes	Included without usable data
Identification	Sponsorship source: no information Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 2000
Notes	A valid e-mail could not be found. Author not contactable.

Lonowski 1978

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: progressive drug reductions were implemented. If a participant's rated behaviour deviated 1 SD or more in the direction of psychological maladjustment, the criterion for decompensation was reached and reductions were stopped. At the time of clinical relapse, participants received 50% increases in their current drug dosage. Fifty per cent of dosage increases were made until the participant's level of function returned to within the baseline statistical range. Weekly dosage increases were ceased when the drug dosage reached 50% higher than the baseline dosage. Decompensated control participants did not receive more than a single 50% dosage increase; rather, they were observed further or placed on other medications. Following the baseline period, all participants in the experimental group received a 50% dosage reduction. Successive 50% dosage reductions were performed every 4 weeks as long as behavioural ratings remained within tolerable limits; until further reductions were not warranted on the basis of clinical action of the drug; or until the end of the experiment at 15 weeks. Duration: 15 weeks Number of study arms: 2 Number of drugs used: 3 (thioridazine, chlorpromazine, haloperidol) Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, investigator) Type of data analysis for overall efficacy: completer analysis Use of prophylactic medication: no

Lonowski 1978 *(Continued)*

	Number of sites: 1 (zero academic sites)
Participants	Diagnosis: schizophrenia; diagnostic criteria: clinical diagnosis Current clinical state: chronically ill Definition of stability: each participant had been given the same medication for at least 6 months (range 6 to 36 months). Participant's rated behaviour remained within 1 SD of his/her mean baseline behaviour. Inclusion criteria: hospitalised schizophrenics Exclusion criteria: no information Setting: inpatients N: 59 Gender: 33 men, 26 women Age in years: mean 47.1 (SD = no information) Continuation arm: participants total: 23 (completers, randomised not available), participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 25 (completers, randomised not available), participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 23 (completers, randomised not available) Antipsychotics used: thioridazine, chlorpromazine, haloperidol. Mean dose: no information, application: oral Description dose scheme: flexible (maintained on matched dosage of neuroleptics) 2. Reduction arm. N = 25 (completers, randomised not available) Antipsychotics used: thioridazine, chlorpromazine, haloperidol. Mean dose: no information, application: oral Description dose scheme: flexible (following the baseline period, all participants in the experimental group received a 50% dosage reduction. Successive 50% dosage reductions were performed every 4 weeks as long as behavioural ratings remained within tolerable limits; until further reductions were not warranted on the basis of clinical action of the drug; or until the end of the experiment at 15 weeks). Degree of antipsychotic dose reduction: 87.5% (maximal dose reduction) Speed of antipsychotic dose reduction: abrupt
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 6 months)
Identification	Sponsorship source: no information Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1978

Lonowski 1978 *(Continued)*

Notes	A valid e-mail could not be found. Author not contactable.

Newcomer 1992

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (chloral hydrate and antiparkinsonians) Compliance measured: yes (assumed since doses were measured throughout the trial) Study phases: two-thirds of an initial group of 27 eligible participants were randomly assigned to receive a 4-week, double-blind trial of 50% of their usual dose of haloperidol. The remaining participants were blindly assigned to continue their usual dose. Of the 27 participants (all assigned to a dose decrease), 3 were dropped from the analysis of the study total sample, and an additional fourth was dropped from the study analysis of the dose-decrease subgroup for administrative reasons (e.g. participated but refused to give blood). Duration: 4 weeks Number of study arms: 2 Number of drugs used: 1 (haloperidol) Randomisation assumed from double-blind: no Type of blinding: double-blind (participant and raters) Type of data analysis for overall efficacy: completers analysis Use of prophylactic medication: no Number of sites: 2
Participants	Diagnosis: schizophrenia; diagnostic criteria: Research Diagnostic Criteria Current clinical state: remission Definition of stability: participants had previously received at least 2 years of neuroleptic treatment and were without evidence of psychotic relapse (i.e. requiring an increase in neuroleptic medication or hospitalisation) for at least 3 months prior to study entry. All participants had been on unchanging doses of haloperidol for at least 3 weeks prior to study entry. Inclusion criteria: male veterans gave written informed consent for their participation and met Research Diagnostic Criteria (RDC; Spitzer et al, 1978) for schizophrenia. Participants were recruited from an outpatient clinic and an inpatient research unit at the Department of Veterans Affairs Medical Center in Palo Alto, California. Participants had previously received at least 2 years of neuroleptic treatment and were without evidence of psychotic relapse (i.e. requiring a 25% increase in neuroleptic medication or hospitalisation) for at least 3 months prior to study entry. All participants had been on unchanging doses of haloperidol for at least 3 weeks prior to study entry. Exclusion criteria: no information Setting: in- and outpatient N: 27 Gender: 27 men

Newcomer 1992 *(Continued)*

	Age in years: mean 38.96 (SD = 13.39) (calculated on the 24 participants consenting to give blood) Continuation arm: participants total: 9, participants male: 9, participants female: 0, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 18, participants male: 18, participants female: 0, age: no information, PANSS total: duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 9 Antipsychotics used: haloperidol. Mean dose: no information, application: oral Description dose scheme: flexible (continue their usual dose) 2. Reduction arm. N = 18 Antipsychotics used: haloperidol. Mean dose: no information, application: oral Description dose scheme: fixed (50% of the usual dose) Speed of antipsychotic dose reduction: abrupt
Outcomes	Study included without usable data.
Identification	Sponsorship source: Department of Veterans Affairs Medical Research Service, Office of Academic Affairs fellowships Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1992
Notes	We received no reply to our e-mail with data request.

Ozawa 2019

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (lorazepam, clonazepam, zolpidem, quetiapine < 50 mg) Compliance measured: no information Study phases: no information Duration: 52 weeks Number of study arms: 2 Number of drugs used: 2 (risperidone or olanzapine) Randomisation assumed from double-blind: no Type of blinding: single-blind (blind raters)

Ozawa 2019 *(Continued)*

	Type of data analysis for overall efficacy: LOCF Use of prophylactic antiparkinson medication: no information Number of sites: 6 (no academic sites)
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV, DSM-5 Current clinical state: partial remission Definition of stability: stable dose of risperidone or olanzapine for the previous 3 months Inclusion criteria: 1) DSM-IV and DSM-5 diagnosis of schizophrenia; 2) having received a stable dose of risperidone or olanzapine for the previous 3 months; 3) age 18 years or older; and 4) capable of providing informed consent Exclusion criteria: patients who had a concomitant use of antipsychotic drugs other than quetiapine at 50 mg or less or its equivalents, history of treatment with long-acting risperidone within 6 months, active suicidal ideations or past suicide attempts, and presence of a severe physical condition, mental retardation, or active substance abuse were excluded. If the target dose (corresponding to 65% D2 occupancy) was greater than the actually prescribed dose upon study enrolment, the patient was excluded from the study. Setting: in- and outpatient N: 35 Gender: 23 men, 12 women Age in years: mean 63.9 (SD = 7.9) Continuation arm: participants total: 18, participants male: 10, participants female: 8, age: mean 63.7 years (SD = 8.5), PANSS total: mean 71.4 (SD = 15.9), duration of illness: mean 34.1 years (SD = 13), baseline weight: mean 58.2 kg (SD = 9.8), height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 17, participants male: 13, participants female: 4, age: mean 64.1 years (SD = 7.4), PANSS total: mean 79.1 (SD = 22), duration of illness: mean 37.4 years (SD = 10.6), baseline weight: mean 57.1 kg (SD = 11.1), height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 18 Antipsychotics used: risperidone or olanzapine. Mean dose: risperidone: 4.3 (1.9), olanzapine: 15.8 (4.6), application: oral (risperidone and olanzapine). Description dose scheme: fixed 2. Reduction arm. N = 17 Antipsychotics used: risperidone or olanzapine. Mean dose: risperidone: 4.2 (1.9), olanzapine: 12.8 (3.9), application: oral (risperidone and olanzapine). Description dose scheme: to predict the oral doses that are going to achieve 65% dopamine D2 receptor occupancy at trough, 2 plasma samples were taken with a minimum interval of 5 hours to measure plasma concentrations of risperidone plus 9-hydroxyrisperidone (active moiety) or olanzapine. Plasma concentrations of risperidone, 9-hydroxyrisperidone, and olanzapine were assayed in heparinised plasma using liquid chromatography with tandem mass spectrometry detection. Oral doses that corresponded to these plasma antipsychotic concentrations at trough were estimated for each individual with measured antipsychotic concentrations on 2 occasions, dosing information for the past 24 hours, times of the blood draws, age, sex, weight, race, and smoking status, using the mixed-effect population PPK approach with the NONMEM IV; fixed. Degree of antipsychotic dose reduction: aimed reduction up to the 65% dopamine D2 receptor occupancy. Actual reduction: risperidone: 57.6%, olanzapine: 46.0% Speed of antipsychotic dose reduction: gradual (4 weeks)

Ozawa 2019 *(Continued)*

Outcomes	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 3 months, < 6 months, < 1 year) Functioning - mean endpoint GAF (< 1 year) Functioning - mean change GAF (< 1 year) Global state - number of participants with relapse/exacerbations of psychosis (< 6 months, < 1 year) Global state - mean change CGI-S (< 1 year) Leaving the study early - for any reason - overall acceptability (< 3 months, < 6 months, < 1 year) Leaving the study early - due to inefficacy - overall efficacy (< 3 months, < 6 months, < 1 year) Mental state - general: mean endpoint PANSS total (< 1 year) Mental state - general: mean change PANSS total (< 1 year) Mental state - specific: mean endpoint PANSS positive (< 1 year) Mental state - specific: mean change PANSS positive (< 1 year) Mental state - specific: mean endpoint PANSS negative (< 1 year) Mental state - specific: mean change PANSS negative (< 1 year) Adverse effects - mean change weight (< 1 year) Adverse effects - mean endpoint SAS (< 1 year) Adverse effects - mean change SAS (< 1 year) Adverse effects - mean endpoint BARS (< 1 year) Adverse effects - mean change BARS (< 1 year) Adverse effects - mean endpoint AIMS (< 1 year) Adverse effects - mean change AIMS (< 1 year) Adverse effects - mean change QTc interval (milliseconds) (< 1 year) Adverse effects - mean change prolactin levels (ng/mL) (< 1 year) Adverse effect - mortality: overall mortality (< 1 year) Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: public (Nakatomi Foundation and Keio Fukuzawa Fund) Country: Japan Trial registration ID: JPRN-UMIN000014976 Number of countries: 1 Publication year: 2019
Notes	The authors provided unpublished data.

Remington 2011

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Study phases: participants were randomised to standard dose or extended dose (every other day) Additional medication allowed: yes (other psychotropic medication prescribed prior to the study were permitted; antipsychotic polypharmacy was not allowed) Compliance measured: yes (pill count, plasma levels) Duration: 26 weeks Number of study arms: 2 Number of drugs used: 3 (loxapine, olanzapine, risperidone) Randomisation assumed from double-blind: no Type of blinding: double-blind (no information) Type of data analysis for overall efficacy: m-ITT (participants who completed at least 1 follow-up visit; ANOVA) Number of sites: 1 academic site
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV Current clinical state: no information (no patient subgroup) Definition of stability: stabilised as outpatients with a single, oral antipsychotic (with the exception of clozapine and quetiapine) >= 3 months Inclusion criteria: 1) DSM-IV diagnosis of schizophrenia based on clinical interview, collaborative history, and chart review; 2) capacity to provide written, informed consent; 3) stabilised as outpatients with a single, oral antipsychotic (with the exception of clozapine and quetiapine) >= 3 months; 4) no exposure to a depot antipsychotic >= 1 year; 5) no current diagnosis of substance abuse according to DSM-IV criteria; and 6) evidence of adherence to current antipsychotic treatment; a patient was deemed adherent to antipsychotic treatment if their clinician and case manager rated this to be >= 80% Exclusion criteria: no information Setting: outpatient N: 35 Gender: 21 men, 14 women Age in years: mean 37.1 (SD = 14.6) Continuation arm: participants total: 18, participants male: 8, participants female: 10, age: mean 37.1 years (SD = 14.6), BPRS total: 25.2 (SD = 4.2), duration of illness: no information, baseline weight: mean 86.3 kg (SD = 23.1), height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 17, participants male: 11, participants female: 6, age: mean 39.8 years (SD = 11.5), BPRS total: mean 25.6 (SD = 5.7), duration of illness: no information, baseline weight: mean 83.6 kg (SD = 22.7), height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 18 Antipsychotics used: loxapine, olanzapine, risperidone. Mean dose: no information, application: oral

Remington 2011 *(Continued)*

	Description dose scheme: participants maintained the same daily dose; fixed
	2. Reduction arm. N = 17
	Antipsychotics used: olanzapine, risperidone. Mean dose: no information, application: oral
	Description dose scheme: the same daily dose administered every other day; fixed
	Degree of antipsychotic dose reduction: 50%
	Speed of antipsychotic dose reduction: abrupt
Outcomes	Service use - readmission to hospital (< 6 months)
	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 3 months, < 6 months)
	Global state - number of participants with relapse/exacerbations of psychosis (< 6 months)
	Leaving the study early - due to inefficacy - overall efficacy (< 6 months)
	Mental state - general: mean endpoint BPRS total (< 3 months, < 6 months)
	Adverse effects - weight change in % from baseline to endpoint (< 6 months)
	Adverse effects - mean endpoint AIMS (< 3 months, < 6 months)
Identification	Sponsorship source: National Alliance for Research on Schizophrenia and Depression (NARSAD) Independent Investigator Award to Dr Remington
	Country: Canada
	Number of countries: 1
	Trial registration ID: NCT00431574
	Publication years: 2011
Notes	We received no reply to our e-mail with data request.
	Dropouts were not extracted, because it was not clear to which arm they belonged. There were a total of 11 dropouts.
	CDSS measured, but data not usable.

Rouillon 2008

Study characteristics	
Methods	Study design: randomised controlled trial
	Study grouping: parallel group
	Additional medication allowed: yes (antidepressants, anxiolytics, hypnotics, other antipsychotics)
	Compliance measured: no information
	Study phases: no information
	Duration: 26 weeks
	Number of study arms: 2

Rouillon 2008 *(Continued)*

	Number of drugs used: no information Randomisation assumed from double-blind: no Type of blinding: open-label Type of data analysis for overall efficacy: ITT Use of prophylactic medication: no information Number of sites: 48
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV Current clinical state: partial remission Definition of stability: patients considered as clinically stable by the investigator and receiving more than 10 mg/day of olanzapine for at least 4 months before entry Inclusion criteria: male or female aged 18 years or over, meeting DSM-IV criteria for schizophrenia, considered as clinically stable by the investigator and receiving more than 10 mg/day of olanzapine for at least 4 months before entry Exclusion criteria: clinically significant or unstable medical illness, patients who were allergic to olanzapine, and pregnant or lactating females. Setting: outpatient N: 97 Gender: 66 men, 31 women Age: mean 39.4 years (SD = 11.9) Continuation arm: participants total: 48, participants male: 34, participants female: 14, age: mean 39.2 years (SD = 11), PANSS total: 68.4 (SD = 18.8), duration of illness: no information, baseline weight: mean 78.3 kg (SD = 13.3), height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 49, participants male: 32, participants female: 17, age: mean 40.2 years (SD = 9.6), PANSS total: mean 61.3 (SD = 15.8), duration of illness: no information, baseline weight: mean 74.4 kg (SD = 13.6), height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 48 Antipsychotics used: olanzapine and others not specified. Mean dose: 17.9 (2.7) mg/day, application: oral Description dose scheme: fixed (the investigator was allowed to increase the dose if needed and before patient relapse) 2. Reduction arm. N = 49 Antipsychotics used: olanzapine and others not specified. Mean dose: 17.6 (2.8) mg/day, application: oral Description dose scheme: dose had to be reduced by 2.5 mg. Afterwards the dose could be decreased again by step of 2.5 mg according to investigator judgement; flexible (the investigator was allowed to increase the dose if needed and before patient relapse). Degree of antipsychotic dose reduction: up to 50% Speed of antipsychotic dose reduction: gradual
Outcomes	Service use - readmission to hospital (< 3 months, < 6 months)

Rouillon 2008 *(Continued)*

	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 6 months)
	Quality of life - mean change score S-QoL (< 6 months)
	Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months)
	Leaving the study early - for any reason - overall acceptability (< 6 months)
	Mental state - general: mean change PANSS total (< 6 months)
	Mental state - specific: mean change PANSS positive (< 6 months)
	Mental state - specific: mean change PANSS negative (< 6 months)
	Mental state - specific: mean change PANSS depression/anxiety (< 6 months)
	Adverse effects - number of participants with at least one adverse effect (< 6 months)
	Adverse effects - mean change weight (< 6 months)
	Adverse effects - mean change SAS (< 6 months)
	Adverse effects - mean change BARS (< 6 months)
	Adverse effects - mean change AIMS (< 6 months)
	Adverse effect - mortality: mortality due to suicide (< 3 months, < 6 months)
	Medication – mean antipsychotic dose at endpoint (< 3 months, < 6 months)
Identification	Sponsorship source: pharma (Eli Lilly France)
	Country: France
	Trial registration ID: no information
	Number of countries: 1
	Publication year: 2008
Notes	We received no reply to our e-mail with data request.

Schooler 1997

Study characteristics	
Methods	Study design: randomised controlled trial
	Study grouping: parallel group
	Additional medication allowed: yes (antiparkinsonians and benzodiazepines)
	Compliance measured: yes (rescue measures with depot drugs were taken if compliance was a concern)
	Study phases: following consent, participants entered a 16- to 24-week stabilisation phase defined by hospital admission date or by study entry for outpatients. Participants were randomly assigned to Applied Family Management or Supportive Family Management, and those treatments began. Participants were discharged, with the goal of stabilisation, to receive assigned family management and injectable fluphenazine decanoate only.
	Duration: 104 weeks

Schooler 1997 *(Continued)*

	Number of study arms: 6 (factorial design 2 x 3: Applied Family Management vs Supportive Family Management; Standard Dose, Low Dose, and Targeted Dose). We used only standard and low doses, combining the family interventions. Number of drugs used: fluphenazine decanoate and oral fluphenazine Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, investigator) Type of data analysis for overall efficacy: no information (main scale missing) Use of prophylactic medication: at least some participants received antiparkinsonians Number of sites: 5 (5 academic sites)
Participants	Diagnosis: schizophrenia, schizoaffective disorder, schizophreniform disorder; diagnostic criteria: DSM-III-R Current clinical state: partial remission (criteria for remission were not strict, and recruited patients were acutely ill) Definition of stability: stable dosage of 12.5 to 50 mg fluphenazine decanoate every 2 weeks for 4 weeks without the use of other antipsychotic or psychotropic medications (e.g. lithium, antidepressants); stable psychotic symptoms assessed by the BPRS for 4 weeks; no psychotic symptom (conceptual disorganisation, grandiosity, hallucinatory behaviour, and unusual thought content) greater than moderate Inclusion criteria: 1) a DSM-III-R diagnosis of schizophrenia (any subtype), schizoaffective disorder, or schizophreniform disorder as determined by the Structured Clinical Interview for DSM-III-R (SCID-Psychotic Disorders); 2) age between 18 and 55 years; 3) living with, or having more than superficial contact with, family of origin defined as a minimum of 4 hours of regular face-to-face contact per week; 4) living close enough to the clinic to permit home visits; and 5) informed consent from the patient and at least 1 family member to participate in both medication and family treatment Exclusion criteria: 1) unequivocal liver damage; 2) acute or chronic organic brain syndrome; 3) DSM-III-R diagnosis of psychoactive substance dependence and, additionally, for patients with schizophreniform disorder, DSM-III-R diagnosis of psychoactive substance abuse; and 4) pregnancy Setting: in- and outpatient N: 213 Gender: no information Age in years: no information Continuation arm: participants total: 107, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 106, participants male: no information, participants female: no information, age: no information, PANSS total: no information, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 107 Antipsychotics used: fluphenazine decanoate or hydrochloride. Mean dose: no information (range 12.5 to 50 mg every 2 weeks), application: oral and depot. Description dose scheme: flexible (12.5 to 50 mg fluphenazine decanoate every 2 weeks maintained over time)

Schooler 1997 *(Continued)*

	2. Reduction arm. N = 106 Antipsychotics used: fluphenazine decanoate or hydrochloride. Mean dose: no information (range 2.5 to 10 mg every 2 weeks), application: oral and depot Description dose scheme: flexible (12.5 to 50 mg of fluphenazine decanoate every 2 weeks for 4 weeks without the use of other antipsychotic or psychotropic medications, then 2.5 to 10 mg every 2 weeks) Degree of antipsychotic dose reduction: 80% Speed of antipsychotic dose reduction: abrupt
Outcomes	Service use - readmission to hospital (> 1 year) Global state - number of participants with relapse/exacerbations of psychosis (< 6 months, < 1 year, > 1 year) Medication – mean antipsychotic dose at endpoint (< 6 months, < 1 year)
Identification	Sponsorship source: public (grants: MH39992, MH39998, MH40007, MH40042, MH40597) Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 1997
Notes	The author replied to our e-mail with the information that data are no longer accessible.

Takeuchi 2014

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Study phase: participants randomised to the reduction or maintenance group Additional medication allowed: yes (concomitant medications were permitted; no other antipsychotic was allowed, except for low doses <= 50 mg/day of chlorpromazine or levomepromazine) Compliance measured: yes (clinical interview) Duration: 28 weeks Number of study arms: 2 Number of drugs used: 2 (olanzapine, risperidone) Randomisation assumed from double-blind: no Type of blinding: open-label Type of data analysis for overall efficacy: ITT (LOCF) Number of sites: 6 (no information about the number of academic sites)
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: DSM-IV

Takeuchi 2014 *(Continued)*

	Current clinical state: remission (symptomatic remission in positive symptoms; no patient subgroup) Definition of stability: patients receiving a stable dose of either risperidone > 2 mg/day or olanzapine > 5 mg/day as antipsychotic monotherapy for at least 3 months, and in remission with respect to positive symptoms, as defined by a score of ≤ 3 (mild) on all of the following PANSS-8 Positive subscale items: delusion (P1), conceptual disorganisation (P2), hallucinatory behaviour (P3), and suspiciousness (P6) Inclusion criteria: participants were ≥ 18 years of age, diagnosed with schizophrenia according to DSM-IV, receiving a stable dose of either risperidone > 2 mg/day or olanzapine > 5 mg/day as antipsychotic monotherapy for at least 3 months, and in remission with respect to positive symptoms, as defined by a score of ≤ 3 (mild) on all of the following PANSS-8 Positive subscale items: delusion (P1), conceptual disorganisation (P2), hallucinatory behaviour (P3), and suspiciousness (P6). Concomitant use of ≤ 50 mg/day of chlorpromazine or levomepromazine was allowed because these medications are often used as hypnotics in Japan, and it was considered that such low doses would not be associated with antipsychotic effects. Concomitant medications other than antipsychotics were allowed. Exclusion criteria: patients on antipsychotic polypharmacy were excluded, although concomitant use of ≤ 50 mg/day of chlorpromazine or levomepromazine was allowed because these medications are often used as hypnotics in Japan, and it was considered that such low doses would not be associated with antipsychotic effects. Concomitant medications other than antipsychotics were allowed. Patients were also excluded if they suffered from any significant medical or neurological illnesses, or were pregnant or lactating. Setting: in- and outpatient N: 61 Gender: 37 men, 24 women Age in years: mean 39.7 (13.3) Continuation arm: participants total: 30, participants male: 19, participants female: 11, age: mean 38.4 years (SD = 14.3), PANSS total: mean 56.3 (SD = 11.7), duration of illness: mean 12.9 years (SD = 13.0), baseline weight: mean 67.3 kg (SD = 15.5), height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 31, participants male: 18, participants female: 13, age: mean 40.9 years (SD = 12.2), PANSS total: mean 56.4 (SD = 15.1), duration of illness: mean 15.5 (SD = 11.3), baseline weight: mean 70.2 kg (SD = 16.2), height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 30 Antipsychotics used: olanzapine, risperidone. Mean dose: 4.5 mg/day (SD = 2.8 mg/day; 3 to 12 mg/day, > 2 mg/day) risperidone and 14.1 (SD = 4.3 mg/day; 10 to 20 mg/day, > 5 mg/day) olanzapine; application: oral Description dose scheme: maintenance of baseline dose; fixed (or no information) 2. Reduction arm. N = 31 Antipsychotics used: olanzapine, risperidone. Mean dose: 3.7 mg/day (SD = 1 mg/day; 3 to 6 mg/day; > 2 mg/day) risperidone and 13.8 mg/day (SD = 5.2 mg/day; 7.5 to 20 mg/day; > 5 mg/day) olanzapine; application: oral Description dose scheme: risperidone or olanzapine were reduced by 25% at baseline and week 4, followed by the treatment with half the baseline dose over the next 24 weeks; fixed (or no information) Degree of antipsychotic dose reduction: up to 50% (for safety reasons > 2 mg/day risperidone and > 5 mg/day olanzapine) Speed of antipsychotic dose reduction: gradual (reduction of 25% of the baseline dose at baseline, reduction of another 25% of baseline dose at 4 weeks)

Takeuchi 2014 *(Continued)*

Outcomes	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 1 year)
	Quality of life - mean change score EQ-5D (< 1 year)
	Quality of life - mean change SWNS (< 1 year)
	Global state - number of participants with relapse/exacerbations of psychosis (< 1 year)
	Global state - mean change CGI-S (< 1 year)
	Leaving the study early - for any reason - overall acceptability (< 1 year)
	Leaving the study early - due to inefficacy - overall efficacy (< 1 year)
	Mental state - general: mean change PANSS total (< 1 year)
	Mental state - specific: mean change PANSS positive (< 1 year)
	Mental state - specific: mean change PANSS negative (< 1 year)
	Mental state - specific: mean change CDSS (< 1 year)
	Mental state - specific: mean change POMS-SF (< 1 year)
	Mental state - specific: mean change SAI (< 1 year)
	Satisfaction with care - mean change DAI-10 (< 1 year)
	Adverse effects - mean change weight (< 1 year)
	Adverse effects - mean change DIEPSS (< 1 year)
	Adverse effects - mean change QTc interval (milliseconds) (< 1 year)
	Adverse effects - mean change prolactin levels (ng/mL) (< 1 year)
	Cognition - mean change RBANS (< 1 year)
	Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: Inokashira Hospital and Research Group for Schizophrenia
	Country: Japan
	Number of countries: 1
	Trial registration ID: UMIN000001834
	Publication year: 2013
Notes	The authors provided unpublished data.

Volavka 2000

Study characteristics	
Methods	Study design: randomised controlled trial
	Study grouping: parallel group
	Additional medication allowed: yes (benztropine)
	Compliance measured: yes (blood samples)

Volavka 2000 *(Continued)*

	Study phases: 3 study periods. Period 1: switching tablet form of haloperidol to liquid oral form, 3 weeks. Period 2: plasma-level-reduction group and control group, 12 weeks. Period 3: plasma-level maintenance, 16 weeks Duration: 28 weeks Number of study arms: 2 Number of drugs used: 1 Randomisation assumed from double-blind: no Type of blinding: double-blind (psychiatrists were blind; participants were also probably blind) Type of data analysis for overall efficacy: ITT Use of prophylactic antiparkinson medication: no Number of sites: 3
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: clinical diagnosis Current clinical state: chronically ill Definition of stability: participants had been consistently ill with no interval of good functioning for at least 18 months immediately before their selection and hospitalised for at least 6 months Inclusion criteria: participants were inpatients with the diagnosis of schizophrenia or schizoaffective disorder. They had been consistently ill with no interval of good functioning for at least 18 months immediately before their selection and hospitalised for at least 6 months (cumulative). The patients were selected because their clinical psychiatrists (using clinical judgement) had prescribed a dose of oral haloperidol exceeding 20 mg/day for at least 1 month before selection. At the time of selection, the participants had not received an injection of a slow-release antipsychotic for the previous 1 month or longer. Exclusion criteria: no information Setting: inpatient N: 23 Gender: 20 men, 3 women Age in years: mean 40.1 (SD = 11.2) Continuation arm: participants total: 12, participants male: no information, participants female: no information, age: no information, PANSS total: mean 92.6, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 11, participants male: no information, participants female: no information, age: no information, PANSS total: mean 82.3, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 12 Antipsychotics used: haloperidol. Mean dose: 34.3 (8.7) mg/day, application: oral (liquid). Description dose scheme: fixed (dose was adjusted as necessary) 2. Reduction arm. N = 11 Antipsychotics used: haloperidol. Mean dose: 32.9 (5.3) mg/day, application: oral (liquid)

Volavka 2000 *(Continued)*

	Description dose scheme: flexible. A gradual dose reduction over a period of 12 weeks. This rate of dose reduction was selected on the basis of results from a previous study in order to minimise the risk of clinical deterioration during the reduction period. The goal of the reduction schedule was to achieve a plasma level range of 8 to 12 ng/mL, with a target of 10 ng/mL. The rationale for this target was based on clinical evidence. The dose reduction was planned individually depending on the participant's baseline plasma level, and doses were adjusted to conform to the individualised plan of gradual plasma level reduction. Degree of antipsychotic dose reduction: 33% Speed of antipsychotic dose reduction: gradual (12 weeks)
Outcomes	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 3 months, < 6 months) Leaving the study early - for any reason - overall acceptability (< 3 months, < 6 months) Leaving the study early - due to inefficacy - overall efficacy (< 3 months) Mental state - general: mean change PANSS total (< 3 months) Mental state - specific: mean change PANSS positive (< 3 months) Adverse effects - mean change SAS (< 3 months) Adverse effect - mortality: overall mortality (< 3 months, < 6 months) Adverse effect - mortality: mortality due to natural causes (< 3 months, < 6 months) Adverse effect - mortality: mortality due to suicide (< 3 months, < 6 months) Medication – mean antipsychotic dose at endpoint (< 3 months, < 6 months)
Identification	Sponsorship source: public (National Institute of Mental Health MH41772) Country: USA Trial registration ID: no information Number of countries: 1 Publication year: 2000
Notes	A valid e-mail could not be found. Author not contactable.

Wang 2010

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes (benzodiazepines, zolpidem, benzatropine, and propranolol) Compliance measured: yes (pills count) Study phases: 3 study groups. Group 1: no dose reduction group (initial optimal therapeutic dose continued troughout the study). Group 2: 4-week group (initial optimal therapeutic dose continued for 4 weeks, followed by a 50% dose reduction). Group 3: 26-week group (initial optimal therapeutic dose continued for 26 weeks, followed by a 50% dose reduction until the end of the study)

Wang 2010 *(Continued)*

	Duration: 4-week group: 4 weeks + 52 weeks of follow-up; 26-week group: 26 weeks + 52 weeks of follow-up; no dose reduction group: 52 weeks. We considered the participants from the start of the antipsychotics dose reduction (52 weeks for all groups). Number of study arms: 3 (we considered only 2 arms: oral aripiprazole 10 to 30 mg/day and aripiprazole long-acting injectable 50 mg/4 weeks; we did not consider the third arm with aripiprazole long-acting injectable 400 mg/4 weeks as it was not a continuation or a reduction arm) Number of drugs used: 1 (risperidone) Randomisation assumed from double-blind: no Type of blinding: open-label Type of data analysis for overall efficacy: LOCF Use of prophylactic antiparkinson medication: no information Number of sites: 19
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV Current clinical state: partial remission Definition of stability: clinical stabilisation following an acute episode for at least 4 weeks but less than 8 weeks, with 'clinical stability' defined as a total score on the BPRS of less than 36 points (acute episodes included all cases of hospitalisation due to an exacerbation of psychotic symptoms) Inclusion criteria: 1) age between 18 and 65 years; 2) either sex; 3) in- or outpatient status with a diagnosis of DSM-IV schizophrenia at study entry; 4) clinical stabilisation following an acute episode for at least 4 weeks but less than 8 weeks, with 'clinical stability' defined as a total score on the BPRS of less than 36 points (8) (acute episodes included all cases of hospitalisation due to an exacerbation of psychotic symptoms); 5) administration of risperidone monotherapy in an optimal therapeutic dose (4 to 8 mg/day) in the acute phase of treatment for the psychotic episode and response to antipsychotic treatment (i.e. being neither a partial responder nor refractory to antipsychotic treatment), as evidenced by a chart review and confirmed by the treating psychiatrist (the treating psychiatrists were not involved in the study design); 6) local residence with at least 1 family member after discharge; 7) satisfactory treatment adherence, defined by a pill count that yielded more than 80% adherence to the risperidone prescription over the past 4 weeks; and 8) an understanding of the aims of the study and a signed consent form Exclusion criteria: 1) use of antidepressants, mood stabilisers, or Chinese herbal remedies concomitantly with risperidone or having received ECT or participated in any other drug trial or interventional study over the 4 weeks before study entry; 2) a history of or an ongoing major chronic medical or neurological condition; 3) past or current abuse of drugs or alcohol other than nicotine; and 4) pregnancy or plans to become pregnant, lactation, or lack of an effective method of birth control Setting: in- and outpatient N: 374 Gender: 172 men, 202 women Age: mean 32.6 years (SD = 10.8) Continuation arm: participants total: 129, participants male: 62, participants female: 67, age: mean 33.8 years (SD = 11.8), PANSS total: 39.7 (SD = 10.2), duration of illness: mean 7.3 years (SD = 7.5), baseline weight: mean 63.2 kg (SD = 11.5), height: no information, BMI: mean 22.8 (SD = 3), average time in study: no information Reduction arms (combined): 4 weeks stabilisation and subsequent dose reduction: participants total: 125, participants male: 51, participants female: 74, age: mean 31.3 years (SD = 10.6), PANSS total: mean 39.7 years (SD = 9.6), dura-

Wang 2010 *(Continued)*

	tion of illness: mean 6.1 years (SD = 6.1), baseline weight: mean 62.2 kg (SD = 10.7), height: no information, BMI: mean 22.8 (SD = 3.2), average time in study: no information 26 weeks stabilisation and subsequent dose reduction: participants total: 120, participants male: 59, participants female: 61, age: mean 32.7 years (SD = 9.8), PANSS total: mean 39.6 (SD = 8.6), duration of illness: mean 6.7 years (SD = 7), baseline weight: mean 62.8 kg (SD = 10.7), height: no information, BMI: mean 22.7 (SD = 3), average time in study: no information
Interventions	1. Continuation arm. N = 129 Antipsychotics used: risperidone. Mean dose: 4.3 mg/day (SD = 0.6 mg/day; range 4 to 8 mg/day), application: oral Description dose scheme: fixed 2. Reduction arm (combined in analysis). N = 245 4 weeks stabilisation and subsequent dose reduction. N = 125 Antipsychotics used: risperidone. Mean dose: 4.4 mg/day (SD = 0.8 mg/day), application: oral Description dose scheme: participants in the 4-week group were maintained at the initial therapeutic risperidone dose for 4 weeks, after which the dose was reduced gradually (0.5 mg every 7 to 10 days, depending on the starting dose) to one-half of the therapeutic dose over the next 8 weeks, which was maintained until the end of the study Degree of antipsychotic dose reduction: 50% Speed of antipsychotic dose reduction: gradual (8 weeks) 26 weeks stabilisation and subsequent dose reduction. N = 120 Antipsychotics used: risperidone. Mean dose: 3.8 mg/day (SD = 0.9 mg/day), application: oral Description dose scheme: participants in the 26-week group were maintained at the initial therapeutic risperidone dose for 4 weeks, after which the dose was reduced gradually (0.5 mg every 7 to 10 days, depending on the starting dose) to one-half of the therapeutic dose over the next 8 weeks, which was maintained until the end of the study Degree of antipsychotic dose reduction: 50% Speed of antipsychotic dose reduction: gradual (8 weeks)
Outcomes	Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months, < 1 year) Mental state - general: mean endpoint PANSS total (< 3 months, < 6 months, < 1 year) Mental state - general: mean change PANSS total (< 1 year) Mental state - specific: mean change PANSS positive (< 1 year) Mental state - specific: mean change PANSS negative (< 1 year) Mental state - specific: mean change PANSS depression/anxiety (< 1 year) Behaviour - mean change PANSS excitement/hostility (< 1 year) Adverse effects - mean change SAS (< 1 year) Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: public (10th National Five-Year Plan Foundation of the Ministry of Science and Technology Program, People's Republic of China (2004BA720A22)) and private (Research Foundation of Xian-Janssen Pharmaceutical)

Wang 2010 *(Continued)*

	Country: China Trial registration ID: NCT00848432, RIS-CN-MCCT-0201 Number of countries: 1 Publication year: 2010
Notes	We received no reply to our e-mail with data request.

Wunderink 2007

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Study phases: T0 (time point 0): first treatment response; T6: 6 months after T0, remission phase: when remitted entering trial; T15: halfway point of trial; T24: 24 months after first treatment response; up to 7 years follow-up after the RCT was completed Additional medication allowed: no information Compliance measured: yes (clinical interview) Duration: 72 years (follow-up within the RCT) Number of study arms: 2 Number of drugs used: no information (risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol were the most frequently used) Randomisation assumed from double-blind: no Type of blinding: single-blind (outcome assessor) Type of data analysis for overall efficacy: ITT (MMRM) Number of sites: 8 (7 district mental health centres and the Department of Psychiatry of the University Medical Center Groningen)
Participants	Diagnosis: schizophrenia, schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified; diagnostic criteria: DSM-IV Current clinical state: remission (symptomatic remission in positive symptoms; first episode) Definition of stability: treatment response was defined by clinical improvement to a non-florid psychotic state of at least 1 week's duration, reported by the clinician and subsequently confirmed by PANSS positive symptom subscale ratings as assessed by a research team member. 1 rating of 4 (moderate) was allowed. Remission required a sustained improvement of positive symptoms, reflected by symptom severity levels at or below the level of response during at least 6 months. Negative and disorganisation symptoms, included in recently proposed remission criteria, were not considered. During remission, mild exacerbations of positive symptoms of less than 1 week's duration were allowed. Inclusion criteria: patients included in the study had first-episode schizophrenia or a related psychotic disorder; were aged 18 to 45 years; lived in the catchment area; had received no prior antipsychotic medication for more than 3 months; had mastered the Dutch language; and had an estimated IQ score above 70. In addition, participants had to show response of positive symptoms within 6 months of antipsychotic treatment and sustained remission during 6 months. Diagnosis was established using the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). A DSM-IV diagnosis of schizophrenia,

Wunderink 2007 *(Continued)*

	schizophreniform disorder, brief psychotic disorder, schizoaffective disorder, delusional disorder, or psychotic disorder not otherwise specified was required. All participants were treated with antipsychotics until remission. Exclusion criteria: no information Setting: likely outpatient N: 131 Gender: 89 men, 39 women (participants with gender given) Age: no information Continuation arm: participants total: 63, participants male: 44, participants female: 19, age: no information, PANSS total baseline: mean 47.3, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information Reduction arm: participants total: 68, participants male: 45, participants female: 20, age: no information, PANSS total baseline: mean 44.1, duration of illness: no information, baseline weight: no information, height: no information, BMI: no information, average time in study: no information
Interventions	1. Continuation arm. N = 63 Antipsychotics used: risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol (most frequently). Mean dose: no information, application: no information Description dose scheme: maintenance treatment was carried out according to American Psychiatric Association guidelines, preferably using low-dose atypical antipsychotics 2. Reduction arm. N = 68 Antipsychotics used: risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol (most frequently). Mean dose: no information, application: no information Description dose scheme: the dosage was gradually tapered and discontinued if feasible. Tapering was allowed to be guided by symptom severity levels and patient preference. If early warning signs of relapse emerged or positive symptoms recurred, clinicians were to restart or increase the dosage of antipsychotics. Flexible Degree of antipsychotic dose reduction: up to 100% Speed of antipsychotic dose reduction: gradual (no further information)
Outcomes	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 3 months, < 6 months, < 1 year, > 1 year) Quality of life - mean endpoint WHOQOL-BREF (< 1 year, > 1 year) Functioning - mean endpoint GSDS (< 1 year, > 1 year) Global state - number of participants with relapse/exacerbations of psychosis (< 3 months, < 6 months, < 1 year, > 1 year) Leaving the study early - for any reason - overall acceptability (> 1 year) Leaving the study early - due to inefficacy - overall efficacy (< 3 months, < 6 months, < 1 year, > 1 year) Mental state - general: mean endpoint PANSS total (< 1 year, > 1 year) Mental state - specific: mean endpoint PANSS positive (< 1 year, > 1 year) Mental state - specific: mean endpoint PANSS negative (< 1 year, > 1 year) Adverse effects - mean endpoint LUNSERS (< 1 year, > 1 year)

Wunderink 2007 *(Continued)*

	Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: The Netherlands Organisation for Health Research and Development (The Hague) (DO945-01-001), Foundation for the Support of the Society for Christian Care of the Nervously and Mentally Ill (Bennekom), Foundation "De Open Ankh" (Soesterberg), and Eli Lilly Nederland B.V. (Houten). Country: the Netherlands Number of countries: 1 Trial registration ID: NTR374; ISRCTN16228411; MESIFOS Publication year: 2007
Notes	A valid e-mail could not be found. Author not contactable. Service use - days in the hospital was reported as % and could not be used.

Zhou 2018

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Study phases: randomised to reduction or maintenance group Additional medication allowed: yes (other concomitant medications were allowed; other antipsychotics were not allowed except for clozapine <= 50 mg/day and quetiapine <= 200 mg/day for sleep) Compliance measured: no (stated as a limitation of the study) Duration: 52 weeks Number of study arms: 2 Number of drugs used: 2 (olanzapine, risperidone) Randomisation assumed from double-blind: no Type of blinding: single-blind (outcome assessor) Type of data analysis for overall efficacy: ITT (MMRM) Number of sites: 2 (1 academic site)
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-IV-TR Current clinical state: partial remission (no patient subgroup) Definition of stability: stabilised phase defined as a score of ≤ 3 (mild) on all of the following PANSS positive subscale items: (P1) delusion, (P2) conceptual disorganisation, (P3) hallucinatory behaviour, and (P6) suspiciousness (Takeuchi et al, 2013), and prescribed antipsychotic monotherapy of either risperidone or olanzapine at a constant dose of ≥ 4 mg/day or ≥ 10 mg/day, respectively, for at least 3 months Inclusion criteria: aged 18 to 60 years; male or female; diagnosed with schizophrenia meeting the DSM-IV-TR (American Psychiatric Association, 2000) criteria at study entry; stabilised phase defined as a score of ≤ 3 (mild) on all of the following PANSS positive subscale items: (P1) delusion, (P2) conceptual disorganisation, (P3) hallucinatory behaviour, and (P6) suspiciousness (Takeuchi et al, 2013); prescribed antipsychotic monotherapy of either risperidone or olanzapine at a constant dose of ≥ 4 mg/

Zhou 2018 *(Continued)*

	day or ≥ 10 mg/day, respectively, for at least 3 months; and could understand the aims of the study and sign the consent form Exclusion criteria: the use of antipsychotic polypharmacy; however, a combined intake of ≤ 50 mg/day of clozapine or ≤ 200 mg/day of quetiapine was allowed to aid sleep (combined medications other than antipsychotics were allowed); a history of or a current major medical or neurological disorder; substance abuse; and pregnancy or lactation. 4 participants receiving combined clozapine and quetiapine were included in study, 2 with combined clozapine in the maintenance group and 2 with combined quetiapine in the reduction group. Given the impact of clozapine on white blood cells, monitoring of white blood cells was required, and was found to be normal throughout the entire study. Setting: outpatients N: 75 Gender: 45 men, 30 women Age: mean 44.6 years (SD = 7.9) Continuation arm: participants total: 38, participants male: 23, participants female: 15, age: mean 44.8 years (SD = 6.6), PANSS baseline: mean 66.5, duration of illness: no information, baseline weight: no information, height: no information, BMI: mean 26.9 kg/m^2 (SD = 5.9), average time in study: no information Reduction arm: participants total: 37, participants male: 22, participants female: 15, age: mean 44.3 years (SD = 9.1), PANSS baseline: mean 66.2, duration of illness: no information, baseline weight: no information, height: no information, BMI: mean 25.3 kg/m^2 (SD = 4.7), average time in study: no information
Interventions	1. Continuation arm. N = 38 Antipsychotics used: olanzapine, risperidone. Mean dose: 4.9 mg/day (SD = 0.9 mg/day; > 2 mg/day) for risperidone and 17.2 mg/day (SD = 3.6 mg/day; > 10 mg/day) for olanzapine at baseline, application: oral Description dose scheme: maintenance of the baseline dose; fixed (unclear information) 2. Reduction arm. N = 37 Antipsychotics used: olanzapine, risperidone. Mean dose: 5.1 mg/day (SD = 0.9 mg/day; > 2 mg/day) for risperidone and 19.5 mg/day (SD = 1.6 mg/day; > 5 mg/day) for olanzapine at baseline and 3.3 mg/day (SD = 0.4 mg/day; > 2 mg/day) for risperidone and 7.8 mg/day (SD = 0.8 mg/day; > 5 mg/day) for olanzapine at endpoint, application: oral Description dose scheme: dose of risperidone or olanzapine was reduced by 25% for the first 4 weeks, then reduced by 50% of the original dose for the next 12 weeks, and then maintained at this dose until the end of the study; fixed (unclear information) Degree of antipsychotic dose reduction: 50% Speed of antipsychotic dose reduction: gradual (25% for the first 4 weeks and 50% for the next 12 weeks)
Outcomes	Adverse effect - leaving the study early due to adverse effects - overall tolerability (< 3 months, < 6 months, < 1 year) Global state - number of participants with relapse/exacerbations of psychosis (< 1 year) Leaving the study early - for any reason - overall acceptability (< 1 year) Leaving the study early - due to inefficacy - overall efficacy (< 1 year) Mental state - general: mean endpoint PANSS total (< 3 months, < 6 months, < 1 year)

Zhou 2018 *(Continued)*

	Mental state - specific: mean endpoint PANSS positive (< 3 months, < 6 months, < 1 year) Mental state - specific: mean endpoint PANSS negative (< 3 months, < 6 months, < 1 year) Mental state - specific: mean endpoint NSA-16 (< 3 months, < 6 months, < 1 year) Adverse effects - mean endpoint BMI (kg/m^2) (< 3 months, < 6 months, < 1 year) Adverse effects - mean endpoint SAS (< 3 months, < 6 months, < 1 year) Cognition - mean endpoint MCCB total (< 3 months, < 6 months, < 1 year) Medication – mean antipsychotic dose at endpoint (< 1 year)
Identification	Sponsorship source: this study was supported by the Planned Science and Technology Projects of Guangzhou (grant number 201607010131), Guangzhou Municipal Key Discipline in Medicine (2017-2019), Science and Technology Department of Guangdong Province major science and technology (grant number 2016B010108003), and National R&D programme focused on precision medical research of China (grant number 2016YFC0906302) Country: China Number of countries: 1 Trial registration ID: ChiCTR-POC-15006642 Publication year: 2018
Notes	We received no reply to our e-mail with data request.

AIMS: Abnormal Involuntary Movement Scale
ANOVA: analysis of variance
BARS: Barnes Akathisia Rating Scale
BMI: body mass index
BPRS: Brief Psychiatric Rating Scale
C-SSRS: Columbia Suicide Severity Rating Scale
CDSS: Calgary Depression Scale for Schizophrenia
CGI-I: Clinical Global Impression - Improvement
CGI-S: Clinical Global Impression - Severity
CGI-SS: Clinical Global Impression - Severity of Suicidality
CNS: central nervous system
DAI-10: Drug Attitude Inventory - 10 items
DAI-30: Drug Attitude Inventory - 30 items
DIEPS: Drug-Induced Extrapyramidal Symptoms Scale
DSM-III-R: Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised
DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision
ECT: electroconvulsive therapy
EPS: extrapyramidal symptoms
GAF: Global Assessment of Functioning
GAS: Global Assessment Scale
GSDS: Groningen Social Disabilities Schedule
IAQ-12: Investigator's Assessment Questionnaire - 12 items
ICD: International Classification of Diseases
IM: intramuscular
IQ: intelligent quotient
ITT: intention to treat
LOCF: last observation carried forward
LUNSERS: Liverpool University Neuroleptic Side Effect Rating Scale
m-ITT: modified intention to treat
MAQ: Medication Adherence Questionnaire
MARS: Medication Adherence Rating Scale
MCCB: MATRICS Consensus Cognitive Battery

MMRM: mixed model repeated measures
MPRC: Maryland Psychiatric Research Center involuntary movement scale
NA: not available
NIMH: National Institute of Mental Health
NONMEM IV: NONlinear Mixed Effects Modeling - Fourth
NSA-16: Negative Symptom Assessment - 16 items
PANSS: Positive and Negative Symptoms Scale
POMS-SF: Profile of Mood States Short Form
PPK: population pharmacokinetic
PSMQ-Modified: Patient Satisfaction with Medication Questionnaire - Modified
PSP: Personal Social Performance Scale
QLS: Quality of Life Scale
RBANS: Repeatable Battery for the Assessment of Neuropsychological Status
RCT: randomised controlled trial
RTDRS: Rockland-Simpson Dyskinesia Rating Scale
S-QoL: Schizophrenia Quality of Life
SAI: Schedule for Assessment of Insight
SAS: Simpson-Angus Scale
SCL-90: Symptom Checklist-90
SCLoF: Strauss-Carpenter Level of Function scale
SD: standard deviation
SF-36: 36-item Short Form Health Survey
SWNS: Subjective Well-being under Neuroleptics Scale
UKU: Udvalg for Kliniske Undersøgelser
WHOQOL-BREF: World Health Organization Quality of Life abbreviated form

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Arato 2002	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
AstraZeneca 2007	Design: randomised Participants: not stable
Baker 2002	Design: randomised Participants: not stable
Bogers 2018	Design: randomised Participants: not stable
Caffey 1971	Design: randomised Participants: not stable Intervention: no dose reduction
Dellva 1997	Design: randomised Participants: not stable Intervention: no dose reduction; study evaluated standard versus low dose
Durgam 2017	Design: randomised

Study	Reason for exclusion
	Participants: not stable Intervention: no dose reduction; study evaluated standard versus low dose
Eli-Lilly F1D-EW-E003 1997	Design: randomised Participants: not stable Intervention: no dose reduction; study evaluated standard versus low dose
Eli-Lilly F1D-MC-HGAD 1997	Design: randomised Participants: not stable Intervention: no dose reduction; study evaluated standard versus low dose
European Medicines Agency 2007	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Faber 2012	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Goldstein 1978	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Harris 1997	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Hirschowitz 1997	Design: randomised Participants: stable individuals with schizophrenia Intervention: dose reduction Comparator: no dose maintenance
Hsiao 2011	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Huttunen 1996	Design: randomised Participants: stable individuals with schizophrenia Intervention: starting dose not clear; likely standard versus low dose
Inderbitzin 1994	Design: not randomised

Study	Reason for exclusion
Kalachnik 1984	Design: randomised Participants: no schizophrenia
Kane 1979	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Kane 2002	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose
Khazaie 2005	Design: concerns related to the data. Study is almost identical to Carpenter 1999 (included), and we had serious concerns that it was a fraudulent trial (e.g. the calculated Chi^2 from 2 x 2 table on gender in Khazaie 2005 is different from the reported one (1.59 vs 3.59). The reported one is similar to the Carpenter 1999 one (3.59 vs 3.57), and this issue applied to all reported data).
Kinon 2004	Design: randomised Participants: insufficient description of stability
Koshikawa 1991	Design: randomised Participants: stable individuals with schizophrenia Intervention: dose reduction Comparator: no dose maintenance (dose increase)
Lecrubier 2006	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose
Lee 2002	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (dose increase)
Lublin 1991	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Mallikaarjun 2013	Design: randomised Participants: stable individuals with schizophrenia Intervention: dose reduction Comparator: no dose maintenance
Marder 1984	Design: randomised Participants: stable individuals with schizophrenia

Study	Reason for exclusion
	Intervention: no dose reduction
Marken 1994	Design: randomised Participants: no diagnosis of schizophrenia
Matkovits Gupta 1999	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (dose increase)
Matkovits Gupta 2001	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (dose increase)
Miller 1965	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
NCT00254787	Design: randomised Participants: not stable
NCT00254813	Design: randomised Participants: not stable
NCT00304473	Design: randomised Participants: not stable
NCT00457899	Design: randomised Participants: not stable
NCT00486798	Design: randomised Participants: not stable
NCT00919607	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction
Nishikawa 1984	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose
Nishikawa 1985	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose

Study	Reason for exclusion
Nishikawa 1989	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose
Pae 2007	Design: randomised Participants: not stable
Schultz 2007	Design: randomised Participants: not stable
Simpson 2007	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose
Smith 2002	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (dose increase)
Soria 1994	Design: not randomised
Sramek 1997	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (dose increase)
Sramek 1998	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (dose increase)
Sukegawa 2008	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (combined dose reduction and polypharmacy reduction)
Sukegawa 2013	Design: not randomised
Suzuki 1992	Design: randomised Participants: stable individuals with schizophrenia Intervention: dose reduction Comparator: no dose maintenance
Townsend 2004	Design: randomised Participants: not stable
Uchida 2006	Design: randomised

Study	Reason for exclusion
	Participants: insufficient description of stability
Velligan 2002	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction; study evaluated standard versus low dose
Yamanouchi 2015	Design: randomised Participants: stable individuals with schizophrenia Intervention: no dose reduction (combined dose reduction and polypharmacy reduction)
Yoon 2016	Design: randomised Participants: stable individuals with schizophrenia Intervention: dose reduction Comparator: no dose maintenance

Characteristics of ongoing studies *[ordered by study ID]*

EUCTR2017 002406 12

Study name	HAMLETT. Handling antipsychotic medication: long-term evaluation of targeted treatment. A pragmatic single blind RCT of continuation versus discontinuation/dose reduction of antipsychotic medication in patients remitted after a first episode of psychosis
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: the study is divided into 2 phases: 1) an experimental phase of 6 months; and 2) a follow-up phase of 3.5 years. The experimental phase consists of a screening visit (−3 to 0 months before participating), a baseline visit, a midterm visit (at 3 months postbaseline), and a close-out visit (6 months postbaseline). The follow-up phase consists of 4 visits (i.e. at 12, 24, 36, and 48 months postbaseline). Duration in weeks: 26 Number of study arms: 2 Randomisation assumed from double-blind: no Type of blinding: single-blind (assessor) Type of data analysis for overall efficacy: ITT Use of prophylactic medication: no Number of sites: 24
Participants	Diagnosis: first episode of schizophrenia, schizoaffective disorder, schizophreniform disorder, brief psychotic disorder, delusional disorder, substance/medication-induced psychotic disorder, or those classified as unspecified schizophrenia spectrum and other psychotic disorder

EUCTR2017 002406 12 *(Continued)*

	Diagnostic criteria: DSM-5 or ICD-10 Current clinical state: remission Definition of stability: no information Inclusion criteria: the participant has had a first episode of psychosis and uses antipsychotic medication; psychotic symptoms are in remission for 3 to 6 months; age 16 to 55 years; the participant understands the study and is able to provide written informed consent; HAMLETT is the only medical-scientific medication study in which the patient participates; sufficient knowledge and ability of the Dutch language Exclusion criteria: dangerous or harmful behaviour (i.e. behaviour with a risk of severe physical injury, or actual physical injury inflicted, to self or others) occurred during first episode of schizophrenia; coercive treatment with antipsychotic medication during first episode of schizophrenia (based on a judicial ruling) Setting: in- and outpatient
Interventions	1. Continuation. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: flexible (medication will be kept within the same range, allowing a 25% dose reduction; increase of dosage is not restricted. After first year, a shared decision is made for further continuation or gradual discontinuation based on the participant's motivation and the clinical situation. 2. Reduction. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: flexible. "Discontinuation schedules were constructed on the following principles: smooth and gradual regular lowering of the serum levels of antipsychotic medication. Since we could not use tapering strips, we needed to diminish antipsychotic medication depending on availability of different dosages and the possibility to divide tablets. Treating physicians prescribe the tapering schedule that fits the patient's type and dose of baseline medication, yet details can be tailored in collaboration with the patient and important relatives. When dose reduction is successful, patients can discontinue their medication completely. [...] In case early warning signs occur, further tapering off of antipsychotic medication will be halted until early warning signs disappear. Stress reduction will be advised. When early warning signs disappear, tapering off antipsychotic medication can be resumed." Degree of antipsychotic dose reduction: up to 100% Speed of antipsychotic dose reduction: gradual
Outcomes	Planned: • Social recovery • Side effects of medication use • Personal well-being • Quality of life • Symptom severity • Physical health (body mass index, somatic comorbidity including metabolic syndrome) • Aggression and self-harm • Cognitive functioning • Movement disorders • Number and duration of psychotic relapses • Number and duration of psychiatric treatments • Cigarette, alcohol, and drug abuse

EUCTR2017 002406 12 *(Continued)*

Starting date	4 April 2019
Contact information	Erna van 't Hag; e.van.t.hag@umcg.nl
Identification	Sponsorship source: independent self-governing organisation (ZonMw grant number 80-84800-98-41015) Country: the Netherlands Trial registration ID: 2017-002406-12 Number of countries: 1 Publication year: 2020
Notes	

JPRN UMIN000037282

Study name	Dose reduction of long-acting injectable second-generation antipsychotics in stable schizophrenia: a multicenter, double-blind, randomized controlled trial
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: yes Study phases: no information Duration in weeks: 52 Number of study arms: 2 Number of drugs used: 2 (LAI risperidone and LAI paliperidone) Randomisation assumed from double-blind: no Type of blinding: double-blind Type of data analysis for overall efficacy: no information Use of prophylactic medication: no information Number of sites: no information
Participants	Diagnosis: schizophrenia or schizoaffective disorder; diagnostic criteria: ICD-10 Current clinical state: remission Definition of stability: remission of positive symptoms defined as a score of <= 3 on all of the following PANSS items: delusion (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganisation (P2), mannerisms and posturing (G5) Inclusion criteria: outpatients having a diagnose of schizophrenia or schizoaffective disorder according to ICD-10; aged >= 20 years old; having regularly and consecutively received LAI risperidone > 25 mg/2 weeks or LAI paliperidone > 50 mg/4 weeks at the same dose for at least 6 months as antipsychotic monotherapy. Antipsychotic polypharmacy is not allowed except for use of quetiapine, chlorpromazine, and levomepromazine <= 50 mg/day as hypnotics; having been in remission

JPRN UMIN000037282 *(Continued)*

	of positive symptoms defined as a score of <= 3 on all of the following PANSS items: delusion (P1), unusual thought content (G9), hallucinatory behaviour (P3), conceptual disorganisation (P2), mannerisms and posturing (G5); having provided written informed consent Exclusion criteria: having a history of obvious harm to him/herself and/or others; having significant physical or neurological illnesses; having a diagnosis of mental and behavioural disorders due to psychoactive substance use according to ICD-10; being pregnant or lactating; having the following contraindications for TMS and MRI (only for patients who take TMS and MRI): using a cardiac pacemaker, having a history of epilepsy, having implanted metal device, having claustrophobia; having been judged as unable to provide informed consent by a person who explains the study; having been judged as unsuitable for the study for another reason by a principal investigator Setting: outpatient
Interventions	1. Continuation. N (no information) Antipsychotics used: LAI risperidone and LAI paliperidone. Mean dose: no information, application: depot Description dose scheme: fixed (LAI-SGAs will be maintained at the same dose as baseline) 2. Reduction. N (no information) Antipsychotics used: LAI risperidone and LAI paliperidone. Mean dose: no information, application: depot Description dose scheme: fixed (each of the LAI-SGAs will be reduced by 50% at baseline and maintained at this dose. For safety reasons, the dose will not be reduced beyond the minimum effective dose.) Degree of antipsychotic dose reduction: 50% Speed of antipsychotic dose reduction: abrupt
Outcomes	Planned: • Change in Brief Assessment of Cognition in Schizophrenia (BACS) • Relapse rate • Time to relapse • Study discontinuation rate • Time to study discontinuation • Positive and Negative Syndrome Scale (PANSS) • Brief Evaluation of Psychosis Symptom Domains (BE-PSD) • Clinical Global Impression -Severity scale (CGI-S) • Personal and Social Performance Scale (PSP) • Specific Levels of Functioning Scale (SLOF) • Subjective Well-being under Neuroleptics scale - Short form (SWNS) • Perceived Deficits Questionnaire (PDQ) • Visual Analogue Scale for Distress Associated with Symptoms (VAS-DAS) • Visual Analogue Scale for Worry and Expectation about Dose Reduction • Drug Induced Extra-Pyramidal Symptoms Scale (DIEPSS) • UKU Side Effect Scale (UKU) • Body weight • Blood biochemistry (triglyceride, LDL cholesterol, HDL cholesterol, fasting blood glucose, plasma prolactin) • Plasma homovanillic acid • Blood concentrations of risperidone and its metabolite (9-O H risperidone) • Proton magnetic resonance spectroscopy (1H-MRS) • Concurrent transcranial magnetic stimulation and electroencephalography (TMS-EEG)

JPRN UMIN000037282 *(Continued)*

- Resting state functional MRI (RS-fMRI)
- Diffusion tensor image (DTI)
- Resting state electroencephalography (RS-EEG)

Starting date	13 March 2020
Contact information	Professor Hiroyoshi Takeuchi; hirotak@dk9.so-net.ne.jp
Identification	Sponsorship source: Keio University School of Medicine Department of Neuropsychiatry Country: Japan Trial registration ID: UMIN000037282 Number of countries: 1 Publication year: 2019
Notes	

Liu 2018

Study name	A proposed alternative between discontinuation and maintenance of antipsychotics: a guided dose reduction trial for patients with remitted psychosis
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: no information Type of data analysis for overall efficacy: no information Use of prophylactic medication: no information Number of sites: 1 (assumed)
Participants	Diagnosis: schizophrenia-related psychotic disorders; diagnostic criteria: no information Current clinical state: remission Definition of stability: no information Inclusion criteria: outpatients with schizophrenia-related psychotic disorders under remitted states Exclusion criteria: no information Setting: outpatient N: no information Gender: no information Age in years: no information

Liu 2018 *(Continued)*

	Continuation arm: participants total: no information, participants male: no information, participants female: no information, age in years: no information; PANSS total: no information, duration ill in years: no information, weight baseline in kg: no information, height in cm: no information, BMI: no information, average time in study in days: no information Reduction arm: participants total: no information, participants male: no information, participants female: no information, age in years: no information; PANSS total: no information, duration ill in years: no information, weight baseline in kg: no information, height in cm: no information, BMI: no information, average time in study in days: no information
Interventions	1. Continuation. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: no information 2. Reduction. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: flexible (participants in the GDR will reduce no more than 25% of their current dose of antipsychotics and be closely monitored every 4 weeks for at least 24 weeks before next dose reduction adjustment) Degree of antipsychotic dose reduction: up to 25% of baseline dose Speed of antipsychotic dose reduction: gradual
Outcomes	Planned: • Number of participants with relapse/exacerbations of psychosis • Personal social performance • Mental state - general (GCI and PANSS) • Quality of life • Drug adherence • Drug-related adverse reactions • Medication satisfaction • Neurocognitive functioning
Starting date	Not available
Contact information	Not available
Identification	Sponsorship source: not available Country: Taiwan Trial registration ID: not available Number of countries: 1 Publication year: 2018
Notes	

NCT03559426

Study name	Research into antipsychotic discontinuation and reduction trial

NCT03559426 *(Continued)*

Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes Compliance measured: yes (by using Medication Adherence Rating Scale) Study phases: no information Duration in weeks: 104 Number of study arms: 2 Number of drugs used: no information Randomisation assumed from double-blind: no Type of blinding: single-blind Type of data analysis for overall efficacy: no information Use of prophylactic medication: no information Number of sites: no information
Participants	Diagnosis: schizophrenia, schizoaffective disorder, delusional disorder or other non-affective psychosis; diagnostic criteria: ICD-10 Current clinical state: partial remission Definition of stability: no information Inclusion criteria: aged 18 years or older; a clinical and/or ICD-10 diagnosis of schizophrenia, schizoaffective disorder, delusional disorder or other non-affective psychosis; more than 1 previous episode or psychotic exacerbation, or a single episode lasting more than 1 year; prescribed continuing antipsychotic medication Exclusion criteria: lack of capacity to consent to the trial; insufficient command of spoken English to understand trial procedures; subject to a section of the Mental Health Act that includes a requirement to take antipsychotic medication; clinician considers there will be a serious risk of harm to self or others; admitted to hospital or treated by a Home Treatment or Crisis Team within the last month; women who have a confirmed pregnancy; women who are breastfeeding; involvement in another Investigational Medicinal Product (IMP) trial Setting: outpatient
Interventions	1. Continuation. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: flexible (participants randomised to maintenance treatment are requested not to make major reductions in their dose of antipsychotic medication during the trial period. Increases in dose are permitted within the protocol, as are changes to a different antipsychotic agent at the same equivalent dose and minor dose reductions to address side effects.) 2. Reduction. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: flexible (the dose is reduced incrementally every 1 or 2 months, focusing on 1 drug at a time where participants are taking more than 1 antipsychotic. The rate of reduction varies according to baseline dose, with most schedules aiming for discontinuation within 12 months, but some lasting longer where baseline doses are high. Treating psychiatrists are asked to see the participants who have been randomised to antipsychotic reduction approximately every

NCT03559426 *(Continued)*

	2 months for the duration of the reduction, to adjust the medication regimen and monitor mental state. Participants are provided the option to discontinue antipsychotic medication completely if the reduction progresses well, or to reduce to a very low dose, defined as the equivalent of 2 mg of haloperidol a day or less, which is lower than the minimum recommended therapeutic dose for most antipsychotics.) Degree of antipsychotic dose reduction: up to 100% Speed of antipsychotic dose reduction: gradual
Outcomes	Planned: • Social Functioning Scale (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Positive and Negative Syndrome Scale (PANSS) (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Modified Glasgow Antipsychotics Side-Effects Scale (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Client Satisfaction Questionnaire (assessing change over time) (CSQ 8) [Time Frame: baseline, 6 months, 12 months, 24 months] • Manchester Short Assessment of Quality of Life (assessing change over time) (MANSA) [Time Frame: baseline, 6 months, 12 months, 24 months] • Digit Span (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • Digit Symbol Coding (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • Rey Auditory Verbal Learning (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • Trail Making Test (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • Verbal Fluency (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • Medication Adherence Rating Scale (MARS-5) (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Relapse Questionnaire (assessing change over time) [Time Frame: 6 months, 12 months, 24 months] • Serious adverse events (assessing change over time) [Time Frame: 6 months, 12 months, 24 months] • EQ-5D-5L (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • ICECAP-A (ICEpop CAPability measure for Adults) (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Client Service Receipt Inventory (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Work Productivity and Activity Questionnaire (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • Schedule for Economic Data from Patient Records [Time Frame: 24 months] • Questionnaire about the Process of Recovery (assessing change over time) • Arizona Sexual Experiences Scale (assessing change over time) [Time Frame: baseline, 6 months, 12 months, 24 months] • The Ambiguous Intentions and Hostility Questionnaire (assessing change over time) (AIHQ) [Time Frame: baseline, 12 months, 24 months] • Hinting Task (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • Bell and Lysaker Emotion Recognition Test (assessing change over time) (BLERT) [Time Frame: baseline, 12 months, 24 months] • The Empathy Quotient (assessing change over time) (EQ) [Time Frame: baseline, 12 months, 24 months] • Trait Emotional Intelligence - Short Form (assessing change over time) [Time Frame: baseline, 12 months, 24 months] • SAT- MC/SAT- MC II (assessing change over time) [Time Frame: baseline, 12 months, 24 months]

NCT03559426 *(Continued)*

Starting date	24 March 2016
Contact information	Professor Joanna Moncrieff; j.moncrieff@ucl.ac.uk
Identification	Sponsorship source: public (Priment Clinical Trials Unit, University College London (Sponsor's reference number: 15/0947); NIHR grant: RP-PG-0514-20004) Country: UK Trial registration ID: NCT03559426 Number of countries: 1 Publication year: 2019
Notes	

NCT03593213

Study name	Clinical trial evaluating the efficacy, safety, and tolerability of cariprazine in a dose-reduction paradigm in the prevention of relapse in participants with schizophrenia
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information Study phases: no information Duration in weeks: 44 Number of study arms: 3 (2 relevant for the review) Number of drugs used: cariprazine Randomisation assumed from double-blind: no Type of blinding: double-blind (participant, care provider) Type of data analysis for overall efficacy: no information Use of prophylactic medication: no information Number of sites: no information
Participants	Diagnosis: schizophrenia; diagnostic criteria: DSM-5 Current clinical state: partial remission Definition of stability: no information Inclusion criteria: diagnosis of schizophrenia for a minimum of 1 year before Visit 1; ability to follow study instructions, complete study assessment tools with minimal assistance and no alteration to the assessment tools, and likely to complete all required visits; patient meets DSM-5 criteria for schizophrenia as determined by SCID-5; PANSS total score ≥ 70 and ≤ 120 at Visit 1 and Visit 2; rating of at least 4 (moderate) on at least 2 of the following PANSS positive symptoms: (P1) delusions, (P2) conceptual disorganisation, (P3) hallucinatory behaviour, (P6) suspiciousness/persecution at Visit 1 and Visit 2

NCT03593213 *(Continued)*

	Exclusion criteria: currently meeting DSM-5 criteria for any of the following: schizoaffective disorder, schizophreniform disorder, and other psychotic disorders bipolar I and II disorder autism spectrum disorder, intellectual development disorder, delirium, major/minor neurocognitive disorder; history of meeting DSM-5 criteria for substance-related disorders (excluding caffeine-related and tobacco-related disorders) within the prior 3 months before Visit 1; prior participation in any clinical trials involving experimental or investigational drugs within 6 months before Visit 1 or planned during the study; female patients who are pregnant, planning to become pregnant during the course of the study, or who are currently lactating Setting: no information
Interventions	1. Continuation. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: no information 2. Reduction. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: no information Degree of antipsychotic dose reduction: 33% Speed of antipsychotic dose reduction: no information
Outcomes	Planned: Time to first relapse during double-blind treatment period [Time Frame: randomisation (Week 18) to end of treatment (Week 44)]
Starting date	30 July 2018
Contact information	Not available
Identification	Sponsorship source: public (Bulgarian Drug Agency) Country: UK Trial registration ID: NCT03593213; EUCTR2017-000818-34 Number of countries: 1
Notes	

Weller 2018

Study name	Does antipsychotic dose reduction in combination with evidence-based intensive recovery treatment (EBIRT) lead to better functional recovery in first episode psychosis: a randomised controlled trial
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: no information Compliance measured: no information

Weller 2018 *(Continued)*

	Study phases: description study interventions/groups: Evidence-Based Intensive Recovery Treatment (EBIRT) combines Individual Placement and Support (IPS) for vocational recovery and CBT for Relapse Prevention, 6 phases of EBIRT intervention: 1) initiation of vocational intervention; 2) formulation and agenda setting; 3) vocational goal setting; 4) engagement and assessment for recovery; 5) psychoeducation with a focus on relapse; and 6) early warning signs and relapse planning, additional optional modules. DRS+: dose reduction strategy with EBIRT groups; AMTx+: antipsychotic maintenance treatment with EBIRT groups Duration in weeks: 12 (104 months follow-up) Number of study arms: 2 Number of drugs used: no information Randomisation assumed from double-blind: no Type of blinding: single-blind Type of data analysis for overall efficacy: ITT Use of prophylactic medication: no information Number of sites: 1 (zero academic sites)
Participants	Diagnosis: first episode of psychotic disorder or mood disorder with psychotic features; diagnostic criteria: DSM-5 Current clinical state: remission Definition of stability: ≥ 3 months of remission on positive symptoms of psychosis in the first year of antipsychotic treatment (participants must currently be taking their prescribed antipsychotic medication) at EPPIC (a score of ≤ 3 (mild) on the hallucinations, unusual thought disorder, conceptual disorganisation, and suspiciousness subscale items of the BPRS for the past 2 weeks and a score ≤ 3 on the hallucinations, unusual thought content, conceptual disorganisation, and suspiciousness subscales of the BRPS for the past 3 months based on a systematic clinical file review and collateral information collected from the participant's treating team in EPPIC) Inclusion criteria: current client of EPPIC; a confirmed diagnosis of first episode of a DSM-5 (American Psychiatric Association, 2013) psychotic disorder or mood disorder with psychotic features (American Psychiatric Association, 2013; First, Karg, & Spitzer, 2015); aged 15 to 25 years (inclusive); ≥ 3 months of remission on positive symptoms of psychosis in the first year of antipsychotic treatment (participants must currently be taking their prescribed antipsychotic medication) at EPPIC (a score of ≤ 3 (mild) on the hallucinations, unusual thought disorder, conceptual disorganisation, and suspiciousness subscale items of the BPRS (Ventura et al, 1993) for the past 2 weeks and a score ≤ 3 on the hallucinations, unusual thought content, conceptual disorganisation, and suspiciousness subscales of the BRPS (Ventura et al, 1993) for the past 3 months based on a systematic clinical file review and collateral information collected from the patient's treating team in EPPIC (as needed)); low suicidality defined as a score of 4 or below on the BPRS (Ventura et al, 1993) sustained for the past 1-month period prior to baseline; the young person is willing for a caregiver to be informed about the study and will have at least weekly contact with their caregiver; ability to provide written informed consent Exclusion criteria: a documented history of an intellectual disability or IQ < 70; inability to converse in or read English; women who are currently pregnant or breastfeeding; neurological disorder (illness of the brain, nerves, or spinal cord which could not better explain the presence of psychosis) Setting: outpatient
Interventions	1. Continuation. N (no information) Antipsychotics used: no information. Mean dose: (SD; range), application: oral Description dose scheme: flexible (a gradual dose reduction of their antipsychotic medication at their next medical review after randomisation. Medication will be tapered under close medical su-

Weller 2018 *(Continued)*

	pervision over 3 months after allocation to the DRS group to minimise the risk of relapse due to abrupt discontinuation. The rate of tapering will be a 25% dose reduction (or as near to 25% as the medication allows) of the pre-reduction dose every month for 3 months, until the participant reduces a dose that is considered clinically safe, whereby some participants will completely cease taking the antipsychotic medication.) 2. Reduction. N (no information) Antipsychotics used: no information. Mean dose: no information, application: oral Description dose scheme: flexible (participants will be prescribed medication as clinically indicated, concordant with the Australian Clinical Practice Guidelines for first episode psychosis. These guidelines recommend the use of the lowest effective dose of atypical antipsychotics.) Degree of antipsychotic dose reduction: up to 75% of the pre-reduction dose Speed of antipsychotic dose reduction: gradual
Outcomes	Planned: • Social and occupational functioning assessed using the Social and Occupational Functioning Scale (SOFAS) [24 months] • Physical health is a composite secondary outcome and will be measured by clinical blood analysis evaluating glucose, haemoglobin A1C, and lipid levels in the treatment groups only. Blood pressure, weight, height, and waist circumference will also be recorded [24 months] • Brain volumes/activity is a composite secondary outcome. Brain volume will be quantified in both treatment groups and healthy controls by high-resolution magnetic resonance imaging (MRI). In addition to structural MRI imaging, functional resting state will also be performed [24 months] • Remission and relapse rates of positive symptoms is a composite secondary outcome and will be assessed using the Brief Psychiatric Rating Scale (exBPRS) in treatment groups only. Remission of negative symptoms will be assessed using the Scale for Assessment of Negative Symptoms (SANS) [24 months] • Cognitive functioning will assessed with neurocognitive tests (including the Brief Assessment of Cognition in Schizophrenia (BACS) will be used to assess neuropsychological functioning in all groups [24 months]
Starting date	20 June 2017
Contact information	Professor Eoin Killackey; eoin.killackey@orygen.org.au
Identification	Sponsorship source: Ronald Philip Griffiths Fellowship; Fellowship from the McCusker Charitable Foundation; NHMRC Senior Research Fellowship, Grant/Award Number: ID Number 1137687; Career Development Fellowship, Grant/Award Number: APP1082934; BB & A Miller Foundation; NHMRC CDF II Fellowship, Grant/Award Number: APP1051891; National Health and Medical Research Council (NHMRC) Project grant, Grant/Award Number: 1102394 Country: Australia Trial registration ID: ACTRN12617000870358 Number of countries: 1 Publication year: 2018
Notes	

BMI: body mass index
BPRS: Brief Psychiatric Rating Scale
CBT: cognitive behavioural therapy
CGI: Clinical Global Impression scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

GDR: guided dose reduction group
HDL: high-density lipoprotein
ICD-10: International Classification of Diseases, 10th Revision
IQ: intelligent quotient
ITT: intention to treat
LAI: long-acting injection
LDL: low-density lipoprotein
MRI: magnetic resonance imaging
NIHR: National Institute for Health and Care Research
PANSS: Positive and Negative Symptoms Scale
SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
SD: standard deviation
TMS: transcranial magnetic stimulation
SGA: second-generation antipsychotic drugs

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 Service use - readmission to hospital (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 Combined time points						
Carpenter 1999	~	✓	✓	✓	~	~
Faraone 1989	~	✓	✓	✓	~	~
Fleischhacker 2014	✓	✓	✓	✓	✓	✓
Huhn 2020	✓	~	✓	✓	✓	~
Kane 1983	~	✓	✓	✓	~	~
Kane 2010	✓	✓	✓	✓	✓	✓
Remington 2011	~	✓	✓	✓	✗	✗
Rouillon 2008	~	✗	✓	✓	~	✗
Schooler 1997	~	✓	✓	~	~	~

Risk of bias for analysis 1.3 Adverse effect - leaving the study early due to adverse effects - overall tolerability (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 Combined time points						
Fleischhacker 2014	✓	✓	✓	✓	✓	✓
Huhn 2020	✓	~	✓	✓	✓	~
Kane 2010	✓	✓	✓	✓	✓	✓
Ozawa 2019	✓	~	✓	✓	✓	~
Remington 2011	~	✓	✓	✓	✓	~
Rouillon 2008	~	✗	✓	✓	✓	✗
Takeuchi 2014	✓	~	✓	✓	✓	~
Volavka 2000	~	✓	✓	✓	✓	~
Wunderink 2007	✓	~	✓	✓	✓	~
Zhou 2018	~	~	✓	✓	✓	~

Risk of bias for analysis 1.13 Quality of life - mean change/endpoint all available scales (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.13.1 Quality of life - combined scales and time points						
Carpenter 1999	~	✓	✓	✓	~	~
Huhn 2020	✓	~	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Kane 2010	✓	✓	✗	✓	✓	✗
Rouillon 2008	~	✗	✓	✗	~	✗
Takeuchi 2014	✓	~	✓	✗	✓	✗
Wunderink 2007	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.22 Functioning - mean endpoint/change all available scales (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.22.1 Functioning - combined scales and time points						
Carpenter 1999	~	✓	✓	✓	~	~
Fleischhacker 2014	✓	✓	✓	✓	~	~
Huhn 2020	✓	~	✓	✓	✓	~
Kane 2010	✓	✓	✓	✓	✓	✓
Ozawa 2019	✓	~	✓	✓	~	~
Wunderink 2007	✓	~	✓	✓	✓	~

Risk of bias for analysis 1.24 Global state - number of participants with relapse/exacerbations of psychosis (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Branchey 1981	✗	✓	✓	~	~	✗
Caffey 1964	~	~	✗	✗	~	✗
Carpenter 1999	~	✓	✓	✓	~	~
Cookson 1987	~	✓	✓	~	~	~
Faraone 1989	~	✓	✓	~	~	~
Fleischhacker 2014	✓	✓	✓	✓	✓	✓
Hogarty 1988	✗	✓	✓	✓	~	✗
Huhn 2020	✓	~	✓	✓	✓	~
Johnson 1987	✓	✓	✓	✓	~	~
Kane 1983	~	✓	✓	~	✓	~
Kane 2010	✓	✓	✓	✓	✓	✓
Lonowski 1978	~	~	✓	✓	~	~
Ozawa 2019	✓	~	✓	✓	✗	✗
Remington 2011	~	✓	✓	✓	✗	✗
Rouillon 2008	~	✗	✓	✓	~	✗
Schooler 1997	~	✓	✓	~	~	~
Takeuchi 2014	✓	~	✓	✗	~	✗
Wang 2010	~	✓	✓	✗	✓	✗

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wunderink 2007	✓	~	✓	✓	✓	~
Zhou 2018	~	~	✓	✓	~	~

Risk of bias for analysis 1.36 Leaving the study early - for any reason - overall acceptability (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.36.1 Combined time points						
Carpenter 1999	~	✓	✓	✓	✓	~
Fleischhacker 2014	✓	✓	✓	✓	✓	✓
Hogarty 1988	✗	✓	✓	✓	✓	✗
Huhn 2020	✓	~	✓	✓	✓	~
Kane 1983	~	✓	✓	✓	~	~
Kane 2010	✓	✓	✓	✓	✓	✓
Ozawa 2019	✓	~	✓	✓	✓	~
Rouillon 2008	~	~	✓	✓	✓	~
Takeuchi 2014	✓	~	✓	✓	✓	~
Volavka 2000	~	✓	✓	✓	✓	~
Wunderink 2007	✓	~	✓	✓	✓	~
Zhou 2018	~	~	✓	✓	✓	~

Risk of bias for analysis 1.77 Adverse effects - number of participants with at least 1 adverse effect (combined time points)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Cookson 1987	~	✓	✓	~	~	~
Fleischhacker 2014	✓	✓	✓	✓	✓	✓
Huhn 2020	✓	~	✓	✓	✓	~
Kane 2010	✓	✓	✓	✓	✓	✓
Rouillon 2008	~	✗	✓	✗	~	✗

DATA AND ANALYSES

Comparison 1. Dose reduction versus dose maintenance

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Service use - readmission to hospital (combined time points)	9	1433	Risk Ratio (IV, Random, 95% CI)	1.53 [0.84, 2.81]
1.1.1 Combined time points	9	1433	Risk Ratio (IV, Random, 95% CI)	1.53 [0.84, 2.81]
1.2 Service use - readmission to hospital (separated time points)	9		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.2.1 < 3 months	3	583	Risk Ratio (IV, Random, 95% CI)	3.05 [1.46, 6.34]
1.2.2 < 6 months	5	647	Risk Ratio (IV, Random, 95% CI)	2.06 [0.88, 4.83]
1.2.3 < 1 year	3	573	Risk Ratio (IV, Random, 95% CI)	1.46 [0.24, 9.05]
1.2.4 > 1 year	1	213	Risk Ratio (IV, Random, 95% CI)	1.01 [0.64, 1.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.3 Adverse effect - leaving the study early due to adverse effects - overall tolerability (combined time points)	10	1340	Risk Ratio (IV, Random, 95% CI)	2.20 [1.39, 3.49]
1.3.1 Combined time points	10	1340	Risk Ratio (IV, Random, 95% CI)	2.20 [1.39, 3.49]
1.4 Adverse effect - leaving the study early due to adverse effects - overall tolerability (separated time points)	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.4.1 < 3 months	6	319	Risk Ratio (IV, Random, 95% CI)	1.06 [0.12, 9.60]
1.4.2 < 6 months	8	882	Risk Ratio (IV, Random, 95% CI)	1.86 [0.80, 4.33]
1.4.3 < 1 year	5	699	Risk Ratio (IV, Random, 95% CI)	2.38 [1.39, 4.09]
1.4.4 > 1 year	1	131	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.5 Quality of life - mean change score EQ-5D	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.5.1 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	0.01 [-0.06, 0.09]
1.6 Quality of life - mean change score S-QoL	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.6.1 < 6 months	1	97	Mean Difference (IV, Fixed, 95% CI)	-2.60 [-9.15, 3.95]
1.7 Quality of life - mean endpoint WHOQOL-BREF	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.7.1 < 1 year	1	128	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-4.62, 4.22]
1.7.2 > 1 year	1	128	Mean Difference (IV, Fixed, 95% CI)	0.90 [-3.59, 5.39]
1.8 Quality of life - mean endpoint QLS (Heinrich)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.8.1 < 1 year	1	50	Mean Difference (IV, Fixed, 95% CI)	2.68 [-8.42, 13.78]
1.9 Quality of life - mean change QLS total (Heinrich)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.9.1 < 6 months	1	364	Mean Difference (IV, Random, 95% CI)	0.30 [-2.95, 3.55]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10 Quality of life - mean endpoint SWNS	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.10.1 < 3 months	1	19	Mean Difference (IV, Fixed, 95% CI)	-6.03 [-14.71, 2.65]
1.10.2 < 6 months	1	19	Mean Difference (IV, Fixed, 95% CI)	0.44 [-8.19, 9.07]
1.11 Quality of life - mean change SWNS	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.11.1 < 3 months	1	16	Mean Difference (IV, Random, 95% CI)	-3.12 [-12.69, 6.44]
1.11.2 < 6 months	1	16	Mean Difference (IV, Random, 95% CI)	2.25 [-11.43, 15.93]
1.11.3 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	-0.10 [-4.58, 4.38]
1.12 Quality of life - mean change/ endpoint SWNS	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.12.1 < 3 months	1	19	Mean Difference (IV, Random, 95% CI)	-6.03 [-14.71, 2.65]
1.12.2 < 6 months	1	19	Mean Difference (IV, Random, 95% CI)	0.44 [-8.19, 9.07]
1.12.3 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	-0.10 [-4.58, 4.38]
1.13 Quality of life - mean change/ endpoint all available scales (combined time points)	6	719	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.17, 0.15]
1.13.1 Quality of life - combined scales and time points	6	719	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.17, 0.15]
1.14 Quality of life - mean change/ endpoint all available scales (separated time points)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.14.1 Quality of life - combined scales (< 3 months)	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.59 [-1.52, 0.35]
1.14.2 Quality of life - combined scales (< 6 months)	3	480	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.23, 0.18]
1.14.3 Quality of life - combined scales (< 1 year)	3	239	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.24, 0.27]
1.14.4 Quality of life - combined scales (> 1 year)	1	128	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.28, 0.42]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.15 Functioning - mean endpoint GSDS	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.15.1 < 1 year	1	128	Mean Difference (IV, Random, 95% CI)	0.10 [-1.32, 1.52]
1.15.2 > 1 year	1	128	Mean Difference (IV, Random, 95% CI)	-0.60 [-2.11, 0.91]
1.16 Functioning - mean endpoint GAF	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.16.1 < 1 year	1	35	Mean Difference (IV, Random, 95% CI)	1.70 [-6.13, 9.53]
1.17 Functioning - mean change GAF	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.17.1 < 1 year	1	35	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.51, 0.31]
1.18 Functioning - mean change PSP	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.18.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	4.49 [-3.27, 12.25]
1.18.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	10.38 [-0.52, 21.28]
1.18.3 < 1 year	1	364	Mean Difference (IV, Random, 95% CI)	2.47 [-0.04, 4.98]
1.19 Functioning - mean endpoint PSP	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.19.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	-3.03 [-12.73, 6.67]
1.19.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	2.85 [-6.53, 12.23]
1.19.3 < 1 year	1	364	Mean Difference (IV, Random, 95% CI)	2.20 [-1.23, 5.63]
1.20 Functioning - mean endpoint SCLoF	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.20.1 < 6 months	1	50	Mean Difference (IV, Random, 95% CI)	-0.18 [-4.06, 3.70]
1.20.2 < 12 months	1	50	Mean Difference (IV, Random, 95% CI)	-2.35 [-6.23, 1.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.21 Functioning - mean change SF-36 mental component summary	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.21.1 < 6 months	1	369	Mean Difference (IV, Random, 95% CI)	-0.61 [-3.07, 1.85]
1.22 Functioning - mean end-point/change all available scales (combined time points)	6	966	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.10, 0.17]
1.22.1 Functioning - combined scales and time points	6	966	Std. Mean Difference (IV, Random, 95% CI)	0.03 [-0.10, 0.17]
1.23 Functioning - mean end-point/change all available scales (separated time points)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.23.1 Functioning - combined scales (< 3 months)	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-1.14, 0.63]
1.23.2 Functioning - combined scales (< 6 months)	3	439	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.25, 0.17]
1.23.3 Functioning - combined scales (< 1 year)	4	577	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.09, 0.25]
1.23.4 Functioning - combined scales (> 1 year)	1	128	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.48, 0.21]
1.24 Global state - number of participants with relapse/exacerbations of psychosis (combined time points)	20	2481	Risk Ratio (IV, Random, 95% CI)	2.16 [1.52, 3.06]
1.25 Global state - number of participants with relapse/exacerbations of psychosis (separated time points)	20		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.25.1 < 3 months	12	1947	Risk Ratio (IV, Random, 95% CI)	2.56 [1.37, 4.78]
1.25.2 < 6 months	15	2224	Risk Ratio (IV, Random, 95% CI)	2.37 [1.54, 3.67]
1.25.3 < 1 year	13	1608	Risk Ratio (IV, Random, 95% CI)	2.31 [1.63, 3.27]
1.25.4 > 1 year	4	474	Risk Ratio (IV, Random, 95% CI)	1.68 [1.29, 2.20]
1.26 Global state - remission	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.26.1 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.82 [0.61, 1.09]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.27 Global state - number of participants with clinically important change in global state	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.27.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	4.17 [0.23, 77.11]
1.27.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	4.17 [0.23, 77.11]
1.28 Global state - mean endpoint CGI-S (high = poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.28.1 < 3 months	2	46	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.86, 0.07]
1.28.2 < 6 months	2	46	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.84, 0.14]
1.29 Global state - mean change CGI-S (high = poor)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.29.1 < 3 months	2	485	Mean Difference (IV, Random, 95% CI)	0.10 [-0.33, 0.53]
1.29.2 < 6 months	2	485	Mean Difference (IV, Random, 95% CI)	0.20 [-0.34, 0.74]
1.29.3 < 1 year	3	488	Mean Difference (IV, Random, 95% CI)	0.03 [-0.21, 0.27]
1.30 Global state - mean endpoint/change CGI-S (high = poor) (combined time points)	6	999	Mean Difference (IV, Random, 95% CI)	0.05 [-0.18, 0.28]
1.31 Global state - mean endpoint/change CGI-S (high = poor) (separated time points)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.31.1 < 3 months	3	511	Std. Mean Difference (IV, Random, 95% CI)	-0.11 [-0.75, 0.52]
1.31.2 < 6 months	3	511	Std. Mean Difference (IV, Random, 95% CI)	-0.02 [-0.71, 0.66]
1.31.3 < 1 year	3	488	Std. Mean Difference (IV, Random, 95% CI)	0.04 [-0.30, 0.37]
1.32 Global state - mean endpoint CGI-I (high = poor) (combined time points)	3	881	Mean Difference (IV, Random, 95% CI)	0.19 [-0.47, 0.85]
1.33 Global state - mean endpoint CGI-I (high = poor) (separated time points)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.33.1 < 3 months	2	484	Mean Difference (IV, Random, 95% CI)	0.07 [-1.07, 1.20]
1.33.2 < 6 months	2	484	Mean Difference (IV, Random, 95% CI)	-0.04 [-1.75, 1.68]
1.33.3 < 1 year	1	397	Mean Difference (IV, Random, 95% CI)	0.36 [0.09, 0.63]
1.34 Global state - mean change IAQ-12 (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.34.1 < 1 year	1	397	Mean Difference (IV, Random, 95% CI)	1.69 [0.47, 2.91]
1.35 Global state - mean endpoint SCL-90 (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.35.1 < 3 months	1	39	Mean Difference (IV, Random, 95% CI)	-0.38 [-0.61, -0.15]
1.35.2 < 6 months	1	39	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.80, -0.24]
1.35.3 < 1 year	1	39	Mean Difference (IV, Random, 95% CI)	-0.59 [-0.91, -0.27]
1.36 Leaving the study early - for any reason - overall acceptability (combined time points)	12	1551	Risk Ratio (IV, Random, 95% CI)	1.38 [1.05, 1.81]
1.36.1 Combined time points	12	1551	Risk Ratio (IV, Random, 95% CI)	1.38 [1.05, 1.81]
1.37 Leaving the study early - for any reason - overall acceptability (separated time points)	12		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.37.1 < 3 months	6	1067	Risk Ratio (IV, Random, 95% CI)	1.53 [1.01, 2.31]
1.37.2 < 6 months	6	767	Risk Ratio (IV, Random, 95% CI)	1.76 [1.27, 2.44]
1.37.3 < 1 year	7	814	Risk Ratio (IV, Random, 95% CI)	1.47 [1.23, 1.76]
1.37.4 > 1 year	2	201	Risk Ratio (IV, Random, 95% CI)	1.68 [0.19, 14.76]
1.38 Leaving the study early - due to inefficacy - overall efficacy (combined time points)	10	1322	Risk Ratio (IV, Random, 95% CI)	2.06 [1.21, 3.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.39 Leaving the study early - due to inefficacy - overall efficacy (separated time points)	10		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.39.1 < 3 months	5	288	Risk Ratio (IV, Random, 95% CI)	0.94 [0.28, 3.12]
1.39.2 < 6 months	5	687	Risk Ratio (IV, Random, 95% CI)	3.48 [2.29, 5.30]
1.39.3 < 1 year	5	699	Risk Ratio (IV, Random, 95% CI)	1.78 [0.68, 4.66]
1.39.4 > 1 year	1	131	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.40 Mental state - general: number of participants with clinically important change in general mental state (combined time points)	2	417	Risk Ratio (IV, Random, 95% CI)	0.84 [0.75, 0.94]
1.40.1 < 1 year	2	417	Risk Ratio (IV, Random, 95% CI)	0.84 [0.75, 0.94]
1.41 Mental state - general: number of participants with clinically important change in general mental state (separated time points)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.41.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.41.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.41.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.84 [0.75, 0.94]
1.42 Mental state - general: mean endpoint BPRS total (high = poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.42.1 < 3 months	1	26	Mean Difference (IV, Random, 95% CI)	0.80 [-2.93, 4.53]
1.42.2 < 6 months	2	76	Mean Difference (IV, Random, 95% CI)	-0.63 [-3.82, 2.55]
1.42.3 < 1 year	1	50	Mean Difference (IV, Random, 95% CI)	-0.60 [-4.48, 3.28]
1.43 Mental state - general: mean change BPRS total (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.43.1 < 3 months	1	466	Mean Difference (IV, Random, 95% CI)	4.03 [2.11, 5.95]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.43.2 < 6 months	1	466	Mean Difference (IV, Random, 95% CI)	5.70 [3.59, 7.81]
1.44 Mental state - general: mean endpoint PANSS total (high = poor)	7		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.44.1 < 3 months	4	901	Mean Difference (IV, Random, 95% CI)	2.37 [-2.90, 7.65]
1.44.2 < 6 months	4	901	Mean Difference (IV, Random, 95% CI)	1.38 [-6.66, 9.42]
1.44.3 < 1 year	5	975	Mean Difference (IV, Random, 95% CI)	-1.25 [-5.44, 2.93]
1.44.4 > 1 year	1	128	Mean Difference (IV, Random, 95% CI)	-1.20 [-4.64, 2.24]
1.45 Mental state - general: mean change PANSS total (high = poor)	8		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.45.1 < 3 months	4	906	Mean Difference (IV, Random, 95% CI)	-0.21 [-6.17, 5.75]
1.45.2 < 6 months	4	980	Mean Difference (IV, Random, 95% CI)	2.50 [-3.46, 8.46]
1.45.3 < 1 year	4	833	Mean Difference (IV, Random, 95% CI)	1.94 [-0.15, 4.02]
1.46 Mental state - general: mean endpoint/change overall symptom scales (PANSS/BPRS) (high = poor) (combined time points)	12	1718	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.24, 0.27]
1.47 Mental state - general: mean endpoint/change overall symptom scales (PANSS/BPRS) (high = poor) (separated time points)	12		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.47.1 < 3 months	7	1347	Std. Mean Difference (IV, Random, 95% CI)	0.14 [-0.11, 0.40]
1.47.2 < 6 months	8	1471	Std. Mean Difference (IV, Random, 95% CI)	0.06 [-0.24, 0.37]
1.47.3 < 1 year	7	1086	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.36, 0.24]
1.47.4 > 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.47, 0.23]
1.48 Mental state - specific: mean endpoint PANSS positive (high = poor)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.48.1 < 3 months	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.86, 0.33]
1.48.2 < 6 months	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.64, 0.17]
1.48.3 < 1 year	4	635	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.26, 0.06]
1.48.4 > 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.30, 0.40]
1.49 Mental state - specific: mean change PANSS positive (high = poor)	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.49.1 < 3 months	3	509	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.70, 0.74]
1.49.2 < 6 months	3	583	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.32, 0.86]
1.49.3 < 1 year	4	833	Std. Mean Difference (IV, Random, 95% CI)	0.24 [0.10, 0.39]
1.50 Mental state - specific: mean endpoint/change positive symptoms (PANSS positive) (high = poor) (combined time points)	10	1337	Std. Mean Difference (IV, Random, 95% CI)	0.07 [-0.22, 0.35]
1.51 Mental state - specific: mean endpoint/change positive symptoms (PANSS positive) (high = poor) (separated time points)	10		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.51.1 < 3 months	4	584	Std. Mean Difference (IV, Random, 95% CI)	0.01 [-0.51, 0.53]
1.51.2 < 6 months	4	658	Std. Mean Difference (IV, Random, 95% CI)	0.10 [-0.45, 0.66]
1.51.3 < 1 year	6	731	Std. Mean Difference (IV, Random, 95% CI)	-0.05 [-0.20, 0.10]
1.51.4 > 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.30, 0.40]
1.52 Mental state - specific: mean endpoint PANSS negative (high = poor)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.52.1 < 3 months	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.75, 0.06]
1.52.2 < 6 months	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.92 [-1.70, -0.13]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.52.3 < 1 year	4	635	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.74, 0.22]
1.52.4 > 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.56, 0.14]
1.53 Mental state - specific: mean change PANSS negative (high = poor)	8		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.53.1 < 3 months	3	509	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-1.26, 0.57]
1.53.2 < 6 months	3	583	Std. Mean Difference (IV, Random, 95% CI)	0.05 [-0.45, 0.54]
1.53.3 < 1 year	4	833	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.32, 0.21]
1.54 Mental state - specific: mean endpoint/change negative symptoms (PANSS negative) (high = poor) (combined time points)	9	1302	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.49, 0.12]
1.55 Mental state - specific: mean endpoint/change negative symptoms (PANSS negative) (high = poor) (separated time points)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.55.1 < 3 months	4	584	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.64, 0.34]
1.55.2 < 6 months	4	658	Std. Mean Difference (IV, Random, 95% CI)	-0.29 [-1.04, 0.45]
1.55.3 < 1 year	5	696	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.71, 0.10]
1.55.4 > 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.56, 0.14]
1.56 Mental state - specific: mean endpoint NSA-16 (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.56.1 < 3 months	1	75	Mean Difference (IV, Random, 95% CI)	-4.80 [-9.72, 0.12]
1.56.2 < 6 months	1	75	Mean Difference (IV, Random, 95% CI)	-6.60 [-12.38, -0.82]
1.56.3 < 1 year	1	75	Mean Difference (IV, Random, 95% CI)	-10.10 [-14.87, -5.33]
1.57 Mental state - specific: mean change CDSS (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.57.1 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	-0.40 [-1.55, 0.75]
1.58 Mental state - specific: mean endpoint PANSS depression/anxiety (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.58.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	0.00 [-1.85, 1.85]
1.58.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	0.97 [-0.55, 2.49]
1.59 Mental state - specific: mean change PANSS depression/anxiety (high = poor)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.59.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	-0.55 [-2.41, 1.31]
1.59.2 < 6 months	2	117	Mean Difference (IV, Random, 95% CI)	0.49 [-0.45, 1.42]
1.59.3 < 1 year	2	737	Mean Difference (IV, Random, 95% CI)	0.26 [-0.08, 0.60]
1.60 Mental state - specific: mean endpoint/change depression (PANSS depression, CDSS) (combined time points)	5	915	Std. Mean Difference (IV, Random, 95% CI)	0.11 [-0.02, 0.25]
1.61 Mental state - specific: mean endpoint/change depression (PANSS depression, CDSS) (separated time points)	5		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.61.1 < 3 months	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.88, 0.88]
1.61.2 < 6 months	2	117	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.12, 0.61]
1.61.3 < 1 year	3	798	Std. Mean Difference (IV, Random, 95% CI)	0.09 [-0.06, 0.23]
1.62 Mental state - specific: mean change POMS-SF (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.62.1 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	3.60 [-1.68, 8.88]
1.63 Mental state - specific: mean change SAI (high = good)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.63.1 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	-0.10 [-2.62, 2.42]
1.64 Behaviour - mean endpoint PANSS excitement/hostility (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.64.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	-1.62 [-2.98, -0.26]
1.64.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	-0.75 [-2.07, 0.57]
1.65 Behaviour - mean change PANSS excitement/hostility (high = poor)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.65.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	-1.62 [-3.05, -0.19]
1.65.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	-0.74 [-2.20, 0.72]
1.65.3 <1 year	2	737	Mean Difference (IV, Random, 95% CI)	0.40 [-0.07, 0.86]
1.66 Behaviour - mean end-point/change aggressive behaviour (PANSS excitement/hostility) (high = poor) (combined time points)	3	757	Mean Difference (IV, Random, 95% CI)	0.25 [-0.32, 0.82]
1.67 Behaviour - mean end-point/change aggressive behaviour (PANSS excitement/hostility) (high = poor) (separated time points)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.67.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	-1.62 [-2.98, -0.26]
1.67.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	-0.75 [-2.07, 0.57]
1.67.3 <1 year	2	737	Mean Difference (IV, Random, 95% CI)	0.40 [-0.07, 0.86]
1.68 Satisfaction with care - number of participants with clinically important change in satisfaction with care (PSMQ-Modified preference to current medication)	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.68.1 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.86 [0.77, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.69 Satisfaction with care - mean endpoint MARS (high = poor)	1	40	Mean Difference (IV, Fixed, 95% CI)	0.61 [-0.09, 1.31]
1.69.1 < 3 months	1	20	Mean Difference (IV, Fixed, 95% CI)	0.80 [-0.19, 1.79]
1.69.2 < 6 months	1	20	Mean Difference (IV, Fixed, 95% CI)	0.42 [-0.57, 1.41]
1.70 Satisfaction with care - mean change MARS (high = poor)	1	40	Mean Difference (IV, Random, 95% CI)	0.27 [-0.39, 0.93]
1.70.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	0.44 [-0.44, 1.32]
1.70.2 < 6 months	1	20	Mean Difference (IV, Random, 95% CI)	0.06 [-0.92, 1.04]
1.71 Satisfaction with care - mean change DAI-10 (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.71.1 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.83, 0.63]
1.72 Satisfaction with care - mean endpoint DAI-30 (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.72.1 < 1 year	1	359	Mean Difference (IV, Random, 95% CI)	-1.00 [-6.65, 4.65]
1.73 Satisfaction with care - mean change MAQ (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.73.1 < 1 year	1	346	Mean Difference (IV, Random, 95% CI)	-0.05 [-0.26, 0.16]
1.74 Satisfaction with care - mean endpoint MAQ (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.74.1 < 1 year	1	362	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.21, 0.19]
1.75 Satisfaction with care - mean endpoint/change adherence scales (MARS, DAI, MAQ) (high = poor) (combined time points)	3	440	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.26, 0.14]
1.76 Satisfaction with care - mean endpoint/change adherence scales (MARS, DAI, MAQ) (high = poor) (separated time points)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.76.1 < 3 months	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.68 [-0.23, 1.59]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.76.2 < 6 months	1	20	Std. Mean Difference (IV, Random, 95% CI)	0.36 [-0.53, 1.25]
1.76.3 < 1 year	2	420	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.29, 0.12]
1.77 Adverse effects - number of participants with at least 1 adverse effect (combined time points)	5	998	Risk Ratio (IV, Random, 95% CI)	1.03 [0.94, 1.12]
1.78 Adverse effects - number of participants with at least 1 adverse effect (separated time points)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.78.1 < 3 months	2	38	Risk Ratio (IV, Random, 95% CI)	0.92 [0.71, 1.19]
1.78.2 < 6 months	4	601	Risk Ratio (IV, Random, 95% CI)	1.06 [0.92, 1.23]
1.78.3 < 1 year	2	415	Risk Ratio (IV, Random, 95% CI)	1.01 [0.91, 1.12]
1.79 Adverse effects - number of participants with at least 1 serious adverse event (combined time points)	2	417	Risk Ratio (IV, Random, 95% CI)	1.49 [0.70, 3.15]
1.80 Adverse effects - number of participants with at least 1 serious adverse event (separated time points)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.80.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.80.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.80.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	1.49 [0.70, 3.15]
1.81 Adverse effects - mean endpoint/change adverse effect scales (LUNSERS, UKU) (high = poor) (combined time points)	2	147	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.34, 0.31]
1.82 Adverse effects - mean endpoint/change adverse effect scales (LUNSERS, UKU) (high = poor) (separated time points)	2		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.82.1 < 3 months	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-1.05, 0.76]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.82.2 < 6 months	1	19	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-1.02, 0.79]
1.82.3 < 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	0.00 [-0.35, 0.35]
1.82.4 > 1 year	1	128	Std. Mean Difference (IV, Random, 95% CI)	0.08 [-0.27, 0.42]
1.83 Adverse effects - mean endpoint LUNSERS (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.83.1 < 1 year	1	128	Mean Difference (IV, Random, 95% CI)	0.00 [-4.97, 4.97]
1.83.2 > 1 year	1	128	Mean Difference (IV, Random, 95% CI)	2.30 [-7.76, 12.36]
1.84 Adverse effects - mean endpoint UKU (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.84.1 < 3 months	1	19	Mean Difference (IV, Random, 95% CI)	-1.21 [-8.16, 5.74]
1.84.2 < 6 months	1	19	Mean Difference (IV, Random, 95% CI)	-1.08 [-9.24, 7.08]
1.85 Adverse effects - number of participants with clinically important weight gain (combined time points)	3	883	Risk Ratio (IV, Random, 95% CI)	0.39 [0.25, 0.61]
1.86 Adverse effects - number of participants with clinically important weight gain (separated time points)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.86.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.86.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.39 [0.22, 0.71]
1.86.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.38 [0.18, 0.78]
1.87 Adverse effects - mean endpoint/change weight (kg, %, BMI) (combined time points)	8	1175	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.50, 0.06]
1.88 Adverse effects - mean endpoint/change weight (kg) (combined time points)	6	1074	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.14, 0.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.89 Adverse effects - mean endpoint/change weight (kg) (separated time points)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.89.1 < 3 months	1	18	Mean Difference (IV, Random, 95% CI)	0.40 [-1.10, 1.90]
1.89.2 < 6 months	3	581	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.71, -0.29]
1.89.3 < 1 year	3	493	Mean Difference (IV, Random, 95% CI)	-0.03 [-2.80, 2.73]
1.90 Adverse effects - mean change weight (kg)	6		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.90.1 < 3 months	1	18	Mean Difference (IV, Random, 95% CI)	0.40 [-1.10, 1.90]
1.90.2 < 6 months	3	581	Mean Difference (IV, Random, 95% CI)	-1.50 [-2.71, -0.29]
1.90.3 < 1 year	3	493	Mean Difference (IV, Random, 95% CI)	-0.03 [-2.80, 2.73]
1.91 Adverse effects - mean weight endpoint (kg)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.91.1 < 3 months	1	19	Mean Difference (IV, Random, 95% CI)	13.58 [0.62, 26.54]
1.91.2 < 6 months	1	19	Mean Difference (IV, Random, 95% CI)	11.52 [-1.40, 24.45]
1.92 Adverse effects - weight change in % from baseline to endpoint	1	26	Mean Difference (IV, Random, 95% CI)	1.00 [-0.60, 2.60]
1.93 Adverse effects - mean endpoint BMI (kg/m^2)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.93.1 < 3 months	1	75	Mean Difference (IV, Random, 95% CI)	-2.30 [-4.66, 0.06]
1.93.2 < 6 months	1	75	Mean Difference (IV, Random, 95% CI)	-2.20 [-4.49, 0.09]
1.93.3 < 1 year	1	75	Mean Difference (IV, Random, 95% CI)	-3.20 [-5.29, -1.11]
1.94 Adverse effects - specific: number of participants that needed antiparkinsonian medication	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.94.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.94.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.94.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.79 [0.48, 1.31]
1.95 Adverse effects - specific: number of participants with at least 1 extrapyramidal symptom (combined time points)	2	417	Risk Ratio (IV, Random, 95% CI)	1.06 [0.63, 1.76]
1.96 Adverse effects - specific: number of participants with at least 1 extrapyramidal symptom (separated time points)	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.96.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.82 [0.34, 1.96]
1.96.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	1.09 [0.33, 3.66]
1.96.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	1.05 [0.60, 1.85]
1.97 Adverse effects - specific: number of participants with parkinsonism	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.97.1 < 6 months	1	466	Risk Ratio (IV, Random, 95% CI)	0.75 [0.08, 7.10]
1.97.2 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	1.29 [0.51, 3.26]
1.98 Adverse effects - specific: number of participants with rigidity	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.98.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.98.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.99 Adverse effects - specific: number of participants with tremors	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.99.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.82 [0.22, 3.11]
1.99.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.57 [0.14, 2.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.100 Adverse effects - specific: number of participants with dystonia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.100.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.100.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.82 [0.06, 11.33]
1.101 Adverse effects - mean endpoint SAS (high = poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.101.1 < 3 months	1	75	Mean Difference (IV, Random, 95% CI)	-1.10 [-2.35, 0.15]
1.101.2 < 6 months	1	75	Mean Difference (IV, Random, 95% CI)	-0.80 [-2.07, 0.47]
1.101.3 < 1 year	2	110	Mean Difference (IV, Random, 95% CI)	-0.66 [-3.79, 2.48]
1.102 Adverse effects - mean change SAS (high = poor)	6		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.102.1 < 3 months	1	20	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-1.12, 0.65]
1.102.2 < 6 months	2	563	Std. Mean Difference (IV, Random, 95% CI)	-0.14 [-0.31, 0.04]
1.102.3 < 1 year	3	763	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.17, 0.12]
1.103 Adverse effects - mean change DIEPSS (high = poor)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.103.1 < 1 year	1	61	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-1.74, -0.26]
1.104 Adverse effects - mean endpoint MPRC parkinsonian scale (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.104.1 < 6 months	1	50	Mean Difference (IV, Random, 95% CI)	0.70 [-0.66, 2.06]
1.104.2 < 1 year	1	50	Mean Difference (IV, Random, 95% CI)	-0.20 [-1.56, 1.16]
1.105 Adverse effects - mean endpoint/change EPS scales (SAS, DIEPSS, MPRC parkinsonian) (high = poor) (combined time points)	9	1532	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.32, -0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.106 Adverse effects - mean endpoint/change EPS scales (SAS, DIEPSS, MPRC parkinsonian) (high = poor) (separated time points)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.106.1 < 3 months	2	95	Std. Mean Difference (IV, Random, 95% CI)	-0.36 [-0.77, 0.04]
1.106.2 < 6 months	4	688	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.28, 0.04]
1.106.3 < 1 year	6	949	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.46, 0.01]
1.107 Adverse effects - specific: number of participants with akathisia (combined time points)	3	883	Risk Ratio (IV, Random, 95% CI)	1.07 [0.55, 2.09]
1.108 Adverse effects - specific: number of participants with akathisia (separated time points)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.108.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	1.23 [0.26, 5.82]
1.108.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.42 [0.07, 2.54]
1.108.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	1.24 [0.60, 2.55]
1.109 Adverse effects - mean endpoint BARS (high = poor)	1	35	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.00, 0.20]
1.109.1 < 1 year	1	35	Mean Difference (IV, Fixed, 95% CI)	0.10 [0.00, 0.20]
1.110 Adverse effects - mean change BARS (high = poor)	4		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.110.1 < 6 months	2	563	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.20, 0.15]
1.110.2 < 1 year	2	423	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-1.08, 0.39]
1.111 Adverse effects - mean endpoint/change BARS (high = poor) (separated and combined time points)	4	986	Std. Mean Difference (IV, Random, 95% CI)	-0.08 [-0.26, 0.11]
1.111.1 < 6 months	2	563	Std. Mean Difference (IV, Random, 95% CI)	-0.03 [-0.20, 0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.111.2 < 1 year	2	423	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-1.08, 0.39]
1.112 Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (combined time points)	4	630	Risk Ratio (IV, Random, 95% CI)	0.83 [0.02, 38.90]
1.113 Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (separated time points)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.113.1 < 3 months	2	38	Risk Ratio (IV, Random, 95% CI)	0.82 [0.06, 11.33]
1.113.2 < 6 months	3	504	Risk Ratio (IV, Random, 95% CI)	5.83 [0.34, 100.03]
1.113.3 < 1 year	2	144	Risk Ratio (IV, Random, 95% CI)	0.11 [0.01, 2.09]
1.114 Adverse effects - mean endpoint AIMS (high = poor)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.114.1 < 3 months	3	105	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.69, 0.18]
1.114.2 < 6 months	3	105	Mean Difference (IV, Random, 95% CI)	-0.27 [-0.71, 0.16]
1.114.3 < 1 year	2	94	Mean Difference (IV, Random, 95% CI)	-0.24 [-2.26, 1.78]
1.115 Adverse effects - mean change AIMS (high = poor)	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.115.1 < 3 months	1	20	Mean Difference (IV, Random, 95% CI)	0.36 [-1.51, 2.23]
1.115.2 < 6 months	3	583	Mean Difference (IV, Random, 95% CI)	0.09 [-0.17, 0.35]
1.115.3 < 1 year	2	423	Mean Difference (IV, Random, 95% CI)	-0.34 [-1.23, 0.54]
1.116 Adverse effects - mean endpoint MPRC dyskinesia scale (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.116.1 < 6 months	1	50	Mean Difference (IV, Random, 95% CI)	1.30 [-2.59, 5.19]
1.116.2 < 12 months	1	50	Mean Difference (IV, Random, 95% CI)	2.30 [-1.59, 6.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.117 Adverse effects - specific: mean endpoint abbreviated RTDRS (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.117.1 < 3 months	1	21	Mean Difference (IV, Random, 95% CI)	-4.80 [-10.51, 0.91]
1.117.2 < 6 months	1	21	Mean Difference (IV, Random, 95% CI)	-3.10 [-8.81, 2.61]
1.118 Adverse effects - mean endpoint/change dyskinesia scales (AIMS, MRCP dyskinesia, RTDRS) (high = poor) (combined time points)	9	1162	Std. Mean Difference (IV, Random, 95% CI)	-0.01 [-0.16, 0.14]
1.119 Adverse effects - mean endpoint/change dyskinesia scales (AIMS, MRCP dyskinesia, RTDRS) (high = poor) (separated time points)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.119.1 < 3 months	4	126	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.57, 0.16]
1.119.2 < 6 months	7	739	Std. Mean Difference (IV, Random, 95% CI)	0.02 [-0.13, 0.17]
1.119.3 < 1 year	4	532	Std. Mean Difference (IV, Random, 95% CI)	-0.06 [-0.37, 0.25]
1.120 Adverse effects - specific: number of participants with QTc prolongation	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.120.1 < 6 months	1	466	Risk Ratio (IV, Random, 95% CI)	2.24 [0.14, 35.50]
1.120.2 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.121 Adverse effects - mean change QTc interval (milliseconds)	3		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.121.1 < 6 months	1	463	Mean Difference (IV, Random, 95% CI)	-0.03 [-2.80, 2.74]
1.121.2 < 1 year	2	81	Mean Difference (IV, Random, 95% CI)	4.13 [-1.89, 10.15]
1.122 Adverse effects - specific: number of participants with arrhythmia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.122.1 < 6 months	1	466	Risk Ratio (IV, Random, 95% CI)	0.74 [0.03, 18.12]
1.123 Adverse effects - specific: number of participants with hypotension	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.123.1 < 6 months	1	466	Risk Ratio (IV, Random, 95% CI)	4.47 [0.41, 48.92]
1.124 Adverse effects - specific: number of participants with bradycardia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.124.1 < 6 months	1	466	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.125 Adverse effects - specific: number of participants with tachycardia	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.125.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.82 [0.06, 11.33]
1.125.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	1.09 [0.25, 4.79]
1.126 Adverse effects - specific: number of participants with dizziness	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.126.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	1.64 [0.18, 15.26]
1.126.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.94 [0.36, 2.46]
1.127 Adverse effects - specific: number of participants with increased prolactin	2		Risk Ratio (IV, Fixed, 95% CI)	Subtotals only
1.127.1 < 6 months	1	248	Risk Ratio (IV, Fixed, 95% CI)	0.72 [0.31, 1.69]
1.127.2 < 1 year	1	397	Risk Ratio (IV, Fixed, 95% CI)	1.35 [0.49, 3.72]
1.128 Adverse effects - mean change prolactin levels (ng/mL)	4		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.128.1 < 6 months	1	466	Mean Difference (IV, Random, 95% CI)	-5.74 [-8.95, -2.53]
1.128.2 < 1 year	3	312	Mean Difference (IV, Random, 95% CI)	-0.24 [-1.48, 1.00]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.129 Adverse effects - specific: number of participants (women) with amenorrhoea	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.129.1 < 3 months	1	8	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.129.2 < 6 months	1	8	Risk Ratio (IV, Random, 95% CI)	2.00 [0.11, 37.83]
1.130 Adverse effects - specific: number of participants (men) with erectile dysfunction	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.130.1 < 3 months	1	12	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.130.2 < 6 months	2	317	Risk Ratio (IV, Random, 95% CI)	4.32 [0.48, 38.83]
1.131 Adverse effects - specific: number of participants with libido decreased	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.131.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.55 [0.11, 2.59]
1.131.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.37 [0.06, 2.11]
1.132 Adverse effects - specific: number of participants with libido increased	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.132.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.132.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.133 Adverse effects - specific: number of participants with sedation	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.133.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.82 [0.14, 4.71]
1.133.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	2.34 [0.56, 9.70]
1.134 Adverse effects - specific: number of participants with insomnia (combined time points)	3	883	Risk Ratio (IV, Random, 95% CI)	1.60 [0.55, 4.67]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.135 Adverse effects - specific: number of participants with insomnia (separated time points)	3		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.135.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.41 [0.10, 1.75]
1.135.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	2.20 [0.52, 9.25]
1.135.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.99 [0.59, 1.67]
1.136 Adverse effects - specific: number of participants with epileptic seizures	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.136.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.136.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.137 Adverse effects - mean change CGI-SS (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.137.1 < 1 year	1	397	Mean Difference (IV, Random, 95% CI)	0.05 [-0.01, 0.11]
1.138 Adverse effects - mean change CSSRS (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.138.1 < 1 year	1	109	Mean Difference (IV, Random, 95% CI)	-0.10 [-0.39, 0.19]
1.139 Adverse effects - specific: number of participants with blurred vision	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.139.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	2.50 [0.11, 54.87]
1.139.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.28 [0.01, 6.10]
1.140 Adverse effects - specific: number of participants with constipation	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.140.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.55 [0.11, 2.59]
1.140.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.35 [0.04, 3.07]

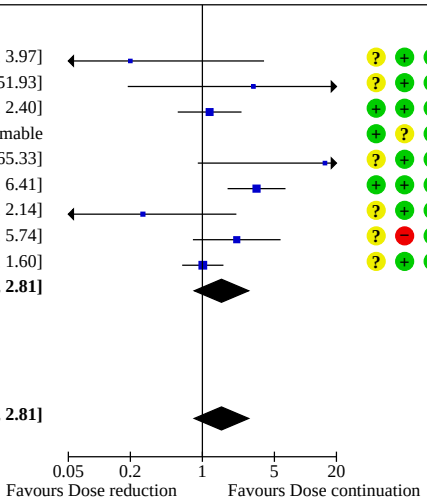
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.141 Adverse effects - specific: number of participants with dry mouth	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.141.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	4.17 [0.23, 77.11]
1.141.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	1.75 [0.36, 8.42]
1.142 Adverse effects - specific: number of participants with hypersalivation	2		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.142.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.17 [0.01, 3.08]
1.142.2 < 6 months	2	486	Risk Ratio (IV, Random, 95% CI)	0.99 [0.03, 36.96]
1.143 Adverse effects - specific: number of participants with urinary retention	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.143.1 < 3 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.17 [0.01, 3.08]
1.143.2 < 6 months	1	20	Risk Ratio (IV, Random, 95% CI)	0.17 [0.01, 3.08]
1.144 Adverse effects - specific: number of participants with leukopenia	1		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.144.1 < 6 months	1	466	Risk Ratio (IV, Random, 95% CI)	6.68 [0.27, 163.06]
1.145 Adverse effects - specific: number of participants with neutropenia	1	466	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.145.1 < 6 months	1	466	Risk Ratio (M-H, Random, 95% CI)	Not estimable
1.146 Adverse effects - specific: number of participants with thrombosis	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.146.1 < 6 months	1	466	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.03, 18.12]
1.147 Adverse effect - mortality: overall mortality (combined time points)	5	941	Risk Ratio (IV, Random, 95% CI)	2.69 [0.48, 15.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.148 Adverse effect - mortality: overall mortality (separated time points)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.148.1 < 3 months	3	509	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.148.2 < 6 months	3	509	Risk Ratio (IV, Random, 95% CI)	3.25 [0.15, 72.36]
1.148.3 < 1 year	2	432	Risk Ratio (IV, Random, 95% CI)	2.47 [0.31, 19.61]
1.149 Adverse effect - mortality: mortality due to natural causes (combined time points)	4	906	Risk Ratio (IV, Random, 95% CI)	1.51 [0.16, 14.02]
1.150 Adverse effect - mortality: mortality due to natural causes (separated time points)	4		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.150.1 < 3 months	3	509	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.150.2 < 6 months	3	509	Risk Ratio (IV, Random, 95% CI)	3.25 [0.15, 72.36]
1.150.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	0.67 [0.03, 16.44]
1.151 Adverse effect - mortality: mortality due to suicide	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.151.1 < 3 months	4	606	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.151.2 < 6 months	4	606	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.151.3 < 1 year	1	397	Risk Ratio (IV, Random, 95% CI)	6.07 [0.25, 147.95]
1.152 Cognition - mean endpoint MCCB total (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.152.1 < 3 months	1	75	Mean Difference (IV, Random, 95% CI)	0.30 [-5.26, 5.86]
1.152.2 < 6 months	1	75	Mean Difference (IV, Random, 95% CI)	-6.00 [-10.47, -1.53]
1.152.3 < 1 year	1	75	Mean Difference (IV, Random, 95% CI)	-6.50 [-11.44, -1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.153 Cognition - mean change RBANS (high = poor)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.153.1 < 1 year	1	61	Mean Difference (IV, Random, 95% CI)	-7.10 [-10.90, -3.30]
1.154 Cognition - mean end-point/change overall cognition (MC-CB, RBANS) (high = poor) (combined time points)	2	136	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.08, -0.39]
1.154.1 < 1 year	2	136	Std. Mean Difference (IV, Random, 95% CI)	-0.74 [-1.08, -0.39]
1.155 Cognition - mean end-point/change overall cognition (MC-CB, RBANS) (high = poor) (separated time points)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.155.1 < 3 months	1	75	Mean Difference (IV, Random, 95% CI)	0.30 [-5.26, 5.86]
1.155.2 < 6 months	1	75	Mean Difference (IV, Random, 95% CI)	-6.00 [-10.47, -1.53]
1.155.3 < 1 year	2	136	Mean Difference (IV, Random, 95% CI)	-6.88 [-9.89, -3.86]
1.156 Medication – mean antipsychotic dose at endpoint (olanzapine equivalents mg/d) (combined time points)	15		Mean Difference (IV, Random, 95% CI)	Totals not selected
1.157 Medication – mean antipsychotic dose at endpoint (olanzapine equivalents mg/d) (separated time points)	17		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.157.1 Baseline	13	1490	Mean Difference (IV, Random, 95% CI)	0.02 [-0.37, 0.41]
1.157.2 < 3 months	4	213	Mean Difference (IV, Random, 95% CI)	-7.71 [-13.53, -1.89]
1.157.3 < 6 months	5	810	Mean Difference (IV, Random, 95% CI)	-10.79 [-18.78, -2.81]
1.157.4 < 1 year	10	1308	Mean Difference (IV, Random, 95% CI)	-8.72 [-11.52, -5.92]
1.157.5 > 1 year	2	229	Mean Difference (IV, Random, 95% CI)	-7.37 [-18.72, 3.99]

Analysis 1.1. Comparison 1: Dose reduction versus dose maintenance , Outcome 1: Service use - readmission to hospital (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
1.1.1 Combined time points							
Carpenter 1999 (1)	0	25	2	25	3.6%	0.20 [0.01 , 3.97]	? + + + ? ?
Faraone 1989 (2)	4	22	0	7	4.0%	3.13 [0.19 , 51.93]	? + + + ? ?
Fleischhacker 2014 (1)	11	131	19	266	20.3%	1.18 [0.58 , 2.40]	+ + + + + +
Huhn 2020 (2)	0	11	0	9		Not estimable	+ ? + + + ?
Kane 1983 (1)	7	62	0	64	3.9%	15.48 [0.90 , 265.33]	? + + + ? ?
Kane 2010 (2)	21	144	14	322	21.3%	3.35 [1.76 , 6.41]	+ + + + + +
Remington 2011 (2)	1	17	4	18	6.5%	0.26 [0.03 , 2.14]	? + + + − −
Rouillon 2008 (2)	11	49	5	48	16.2%	2.16 [0.81 , 5.74]	? − + + ? −
Schooler 1997 (3)	27	106	27	107	24.2%	1.01 [0.64 , 1.60]	? + + ? ? ?
Subtotal (95% CI)		**567**		**866**	**100.0%**	**1.53 [0.84 , 2.81]**	
Total events:	82		71				
Heterogeneity: Tau² = 0.34; Chi² = 16.98, df = 7 (P = 0.02); I² = 59%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Total (95% CI)		**567**		**866**	**100.0%**	**1.53 [0.84 , 2.81]**	
Total events:	82		71				
Heterogeneity: Tau² = 0.34; Chi² = 16.98, df = 7 (P = 0.02); I² = 59%							
Test for overall effect: Z = 1.38 (P = 0.17)							
Test for subgroup differences: Not applicable							



Footnotes

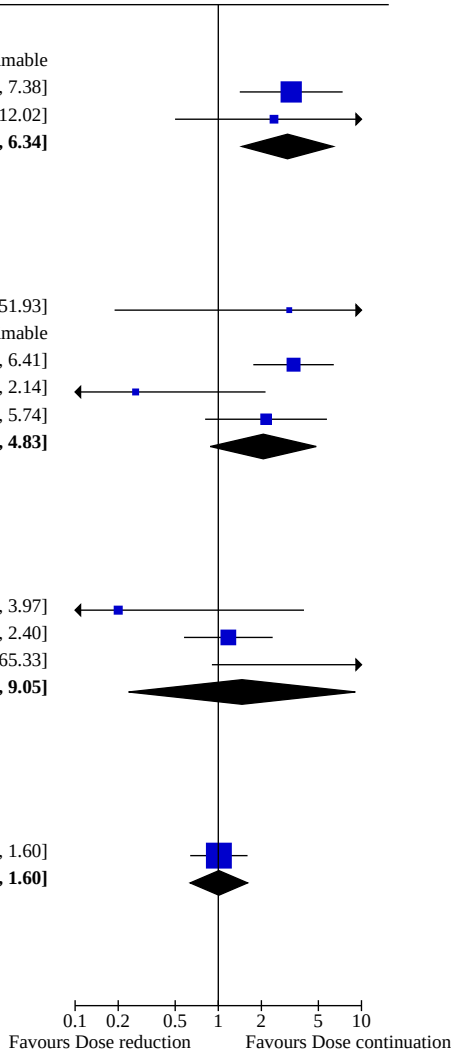
(1) < 1 year
(2) < 6 months
(3) > 1 year

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

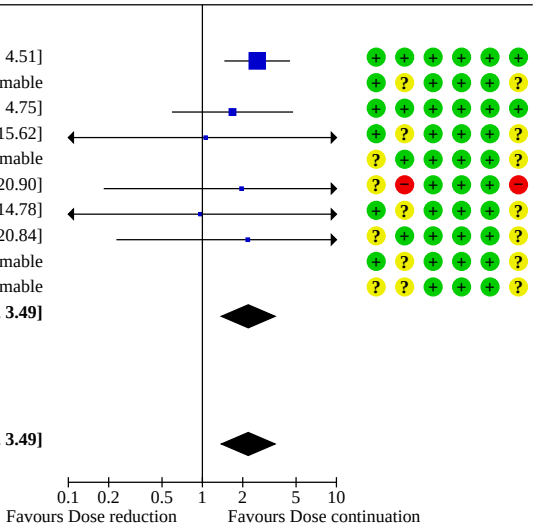
Analysis 1.2. Comparison 1: Dose reduction versus dose maintenance , Outcome 2: Service use - readmission to hospital (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	13	144	9	322	78.7%	3.23 [1.41 , 7.38]
Rouillon 2008	5	49	2	48	21.3%	2.45 [0.50 , 12.02]
Subtotal (95% CI)		**204**		**379**	**100.0%**	**3.05 [1.46 , 6.34]**
Total events:	18		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.76); I² = 0%						
Test for overall effect: Z = 2.97 (P = 0.003)						
1.2.2 < 6 months						
Faraone 1989	4	22	0	7	8.0%	3.13 [0.19 , 51.93]
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	21	144	14	322	45.2%	3.35 [1.76 , 6.41]
Remington 2011	1	17	4	18	13.1%	0.26 [0.03 , 2.14]
Rouillon 2008	11	49	5	48	33.8%	2.16 [0.81 , 5.74]
Subtotal (95% CI)		**243**		**404**	**100.0%**	**2.06 [0.88 , 4.83]**
Total events:	37		23			
Heterogeneity: Tau² = 0.31; Chi² = 5.34, df = 3 (P = 0.15); I² = 44%						
Test for overall effect: Z = 1.67 (P = 0.10)						
1.2.3 < 1 year						
Carpenter 1999	0	25	2	25	22.7%	0.20 [0.01 , 3.97]
Fleischhacker 2014	11	131	19	266	53.3%	1.18 [0.58 , 2.40]
Kane 1983	7	62	0	64	24.1%	15.48 [0.90 , 265.33]
Subtotal (95% CI)		**218**		**355**	**100.0%**	**1.46 [0.24 , 9.05]**
Total events:	18		21			
Heterogeneity: Tau² = 1.49; Chi² = 4.49, df = 2 (P = 0.11); I² = 55%						
Test for overall effect: Z = 0.41 (P = 0.68)						
1.2.4 > 1 year						
Schooler 1997	27	106	27	107	100.0%	1.01 [0.64 , 1.60]
Subtotal (95% CI)		**106**		**107**	**100.0%**	**1.01 [0.64 , 1.60]**
Total events:	27		27			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.04 (P = 0.97)						
Test for subgroup differences: Chi² = 6.95, df = 3 (P = 0.07), I² = 56.8%						



Analysis 1.3. Comparison 1: Dose reduction versus dose maintenance , Outcome 3: Adverse effect - leaving the study early due to adverse effects - overall tolerability (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.3.1 Combined time points						
Fleischhacker 2014 (1)	24	131	19	266	66.6%	2.56 [1.46 , 4.51]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (2)	6	144	8	322	19.6%	1.68 [0.59 , 4.75]
Ozawa 2019 (1)	1	17	1	18	2.9%	1.06 [0.07 , 15.62]
Remington 2011 (2)	0	17	0	18		Not estimable
Rouillon 2008 (2)	2	49	1	48	3.8%	1.96 [0.18 , 20.90]
Takeuchi 2014 (1)	1	31	1	30	2.9%	0.97 [0.06 , 14.78]
Volavka 2000 (2)	2	11	1	12	4.2%	2.18 [0.23 , 20.84]
Wunderink 2007 (1)	0	68	0	63		Not estimable
Zhou 2018 (1)	0	37	0	38		Not estimable
Subtotal (95% CI)		**516**		**824**	**100.0%**	**2.20 [1.39 , 3.49]**
Total events:	36		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Total (95% CI)		**516**		**824**	**100.0%**	**2.20 [1.39 , 3.49]**
Total events:	36		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Test for subgroup differences: Not applicable						



Footnotes

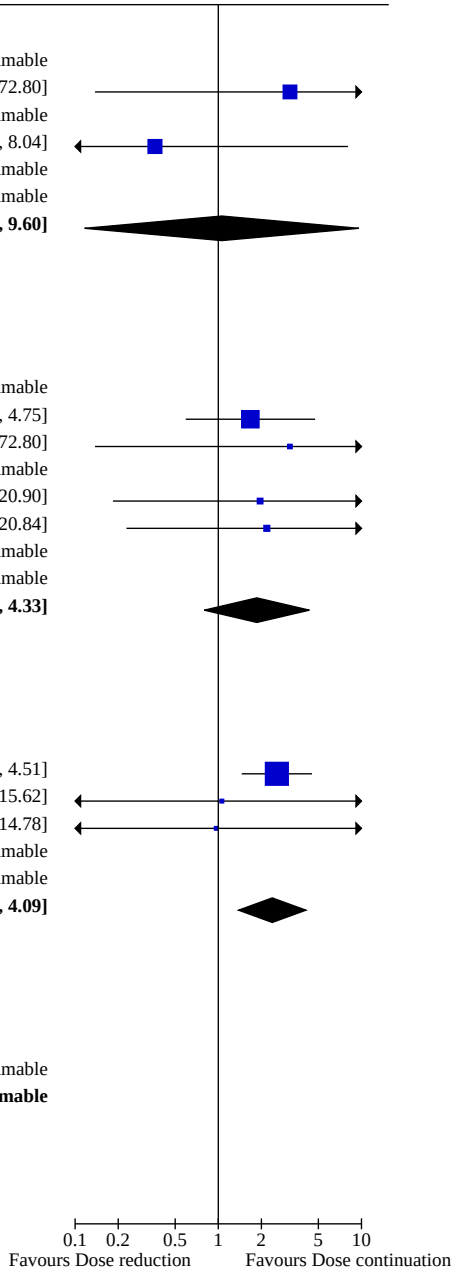
(1) < 1 year
(2) < 6 months

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

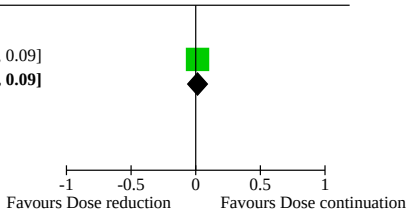
Analysis 1.4. Comparison 1: Dose reduction versus dose maintenance , Outcome 4: Adverse effect - leaving the study early due to adverse effects - overall tolerability (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.4.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Ozawa 2019	1	17	0	18	49.5%	3.17 [0.14 , 72.80]
Remington 2011	0	17	0	18		Not estimable
Volavka 2000	0	11	1	12	50.5%	0.36 [0.02 , 8.04]
Wunderink 2007	0	68	0	63		Not estimable
Zhou 2018	0	37	0	38		Not estimable
Subtotal (95% CI)		**161**		**158**	**100.0%**	**1.06 [0.12 , 9.60]**
Total events:	1		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.93, df = 1 (P = 0.33); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
1.4.2 < 6 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	6	144	8	322	66.0%	1.68 [0.59 , 4.75]
Ozawa 2019	1	17	0	18	7.3%	3.17 [0.14 , 72.80]
Remington 2011	0	17	0	18		Not estimable
Rouillon 2008	2	49	1	48	12.7%	1.96 [0.18 , 20.90]
Volavka 2000	2	11	1	12	14.0%	2.18 [0.23 , 20.84]
Wunderink 2007	0	68	0	63		Not estimable
Zhou 2018	0	37	0	38		Not estimable
Subtotal (95% CI)		**354**		**528**	**100.0%**	**1.86 [0.80 , 4.33]**
Total events:	11		10			
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 1.44 (P = 0.15)						
1.4.3 < 1 year						
Fleischhacker 2014	24	131	19	266	92.0%	2.56 [1.46 , 4.51]
Ozawa 2019	1	17	1	18	4.0%	1.06 [0.07 , 15.62]
Takeuchi 2014	1	31	1	30	3.9%	0.97 [0.06 , 14.78]
Wunderink 2007	0	68	0	63		Not estimable
Zhou 2018	0	37	0	38		Not estimable
Subtotal (95% CI)		**284**		**415**	**100.0%**	**2.38 [1.39 , 4.09]**
Total events:	26		21			
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 2 (P = 0.66); I² = 0%						
Test for overall effect: Z = 3.14 (P = 0.002)						
1.4.4 > 1 year						
Wunderink 2007	0	68	0	63		Not estimable
Subtotal (95% CI)		**68**		**63**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 0.65, df = 2 (P = 0.72), I² = 0%						



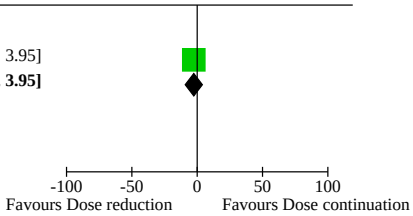
Analysis 1.5. Comparison 1: Dose reduction versus dose maintenance , Outcome 5: Quality of life - mean change score EQ-5D

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.5.1 < 1 year								
Takeuchi 2014	0.008	0.178	31	-0.006	0.122	30	100.0%	0.01 [-0.06 , 0.09]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**0.01 [-0.06 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.36 (P = 0.72)								



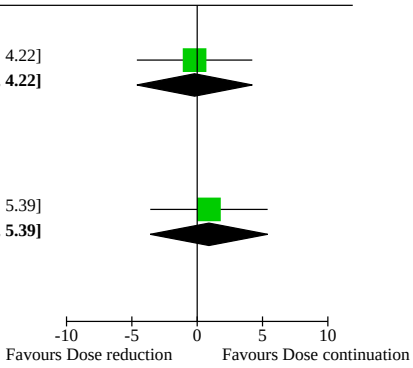
Analysis 1.6. Comparison 1: Dose reduction versus dose maintenance , Outcome 6: Quality of life - mean change score S-QoL

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.6.1 < 6 months								
Rouillon 2008	-10.1	16.7	49	-7.5	16.2	48	100.0%	-2.60 [-9.15 , 3.95]
Subtotal (95% CI)			**49**			**48**	**100.0%**	**-2.60 [-9.15 , 3.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.44)								



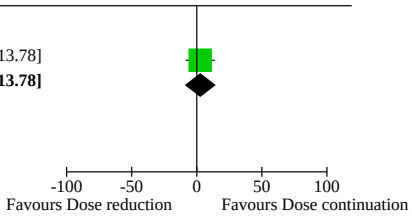
Analysis 1.7. Comparison 1: Dose reduction versus dose maintenance , Outcome 7: Quality of life - mean endpoint WHOQOL-BREF

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.7.1 < 1 year								
Wunderink 2007	-96	11.8	65	-95.8	13.6	63	100.0%	-0.20 [-4.62 , 4.22]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-0.20 [-4.62 , 4.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.7.2 > 1 year								
Wunderink 2007	-96.9	12.6	65	-97.8	13.3	63	100.0%	0.90 [-3.59 , 5.39]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.90 [-3.59 , 5.39]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.69)								
Test for subgroup differences: Chi² = 0.12, df = 1 (P = 0.73), I² = 0%								



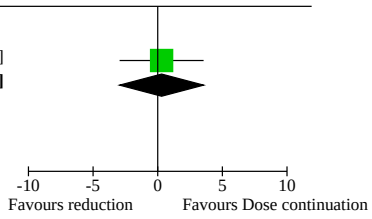
Analysis 1.8. Comparison 1: Dose reduction versus dose maintenance , Outcome 8: Quality of life - mean endpoint QLS (Heinrich)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.8.1 < 1 year								
Carpenter 1999	-63.17	21	25	-65.85	19	25	100.0%	2.68 [-8.42 , 13.78]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**2.68 [-8.42 , 13.78]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								



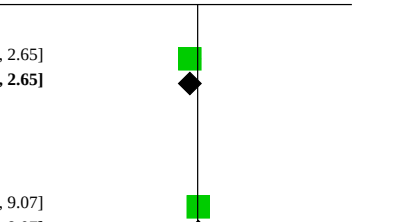
Analysis 1.9. Comparison 1: Dose reduction versus dose maintenance , Outcome 9: Quality of life - mean change QLS total (Heinrich)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.9.1 < 6 months								
Kane 2010	-3.48	12.98	86	-3.78	14.79	278	100.0%	0.30 [-2.95 , 3.55]
Subtotal (95% CI)			**86**			**278**	**100.0%**	**0.30 [-2.95 , 3.55]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.18 (P = 0.86)								



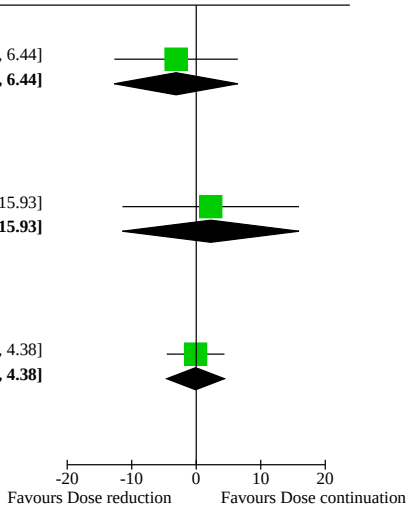
Analysis 1.10. Comparison 1: Dose reduction versus dose maintenance , Outcome 10: Quality of life - mean endpoint SWNS

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.10.1 < 3 months								
Huhn 2020	-94.91	10.511	11	-88.88	8.757	8	100.0%	-6.03 [-14.71 , 2.65]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**-6.03 [-14.71 , 2.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								
1.10.2 < 6 months								
Huhn 2020	-93.18	8.28	11	-93.62	10.266	8	100.0%	0.44 [-8.19 , 9.07]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**0.44 [-8.19 , 9.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								



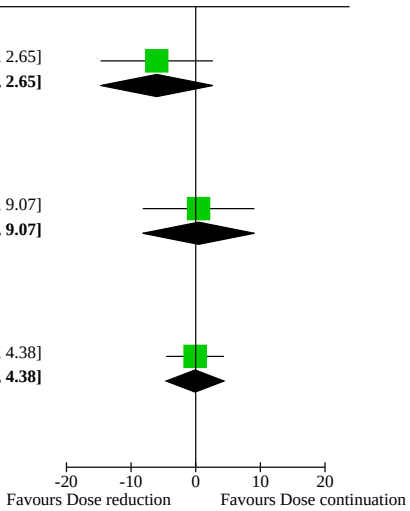
Analysis 1.11. Comparison 1: Dose reduction versus dose maintenance , Outcome 11: Quality of life - mean change SWNS

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 < 3 months								
Huhn 2020	-2.25	10.14	8	0.875	9.372	8	100.0%	-3.13 [-12.69 , 6.44]
Subtotal (95% CI)			**8**			**8**	**100.0%**	**-3.13 [-12.69 , 6.44]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.64 (P = 0.52)								
1.11.2 < 6 months								
Huhn 2020	-1.63	16.34	8	-3.88	11.08	8	100.0%	2.25 [-11.43 , 15.93]
Subtotal (95% CI)			**8**			**8**	**100.0%**	**2.25 [-11.43 , 15.93]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								
1.11.3 < 1 year								
Takeuchi 2014	-3.9	10.1	31	-3.8	7.6	30	100.0%	-0.10 [-4.58 , 4.38]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-0.10 [-4.58 , 4.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.04 (P = 0.97)								
Test for subgroup differences: Chi² = 0.47, df = 2 (P = 0.79), I² = 0%								



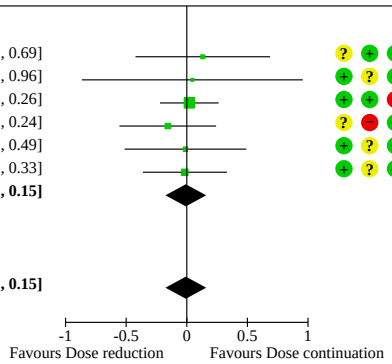
Analysis 1.12. Comparison 1: Dose reduction versus dose maintenance , Outcome 12: Quality of life - mean change/endpoint SWNS

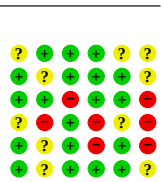
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.12.1 < 3 months								
Huhn 2020	-94.91	10.511	11	-88.88	8.757	8	100.0%	-6.03 [-14.71 , 2.65]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**-6.03 [-14.71 , 2.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.36 (P = 0.17)								
1.12.2 < 6 months								
Huhn 2020	-93.18	8.28	11	-93.62	10.266	8	100.0%	0.44 [-8.19 , 9.07]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**0.44 [-8.19 , 9.07]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								
1.12.3 < 1 year								
Takeuchi 2014	-3.9	10.1	31	-3.8	7.6	30	100.0%	-0.10 [-4.58 , 4.38]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-0.10 [-4.58 , 4.38]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.04 (P = 0.97)								
Test for subgroup differences: Chi² = 1.55, df = 2 (P = 0.46), I² = 0%								



Analysis 1.13. Comparison 1: Dose reduction versus dose maintenance , Outcome 13: Quality of life - mean change/endpoint all available scales (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.13.1 Quality of life - combined scales and time points								
Carpenter 1999 (1)	-63.17	21	25	-65.85	19	25	8.1%	0.13 [-0.42 , 0.69]
Huhn 2020 (2)	-93.18	8.28	11	-93.62	10.266	8	3.0%	0.05 [-0.86 , 0.96]
Kane 2010 (3)	-3.48	12.98	86	-3.78	14.79	278	42.6%	0.02 [-0.22 , 0.26]
Rouillon 2008 (4)	-10.1	16.7	49	-7.5	16.2	48	15.7%	-0.16 [-0.56 , 0.24]
Takeuchi 2014 (5)	-3.9	10.1	31	-3.8	7.6	30	9.9%	-0.01 [-0.51 , 0.49]
Wunderink 2007 (6)	-96	11.8	65	-95.8	13.6	63	20.7%	-0.02 [-0.36 , 0.33]
Subtotal (95% CI)			**267**			**452**	**100.0%**	**-0.01 [-0.17 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 5 (P = 0.97); I² = 0%								
Test for overall effect: Z = 0.10 (P = 0.92)								
Total (95% CI)			**267**			**452**	**100.0%**	**-0.01 [-0.17 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.85, df = 5 (P = 0.97); I² = 0%								
Test for overall effect: Z = 0.10 (P = 0.92)								
Test for subgroup differences: Not applicable								





Footnotes

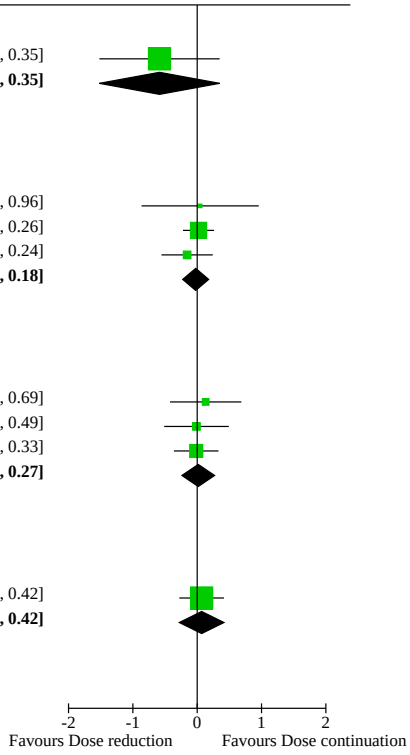
(1) mean endpoint QoL Scale (Heinrich) - < 1 year
(2) mean endpoint SWNS - < 6 months
(3) mean change QLS Total (Heinrich) - < 6 months
(4) mean change score S-QoL - < 6 months
(5) mean change SWNS - < 1 year
(6) mean endpoint WHOQoL-BREF - < 1 year

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.14. Comparison 1: Dose reduction versus dose maintenance , Outcome 14: Quality of life - mean change/endpoint all available scales (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.14.1 Quality of life - combined scales (< 3 months)								
Huhn 2020 (1)	-94.91	10.511	11	-88.88	8.757	8	100.0%	-0.59 [-1.52 , 0.35]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**-0.59 [-1.52 , 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.23 (P = 0.22)								
1.14.2 Quality of life - combined scales (< 6 months)								
Huhn 2020 (2)	-93.18	8.28	11	-93.62	10.266	8	4.9%	0.05 [-0.86 , 0.96]
Kane 2010 (3)	-3.48	12.98	86	-3.78	14.79	278	69.5%	0.02 [-0.22 , 0.26]
Rouillon 2008 (4)	-10.1	16.7	49	-7.5	16.2	48	25.6%	-0.16 [-0.56 , 0.24]
Subtotal (95% CI)			**146**			**334**	**100.0%**	**-0.02 [-0.23 , 0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.58, df = 2 (P = 0.75); I² = 0%								
Test for overall effect: Z = 0.23 (P = 0.82)								
1.14.3 Quality of life - combined scales (< 1 year)								
Carpenter 1999 (5)	-63.17	21	25	-65.85	19	25	20.9%	0.13 [-0.42 , 0.69]
Takeuchi 2014 (6)	-3.9	10.1	31	-3.8	7.6	30	25.5%	-0.01 [-0.51 , 0.49]
Wunderink 2007 (7)	-96	11.8	65	-95.8	13.6	63	53.6%	-0.02 [-0.36 , 0.33]
Subtotal (95% CI)			**121**			**118**	**100.0%**	**0.02 [-0.24 , 0.27]**
Heterogeneity: Tau² = 0.00; Chi² = 0.21, df = 2 (P = 0.90); I² = 0%								
Test for overall effect: Z = 0.13 (P = 0.90)								
1.14.4 Quality of life - combined scales (> 1 year)								
Wunderink 2007 (8)	-96.9	12.6	65	-97.8	13.3	63	100.0%	0.07 [-0.28 , 0.42]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.07 [-0.28 , 0.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.39 (P = 0.70)								
Test for subgroup differences: Chi² = 1.72, df = 3 (P = 0.63), I² = 0%								

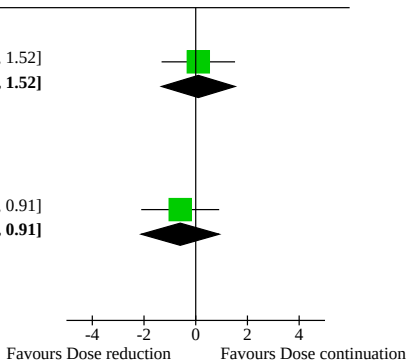


Footnotes

(1) mean endpoint SWNS - < 3 months
(2) mean endpoint SWNS - < 6 months
(3) mean change QLS Total (Heinrich) - < 6 months
(4) mean change score S-QoL - < 6 months
(5) mean endpoint QoL Scale (Heinrich) - < 1 year
(6) mean change SWNS - < 1 year
(7) mean endpoint WHOQoL-BREF - < 1 year
(8) mean endpoint WHOQoL-BREF - > 1 year

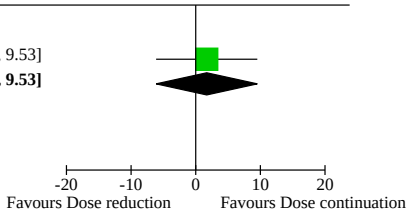
Analysis 1.15. Comparison 1: Dose reduction versus dose maintenance , Outcome 15: Functioning - mean endpoint GSDS

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.15.1 < 1 year								
Wunderink 2007	5.8	4.1	65	5.7	4.1	63	100.0%	0.10 [-1.32 , 1.52]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.10 [-1.32 , 1.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.14 (P = 0.89)								
1.15.2 > 1 year								
Wunderink 2007	5.8	4.5	65	6.4	4.2	63	100.0%	-0.60 [-2.11 , 0.91]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-0.60 [-2.11 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.44)								
Test for subgroup differences: Chi² = 0.44, df = 1 (P = 0.51), I² = 0%								



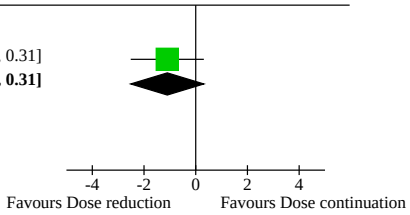
Analysis 1.16. Comparison 1: Dose reduction versus dose maintenance , Outcome 16: Functioning - mean endpoint GAF

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.16.1 < 1 year								
Ozawa 2019	-39.2	12	17	-40.9	11.6	18	100.0%	1.70 [-6.13 , 9.53]
Subtotal (95% CI)			**17**			**18**	**100.0%**	**1.70 [-6.13 , 9.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.43 (P = 0.67)								



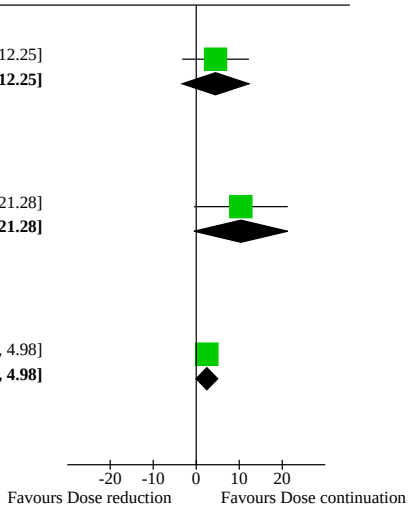
Analysis 1.17. Comparison 1: Dose reduction versus dose maintenance , Outcome 17: Functioning - mean change GAF

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.17.1 < 1 year								
Ozawa 2019	0	1.4	17	1.1	2.7	18	100.0%	-1.10 [-2.51 , 0.31]
Subtotal (95% CI)			**17**			**18**	**100.0%**	**-1.10 [-2.51 , 0.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.52 (P = 0.13)								



Analysis 1.18. Comparison 1: Dose reduction versus dose maintenance , Outcome 18: Functioning - mean change PSP

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.18.1 < 3 months								
Huhn 2020	2.27	7.54	11	-2.22	9.72	9	100.0%	4.49 [-3.27 , 12.25]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**4.49 [-3.27 , 12.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.13 (P = 0.26)								
1.18.2 < 6 months								
Huhn 2020	6.82	11.24	11	-3.56	13.23	9	100.0%	10.38 [-0.52 , 21.28]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**10.38 [-0.52 , 21.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.87 (P = 0.06)								
1.18.3 < 1 year								
Fleischhacker 2014 (1)	2.39	11.4	116	-0.08	11.4	248	100.0%	2.47 [-0.04 , 4.98]
Subtotal (95% CI)			**116**			**248**	**100.0%**	**2.47 [-0.04 , 4.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.93 (P = 0.05)								
Test for subgroup differences: Chi^2 = 2.07, df = 2 (P = 0.35), I^2 = 3.5%								

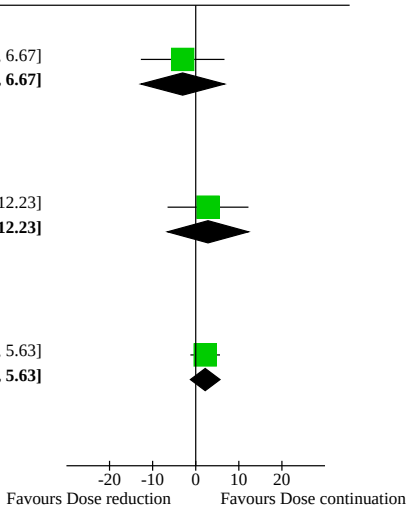


Footnotes

(1) Pooled SD as estimated from the p-value between 400mg/4 weeks vs 50mg/4weeks

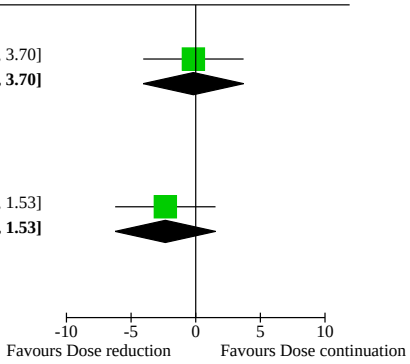
Analysis 1.19. Comparison 1: Dose reduction versus dose maintenance , Outcome 19: Functioning - mean endpoint PSP

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.19.1 < 3 months								
Huhn 2020	-76.36	13.62	11	-73.33	8.29	9	100.0%	-3.03 [-12.73 , 6.67]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-3.03 [-12.73 , 6.67]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.61 (P = 0.54)								
1.19.2 < 6 months								
Huhn 2020	-71.82	12.5	11	-74.67	8.86	9	100.0%	2.85 [-6.53 , 12.23]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**2.85 [-6.53 , 12.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
1.19.3 < 1 year								
Fleischhacker 2014	-64.6	16.6	116	-66.8	13.1	248	100.0%	2.20 [-1.23 , 5.63]
Subtotal (95% CI)			**116**			**248**	**100.0%**	**2.20 [-1.23 , 5.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.26 (P = 0.21)								
Test for subgroup differences: Chi² = 1.05, df = 2 (P = 0.59), I² = 0%								



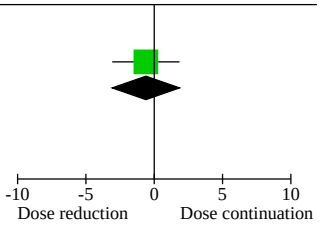
Analysis 1.20. Comparison 1: Dose reduction versus dose maintenance , Outcome 20: Functioning - mean endpoint SCLoF

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.20.1 < 6 months								
Carpenter 1999	-23.42	7	25	-23.24	7	25	100.0%	-0.18 [-4.06 , 3.70]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-0.18 [-4.06 , 3.70]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.20.2 < 12 months								
Carpenter 1999	-23.67	7	25	-21.32	7	25	100.0%	-2.35 [-6.23 , 1.53]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-2.35 [-6.23 , 1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.19 (P = 0.24)								
Test for subgroup differences: Chi² = 0.60, df = 1 (P = 0.44), I² = 0%								



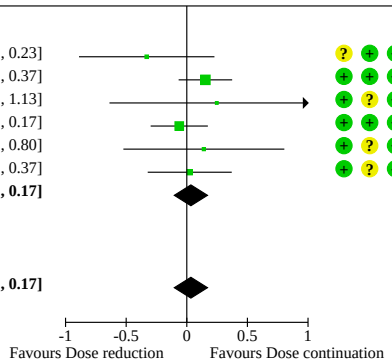
Analysis 1.21. Comparison 1: Dose reduction versus dose maintenance , Outcome 21: Functioning - mean change SF-36 mental component summary

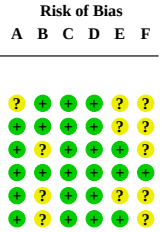
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.21.1 < 6 months								
Kane 2010	-2.28	10.74	92	-1.67	9.47	277	100.0%	-0.61 [-3.07 , 1.85]
Subtotal (95% CI)			**92**			**277**	**100.0%**	**-0.61 [-3.07 , 1.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.49 (P = 0.63)								



Analysis 1.22. Comparison 1: Dose reduction versus dose maintenance , Outcome 22: Functioning - mean endpoint/change all available scales (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.22.1 Functioning - combined scales and time points								
Carpenter 1999 (1)	-23.67	7	25	-21.32	7	25	6.0%	-0.33 [-0.89 , 0.23]
Fleischhacker 2014 (2)	-64.6	16.6	116	-66.8	13.1	248	38.3%	0.15 [-0.07 , 0.37]
Huhn 2020 (3)	-71.82	12.5	11	-74.67	8.86	9	2.4%	0.25 [-0.64 , 1.13]
Kane 2010 (4)	-2.28	10.74	92	-1.67	9.47	277	33.5%	-0.06 [-0.30 , 0.17]
Ozawa 2019 (5)	-39.2	12	17	-40.9	11.6	18	4.2%	0.14 [-0.52 , 0.80]
Wunderink 2007 (6)	5.8	4.1	65	5.7	4.1	63	15.5%	0.02 [-0.32 , 0.37]
Subtotal (95% CI)			**326**			**640**	**100.0%**	**0.03 [-0.10 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 5 (P = 0.59); I² = 0%								
Test for overall effect: Z = 0.48 (P = 0.63)								
Total (95% CI)			**326**			**640**	**100.0%**	**0.03 [-0.10 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 3.72, df = 5 (P = 0.59); I² = 0%								
Test for overall effect: Z = 0.48 (P = 0.63)								
Test for subgroup differences: Not applicable								





Footnotes

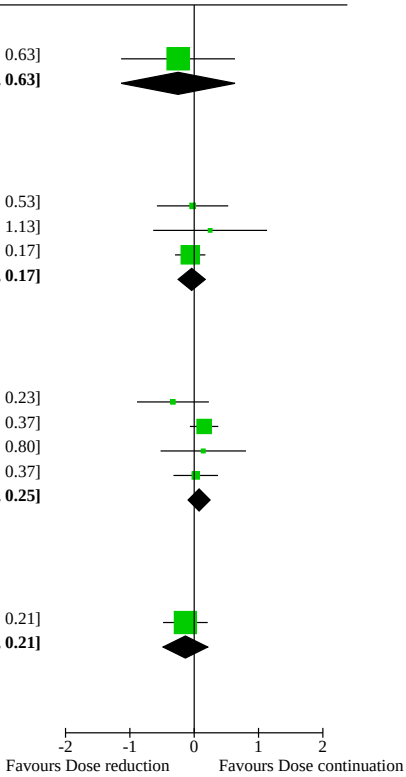
(1) mean endpoint SCLoF - < 1 year
(2) mean endpoint PSP - < 1 year
(3) mean endpoint PSP - < 6 months
(4) mean change SF-36 mental component summary< 6 months
(5) mean endpoint GAF - < 1 year
(6) mean endpoint GSDS - < 1 year

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.23. Comparison 1: Dose reduction versus dose maintenance , Outcome 23: Functioning - mean endpoint/change all available scales (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.23.1 Functioning - combined scales (< 3 months)								
Huhn 2020 (1)	-76.36	13.62	11	-73.33	8.29	9	100.0%	-0.25 [-1.14 , 0.63]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-0.25 [-1.14 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.56 (P = 0.58)								
1.23.2 Functioning - combined scales (< 6 months)								
Carpenter 1999 (2)	-23.42	7	25	-23.24	7	25	14.5%	-0.03 [-0.58 , 0.53]
Huhn 2020 (3)	-71.82	12.5	11	-74.67	8.86	9	5.7%	0.25 [-0.64 , 1.13]
Kane 2010 (4)	-2.28	10.74	92	-1.67	9.47	277	79.9%	-0.06 [-0.30 , 0.17]
Subtotal (95% CI)			**128**			**311**	**100.0%**	**-0.04 [-0.25 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 2 (P = 0.80); I² = 0%								
Test for overall effect: Z = 0.36 (P = 0.72)								
1.23.3 Functioning - combined scales (< 1 year)								
Carpenter 1999 (5)	-23.67	7	25	-21.32	7	25	9.3%	-0.33 [-0.89 , 0.23]
Fleischhacker 2014 (6)	-64.6	16.6	116	-66.8	13.1	248	59.8%	0.15 [-0.07 , 0.37]
Ozawa 2019 (7)	-39.2	12	17	-40.9	11.6	18	6.6%	0.14 [-0.52 , 0.80]
Wunderink 2007 (8)	5.8	4.1	65	5.7	4.1	63	24.3%	0.02 [-0.32 , 0.37]
Subtotal (95% CI)			**223**			**354**	**100.0%**	**0.08 [-0.09 , 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 3 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.87 (P = 0.38)								
1.23.4 Functioning - combined scales (> 1 year)								
Wunderink 2007 (9)	5.8	4.5	65	6.4	4.2	63	100.0%	-0.14 [-0.48 , 0.21]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-0.14 [-0.48 , 0.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.77 (P = 0.44)								
Test for subgroup differences: Chi² = 1.80, df = 3 (P = 0.62), I² = 0%								



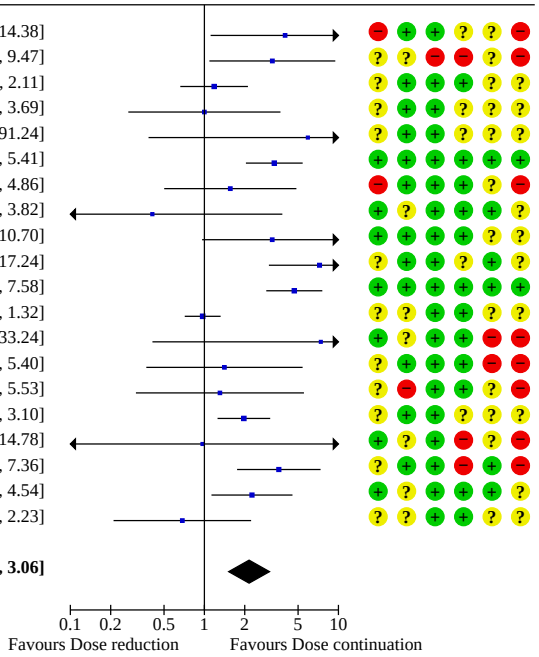
Footnotes

(1) mean endpoint PSP - < 3 months
(2) mean endpoint SCLoF - < 6 months
(3) mean endpoint PSP - < 6 months
(4) mean change SF-36 mental component summary - < 6 months
(5) mean endpoint SCLoF - < 12 months
(6) mean endpoint PSP - < 1 year
(7) mean endpoint GAF - < 1 year
(8) mean endpoint GSDS - < 1 year
(9) mean endpoint GSDS - > 1 year

Analysis 1.24. Comparison 1: Dose reduction versus dose maintenance , Outcome 24: Global state - number of participants with relapse/exacerbations of psychosis (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Branchey 1981 (1)	16	22	2	11	4.2%	4.00 [1.11 , 14.38]
Caffey 1964 (2)	13	89	4	88	4.9%	3.21 [1.09 , 9.47]
Carpenter 1999 (3)	13	25	11	25	7.4%	1.18 [0.66 , 2.11]
Cookson 1987 (3)	3	9	3	9	4.1%	1.00 [0.27 , 3.69]
Faraone 1989 (2)	8	22	0	7	1.4%	5.91 [0.38 , 91.24]
Fleischhacker 2014 (3)	36	131	22	266	7.9%	3.32 [2.04 , 5.41]
Hogarty 1988 (3)	7	37	4	33	4.7%	1.56 [0.50 , 4.86]
Huhn 2020 (4)	1	11	2	9	2.0%	0.41 [0.04 , 3.82]
Johnson 1987 (3)	9	29	3	31	4.4%	3.21 [0.96 , 10.70]
Kane 1983 (3)	35	62	5	64	5.9%	7.23 [3.03 , 17.24]
Kane 2010 (4)	44	144	21	322	7.9%	4.69 [2.90 , 7.58]
Lonowski 1978 (4)	19	25	18	23	8.7%	0.97 [0.71 , 1.32]
Ozawa 2019 (5)	3	17	0	18	1.3%	7.39 [0.41 , 133.24]
Remington 2011 (4)	4	17	3	18	3.9%	1.41 [0.37 , 5.40]
Rouillon 2008 (6)	4	49	3	48	3.6%	1.31 [0.31 , 5.53]
Schooler 1997 (7)	41	106	21	107	8.1%	1.97 [1.25 , 3.10]
Takeuchi 2014 (3)	1	31	1	30	1.4%	0.97 [0.06 , 14.78]
Wang 2010 (3)	47	211	8	129	6.7%	3.59 [1.75 , 7.36]
Wunderink 2007 (3)	22	68	9	63	6.8%	2.26 [1.13 , 4.54]
Zhou 2018 (3)	4	37	6	38	4.5%	0.68 [0.21 , 2.23]
Total (95% CI)		**1142**		**1339**	**100.0%**	**2.16 [1.52 , 3.06]**
Total events:	330		146			

Heterogeneity: Tau² = 0.34; Chi² = 62.50, df = 19 (P < 0.00001); I² = 70%
Test for overall effect: Z = 4.29 (P < 0.0001)
Test for subgroup differences: Not applicable



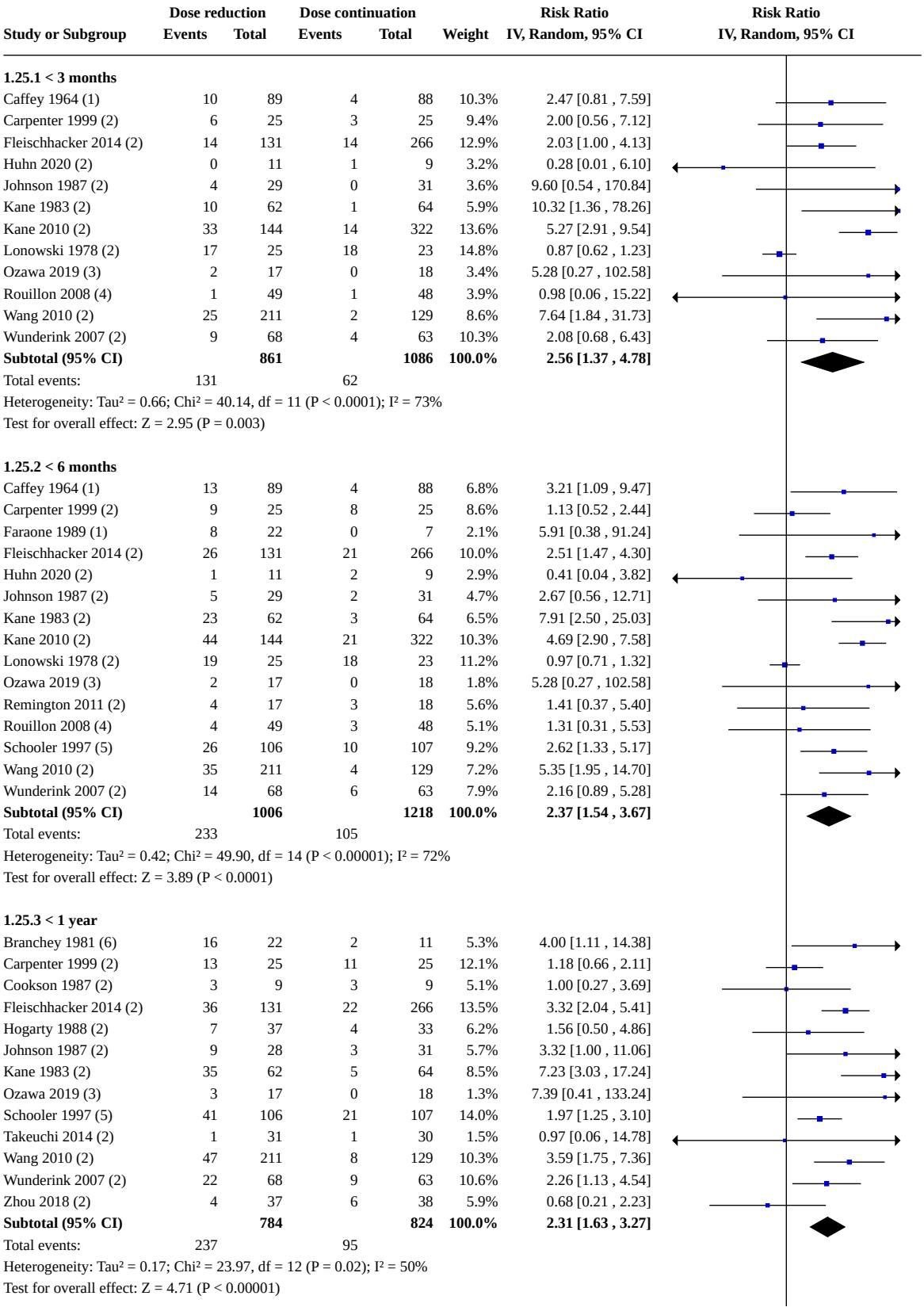
Footnotes

(1) < 1 year; severe or persistent (> 1 week) clinical worsening
(2) < 6 months; relapse by clinical judgement
(3) < 1 year; scale defined relapse
(4) < 6 months; scale defined relapse
(5) < 1 year; dropouts due to clinical worsening
(6) < 6 months; hospitalisation
(7) < 1 year; clinical worsening needing rescue medication

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.25. Comparison 1: Dose reduction versus dose maintenance , Outcome 25: Global state - number of participants with relapse/exacerbations of psychosis (separated time points)



Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.25.1 < 3 months						
Caffey 1964 (1)	10	89	4	88	10.3%	2.47 [0.81 , 7.59]
Carpenter 1999 (2)	6	25	3	25	9.4%	2.00 [0.56 , 7.12]
Fleischhacker 2014 (2)	14	131	14	266	12.9%	2.03 [1.00 , 4.13]
Huhn 2020 (2)	0	11	1	9	3.2%	0.28 [0.01 , 6.10]
Johnson 1987 (2)	4	29	0	31	3.6%	9.60 [0.54 , 170.84]
Kane 1983 (2)	10	62	1	64	5.9%	10.32 [1.36 , 78.26]
Kane 2010 (2)	33	144	14	322	13.6%	5.27 [2.91 , 9.54]
Lonowski 1978 (2)	17	25	18	23	14.8%	0.87 [0.62 , 1.23]
Ozawa 2019 (3)	2	17	0	18	3.4%	5.28 [0.27 , 102.58]
Rouillon 2008 (4)	1	49	1	48	3.9%	0.98 [0.06 , 15.22]
Wang 2010 (2)	25	211	2	129	8.6%	7.64 [1.84 , 31.73]
Wunderink 2007 (2)	9	68	4	63	10.3%	2.08 [0.68 , 6.43]
Subtotal (95% CI)		**861**		**1086**	**100.0%**	**2.56 [1.37 , 4.78]**
Total events:	131		62			
Heterogeneity: Tau² = 0.66; Chi² = 40.14, df = 11 (P < 0.0001); I² = 73%						
Test for overall effect: Z = 2.95 (P = 0.003)						
1.25.2 < 6 months						
Caffey 1964 (1)	13	89	4	88	6.8%	3.21 [1.09 , 9.47]
Carpenter 1999 (2)	9	25	8	25	8.6%	1.13 [0.52 , 2.44]
Faraone 1989 (1)	8	22	0	7	2.1%	5.91 [0.38 , 91.24]
Fleischhacker 2014 (2)	26	131	21	266	10.0%	2.51 [1.47 , 4.30]
Huhn 2020 (2)	1	11	2	9	2.9%	0.41 [0.04 , 3.82]
Johnson 1987 (2)	5	29	2	31	4.7%	2.67 [0.56 , 12.71]
Kane 1983 (2)	23	62	3	64	6.5%	7.91 [2.50 , 25.03]
Kane 2010 (2)	44	144	21	322	10.3%	4.69 [2.90 , 7.58]
Lonowski 1978 (2)	19	25	18	23	11.2%	0.97 [0.71 , 1.32]
Ozawa 2019 (3)	2	17	0	18	1.8%	5.28 [0.27 , 102.58]
Remington 2011 (2)	4	17	3	18	5.6%	1.41 [0.37 , 5.40]
Rouillon 2008 (4)	4	49	3	48	5.1%	1.31 [0.31 , 5.53]
Schooler 1997 (5)	26	106	10	107	9.2%	2.62 [1.33 , 5.17]
Wang 2010 (2)	35	211	4	129	7.2%	5.35 [1.95 , 14.70]
Wunderink 2007 (2)	14	68	6	63	7.9%	2.16 [0.89 , 5.28]
Subtotal (95% CI)		**1006**		**1218**	**100.0%**	**2.37 [1.54 , 3.67]**
Total events:	233		105			
Heterogeneity: Tau² = 0.42; Chi² = 49.90, df = 14 (P < 0.00001); I² = 72%						
Test for overall effect: Z = 3.89 (P < 0.0001)						
1.25.3 < 1 year						
Branchey 1981 (6)	16	22	2	11	5.3%	4.00 [1.11 , 14.38]
Carpenter 1999 (2)	13	25	11	25	12.1%	1.18 [0.66 , 2.11]
Cookson 1987 (2)	3	9	3	9	5.1%	1.00 [0.27 , 3.69]
Fleischhacker 2014 (2)	36	131	22	266	13.5%	3.32 [2.04 , 5.41]
Hogarty 1988 (2)	7	37	4	33	6.2%	1.56 [0.50 , 4.86]
Johnson 1987 (2)	9	28	3	31	5.7%	3.32 [1.00 , 11.06]
Kane 1983 (2)	35	62	5	64	8.5%	7.23 [3.03 , 17.24]
Ozawa 2019 (3)	3	17	0	18	1.3%	7.39 [0.41 , 133.24]
Schooler 1997 (5)	41	106	21	107	14.0%	1.97 [1.25 , 3.10]
Takeuchi 2014 (2)	1	31	1	30	1.5%	0.97 [0.06 , 14.78]
Wang 2010 (2)	47	211	8	129	10.3%	3.59 [1.75 , 7.36]
Wunderink 2007 (2)	22	68	9	63	10.6%	2.26 [1.13 , 4.54]
Zhou 2018 (2)	4	37	6	38	5.9%	0.68 [0.21 , 2.23]
Subtotal (95% CI)		**784**		**824**	**100.0%**	**2.31 [1.63 , 3.27]**
Total events:	237		95			
Heterogeneity: Tau² = 0.17; Chi² = 23.97, df = 12 (P = 0.02); I² = 50%						
Test for overall effect: Z = 4.71 (P < 0.00001)						

Analysis 1.25. (Continued)

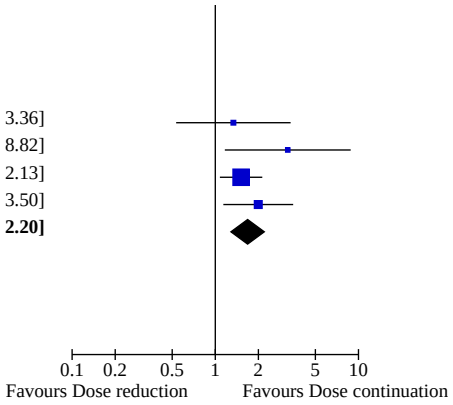
Heterogeneity: Tau² = 0.17; Chi² = 23.97, df = 12 (P = 0.02); I² = 50%
Test for overall effect: Z = 4.71 (P < 0.00001)

1.25.4 > 1 year

Hogarty 1988 (2)	9	37	6	33	8.5%	1.34 [0.53 , 3.36]
Johnson 1987 (2)	12	29	4	31	7.0%	3.21 [1.17 , 8.82]
Schooler 1997 (5)	51	106	34	107	61.8%	1.51 [1.08 , 2.13]
Wunderink 2007 (2)	28	68	13	63	22.8%	2.00 [1.14 , 3.50]
Subtotal (95% CI)		**240**		**234**	**100.0%**	**1.68 [1.29 , 2.20]**
Total events:	100		57			

Heterogeneity: Tau² = 0.00; Chi² = 2.52, df = 3 (P = 0.47); I² = 0%
Test for overall effect: Z = 3.80 (P = 0.0001)

Test for subgroup differences: Chi² = 3.45, df = 3 (P = 0.33), I² = 13.0%

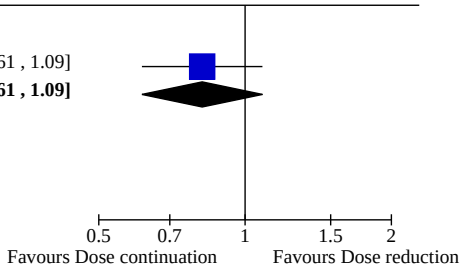


Footnotes
(1) relapse by clinical judgement
(2) scale defined relapse
(3) dropouts due to clinical worsening
(4) hospitalisation
(5) clinical worsening needing rescue medication
(6) severe or persistent (> 1 week) clinical worsening

Analysis 1.26. Comparison 1: Dose reduction versus dose maintenance , Outcome 26: Global state - remission

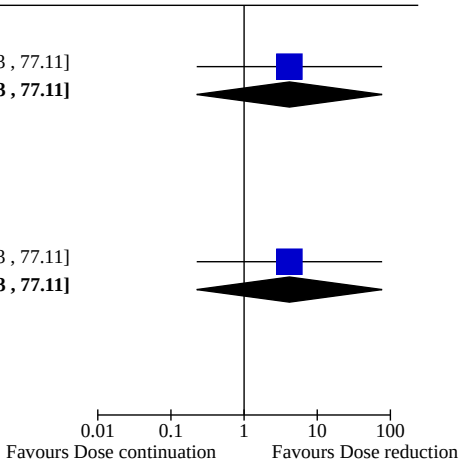
	Dose reduction		Dose continuation			Risk Ratio	Risk Ratio
Study or Subgroup	**Events**	**Total**	**Events**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
1.26.1 < 1 year							
Fleischhacker 2014	43	131	107	266	100.0%	0.82 [0.61 , 1.09]	
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.82 [0.61 , 1.09]**	
Total events:	43		107				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.40 (P = 0.16)



Analysis 1.27. Comparison 1: Dose reduction versus dose maintenance , Outcome 27: Global state - number of participants with clinically important change in global state

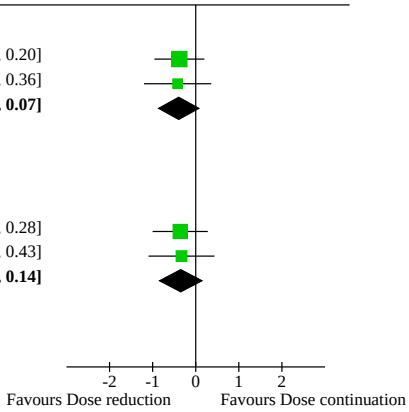
Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.27.1 < 3 months						
Huhn 2020 (1)	2	11	0	9	100.0%	4.17 [0.23 , 77.11]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**4.17 [0.23 , 77.11]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.27.2 < 6 months						
Huhn 2020 (1)	2	11	0	9	100.0%	4.17 [0.23 , 77.11]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**4.17 [0.23 , 77.11]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						



Footnotes
(1) CGI-I 1 or 2

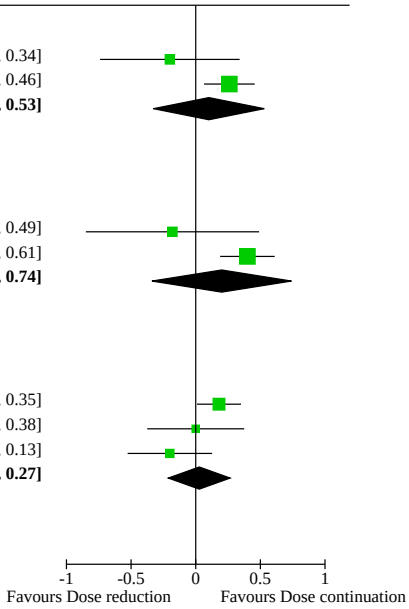
Analysis 1.28. Comparison 1: Dose reduction versus dose maintenance , Outcome 28: Global state - mean endpoint CGI-S (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.28.1 < 3 months								
Huhn 2020	2.73	0.47	11	3.11	0.78	9	64.4%	-0.38 [-0.96 , 0.20]
Remington 2011	2.83	0.84	14	3.25	1.14	12	35.6%	-0.42 [-1.20 , 0.36]
Subtotal (95% CI)			**25**			**21**	**100.0%**	**-0.39 [-0.86 , 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.94); I² = 0%								
Test for overall effect: Z = 1.66 (P = 0.10)								
1.28.2 < 6 months								
Huhn 2020	2.64	0.5	11	3	0.87	9	58.8%	-0.36 [-1.00 , 0.28]
Remington 2011	2.75	0.75	14	3.08	1.16	12	41.2%	-0.33 [-1.09 , 0.43]
Subtotal (95% CI)			**25**			**21**	**100.0%**	**-0.35 [-0.84 , 0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.39 (P = 0.17)								
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%								



Analysis 1.29. Comparison 1: Dose reduction versus dose maintenance , Outcome 29: Global state - mean change CGI-S (high = poor)

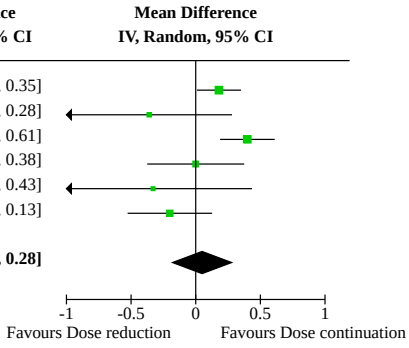
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.29.1 < 3 months								
Huhn 2020	-0.09	0.3	11	0.11	0.78	9	34.5%	-0.20 [-0.74 , 0.34]
Kane 2010	0.23	1.1	143	-0.03	0.7	322	65.5%	0.26 [0.06 , 0.46]
Subtotal (95% CI)			**154**			**331**	**100.0%**	**0.10 [-0.33 , 0.53]**
Heterogeneity: Tau² = 0.06; Chi² = 2.47, df = 1 (P = 0.12); I² = 59%								
Test for overall effect: Z = 0.46 (P = 0.64)								
1.29.2 < 6 months								
Huhn 2020	-0.18	0.6	11	0	0.87	9	34.4%	-0.18 [-0.85 , 0.49]
Kane 2010	0.3	1.2	143	-0.1	0.7	322	65.6%	0.40 [0.19 , 0.61]
Subtotal (95% CI)			**154**			**331**	**100.0%**	**0.20 [-0.34 , 0.74]**
Heterogeneity: Tau² = 0.10; Chi² = 2.62, df = 1 (P = 0.11); I² = 62%								
Test for overall effect: Z = 0.73 (P = 0.47)								
1.29.3 < 1 year								
Fleischhacker 2014	0.23	0.8	129	0.05	0.82	263	46.9%	0.18 [0.01 , 0.35]
Ozawa 2019 (1)	0.1	0.4	17	0.1	0.7	18	24.5%	0.00 [-0.38 , 0.38]
Takeuchi 2014	-0.2	0.7	31	0	0.6	30	28.6%	-0.20 [-0.53 , 0.13]
Subtotal (95% CI)			**177**			**311**	**100.0%**	**0.03 [-0.21 , 0.27]**
Heterogeneity: Tau² = 0.02; Chi² = 4.32, df = 2 (P = 0.12); I² = 54%								
Test for overall effect: Z = 0.22 (P = 0.82)								
Test for subgroup differences: Chi² = 0.37, df = 2 (P = 0.83), I² = 0%								



Footnotes
(1) CGI-SCH

Analysis 1.30. Comparison 1: Dose reduction versus dose maintenance , Outcome 30: Global state - mean endpoint/change CGI-S (high = poor) (combined time points)

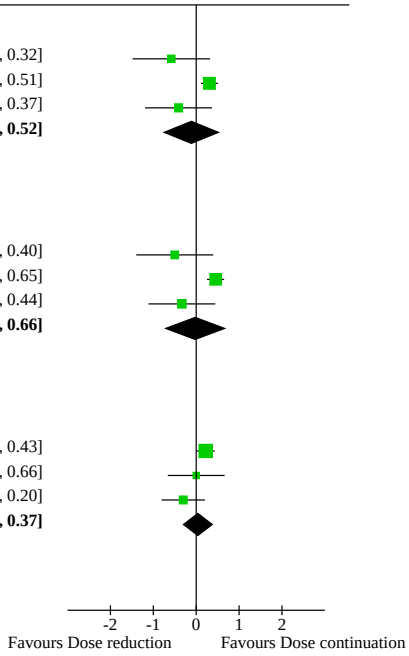
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	0.23	0.8	129	0.05	0.82	263	25.5%	0.18 [0.01 , 0.35]
Huhn 2020 (2)	2.64	0.5	11	3	0.87	9	8.9%	-0.36 [-1.00 , 0.28]
Kane 2010 (3)	0.3	1.2	143	-0.1	0.7	322	23.7%	0.40 [0.19 , 0.61]
Ozawa 2019 (4)	0.1	0.4	17	0.1	0.7	18	16.5%	0.00 [-0.38 , 0.38]
Remington 2011 (2)	2.75	0.75	14	3.08	1.16	12	6.9%	-0.33 [-1.09 , 0.43]
Takeuchi 2014 (1)	-0.2	0.7	31	0	0.6	30	18.5%	-0.20 [-0.53 , 0.13]
Total (95% CI)			**345**			**654**	**100.0%**	**0.05 [-0.18 , 0.28]**
Heterogeneity: Tau² = 0.05; Chi² = 14.48, df = 5 (P = 0.01); I² = 65%								
Test for overall effect: Z = 0.42 (P = 0.67)								
Test for subgroup differences: Not applicable								



Footnotes
(1) CGI-S; change; <1 year
(2) CGI-S; endpoint; <6 months
(3) CGI-S; change; <3 months
(4) CGI-SCH; change; < 1 year

Analysis 1.31. Comparison 1: Dose reduction versus dose maintenance , Outcome 31: Global state - mean endpoint/change CGI-S (high = poor) (separated time points)

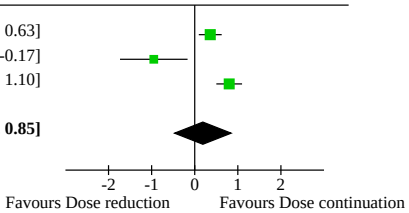
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.31.1 < 3 months								
Huhn 2020 (1)	2.73	0.47	11	3.11	0.78	9	24.6%	-0.58 [-1.48 , 0.32]
Kane 2010 (2)	0.23	1.1	143	-0.03	0.7	322	47.2%	0.31 [0.11 , 0.51]
Remington 2011 (1)	2.83	0.84	14	3.25	1.14	12	28.2%	-0.41 [-1.19 , 0.37]
Subtotal (95% CI)			**168**			**343**	**100.0%**	**-0.11 [-0.75 , 0.52]**
Heterogeneity: Tau² = 0.21; Chi² = 6.28, df = 2 (P = 0.04); I² = 68%								
Test for overall effect: Z = 0.35 (P = 0.72)								
1.31.2 < 6 months								
Huhn 2020 (3)	2.64	0.5	11	3	0.87	9	25.9%	-0.50 [-1.40 , 0.40]
Kane 2010 (2)	0.3	1.2	143	-0.1	0.7	322	44.9%	0.45 [0.25 , 0.65]
Remington 2011 (3)	2.75	0.75	14	3.08	1.16	12	29.2%	-0.33 [-1.11 , 0.44]
Subtotal (95% CI)			**168**			**343**	**100.0%**	**-0.02 [-0.71 , 0.66]**
Heterogeneity: Tau² = 0.26; Chi² = 7.39, df = 2 (P = 0.02); I² = 73%								
Test for overall effect: Z = 0.07 (P = 0.95)								
1.31.3 < 1 year								
Fleischhacker 2014 (4)	0.23	0.8	129	0.05	0.82	263	54.4%	0.22 [0.01 , 0.43]
Ozawa 2019 (5)	0.1	0.4	17	0.1	0.7	18	18.7%	0.00 [-0.66 , 0.66]
Takeuchi 2014 (4)	-0.2	0.7	31	0	0.6	30	26.9%	-0.30 [-0.81 , 0.20]
Subtotal (95% CI)			**177**			**311**	**100.0%**	**0.04 [-0.30 , 0.37]**
Heterogeneity: Tau² = 0.04; Chi² = 3.67, df = 2 (P = 0.16); I² = 46%								
Test for overall effect: Z = 0.23 (P = 0.82)								
Test for subgroup differences: Chi² = 0.18, df = 2 (P = 0.91), I² = 0%								



Footnotes
(1) CGI-S; endpoint; <3 months
(2) CGI-S; change; <3 months
(3) CGI-S; endpoint; <6 months
(4) CGI-S; change; <1 year
(5) CGI-SCH; change; < 1 year

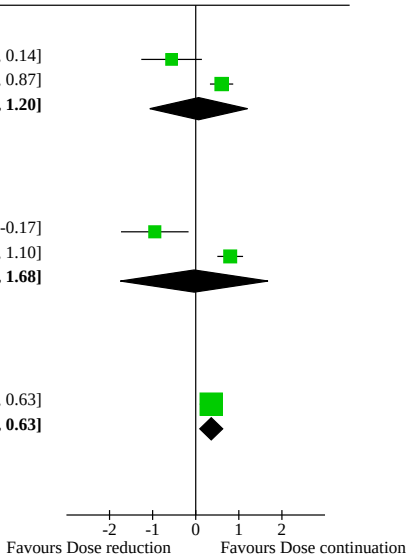
Analysis 1.32. Comparison 1: Dose reduction versus dose maintenance , Outcome 32: Global state - mean endpoint CGI-I (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fleischhacker 2014	4.02	1.32	131	3.66	1.16	266	37.6%	0.36 [0.09 , 0.63]
Huhn 2020	3.27	1.1	11	4.22	0.67	9	25.5%	-0.95 [-1.73 , -0.17]
Kane 2010	3.9	1.6	143	3.1	1.3	321	37.0%	0.80 [0.50 , 1.10]
Total (95% CI)			**285**			**596**	**100.0%**	**0.19 [-0.47 , 0.85]**
Heterogeneity: Tau² = 0.28; Chi² = 17.97, df = 2 (P = 0.0001); I² = 89%								
Test for overall effect: Z = 0.56 (P = 0.57)								
Test for subgroup differences: Not applicable								



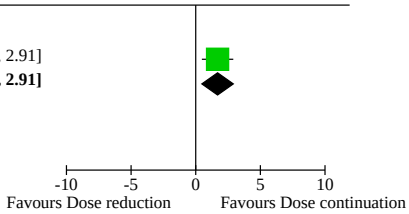
Analysis 1.33. Comparison 1: Dose reduction versus dose maintenance , Outcome 33: Global state - mean endpoint CGI-I (high = poor) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.33.1 < 3 months								
Huhn 2020	3.55	0.82	11	4.11	0.78	9	45.9%	-0.56 [-1.26 , 0.14]
Kane 2010	3.8	1.4	143	3.2	1.3	321	54.1%	0.60 [0.33 , 0.87]
Subtotal (95% CI)			**154**			**330**	**100.0%**	**0.07 [-1.07 , 1.20]**
Heterogeneity: Tau² = 0.60; Chi² = 9.11, df = 1 (P = 0.003); I² = 89%								
Test for overall effect: Z = 0.12 (P = 0.91)								
1.33.2 < 6 months								
Huhn 2020	3.27	1.1	11	4.22	0.67	9	47.8%	-0.95 [-1.73 , -0.17]
Kane 2010	3.9	1.6	143	3.1	1.3	321	52.2%	0.80 [0.50 , 1.10]
Subtotal (95% CI)			**154**			**330**	**100.0%**	**-0.04 [-1.75 , 1.68]**
Heterogeneity: Tau² = 1.44; Chi² = 16.73, df = 1 (P < 0.0001); I² = 94%								
Test for overall effect: Z = 0.04 (P = 0.97)								
1.33.3 < 1 year								
Fleischhacker 2014	4.02	1.32	131	3.66	1.16	266	100.0%	0.36 [0.09 , 0.63]
Subtotal (95% CI)			**131**			**266**	**100.0%**	**0.36 [0.09 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.66 (P = 0.008)								
Test for subgroup differences: Chi² = 0.43, df = 2 (P = 0.81), I² = 0%								



Analysis 1.34. Comparison 1: Dose reduction versus dose maintenance , Outcome 34: Global state - mean change IAQ-12 (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.34.1 < 1 year								
Fleischhacker 2014 (1)	2.04	5.81	131	0.35	5.81	266	100.0%	1.69 [0.47 , 2.91]
Subtotal (95% CI)			**131**			**266**	**100.0%**	**1.69 [0.47 , 2.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.73 (P = 0.006)								

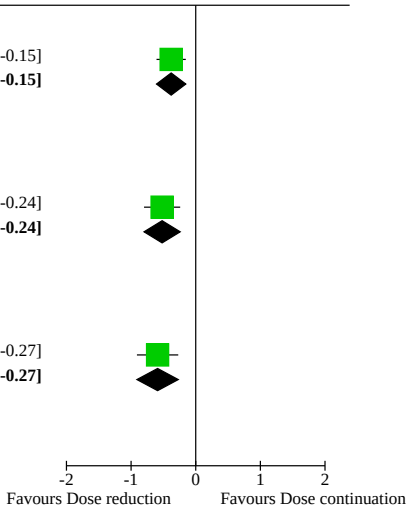


Footnotes

(1) SD estimated from the p-value of the comparison between 400mg/4 weeks and 50mg/4weeks

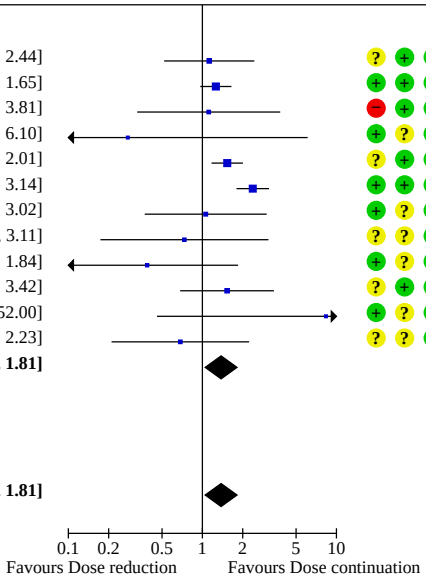
Analysis 1.35. Comparison 1: Dose reduction versus dose maintenance , Outcome 35: Global state - mean endpoint SCL-90 (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.35.1 < 3 months								
Kane 1983	0.25	0.34	13	0.63	0.34	26	100.0%	-0.38 [-0.61 , -0.15]
Subtotal (95% CI)			**13**			**26**	**100.0%**	**-0.38 [-0.61 , -0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.29 (P = 0.001)								
1.35.2 < 6 months								
Kane 1983	0.15	0.42	13	0.67	0.42	26	100.0%	-0.52 [-0.80 , -0.24]
Subtotal (95% CI)			**13**			**26**	**100.0%**	**-0.52 [-0.80 , -0.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.64 (P = 0.0003)								
1.35.3 < 1 year								
Kane 1983	0.1	0.48	13	0.69	0.48	26	100.0%	-0.59 [-0.91 , -0.27]
Subtotal (95% CI)			**13**			**26**	**100.0%**	**-0.59 [-0.91 , -0.27]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.62 (P = 0.0003)								
Test for subgroup differences: Chi² = 1.27, df = 2 (P = 0.53), I² = 0%								



Analysis 1.36. Comparison 1: Dose reduction versus dose maintenance , Outcome 36: Leaving the study early - for any reason - overall acceptability (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
1.36.1 Combined time points							
Carpenter 1999 (1)	9	25	8	25	8.4%	1.13 [0.52 , 2.44]	? + + + + ?
Fleischhacker 2014 (1)	54	131	87	266	20.8%	1.26 [0.96 , 1.65]	+ + + + + +
Hogarty 1988 (1)	5	37	4	33	4.2%	1.11 [0.33 , 3.81]	− + + + + −
Huhn 2020 (2)	0	11	1	9	0.8%	0.28 [0.01 , 6.10]	+ ? + + + ?
Kane 1983 (1)	49	62	33	64	20.8%	1.53 [1.17 , 2.01]	? + + + ? ?
Kane 2010 (2)	68	144	64	322	20.5%	2.38 [1.80 , 3.14]	+ + + + + +
Ozawa 2019 (1)	5	17	5	18	5.4%	1.06 [0.37 , 3.02]	+ ? + + + ?
Rouillon 2008 (2)	3	49	4	48	3.1%	0.73 [0.17 , 3.11]	? ? + + + ?
Takeuchi 2014 (1)	2	31	5	30	2.7%	0.39 [0.08 , 1.84]	+ ? + + + ?
Volavka 2000 (2)	7	11	5	12	8.0%	1.53 [0.68 , 3.42]	? + + + + ?
Wunderink 2007 (3)	4	68	0	63	0.9%	8.35 [0.46 , 152.00]	+ ? + + + ?
Zhou 2018 (1)	4	37	6	38	4.4%	0.68 [0.21 , 2.23]	? ? + + + ?
Subtotal (95% CI)		**623**		**928**	**100.0%**	**1.38 [1.05 , 1.81]**	
Total events:	210		222				
Heterogeneity: Tau² = 0.07; Chi² = 21.12, df = 11 (P = 0.03); I² = 48%							
Test for overall effect: Z = 2.31 (P = 0.02)							
Total (95% CI)		**623**		**928**	**100.0%**	**1.38 [1.05 , 1.81]**	
Total events:	210		222				
Heterogeneity: Tau² = 0.07; Chi² = 21.12, df = 11 (P = 0.03); I² = 48%							
Test for overall effect: Z = 2.31 (P = 0.02)							
Test for subgroup differences: Not applicable							



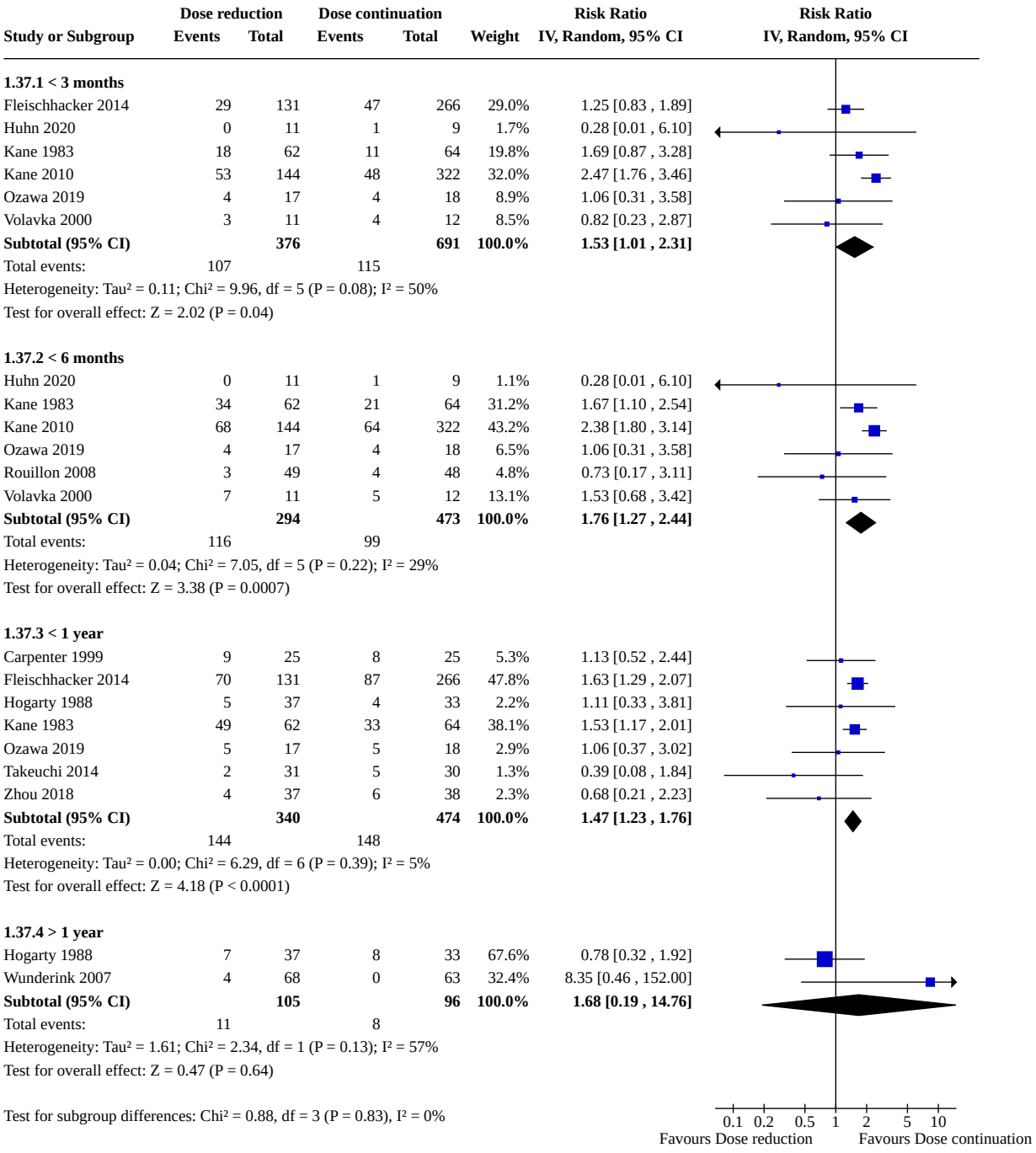
Footnotes

(1) < 1 year
(2) < 6 months
(3) > 1 year

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

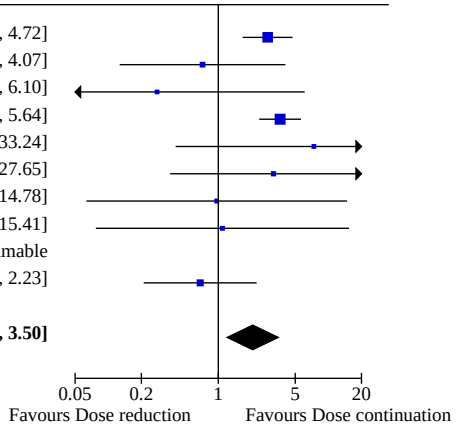
Analysis 1.37. Comparison 1: Dose reduction versus dose maintenance , Outcome 37: Leaving the study early - for any reason - overall acceptability (separated time points)



Analysis 1.38. Comparison 1: Dose reduction versus dose maintenance , Outcome 38: Leaving the study early - due to inefficacy - overall efficacy (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014 (1)	29	131	21	266	29.0%	2.80 [1.67 , 4.72]
Hogarty 1995 (2)	2	38	3	41	7.6%	0.72 [0.13 , 4.07]
Huhn 2020 (3)	0	11	1	9	2.8%	0.28 [0.01 , 6.10]
Kane 2010 (3)	44	144	27	322	31.6%	3.64 [2.35 , 5.64]
Ozawa 2019 (1)	3	17	0	18	3.1%	7.39 [0.41 , 133.24]
Remington 2011 (3)	3	17	1	18	5.3%	3.18 [0.36 , 27.65]
Takeuchi 2014 (1)	1	31	1	30	3.5%	0.97 [0.06 , 14.78]
Volavka 2000 (2)	1	11	1	12	3.7%	1.09 [0.08 , 15.41]
Wunderink 2007 (1)	0	68	0	63		Not estimable
Zhou 2018 (1)	4	37	6	38	13.5%	0.68 [0.21 , 2.23]
Total (95% CI)		**505**		**817**	**100.0%**	**2.06 [1.21 , 3.50]**
Total events:	87		61			

Heterogeneity: Tau² = 0.18; Chi² = 12.81, df = 8 (P = 0.12); I² = 38%
Test for overall effect: Z = 2.65 (P = 0.008)
Test for subgroup differences: Not applicable

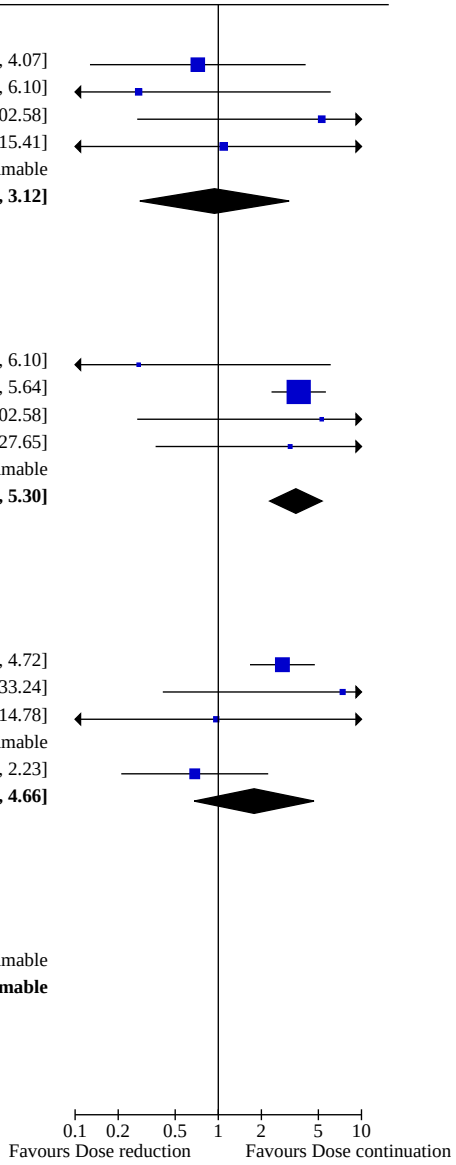


Footnotes

(1) < 1 year
(2) < 3 months
(3) < 6 months

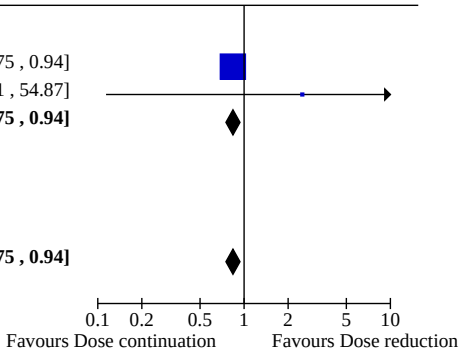
Analysis 1.39. Comparison 1: Dose reduction versus dose maintenance , Outcome 39: Leaving the study early - due to inefficacy - overall efficacy (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.39.1 < 3 months						
Hogarty 1995	2	38	3	41	48.0%	0.72 [0.13 , 4.07]
Huhn 2020	0	11	1	9	15.1%	0.28 [0.01 , 6.10]
Ozawa 2019	2	17	0	18	16.4%	5.28 [0.27 , 102.58]
Volavka 2000	1	11	1	12	20.6%	1.09 [0.08 , 15.41]
Wunderink 2007	0	68	0	63		Not estimable
Subtotal (95% CI)		**145**		**143**	**100.0%**	**0.94 [0.28 , 3.12]**
Total events:	5		5			
Heterogeneity: Tau² = 0.00; Chi² = 2.00, df = 3 (P = 0.57); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
1.39.2 < 6 months						
Huhn 2020	0	11	1	9	1.8%	0.28 [0.01 , 6.10]
Kane 2010	44	144	27	322	92.4%	3.64 [2.35 , 5.64]
Ozawa 2019	2	17	0	18	2.0%	5.28 [0.27 , 102.58]
Remington 2011	3	17	1	18	3.8%	3.18 [0.36 , 27.65]
Wunderink 2007	0	68	0	63		Not estimable
Subtotal (95% CI)		**257**		**430**	**100.0%**	**3.48 [2.29 , 5.30]**
Total events:	49		29			
Heterogeneity: Tau² = 0.00; Chi² = 2.70, df = 3 (P = 0.44); I² = 0%						
Test for overall effect: Z = 5.82 (P < 0.00001)						
1.39.3 < 1 year						
Fleischhacker 2014	29	131	21	266	49.5%	2.80 [1.67 , 4.72]
Ozawa 2019	3	17	0	18	9.3%	7.39 [0.41 , 133.24]
Takeuchi 2014	1	31	1	30	10.3%	0.97 [0.06 , 14.78]
Wunderink 2007	0	68	0	63		Not estimable
Zhou 2018	4	37	6	38	30.9%	0.68 [0.21 , 2.23]
Subtotal (95% CI)		**284**		**415**	**100.0%**	**1.78 [0.68 , 4.66]**
Total events:	37		28			
Heterogeneity: Tau² = 0.42; Chi² = 5.60, df = 3 (P = 0.13); I² = 46%						
Test for overall effect: Z = 1.17 (P = 0.24)						
1.39.4 > 1 year						
Wunderink 2007	0	68	0	63		Not estimable
Subtotal (95% CI)		**68**		**63**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Chi² = 5.06, df = 2 (P = 0.08), I² = 60.5%						



Analysis 1.40. Comparison 1: Dose reduction versus dose maintenance , Outcome 40: Mental state - general: number of participants with clinically important change in general mental state (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.40.1 < 1 year						
Fleischhacker 2014 (1)	97	131	235	266	99.9%	0.84 [0.75 , 0.94]
Huhn 2020 (2)	1	11	0	9	0.1%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**142**		**275**	**100.0%**	**0.84 [0.75 , 0.94]**
Total events:	98		235			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 3.11 (P = 0.002)						
Total (95% CI)		**142**		**275**	**100.0%**	**0.84 [0.75 , 0.94]**
Total events:	98		235			
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%						
Test for overall effect: Z = 3.11 (P = 0.002)						
Test for subgroup differences: Not applicable						



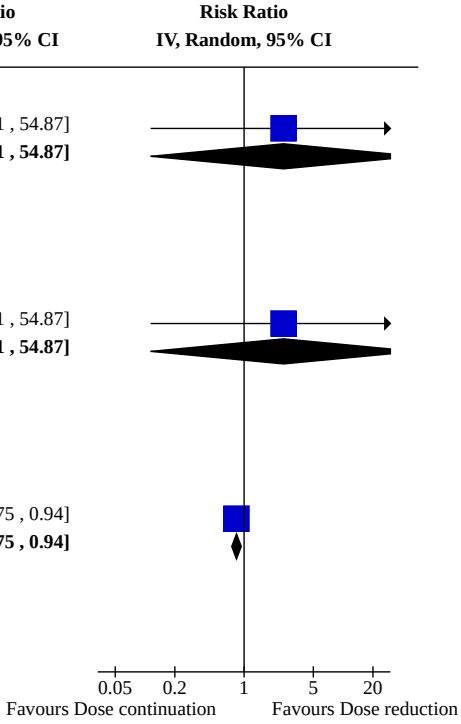
Footnotes

(1) <1 year

(2) <6 months; At least 50% reduction in PANSS total

Analysis 1.41. Comparison 1: Dose reduction versus dose maintenance , Outcome 41: Mental state - general: number of participants with clinically important change in general mental state (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.41.1 < 3 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.41.2 < 6 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.41.3 < 1 year						
Fleischhacker 2014	97	131	235	266	100.0%	0.84 [0.75 , 0.94]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.84 [0.75 , 0.94]**
Total events:	97		235			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.14 (P = 0.002)						
Test for subgroup differences: Chi² = 0.96, df = 2 (P = 0.62), I² = 0%						

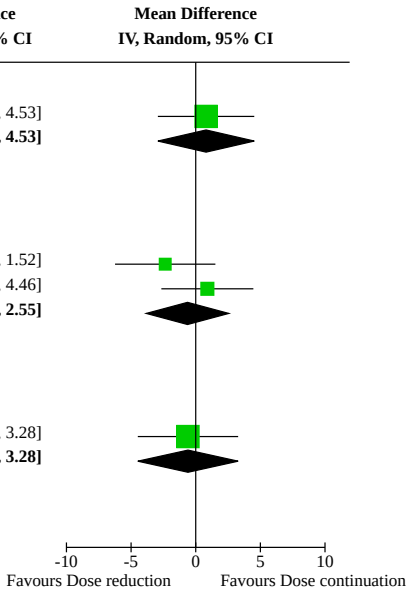


Footnotes

(1) At least 50% reduction in PANSS total

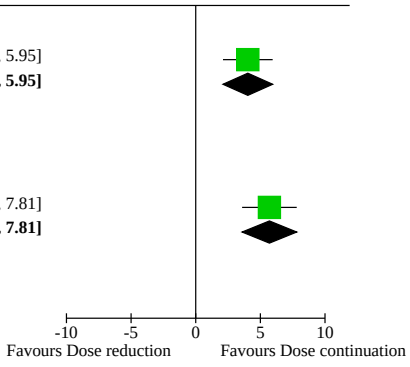
Analysis 1.42. Comparison 1: Dose reduction versus dose maintenance , Outcome 42: Mental state - general: mean endpoint BPRS total (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.42.1 < 3 months								
Remington 2011	24.9	5.58	14	24.1	4.09	12	100.0%	0.80 [-2.93 , 4.53]
Subtotal (95% CI)			**14**			**12**	**100.0%**	**0.80 [-2.93 , 4.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.42 (P = 0.67)								
1.42.2 < 6 months								
Carpenter 1999	24.48	7	25	26.84	7	25	47.1%	-2.36 [-6.24 , 1.52]
Remington 2011	24.4	5.16	14	23.5	4.09	12	52.9%	0.90 [-2.66 , 4.46]
Subtotal (95% CI)			**39**			**37**	**100.0%**	**-0.63 [-3.82 , 2.55]**
Heterogeneity: Tau² = 1.71; Chi² = 1.47, df = 1 (P = 0.22); I² = 32%								
Test for overall effect: Z = 0.39 (P = 0.70)								
1.42.3 < 1 year								
Carpenter 1999	24.36	7	25	24.96	7	25	100.0%	-0.60 [-4.48 , 3.28]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-0.60 [-4.48 , 3.28]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.30 (P = 0.76)								
Test for subgroup differences: Chi² = 0.39, df = 2 (P = 0.82), I² = 0%								



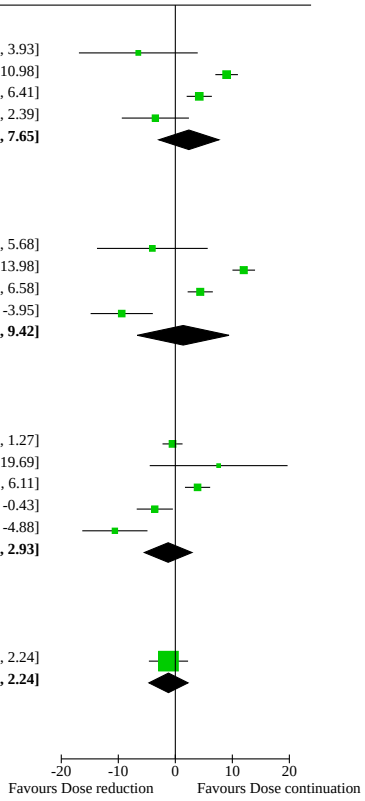
Analysis 1.43. Comparison 1: Dose reduction versus dose maintenance , Outcome 43: Mental state - general: mean change BPRS total (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.43.1 < 3 months								
Kane 2010	3.25	10.9	144	-0.78	6.6	322	100.0%	4.03 [2.11 , 5.95]
Subtotal (95% CI)			**144**			**322**	**100.0%**	**4.03 [2.11 , 5.95]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.11 (P < 0.0001)								
1.43.2 < 6 months								
Kane 2010	4.6	12	144	-1.1	7.2	322	100.0%	5.70 [3.59 , 7.81]
Subtotal (95% CI)			**144**			**322**	**100.0%**	**5.70 [3.59 , 7.81]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.29 (P < 0.00001)								
Test for subgroup differences: Chi² = 1.31, df = 1 (P = 0.25), I² = 23.9%								



Analysis 1.44. Comparison 1: Dose reduction versus dose maintenance , Outcome 44: Mental state - general: mean endpoint PANSS total (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.44.1 < 3 months								
Huhn 2020	46.73	10.257	11	53.22	12.968	9	14.4%	-6.49 [-16.91 , 3.93]
Kane 2010 (1)	63	10.07975772	144	54	10.07975772	322	31.3%	9.00 [7.02 , 10.98]
Wang 2010 (1)	40.2	10.07975772	211	36	10.07975772	129	31.0%	4.20 [1.99 , 6.41]
Zhou 2018 (2)	64.2	12.6	37	67.7	13.4	38	23.3%	-3.50 [-9.39 , 2.39]
Subtotal (95% CI)			**403**			**498**	**100.0%**	**2.37 [-2.90 , 7.65]**
Heterogeneity: Tau² = 22.11; Chi² = 26.90, df = 3 (P < 0.00001); I² = 89%								
Test for overall effect: Z = 0.88 (P = 0.38)								
1.44.2 < 6 months								
Huhn 2020	46.63636364	6.845038017	11	50.66666667	13.50925609	9	19.9%	-4.03 [-13.74 , 5.68]
Kane 2010 (1)	65	10.07975772	144	53	10.07975772	322	27.6%	12.00 [10.02 , 13.98]
Wang 2010 (1)	41.7	10.07975772	211	37.33	10.07975772	129	27.5%	4.37 [2.16 , 6.58]
Zhou 2018 (2)	61.2	11.9	37	70.6	12.2	38	24.9%	-9.40 [-14.85 , -3.95]
Subtotal (95% CI)			**403**			**498**	**100.0%**	**1.38 [-6.66 , 9.42]**
Heterogeneity: Tau² = 59.88; Chi² = 69.59, df = 3 (P < 0.00001); I² = 96%								
Test for overall effect: Z = 0.34 (P = 0.74)								
1.44.3 < 1 year								
Fleischhacker 2014 (2)	56.08	8.44	131	56.57	8.3	266	25.6%	-0.49 [-2.25 , 1.27]
Ozawa 2019	79.2	21.1	17	71.6	14.6	18	8.3%	7.60 [-4.49 , 19.69]
Wang 2010 (1)	41.8	10.07975772	211	37.9	10.07975772	129	25.0%	3.90 [1.69 , 6.11]
Wunderink 2007 (2)	44.4	7.97	65	48	10.16	63	23.3%	-3.60 [-6.77 , -0.43]
Zhou 2018 (2)	59.4	11.6	37	70	13.6	38	17.9%	-10.60 [-16.32 , -4.88]
Subtotal (95% CI)			**461**			**514**	**100.0%**	**-1.25 [-5.44 , 2.93]**
Heterogeneity: Tau² = 16.97; Chi² = 31.97, df = 4 (P < 0.00001); I² = 87%								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.44.4 > 1 year								
Wunderink 2007 (2)	47.8	9.94	65	49	9.89	63	100.0%	-1.20 [-4.64 , 2.24]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-1.20 [-4.64 , 2.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.49)								
Test for subgroup differences: Chi² = 1.61, df = 3 (P = 0.66), I² = 0%								



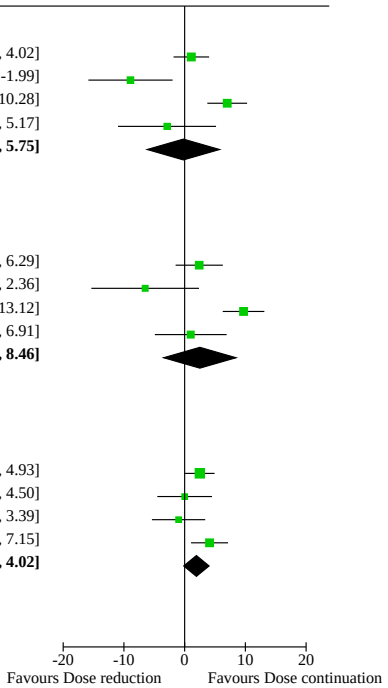
Footnotes

(1) imputed SD

(2) SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)

Analysis 1.45. Comparison 1: Dose reduction versus dose maintenance , Outcome 45: Mental state - general: mean change PANSS total (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.45.1 < 3 months								
Fleischhacker 2014	1.3	14.9	131	0.2	11.9	266	29.2%	1.10 [-1.82 , 4.02]
Huhn 2020	-3.364	7.187	11	5.555555556	8.383184227	9	22.1%	-8.92 [-15.85 , -1.99]
Kane 2010	5.35	18.7	144	-1.66	10.8	322	28.7%	7.01 [3.74 , 10.28]
Volavka 2000 (1)	-6.1	8.2	11	-3.2	11.4	12	20.0%	-2.90 [-10.97 , 5.17]
Subtotal (95% CI)			**297**			**609**	**100.0%**	**-0.21 [-6.17 , 5.75]**
Heterogeneity: Tau² = 29.39; Chi² = 20.26, df = 3 (P = 0.0002); I² = 85%								
Test for overall effect: Z = 0.07 (P = 0.94)								
1.45.2 < 6 months								
Fleischhacker 2014	2.6	21.1	131	0.2	11.9	266	28.1%	2.40 [-1.49 , 6.29]
Huhn 2020	-3.5	10.6	11	3	9.6	9	18.7%	-6.50 [-15.36 , 2.36]
Kane 2010	7.2	19.2	144	-2.5	12.6	322	28.9%	9.70 [6.28 , 13.12]
Rouillon 2008	-5.4	10	49	-6.4	18.4	48	24.3%	1.00 [-4.91 , 6.91]
Subtotal (95% CI)			**335**			**645**	**100.0%**	**2.50 [-3.46 , 8.46]**
Heterogeneity: Tau² = 28.95; Chi² = 17.16, df = 3 (P = 0.0007); I² = 83%								
Test for overall effect: Z = 0.82 (P = 0.41)								
1.45.3 < 1 year								
Fleischhacker 2014	3.1	11.6	131	0.6	11.6	266	37.1%	2.50 [0.07 , 4.93]
Ozawa 2019	0.1	5.4	17	0.1	8	18	16.7%	0.00 [-4.50 , 4.50]
Takeuchi 2014	-6.7	10.3	31	-5.7	6.9	30	17.4%	-1.00 [-5.39 , 3.39]
Wang 2010 (2)	2.9	13.4	211	-1.2	14.2	129	28.8%	4.10 [1.05 , 7.15]
Subtotal (95% CI)			**390**			**443**	**100.0%**	**1.94 [-0.15 , 4.02]**
Heterogeneity: Tau² = 1.52; Chi² = 4.51, df = 3 (P = 0.21); I² = 34%								
Test for overall effect: Z = 1.82 (P = 0.07)								
Test for subgroup differences: Chi² = 0.51, df = 2 (P = 0.78), I² = 0%								



Footnotes

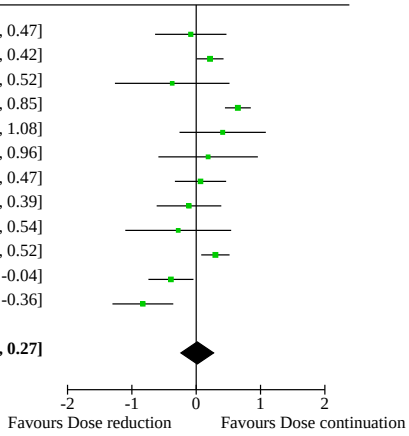
(1) minus transformed, it was reproted as improvement

(2) Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.46. Comparison 1: Dose reduction versus dose maintenance , Outcome 46: Mental state - general: mean endpoint/change overall symptom scales (PANSS/BPRS) (high = poor) (combined time points)

	Dose reduction			Dose continuation				Std. Mean Difference
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI
Carpenter 1999 (1)	24.36	7	25	24.96	7	25	7.7%	-0.08 [-0.64 , 0.47]
Fleischhacker 2014 (2)	3.1	11.6	131	0.6	11.6	266	11.2%	0.22 [0.01 , 0.42]
Huhn 2020 (3)	46.64	6.85	11	50.67	13.51	9	4.9%	-0.37 [-1.26 , 0.52]
Kane 2010 (4)	7.2	19.2	144	-2.5	12.6	322	11.3%	0.65 [0.45 , 0.85]
Ozawa 2019 (5)	79.2	21.1	17	71.6	14.6	18	6.6%	0.41 [-0.26 , 1.08]
Remington 2011 (6)	24.4	5.16	14	23.5	4.09	12	5.7%	0.19 [-0.59 , 0.96]
Rouillon 2008 (7)	-5.4	10	49	-6.4	18.4	48	9.4%	0.07 [-0.33 , 0.47]
Takeuchi 2014 (8)	-6.7	10.3	31	-5.7	6.9	30	8.2%	-0.11 [-0.61 , 0.39]
Volavka 2000 (9)	-6.1	8.2	11	-3.2	11.4	12	5.3%	-0.28 [-1.10 , 0.54]
Wang 2010 (10)	2.9	13.4	211	-1.2	14.2	129	11.2%	0.30 [0.08 , 0.52]
Wunderink 2007 (11)	44.4	7.97	65	48	10.16	63	9.9%	-0.39 [-0.74 , -0.04]
Zhou 2018 (12)	59.4	11.6	37	70	13.6	38	8.6%	-0.83 [-1.30 , -0.36]
Total (95% CI)			**746**			**972**	**100.0%**	**0.02 [-0.24 , 0.27]**

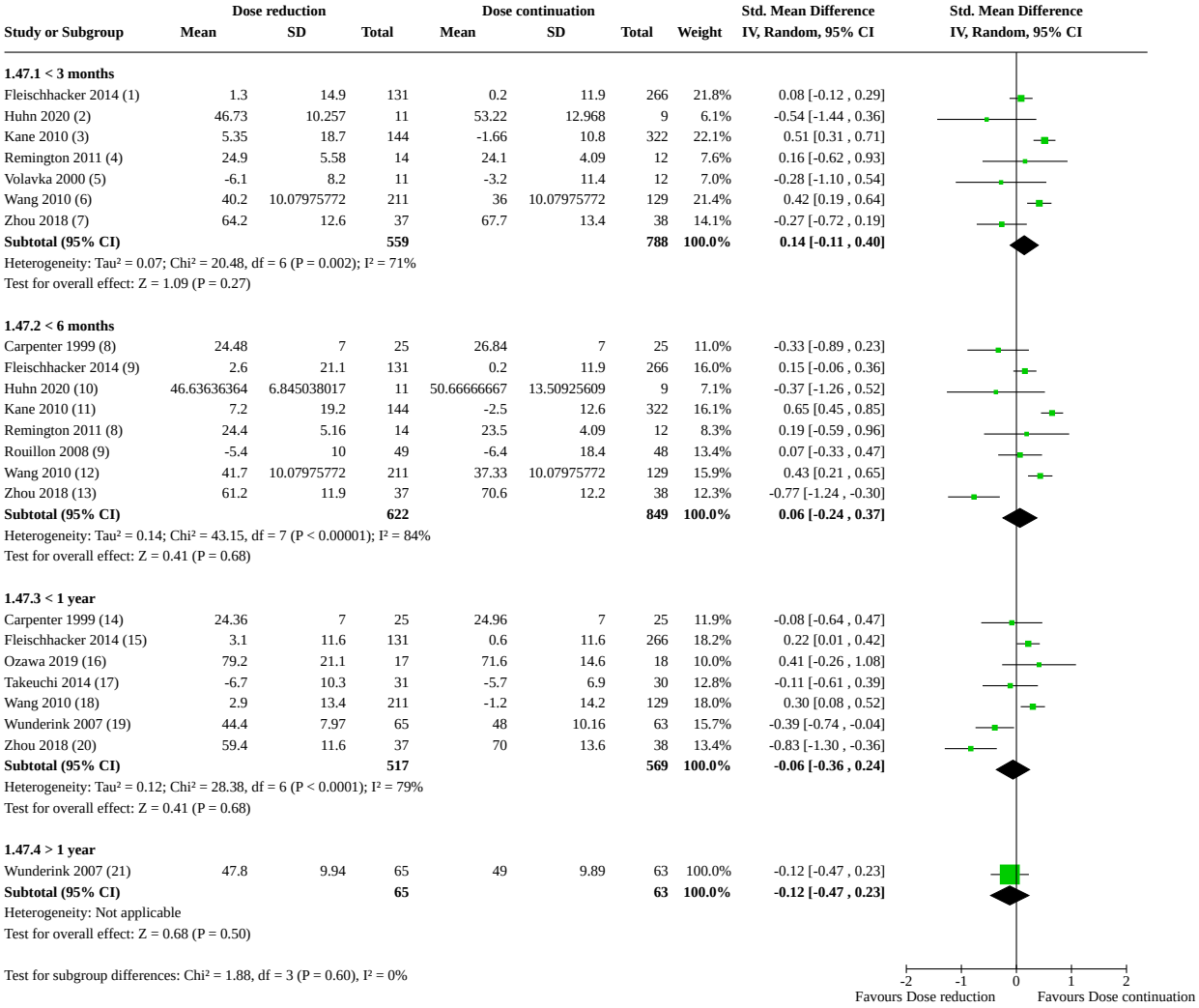
Heterogeneity: Tau² = 0.14; Chi² = 55.30, df = 11 (P < 0.00001); I² = 80%
Test for overall effect: Z = 0.12 (P = 0.90)
Test for subgroup differences: Not applicable



Footnotes

(1) BPRS; endpoint; < 1 year
(2) PANSS; change < 1 year; change was used because provided the original SD
(3) PANSS; endpoint; < 6 year;
(4) PANSS; change; < 6 months; change was used because provided the original SD
(5) PANSS; endpoint; < 1 year;
(6) BPRS; endpoint; < 6 months
(7) PANSS; change; < 6 months
(8) PANSS; change; < 1 year
(9) PANSS; change; < 3 months; minus transformed it was reported as improvement
(10) PANSS; change; < 1 year; change was used because provided the original SD
(11) PANSS; endpoint; < 1 year; SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(12) PANSS; endpoint; <1 year; SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)

Analysis 1.47. Comparison 1: Dose reduction versus dose maintenance , Outcome 47: Mental state - general: mean endpoint/change overall symptom scales (PANSS/BPRS) (high = poor) (separated time points)

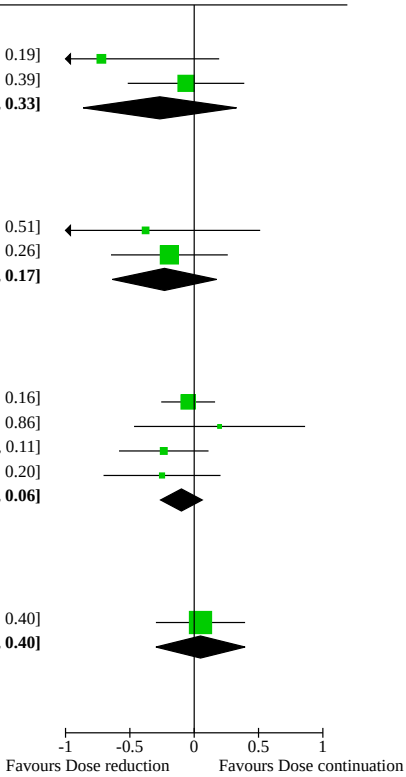


Footnotes

(1) PANSS; change; < 3 months
(2) PANSS; endpoint; < 3 months
(3) PANSS; CHANGE; < 3 months; change was used because provided original SD
(4) BPRS; endpoint; < 3 months
(5) PANSS; change; < 3 months; minus transformed it was reported as improvement
(6) PANSS; endpoint; < 3 months; imputed SD
(7) PANSS; endpoint; < 3 monthsSD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(8) BPRS; endpoint; < 6 months
(9) PANSS; change; < 6 months
(10) PANSS; endpoint; < 6 year;
(11) PANSS; change; < 6 months; change was used because provided original SD
(12) PANSS; endpoint; < 6 months; imputed SD
(13) PANSS; endpoint; < 6 months; SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(14) BPRS; endpoint; < 1 year
(15) PANSS; change; < 1 year; chane was used because provided the original SD
(16) PANSS; endpoint; < 1 year;
(17) PANSS; change; < 1 year
(18) PANSS; change; < 1 year; change was used because provided original SD
(19) PANSS; endpoint; < 1 year; SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(20) PANSS; endpoint; <1 year; SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(21) PANSS; endpoint; >1 year; SD calculated by adding the subscales (assuming a correlation of 0; conservative assumption)

Analysis 1.48. Comparison 1: Dose reduction versus dose maintenance , Outcome 48: Mental state - specific: mean endpoint PANSS positive (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.48.1 < 3 months								
Huhn 2020	9.55	2.25	11	12	4.18	9	31.0%	-0.72 [-1.64 , 0.19]
Zhou 2018 (1)	11.6	4.3	37	11.9	5	38	69.0%	-0.06 [-0.52 , 0.39]
Subtotal (95% CI)			**48**			**47**	**100.0%**	**-0.27 [-0.86 , 0.33]**
Heterogeneity: Tau² = 0.08; Chi² = 1.59, df = 1 (P = 0.21); I² = 37%								
Test for overall effect: Z = 0.88 (P = 0.38)								
1.48.2 < 6 months								
Huhn 2020	10.18	2.44	11	11.44	3.94	9	20.6%	-0.38 [-1.27 , 0.51]
Zhou 2018 (1)	10.9	4.2	37	11.9	5.9	38	79.4%	-0.19 [-0.65 , 0.26]
Subtotal (95% CI)			**48**			**47**	**100.0%**	**-0.23 [-0.64 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%								
Test for overall effect: Z = 1.12 (P = 0.26)								
1.48.3 < 1 year								
Fleischhacker 2014 (2)	14.86	4.19	131	15.06	4.27	266	59.8%	-0.05 [-0.26 , 0.16]
Ozawa 2019	15.5	5.8	17	14.4	5.1	18	5.9%	0.20 [-0.47 , 0.86]
Wunderink 2007	9.7	3	65	10.5	3.7	63	21.6%	-0.24 [-0.58 , 0.11]
Zhou 2018 (1)	10.8	4.9	37	12.2	6.1	38	12.7%	-0.25 [-0.70 , 0.20]
Subtotal (95% CI)			**250**			**385**	**100.0%**	**-0.10 [-0.26 , 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 2.02, df = 3 (P = 0.57); I² = 0%								
Test for overall effect: Z = 1.20 (P = 0.23)								
1.48.4 > 1 year								
Wunderink 2007	11	4.3	65	10.8	3.8	63	100.0%	0.05 [-0.30 , 0.40]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.05 [-0.30 , 0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								



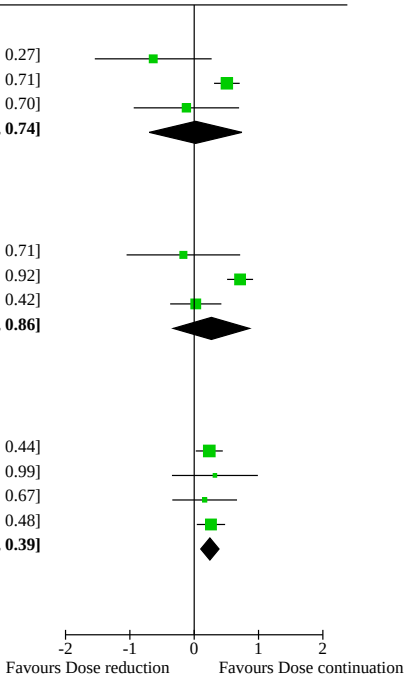
Footnotes

(1) calculated by adding the subscales (assuming a correlation of 0; conservative assumption)

(2) Positive symptoms Marder factor

Analysis 1.49. Comparison 1: Dose reduction versus dose maintenance , Outcome 49: Mental state - specific: mean change PANSS positive (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.49.1 < 3 months								
Huhn 2020	0.27	2	11	1.89	2.89	9	26.6%	-0.64 [-1.54 , 0.27]
Kane 2010	2.22	6.1	144	-0.08	3.6	322	44.5%	0.51 [0.31 , 0.71]
Volavka 2000 (1)	-1.5	4.9	11	-1	2.9	12	28.9%	-0.12 [-0.94 , 0.70]
Subtotal (95% CI)			**166**			**343**	**100.0%**	**0.02 [-0.70 , 0.74]**
Heterogeneity: Tau² = 0.29; Chi² = 7.63, df = 2 (P = 0.02); I² = 74%								
Test for overall effect: Z = 0.06 (P = 0.95)								
1.49.2 < 6 months								
Huhn 2020	0.91	1.97	11	1.33	2.83	9	22.1%	-0.17 [-1.05 , 0.71]
Kane 2010	3	6	144	-0.2	3.6	322	41.5%	0.71 [0.51 , 0.92]
Rouillon 2008 (2)	-0.8	2.7	49	-0.9	5.1	48	36.4%	0.02 [-0.37 , 0.42]
Subtotal (95% CI)			**204**			**379**	**100.0%**	**0.27 [-0.32 , 0.86]**
Heterogeneity: Tau² = 0.21; Chi² = 11.75, df = 2 (P = 0.003); I² = 83%								
Test for overall effect: Z = 0.88 (P = 0.38)								
1.49.3 < 1 year								
Fleischhacker 2014	1.46	4	131	0.52	4	266	45.8%	0.23 [0.02 , 0.44]
Ozawa 2019	0.4	3.2	17	-0.5	2.2	18	4.5%	0.32 [-0.35 , 0.99]
Takeuchi 2014	-1	2	31	-1.4	2.8	30	8.0%	0.16 [-0.34 , 0.67]
Wang 2010 (3)	1.2	4.4	211	0	4.9	129	41.7%	0.26 [0.04 , 0.48]
Subtotal (95% CI)			**390**			**443**	**100.0%**	**0.24 [0.10 , 0.39]**
Heterogeneity: Tau² = 0.00; Chi² = 0.18, df = 3 (P = 0.98); I² = 0%								
Test for overall effect: Z = 3.36 (P = 0.0008)								
Test for subgroup differences: Chi² = 0.36, df = 2 (P = 0.83), I² = 0%								

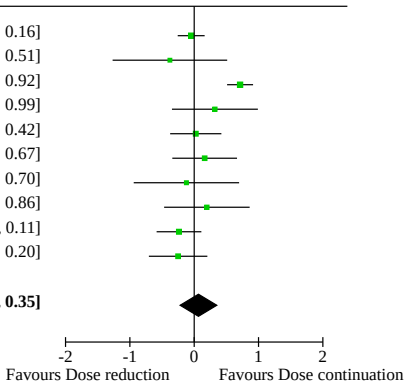


Footnotes

(1) minus transformed
(2) Not clear if it si PANSS Marder factorialization
(3) Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.50. Comparison 1: Dose reduction versus dose maintenance , Outcome 50: Mental state - specific: mean endpoint/change positive symptoms (PANSS positive) (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	14.86	4.19	131	15.06	4.27	266	13.5%	-0.05 [-0.26 , 0.16]
Huhn 2020 (2)	10.18	2.44	11	11.44	3.94	9	6.0%	-0.38 [-1.27 , 0.51]
Kane 2010 (3)	3	6	144	-0.2	3.6	322	13.6%	0.71 [0.51 , 0.92]
Ozawa 2019 (4)	0.4	3.2	17	-0.5	2.2	18	8.1%	0.32 [-0.35 , 0.99]
Rouillon 2008 (3)	-0.8	2.7	49	-0.9	5.1	48	11.4%	0.02 [-0.37 , 0.42]
Takeuchi 2014 (4)	-1	2	31	-1.4	2.8	30	10.0%	0.16 [-0.34 , 0.67]
Volavka 2000 (5)	-1.5	4.9	11	-1	2.9	12	6.6%	-0.12 [-0.94 , 0.70]
Wang 2010 (6)	15.5	5.8	17	14.4	5.1	18	8.1%	0.20 [-0.47 , 0.86]
Wunderink 2007 (6)	9.7	3	65	10.5	3.7	63	12.0%	-0.24 [-0.58 , 0.11]
Zhou 2018 (7)	10.8	4.9	37	12.2	6.1	38	10.6%	-0.25 [-0.70 , 0.20]
Total (95% CI)			**513**			**824**	**100.0%**	**0.07 [-0.22 , 0.35]**
Heterogeneity: Tau² = 0.14; Chi² = 43.08, df = 9 (P < 0.00001); I² = 79%								
Test for overall effect: Z = 0.46 (P = 0.65)								
Test for subgroup differences: Not applicable								

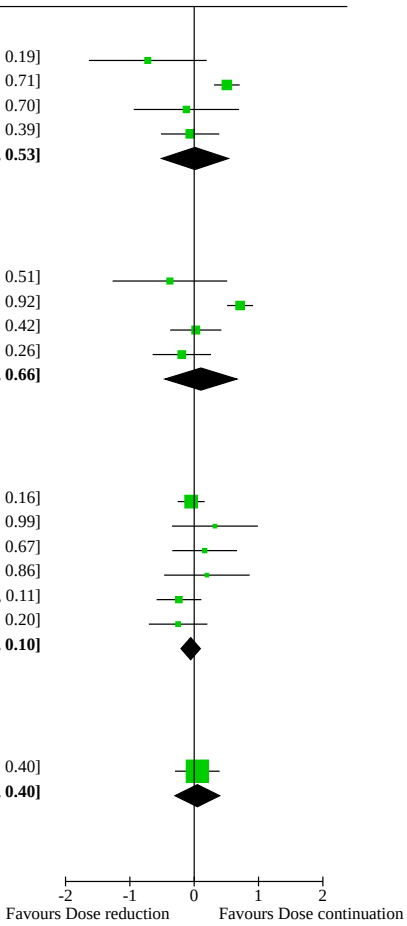


Footnotes

(1) endpoint; <1 year; Positive symptoms Marder factor
(2) endpoint; <6 months
(3) change; <6 months
(4) change; < 1 year
(5) change; <3 months; minus transformed
(6) endpoint; <1 year;
(7) endpoint; <1 year

Analysis 1.51. Comparison 1: Dose reduction versus dose maintenance , Outcome 51: Mental state - specific: mean endpoint/change positive symptoms (PANSS positive) (high = poor) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.51.1 < 3 months								
Huhn 2020 (1)	9.55	2.25	11	12	4.18	9	17.1%	-0.72 [-1.64 , 0.19]
Kane 2010 (2)	2.22	6.1	144	-0.08	3.6	322	34.9%	0.51 [0.31 , 0.71]
Volavka 2000 (3)	-1.5	4.9	11	-1	2.9	12	19.2%	-0.12 [-0.94 , 0.70]
Zhou 2018 (4)	11.6	4.3	37	11.9	5	38	28.7%	-0.06 [-0.52 , 0.39]
Subtotal (95% CI)			**203**			**381**	**100.0%**	**0.01 [-0.51 , 0.53]**
Heterogeneity: Tau² = 0.19; Chi² = 12.15, df = 3 (P = 0.007); I² = 75%								
Test for overall effect: Z = 0.05 (P = 0.96)								
1.51.2 < 6 months								
Huhn 2020 (5)	10.18	2.44	11	11.44	3.94	9	17.4%	-0.38 [-1.27 , 0.51]
Kane 2010 (6)	3	6	144	-0.2	3.6	322	29.9%	0.71 [0.51 , 0.92]
Rouillon 2008 (6)	-0.8	2.7	49	-0.9	5.1	48	26.9%	0.02 [-0.37 , 0.42]
Zhou 2018 (7)	10.9	4.2	37	11.9	5.9	38	25.8%	-0.19 [-0.65 , 0.26]
Subtotal (95% CI)			**241**			**417**	**100.0%**	**0.10 [-0.45 , 0.66]**
Heterogeneity: Tau² = 0.26; Chi² = 21.94, df = 3 (P < 0.0001); I² = 86%								
Test for overall effect: Z = 0.37 (P = 0.71)								
1.51.3 < 1 year								
Fleischhacker 2014 (8)	14.86	4.19	131	15.06	4.27	266	51.4%	-0.05 [-0.26 , 0.16]
Ozawa 2019 (9)	0.4	3.2	17	-0.5	2.2	18	5.1%	0.32 [-0.35 , 0.99]
Takeuchi 2014 (9)	-1	2	31	-1.4	2.8	30	8.9%	0.16 [-0.34 , 0.67]
Wang 2010 (10)	15.5	5.8	17	14.4	5.1	18	5.1%	0.20 [-0.47 , 0.86]
Wunderink 2007 (10)	9.7	3	65	10.5	3.7	63	18.6%	-0.24 [-0.58 , 0.11]
Zhou 2018 (11)	10.8	4.9	37	12.2	6.1	38	10.9%	-0.25 [-0.70 , 0.20]
Subtotal (95% CI)			**298**			**433**	**100.0%**	**-0.05 [-0.20 , 0.10]**
Heterogeneity: Tau² = 0.00; Chi² = 4.26, df = 5 (P = 0.51); I² = 0%								
Test for overall effect: Z = 0.71 (P = 0.48)								
1.51.4 > 1 year								
Wunderink 2007 (12)	11	4.3	65	10.8	3.8	63	100.0%	0.05 [-0.30 , 0.40]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.05 [-0.30 , 0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.28 (P = 0.78)								
Test for subgroup differences: Chi² = 0.55, df = 3 (P = 0.91), I² = 0%								

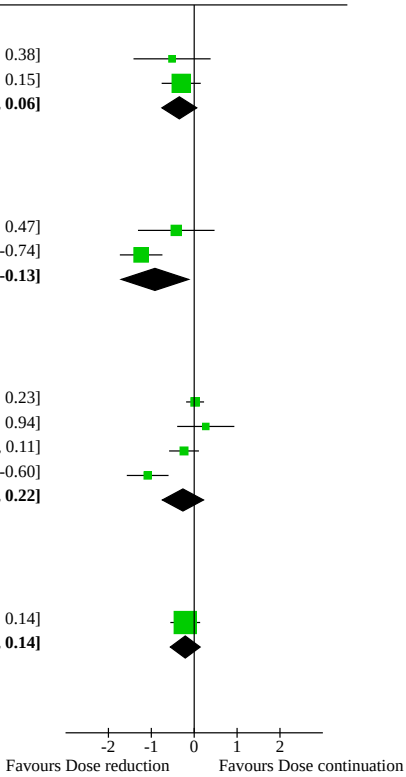


Footnotes

(1) endpoint; <3 months
(2) change; <3 months
(3) change; <3 months; minus transformed
(4) endpoint; <3 months; calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(5) endpoint; <6 months
(6) change; <6 months
(7) endpoint; <6 months; calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(8) endpoint; <1 year; Positive symptoms Marder factor
(9) change; < 1 year
(10) endpoint; <1 year;
(11) endpoint; <1 year; calculated by adding the subscales (assuming a correlation of 0; conservative assumption)
(12) endpoint; >1 year;

Analysis 1.52. Comparison 1: Dose reduction versus dose maintenance , Outcome 52: Mental state - specific: mean endpoint PANSS negative (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.52.1 < 3 months								
Huhn 2020	11.55	3.503	11	13.78	4.81	9	20.4%	-0.52 [-1.42 , 0.38]
Zhou 2018	20.1	7.1	37	22.2	6.6	38	79.6%	-0.30 [-0.76 , 0.15]
Subtotal (95% CI)			**48**			**47**	**100.0%**	**-0.35 [-0.75 , 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 0.17, df = 1 (P = 0.68); I² = 0%								
Test for overall effect: Z = 1.67 (P = 0.09)								
1.52.2 < 6 months								
Huhn 2020	9.91	1.87	11	11.44	4.82	9	39.3%	-0.42 [-1.31 , 0.47]
Zhou 2018	18.8	6.4	37	25.7	4.5	38	60.7%	-1.24 [-1.73 , -0.74]
Subtotal (95% CI)			**48**			**47**	**100.0%**	**-0.92 [-1.70 , -0.13]**
Heterogeneity: Tau² = 0.20; Chi² = 2.47, df = 1 (P = 0.12); I² = 60%								
Test for overall effect: Z = 2.29 (P = 0.02)								
1.52.3 < 1 year								
Fleischhacker 2014 (1)	16.14	5.63	131	16.03	5.09	266	29.7%	0.02 [-0.19 , 0.23]
Ozawa 2019	25.5	7.2	17	23.7	5.8	18	19.6%	0.27 [-0.40 , 0.94]
Wunderink 2007	11.8	4	65	13	5.9	63	27.0%	-0.24 [-0.59 , 0.11]
Zhou 2018	17.3	6.5	37	24.1	5.9	38	23.8%	-1.08 [-1.57 , -0.60]
Subtotal (95% CI)			**250**			**385**	**100.0%**	**-0.26 [-0.74 , 0.22]**
Heterogeneity: Tau² = 0.19; Chi² = 18.51, df = 3 (P = 0.0003); I² = 84%								
Test for overall effect: Z = 1.08 (P = 0.28)								
1.52.4 > 1 year								
Wunderink 2007	12.1	5.2	65	13.3	6.2	63	100.0%	-0.21 [-0.56 , 0.14]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-0.21 [-0.56 , 0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.18 (P = 0.24)								
Test for subgroup differences: Chi² = 2.68, df = 3 (P = 0.44), I² = 0%								

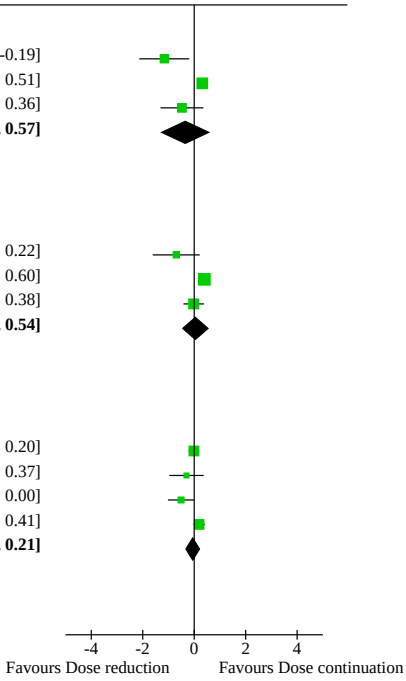


Footnotes

(1) Negative symptoms - Marder factor

Analysis 1.53. Comparison 1: Dose reduction versus dose maintenance , Outcome 53: Mental state - specific: mean change PANSS negative (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.53.1 < 3 months								
Huhn 2020	-2.18	2.86	11	1.78	3.7	9	28.3%	-1.16 [-2.13 , -0.19]
Kane 2010	0.4	4.9	144	-0.8	3.2	322	40.8%	0.31 [0.12 , 0.51]
Volavka 2000 (1)	-1.1	2.9	11	0.1	1.9	12	30.9%	-0.48 [-1.31 , 0.36]
Subtotal (95% CI)			**166**			**343**	**100.0%**	**-0.35 [-1.26 , 0.57]**
Heterogeneity: Tau² = 0.52; Chi² = 11.41, df = 2 (P = 0.003); I² = 82%								
Test for overall effect: Z = 0.75 (P = 0.45)								
1.53.2 < 6 months								
Huhn 2020	-3.8	3.5	11	-0.6	5.3	9	18.1%	-0.70 [-1.61 , 0.22]
Kane 2010	0.5	4.8	144	-1.1	3.6	322	45.0%	0.40 [0.20 , 0.60]
Rouillon 2008 (2)	-2	3.6	49	-1.9	5.6	48	36.8%	-0.02 [-0.42 , 0.38]
Subtotal (95% CI)			**204**			**379**	**100.0%**	**0.05 [-0.45 , 0.54]**
Heterogeneity: Tau² = 0.13; Chi² = 7.97, df = 2 (P = 0.02); I² = 75%								
Test for overall effect: Z = 0.18 (P = 0.86)								
1.53.3 < 1 year								
Fleischhacker 2014	-0.19	3.6	131	-0.15	3.6	266	36.1%	-0.01 [-0.22 , 0.20]
Ozawa 2019	-0.3	1.1	17	0.3	2.5	18	11.7%	-0.30 [-0.97 , 0.37]
Takeuchi 2014	-3	3.7	31	-1.3	2.8	30	17.0%	-0.51 [-1.02 , 0.00]
Wang 2010 (3)	-0.2	3.9	211	-1.3	7.8	129	35.3%	0.19 [-0.03 , 0.41]
Subtotal (95% CI)			**390**			**443**	**100.0%**	**-0.06 [-0.32 , 0.21]**
Heterogeneity: Tau² = 0.04; Chi² = 7.49, df = 3 (P = 0.06); I² = 60%								
Test for overall effect: Z = 0.43 (P = 0.67)								
Test for subgroup differences: Chi² = 0.56, df = 2 (P = 0.76), I² = 0%								

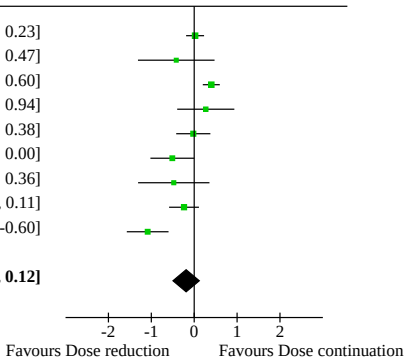


Footnotes

(1) minus transformed
(2) Not clear if it is Marder Factorialization
(3) Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.54. Comparison 1: Dose reduction versus dose maintenance , Outcome 54: Mental state - specific: mean endpoint/change negative symptoms (PANSS negative) (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	16.14	5.63	131	16.03	5.09	266	14.6%	0.02 [-0.19 , 0.23]
Huhn 2020 (2)	9.91	1.87	11	11.44	4.82	9	6.7%	-0.42 [-1.31 , 0.47]
Kane 2010 (3)	0.5	4.8	144	-1.1	3.6	322	14.7%	0.40 [0.20 , 0.60]
Ozawa 2019 (4)	25.5	7.2	17	23.7	5.8	18	9.0%	0.27 [-0.40 , 0.94]
Rouillon 2008 (3)	-2	3.6	49	-1.9	5.6	48	12.4%	-0.02 [-0.42 , 0.38]
Takeuchi 2014 (5)	-3	3.7	31	-1.3	2.8	30	10.9%	-0.51 [-1.02 , 0.00]
Volavka 2000 (6)	-1.1	2.9	11	0.1	1.9	12	7.3%	-0.48 [-1.31 , 0.36]
Wunderink 2007 (4)	11.8	4	65	13	5.9	63	13.1%	-0.24 [-0.59 , 0.11]
Zhou 2018 (4)	17.3	6.5	37	24.1	5.9	38	11.2%	-1.08 [-1.57 , -0.60]
Total (95% CI)			**496**			**806**	**100.0%**	**-0.19 [-0.49 , 0.12]**
Heterogeneity: Tau² = 0.16; Chi² = 42.95, df = 8 (P < 0.00001); I² = 81%								
Test for overall effect: Z = 1.20 (P = 0.23)								
Test for subgroup differences: Not applicable								

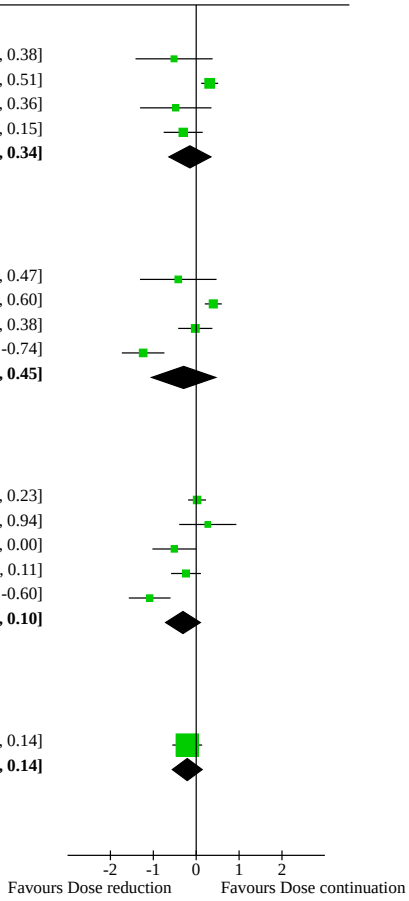


Footnotes

(1) Negative symptoms - Marder factor
(2) endpoint; < 6 months
(3) change; <6 months
(4) endpoint; <1 year;
(5) change; < 1 year
(6) change; < 3 months; minus transformed

Analysis 1.55. Comparison 1: Dose reduction versus dose maintenance , Outcome 55: Mental state - specific: mean endpoint/change negative symptoms (PANSS negative) (high = poor) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.55.1 < 3 months								
Huhn 2020 (1)	11.55	3.503	11	13.78	4.81	9	16.7%	-0.52 [-1.42 , 0.38]
Kane 2010 (2)	0.4	4.9	144	-0.8	3.2	322	36.2%	0.31 [0.12 , 0.51]
Volavka 2000 (3)	-1.1	2.9	11	0.1	1.9	12	18.2%	-0.48 [-1.31 , 0.36]
Zhou 2018 (1)	20.1	7.1	37	22.2	6.6	38	28.9%	-0.30 [-0.76 , 0.15]
Subtotal (95% CI)			**203**			**381**	**100.0%**	**-0.15 [-0.64 , 0.34]**
Heterogeneity: Tau² = 0.16; Chi² = 10.76, df = 3 (P = 0.01); I² = 72%								
Test for overall effect: Z = 0.59 (P = 0.56)								
1.55.2 < 6 months								
Huhn 2020 (4)	9.91	1.87	11	11.44	4.82	9	20.3%	-0.42 [-1.31 , 0.47]
Kane 2010 (5)	0.5	4.8	144	-1.1	3.6	322	28.0%	0.40 [0.20 , 0.60]
Rouillon 2008 (5)	-2	3.6	49	-1.9	5.6	48	26.4%	-0.02 [-0.42 , 0.38]
Zhou 2018 (6)	18.8	6.4	37	25.7	4.5	38	25.3%	-1.24 [-1.73 , -0.74]
Subtotal (95% CI)			**241**			**417**	**100.0%**	**-0.29 [-1.04 , 0.45]**
Heterogeneity: Tau² = 0.51; Chi² = 38.20, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 0.77 (P = 0.44)								
1.55.3 < 1 year								
Fleischhacker 2014 (7)	16.14	5.63	131	16.03	5.09	266	24.7%	0.02 [-0.19 , 0.23]
Ozawa 2019 (8)	25.5	7.2	17	23.7	5.8	18	15.4%	0.27 [-0.40 , 0.94]
Takeuchi 2014 (9)	-3	3.7	31	-1.3	2.8	30	18.6%	-0.51 [-1.02 , 0.00]
Wunderink 2007 (8)	11.8	4	65	13	5.9	63	22.1%	-0.24 [-0.59 , 0.11]
Zhou 2018 (8)	17.3	6.5	37	24.1	5.9	38	19.1%	-1.08 [-1.57 , -0.60]
Subtotal (95% CI)			**281**			**415**	**100.0%**	**-0.31 [-0.71 , 0.10]**
Heterogeneity: Tau² = 0.16; Chi² = 20.29, df = 4 (P = 0.0004); I² = 80%								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.55.4 > 1 year								
Wunderink 2007 (10)	12.1	5.2	65	13.3	6.2	63	100.0%	-0.21 [-0.56 , 0.14]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**-0.21 [-0.56 , 0.14]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.18 (P = 0.24)								
Test for subgroup differences: Chi² = 0.30, df = 3 (P = 0.96), I² = 0%								

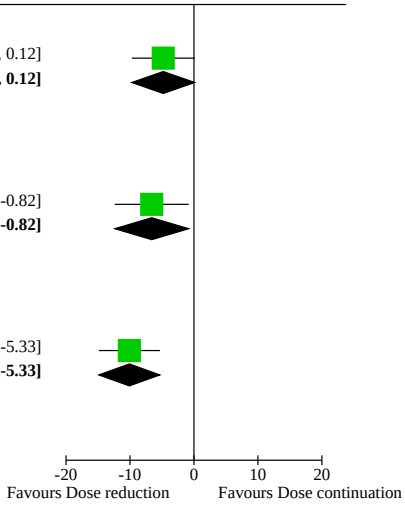


Footnotes

(1) endpoint; <3 months
(2) change; < 3 months
(3) change; < 3 months; minus transformed
(4) endpoint; <6 months
(5) change; <6 months
(6) endpoint; < 6 months
(7) Negative symptoms - Marder factor
(8) endpoint; <1 year;
(9) change; < 1 year
(10) endpoint; > 1 year

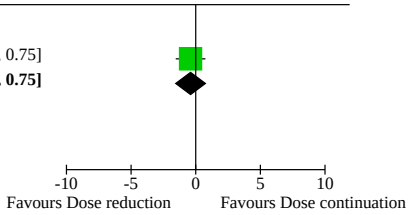
Analysis 1.56. Comparison 1: Dose reduction versus dose maintenance , Outcome 56: Mental state - specific: mean endpoint NSA-16 (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.56.1 < 3 months								
Zhou 2018	61	12.2	37	65.8	9.3	38	100.0%	-4.80 [-9.72 , 0.12]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-4.80 [-9.72 , 0.12]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.91 (P = 0.06)								
1.56.2 < 6 months								
Zhou 2018	61.9	13.1	37	68.5	12.4	38	100.0%	-6.60 [-12.38 , -0.82]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-6.60 [-12.38 , -0.82]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.24 (P = 0.03)								
1.56.3 < 1 year								
Zhou 2018	59.6	13.3	37	69.7	6.6	38	100.0%	-10.10 [-14.87 , -5.33]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-10.10 [-14.87 , -5.33]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 4.15 (P < 0.0001)								
Test for subgroup differences: Chi² = 2.37, df = 2 (P = 0.31), I² = 15.7%								



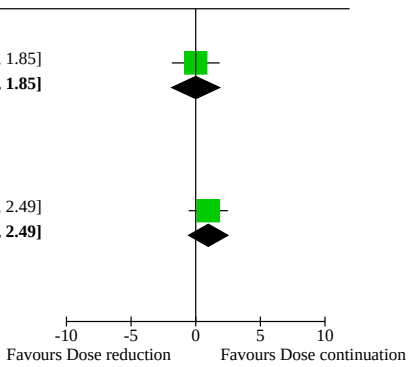
Analysis 1.57. Comparison 1: Dose reduction versus dose maintenance , Outcome 57: Mental state - specific: mean change CDSS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.57.1 < 1 year								
Takeuchi 2014	-0.9	2.7	31	-0.5	1.8	30	100.0%	-0.40 [-1.55 , 0.75]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-0.40 [-1.55 , 0.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.49)								



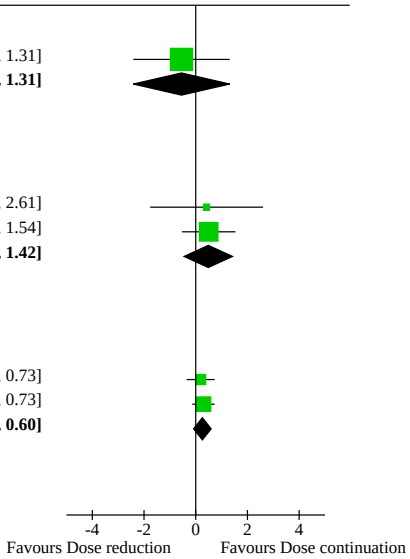
Analysis 1.58. Comparison 1: Dose reduction versus dose maintenance , Outcome 58: Mental state - specific: mean endpoint PANSS depression/anxiety (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.58.1 < 3 months								
Huhn 2020	5	2.28	11	5	1.94	9	100.0%	0.00 [-1.85 , 1.85]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**0.00 [-1.85 , 1.85]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.58.2 < 6 months								
Huhn 2020	5.64	1.96	11	4.67	1.5	9	100.0%	0.97 [-0.55 , 2.49]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**0.97 [-0.55 , 2.49]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								
Test for subgroup differences: Chi² = 0.63, df = 1 (P = 0.43), I² = 0%								



Analysis 1.59. Comparison 1: Dose reduction versus dose maintenance , Outcome 59: Mental state - specific: mean change PANSS depression/anxiety (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.59.1 < 3 months								
Huhn 2020	-0.55	2.38	11	0	1.87	9	100.0%	-0.55 [-2.41 , 1.31]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-0.55 [-2.41 , 1.31]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.58 (P = 0.56)								
1.59.2 < 6 months								
Huhn 2020	0.09	3.21	11	-0.33	1.66	9	18.4%	0.42 [-1.77 , 2.61]
Rouillon 2008 (1)	-0.8	2.5	49	-1.3	2.7	48	81.6%	0.50 [-0.54 , 1.54]
Subtotal (95% CI)			**60**			**57**	**100.0%**	**0.49 [-0.45 , 1.42]**
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%								
Test for overall effect: Z = 1.02 (P = 0.31)								
1.59.3 < 1 year								
Fleischhacker 2014	0.02	2.7	131	-0.17	2.4	266	38.8%	0.19 [-0.35 , 0.73]
Wang 2010 (2)	0.3	1.9	211	0	2.03	129	61.2%	0.30 [-0.13 , 0.73]
Subtotal (95% CI)			**342**			**395**	**100.0%**	**0.26 [-0.08 , 0.60]**
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.76); I² = 0%								
Test for overall effect: Z = 1.49 (P = 0.14)								
Test for subgroup differences: Chi² = 0.95, df = 2 (P = 0.62), I² = 0%								



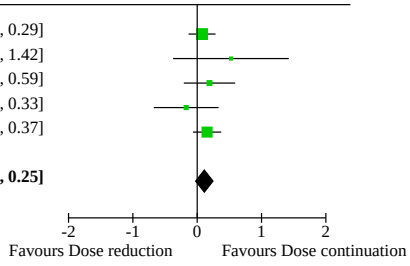
Footnotes

(1) Not clearly stated if it is the Marder Factor

(2) Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.60. Comparison 1: Dose reduction versus dose maintenance , Outcome 60: Mental state - specific: mean endpoint/change depression (PANSS depression, CDSS) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	0.02	2.7	131	-0.17	2.4	266	41.5%	0.08 [-0.13 , 0.29]
Huhn 2020 (2)	5.64	1.96	11	4.67	1.5	9	2.2%	0.52 [-0.37 , 1.42]
Rouillon 2008 (3)	-0.8	2.5	49	-1.3	2.7	48	11.4%	0.19 [-0.21 , 0.59]
Takeuchi 2014 (4)	-0.9	2.7	31	-0.5	1.8	30	7.2%	-0.17 [-0.67 , 0.33]
Wang 2010 (5)	0.3	1.9	211	0	2.03	129	37.7%	0.15 [-0.07 , 0.37]
Total (95% CI)			**433**			**482**	**100.0%**	**0.11 [-0.02 , 0.25]**
Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 4 (P = 0.66); I² = 0%								
Test for overall effect: Z = 1.61 (P = 0.11)								
Test for subgroup differences: Not applicable								



Footnotes

(1) PANSS depression; change; <1 year;

(2) PANSS depression; endpoint; < 6 months

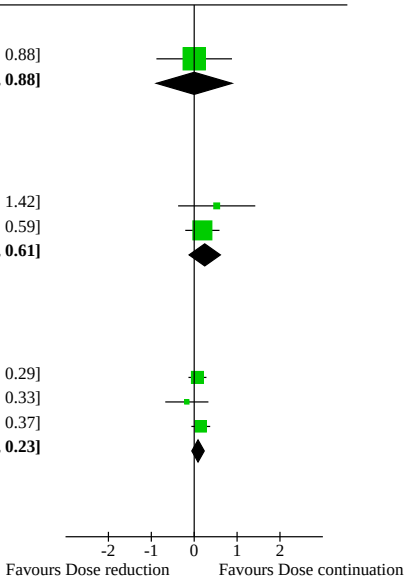
(3) PANSS depression; change; < 6 months

(4) CDSS; change; < 1 year

(5) PANSS depression; change; <1 year; Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.61. Comparison 1: Dose reduction versus dose maintenance , Outcome 61: Mental state - specific: mean endpoint/change depression (PANSS depression, CDSS) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.61.1 < 3 months								
Huhn 2020 (1)	5	2.28	11	5	1.94	9	100.0%	0.00 [-0.88 , 0.88]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**0.00 [-0.88 , 0.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.61.2 < 6 months								
Huhn 2020 (2)	5.64	1.96	11	4.67	1.5	9	16.4%	0.52 [-0.37 , 1.42]
Rouillon 2008 (3)	-0.8	2.5	49	-1.3	2.7	48	83.6%	0.19 [-0.21 , 0.59]
Subtotal (95% CI)			**60**			**57**	**100.0%**	**0.25 [-0.12 , 0.61]**
Heterogeneity: Tau² = 0.00; Chi² = 0.44, df = 1 (P = 0.51); I² = 0%								
Test for overall effect: Z = 1.32 (P = 0.19)								
1.61.3 < 1 year								
Fleischhacker 2014 (4)	0.02	2.7	131	-0.17	2.4	266	48.0%	0.08 [-0.13 , 0.29]
Takeuchi 2014 (5)	-0.9	2.7	31	-0.5	1.8	30	8.3%	-0.17 [-0.67 , 0.33]
Wang 2010 (6)	0.3	1.9	211	0	2.03	129	43.7%	0.15 [-0.07 , 0.37]
Subtotal (95% CI)			**373**			**425**	**100.0%**	**0.09 [-0.06 , 0.23]**
Heterogeneity: Tau² = 0.00; Chi² = 1.38, df = 2 (P = 0.50); I² = 0%								
Test for overall effect: Z = 1.21 (P = 0.23)								
Test for subgroup differences: Chi² = 0.67, df = 2 (P = 0.72), I² = 0%								

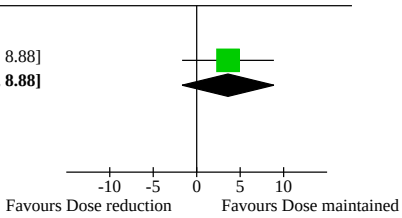


Footnotes

(1) PANSS depression; endpoint; < 3 months
(2) PANSS depression; endpoint; < 6 months
(3) PANSS depression; change; < 6 months
(4) PANSS depression; change; <1 year;
(5) CDSS; change; < 1 year
(6) PANSS depression; change; <1 year; Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

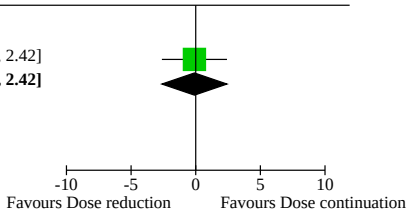
Analysis 1.62. Comparison 1: Dose reduction versus dose maintenance , Outcome 62: Mental state - specific: mean change POMS-SF (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.62.1 < 1 year								
Takeuchi 2014	-1	12.6	31	-4.6	8	30	100.0%	3.60 [-1.68 , 8.88]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**3.60 [-1.68 , 8.88]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.34 (P = 0.18)								



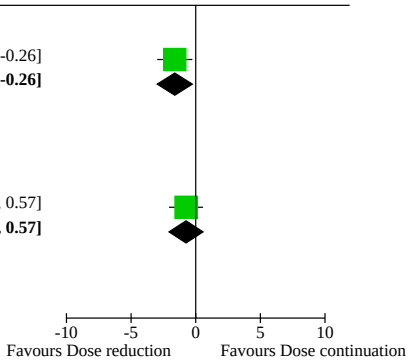
Analysis 1.63. Comparison 1: Dose reduction versus dose maintenance , Outcome 63: Mental state - specific: mean change SAI (high = good)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.63.1 < 1 year								
Takeuchi 2014	-0.7	4.7	31	-0.6	5.3	30	100.0%	-0.10 [-2.62 , 2.42]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-0.10 [-2.62 , 2.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.08 (P = 0.94)								



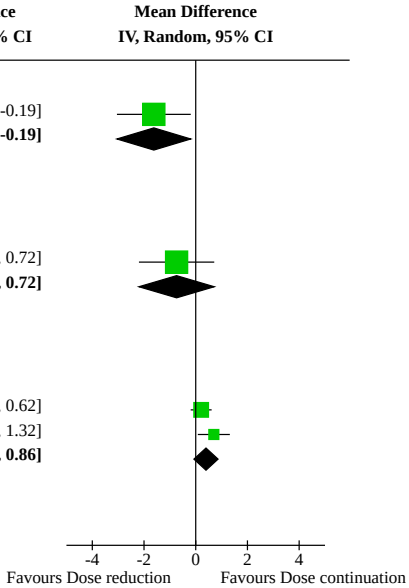
Analysis 1.64. Comparison 1: Dose reduction versus dose maintenance , Outcome 64: Behaviour - mean endpoint PANSS excitement/hostility (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.64.1 < 3 months								
Huhn 2020	4.82	0.98	11	6.44	1.88	9	100.0%	-1.62 [-2.98 , -0.26]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-1.62 [-2.98 , -0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.34 (P = 0.02)								
1.64.2 < 6 months								
Huhn 2020	5.36	1.21	11	6.11	1.69	9	100.0%	-0.75 [-2.07 , 0.57]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-0.75 [-2.07 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
Test for subgroup differences: Chi² = 0.81, df = 1 (P = 0.37), I² = 0%								



Analysis 1.65. Comparison 1: Dose reduction versus dose maintenance , Outcome 65: Behaviour - mean change PANSS excitement/hostility (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.65.1 < 3 months								
Huhn 2020	-0.73	1.62	11	0.89	1.62	9	100.0%	-1.62 [-3.05 , -0.19]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-1.62 [-3.05 , -0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.22 (P = 0.03)								
1.65.2 < 6 months								
Huhn 2020	-0.18	1.54	11	0.56	1.74	9	100.0%	-0.74 [-2.20 , 0.72]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-0.74 [-2.20 , 0.72]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.00 (P = 0.32)								
1.65.3 <1 year								
Fleischhacker 2014	0.33	2	131	0.12	1.8	266	61.9%	0.21 [-0.20 , 0.62]
Wang 2010 (1)	1.2	2.7	211	0.5	2.9	129	38.1%	0.70 [0.08 , 1.32]
Subtotal (95% CI)			**342**			**395**	**100.0%**	**0.40 [-0.07 , 0.86]**
Heterogeneity: Tau² = 0.05; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%								
Test for overall effect: Z = 1.67 (P = 0.10)								
Test for subgroup differences: Chi² = 8.40, df = 2 (P = 0.01), I² = 76.2%								



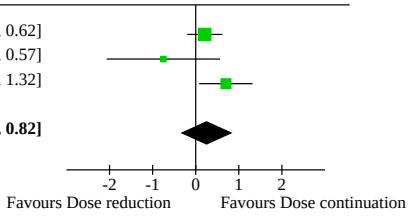
Footnotes

(1) Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.66. Comparison 1: Dose reduction versus dose maintenance , Outcome 66: Behaviour - mean endpoint/change aggressive behaviour (PANSS excitement/hostility) (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	0.33	2	131	0.12	1.8	266	48.8%	0.21 [-0.20 , 0.62]
Huhn 2020 (2)	5.36	1.21	11	6.11	1.69	9	14.5%	-0.75 [-2.07 , 0.57]
Wang 2010 (3)	1.2	2.7	211	0.5	2.9	129	36.7%	0.70 [0.08 , 1.32]
Total (95% CI)			**353**			**404**	**100.0%**	**0.25 [-0.32 , 0.82]**

Heterogeneity: Tau² = 0.13; Chi² = 4.24, df = 2 (P = 0.12); I² = 53%
Test for overall effect: Z = 0.87 (P = 0.39)
Test for subgroup differences: Not applicable

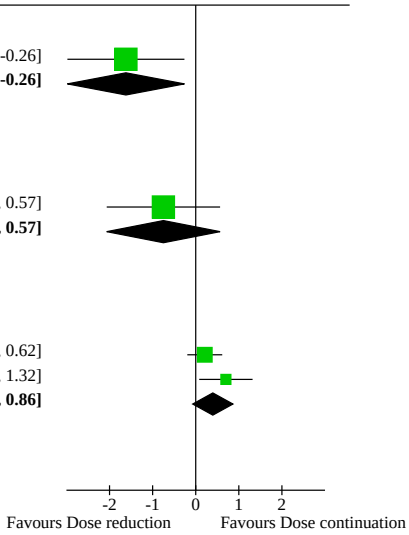


Footnotes
(1) change; <1 year
(2) endpoint; <6 months
(3) change; < 1year; Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

Analysis 1.67. Comparison 1: Dose reduction versus dose maintenance , Outcome 67: Behaviour - mean endpoint/change aggressive behaviour (PANSS excitement/hostility) (high = poor) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.67.1 < 3 months								
Huhn 2020 (1)	4.82	0.98	11	6.44	1.88	9	100.0%	-1.62 [-2.98 , -0.26]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-1.62 [-2.98 , -0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.34 (P = 0.02)								
1.67.2 < 6 months								
Huhn 2020 (2)	5.36	1.21	11	6.11	1.69	9	100.0%	-0.75 [-2.07 , 0.57]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**-0.75 [-2.07 , 0.57]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.12 (P = 0.26)								
1.67.3 <1 year								
Fleischhacker 2014 (3)	0.33	2	131	0.12	1.8	266	61.9%	0.21 [-0.20 , 0.62]
Wang 2010 (4)	1.2	2.7	211	0.5	2.9	129	38.1%	0.70 [0.08 , 1.32]
Subtotal (95% CI)			**342**			**395**	**100.0%**	**0.40 [-0.07 , 0.86]**
Heterogeneity: Tau² = 0.05; Chi² = 1.69, df = 1 (P = 0.19); I² = 41%								
Test for overall effect: Z = 1.67 (P = 0.10)								

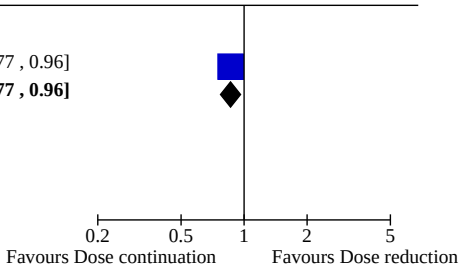
Test for subgroup differences: Chi² = 9.32, df = 2 (P = 0.009), I² = 78.5%



Footnotes
(1) endpoint; <3 months
(2) endpoint; <6 months
(3) change; <1 year
(4) change; < 1year; Total participants of the dose reduction ar are based on the remaining subjects, after the stabilization phase of the 4-weeks and 26-weeks arms

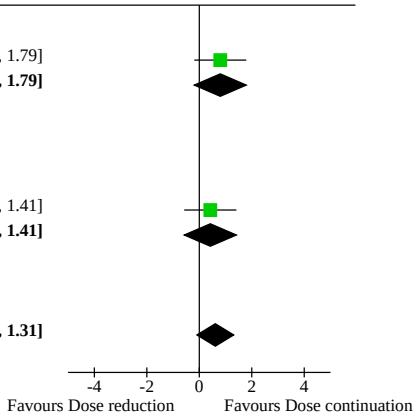
Analysis 1.68. Comparison 1: Dose reduction versus dose maintenance , Outcome 68: Satisfaction with care - number of participants with clinically important change in satisfaction with care (PSMQ-Modified preference to current medication)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.68.1 < 1 year						
Fleischhacker 2014	98	131	231	266	100.0%	0.86 [0.77 , 0.96]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.86 [0.77 , 0.96]**
Total events:	98		231			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.66 (P = 0.008)						



Analysis 1.69. Comparison 1: Dose reduction versus dose maintenance , Outcome 69: Satisfaction with care - mean endpoint MARS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.69.1 < 3 months								
Huhn 2020 (1)	-1.64	1.12	11	-2.44	1.13	9	50.2%	0.80 [-0.19 , 1.79]
Subtotal (95% CI)			**11**			**9**	**50.2%**	**0.80 [-0.19 , 1.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
1.69.2 < 6 months								
Huhn 2020 (1)	-1.91	1.14	11	-2.33	1.12	9	49.8%	0.42 [-0.57 , 1.41]
Subtotal (95% CI)			**11**			**9**	**49.8%**	**0.42 [-0.57 , 1.41]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.83 (P = 0.41)								
Total (95% CI)			**22**			**18**	**100.0%**	**0.61 [-0.09 , 1.31]**
Heterogeneity: Chi² = 0.28, df = 1 (P = 0.60); I² = 0%								
Test for overall effect: Z = 1.70 (P = 0.09)								
Test for subgroup differences: Chi² = 0.28, df = 1 (P = 0.60), I² = 0%								

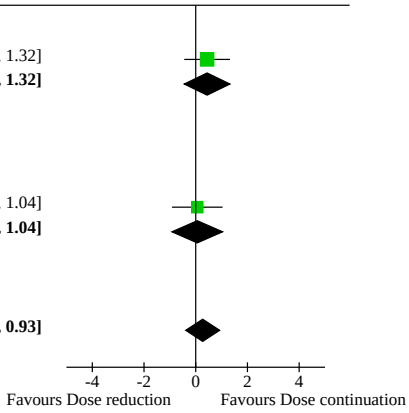


Footnotes

(1) minus transformed

Analysis 1.70. Comparison 1: Dose reduction versus dose maintenance , Outcome 70: Satisfaction with care - mean change MARS (high = poor)

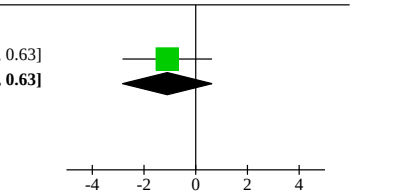
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.70.1 < 3 months								
Huhn 2020 (1)	0	1.26	11	-0.44	0.73	9	55.1%	0.44 [-0.44 , 1.32]
Subtotal (95% CI)			**11**			**9**	**55.1%**	**0.44 [-0.44 , 1.32]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.98 (P = 0.33)								
1.70.2 < 6 months								
Huhn 2020 (2)	-0.27	1.35	11	-0.33	0.87	9	44.9%	0.06 [-0.92 , 1.04]
Subtotal (95% CI)			**11**			**9**	**44.9%**	**0.06 [-0.92 , 1.04]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.12 (P = 0.90)								
Total (95% CI)			**22**			**18**	**100.0%**	**0.27 [-0.39 , 0.93]**
Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%								
Test for overall effect: Z = 0.80 (P = 0.42)								
Test for subgroup differences: Chi² = 0.32, df = 1 (P = 0.57), I² = 0%								



Footnotes
(1) minus transformed
(2) LOCF from the provided data ; minus transformed

Analysis 1.71. Comparison 1: Dose reduction versus dose maintenance , Outcome 71: Satisfaction with care - mean change DAI-10 (high = poor)

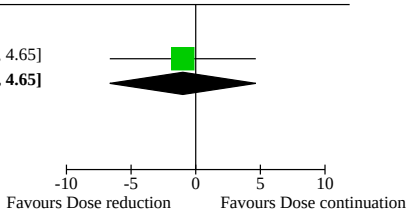
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.71.1 < 1 year								
Takeuchi 2014 (1)	-0.8	3.5	31	0.3	3.4	30	100.0%	-1.10 [-2.83 , 0.63]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-1.10 [-2.83 , 0.63]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.25 (P = 0.21)								



Footnotes
(1) minus transformed

Analysis 1.72. Comparison 1: Dose reduction versus dose maintenance , Outcome 72: Satisfaction with care - mean endpoint DAI-30 (high = poor)

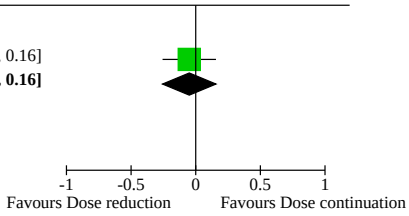
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.72.1 < 1 year								
Fleischhacker 2014 (1)	-21.8	25.41	114	-20.8	25.41	245	100.0%	-1.00 [-6.65 , 4.65]
Subtotal (95% CI)			**114**			**245**	**100.0%**	**-1.00 [-6.65 , 4.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.73)								



Footnotes
(1) Pooled SD estimated from the p-value from the comparison of 50mg/4week vs 400mg/4week ; minus transformed

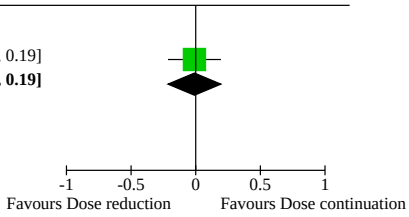
Analysis 1.73. Comparison 1: Dose reduction versus dose maintenance , Outcome 73: Satisfaction with care - mean change MAQ (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.73.1 < 1 year								
Fleischhacker 2014	-0.07	0.9	110	-0.02	0.94	236	100.0%	-0.05 [-0.26 , 0.16]
Subtotal (95% CI)			**110**			**236**	**100.0%**	**-0.05 [-0.26 , 0.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.47 (P = 0.64)								



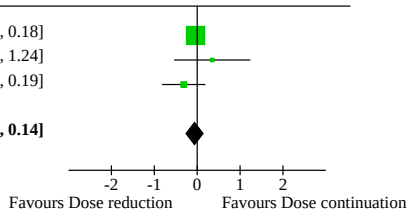
Analysis 1.74. Comparison 1: Dose reduction versus dose maintenance , Outcome 74: Satisfaction with care - mean endpoint MAQ (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.74.1 < 1 year								
Fleischhacker 2014	0.63	0.95	115	0.64	0.87	247	100.0%	-0.01 [-0.21 , 0.19]
Subtotal (95% CI)			**115**			**247**	**100.0%**	**-0.01 [-0.21 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.10 (P = 0.92)								



Analysis 1.75. Comparison 1: Dose reduction versus dose maintenance , Outcome 75: Satisfaction with care - mean endpoint/change adherence scales (MARS, DAI, MAQ) (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	-21.8	25.41	114	-20.8	25.41	245	79.6%	-0.04 [-0.26 , 0.18]
Huhn 2020 (2)	-1.91	1.17	11	-2.33	1.12	9	5.0%	0.35 [-0.54 , 1.24]
Takeuchi 2014 (3)	-0.8	3.5	31	0.3	3.4	30	15.4%	-0.31 [-0.82 , 0.19]
Total (95% CI)			**156**			**284**	**100.0%**	**-0.06 [-0.26 , 0.14]**
Heterogeneity: Tau² = 0.00; Chi² = 1.83, df = 2 (P = 0.40); I² = 0%								
Test for overall effect: Z = 0.62 (P = 0.54)								
Test for subgroup differences: Not applicable								

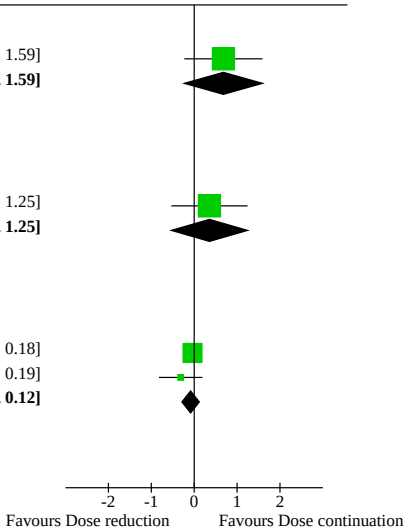


Footnotes

(1) DAI-30; endpoint; < 1 year; minus transformed
(2) MARS; endpoint; < 6 months; minus transformed
(3) DAI-10; change; < 1 year; minus transformed

Analysis 1.76. Comparison 1: Dose reduction versus dose maintenance , Outcome 76: Satisfaction with care - mean endpoint/change adherence scales (MARS, DAI, MAQ) (high = poor) (separated time points)

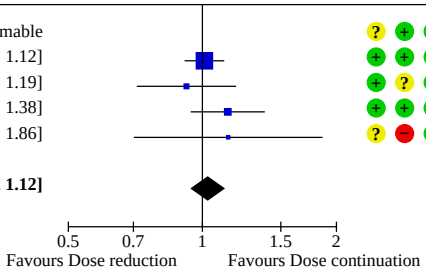
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.76.1 < 3 months								
Huhn 2020 (1)	-1.64	1.12	11	-2.44	1.13	9	100.0%	0.68 [-0.23 , 1.59]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**0.68 [-0.23 , 1.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.46 (P = 0.14)								
1.76.2 < 6 months								
Huhn 2020 (2)	-1.91	1.14	11	-2.33	1.12	9	100.0%	0.36 [-0.53 , 1.25]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**0.36 [-0.53 , 1.25]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.78 (P = 0.43)								
1.76.3 < 1 year								
Fleischhacker 2014 (3)	-21.8	25.41	114	-20.8	25.41	245	83.8%	-0.04 [-0.26 , 0.18]
Takeuchi 2014 (4)	-0.8	3.5	31	0.3	3.4	30	16.2%	-0.31 [-0.82 , 0.19]
Subtotal (95% CI)			**145**			**275**	**100.0%**	**-0.08 [-0.29 , 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 0.96, df = 1 (P = 0.33); I² = 0%								
Test for overall effect: Z = 0.81 (P = 0.42)								
Test for subgroup differences: Chi² = 3.33, df = 2 (P = 0.19), I² = 39.9%								



Footnotes
(1) MARS; endpoint; < 3 months; minus transformed
(2) MARS; endpoint; < 6 months; minus transformed
(3) DAI-30; endpoint; < 1 year; minus transformed
(4) DAI-10; change; < 1 year; minus transformed

Analysis 1.77. Comparison 1: Dose reduction versus dose maintenance , Outcome 77: Adverse effects - number of participants with at least 1 adverse effect (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Cookson 1987 (1)	0	9	0	9		Not estimable	?	+	+	?	?	?
Fleischhacker 2014 (1)	106	131	213	266	67.1%	1.01 [0.91 , 1.12]	+	+	+	+	+	+
Huhn 2020 (2)	10	11	9	9	10.7%	0.92 [0.71 , 1.19]	+	?	+	+	+	?
Kane 2010 (3)	77	144	151	322	19.2%	1.14 [0.94 , 1.38]	+	+	+	+	+	+
Rouillon 2008 (3)	21	49	18	48	3.0%	1.14 [0.70 , 1.86]	?	−	+	−	?	−
Total (95% CI)		**344**		**654**	**100.0%**	**1.03 [0.94 , 1.12]**						
Total events:	214		391									
Heterogeneity: Tau² = 0.00; Chi² = 2.12, df = 3 (P = 0.55); I² = 0%												
Test for overall effect: Z = 0.64 (P = 0.52)												
Test for subgroup differences: Not applicable												

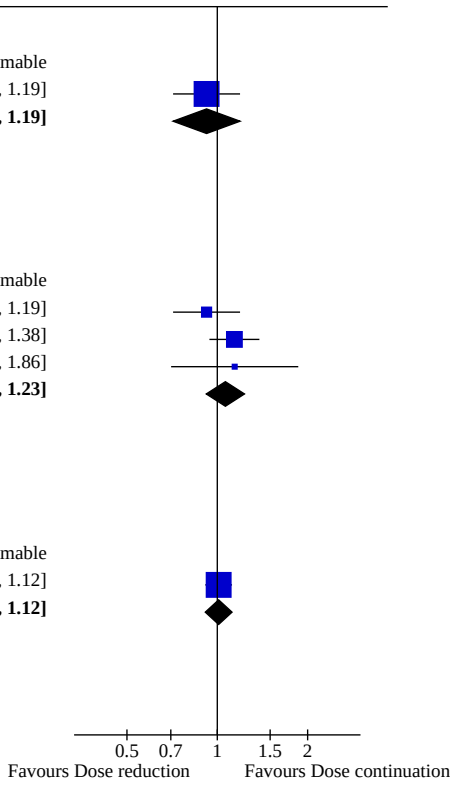


Footnotes
(1) <1 year
(2) < 6 months; Patients having a score of at least 1 in at least one item of the UKU scale (LOCF).
(3) < 6 months

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.78. Comparison 1: Dose reduction versus dose maintenance , Outcome 78: Adverse effects - number of participants with at least 1 adverse effect (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.78.1 < 3 months						
Cookson 1987 (1)	0	9	0	9		Not estimable
Huhn 2020 (2)	10	11	9	9	100.0%	0.92 [0.71 , 1.19]
Subtotal (95% CI)		**20**		**18**	**100.0%**	**0.92 [0.71 , 1.19]**
Total events:	10		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.63 (P = 0.53)						
1.78.2 < 6 months						
Cookson 1987 (3)	0	9	0	9		Not estimable
Huhn 2020 (4)	10	11	9	9	32.5%	0.92 [0.71 , 1.19]
Kane 2010 (3)	77	144	151	322	58.4%	1.14 [0.94 , 1.38]
Rouillon 2008 (3)	21	49	18	48	9.0%	1.14 [0.70 , 1.86]
Subtotal (95% CI)		**213**		**388**	**100.0%**	**1.06 [0.92 , 1.23]**
Total events:	108		178			
Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
1.78.3 < 1 year						
Cookson 1987 (5)	0	9	0	9		Not estimable
Fleischhacker 2014 (5)	106	131	213	266	100.0%	1.01 [0.91 , 1.12]
Subtotal (95% CI)		**140**		**275**	**100.0%**	**1.01 [0.91 , 1.12]**
Total events:	106		213			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.20 (P = 0.84)						
Test for subgroup differences: Chi² = 0.95, df = 2 (P = 0.62), I² = 0%						

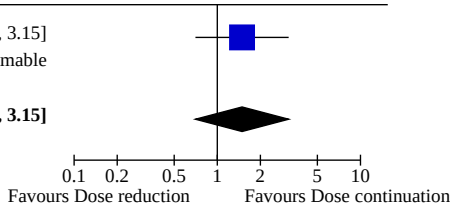


Footnotes

(1) <3 months
(2) <3 months; Patients having a score of at least 1 in at least one item of the UKU scale (LOCF).
(3) < 6 months
(4) < 6 months; Patients having a score of at least 1 in at least one item of the UKU scale (LOCF).
(5) <1 year

Analysis 1.79. Comparison 1: Dose reduction versus dose maintenance , Outcome 79: Adverse effects - number of participants with at least 1 serious adverse event (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014 (1)	11	131	15	266	100.0%	1.49 [0.70 , 3.15]
Huhn 2020 (2)	0	11	0	9		Not estimable
Total (95% CI)		**142**		**275**	**100.0%**	**1.49 [0.70 , 3.15]**
Total events:	11		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Test for subgroup differences: Not applicable						

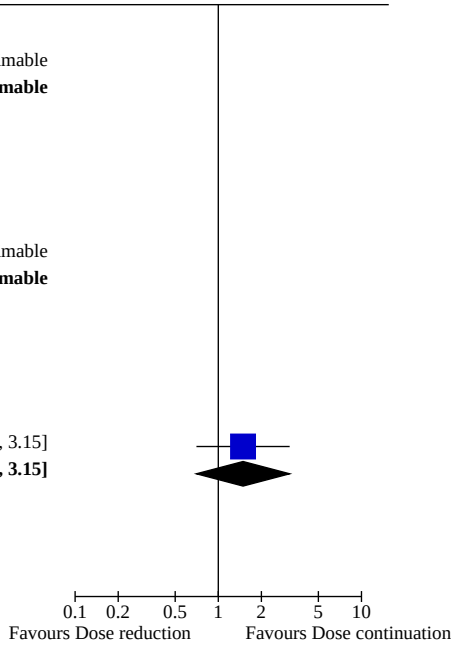


Footnotes

(1) <1 year
(2) < 6 months

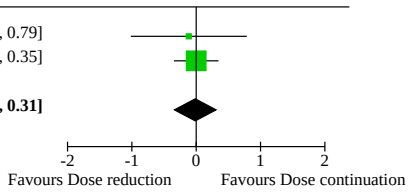
Analysis 1.80. Comparison 1: Dose reduction versus dose maintenance , Outcome 80: Adverse effects - number of participants with at least 1 serious adverse event (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.80.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.80.2 < 6 months						
Huhn 2020	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.80.3 < 1 year						
Fleischhacker 2014	11	131	15	266	100.0%	1.49 [0.70 , 3.15]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**1.49 [0.70 , 3.15]**
Total events:	11		15			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.04 (P = 0.30)						
Test for subgroup differences: Not applicable						



Analysis 1.81. Comparison 1: Dose reduction versus dose maintenance , Outcome 81: Adverse effects - mean endpoint/change adverse effect scales (LUNSERS, UKU) (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Huhn 2020 (1)	10.7	8.08	10	11.78	9.86	9	12.9%	-0.12 [-1.02 , 0.79]
Wunderink 2007 (2)	19.3	13.4	65	19.3	15.2	63	87.1%	0.00 [-0.35 , 0.35]
Total (95% CI)			**75**			**72**	**100.0%**	**-0.01 [-0.34 , 0.31]**
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.82); I² = 0%								
Test for overall effect: Z = 0.09 (P = 0.93)								
Test for subgroup differences: Not applicable								



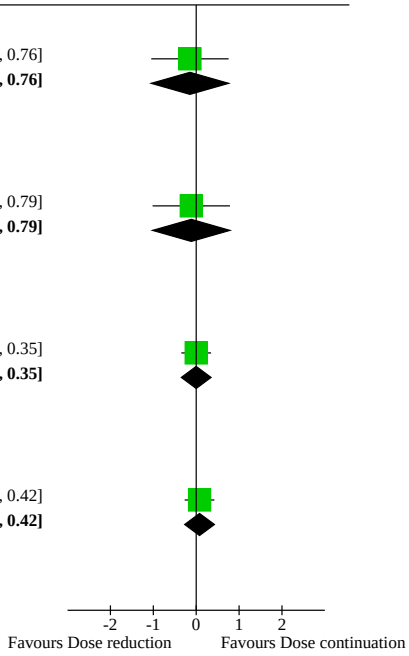
Footnotes

(1) UKU; endpoint; <6 months

(2) LUNSERS; endpoint; < 1 year

Analysis 1.82. Comparison 1: Dose reduction versus dose maintenance , Outcome 82: Adverse effects - mean endpoint/change adverse effect scales (LUNSERS, UKU) (high = poor) (separated time points)

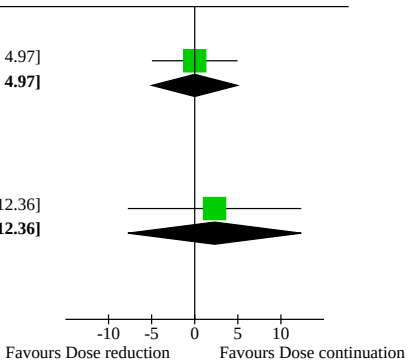
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.82.1 < 3 months								
Huhn 2020 (1)	10.9	9.527	10	12.11	5.622	9	100.0%	-0.15 [-1.05 , 0.76]
Subtotal (95% CI)			**10**			**9**	**100.0%**	**-0.15 [-1.05 , 0.76]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.32 (P = 0.75)								
1.82.2 < 6 months								
Huhn 2020 (2)	10.7	8.084	10	11.78	9.864	9	100.0%	-0.12 [-1.02 , 0.79]
Subtotal (95% CI)			**10**			**9**	**100.0%**	**-0.12 [-1.02 , 0.79]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.25 (P = 0.80)								
1.82.3 < 1 year								
Wunderink 2007 (3)	19.3	13.4	65	19.3	15.2	63	100.0%	0.00 [-0.35 , 0.35]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.00 [-0.35 , 0.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.82.4 > 1 year								
Wunderink 2007 (4)	24.5	36.6	65	22.2	19	63	100.0%	0.08 [-0.27 , 0.42]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.08 [-0.27 , 0.42]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.44 (P = 0.66)								
Test for subgroup differences: Chi² = 0.34, df = 3 (P = 0.95), I² = 0%								



Footnotes
(1) UKU; endpoint; <3 months
(2) UKU; endpoint; <6 months
(3) LUNSERS; endpoint; < 1 year
(4) LUNSERS; endpoint; >1 year

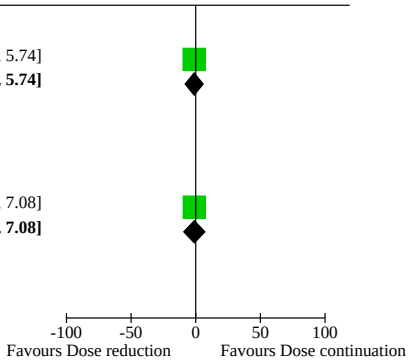
Analysis 1.83. Comparison 1: Dose reduction versus dose maintenance , Outcome 83: Adverse effects - mean endpoint LUNSERS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.83.1 < 1 year								
Wunderink 2007	19.3	13.4	65	19.3	15.2	63	100.0%	0.00 [-4.97 , 4.97]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**0.00 [-4.97 , 4.97]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.00 (P = 1.00)								
1.83.2 > 1 year								
Wunderink 2007	24.5	36.6	65	22.2	19	63	100.0%	2.30 [-7.76 , 12.36]
Subtotal (95% CI)			**65**			**63**	**100.0%**	**2.30 [-7.76 , 12.36]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.45 (P = 0.65)								
Test for subgroup differences: Chi² = 0.16, df = 1 (P = 0.69), I² = 0%								



Analysis 1.84. Comparison 1: Dose reduction versus dose maintenance , Outcome 84: Adverse effects - mean endpoint UKU (high = poor)

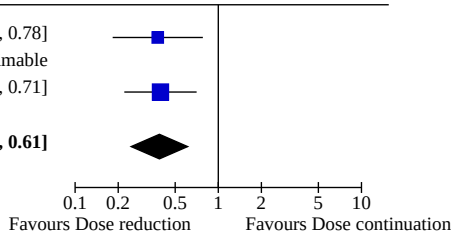
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.84.1 < 3 months								
Huhn 2020 (1)	10.9	9.53	10	12.11	5.62	9	100.0%	-1.21 [-8.16 , 5.74]
Subtotal (95% CI)			**10**			**9**	**100.0%**	**-1.21 [-8.16 , 5.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.34 (P = 0.73)								
1.84.2 < 6 months								
Huhn 2020 (1)	10.7	8.08	10	11.78	9.86	9	100.0%	-1.08 [-9.24 , 7.08]
Subtotal (95% CI)			**10**			**9**	**100.0%**	**-1.08 [-9.24 , 7.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.98), I² = 0%								



Footnotes
(1) UKU total (LOCF)

Analysis 1.85. Comparison 1: Dose reduction versus dose maintenance , Outcome 85: Adverse effects - number of participants with clinically important weight gain (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014 (1)	8	131	43	266	39.1%	0.38 [0.18 , 0.78]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (2)	12	144	68	322	60.9%	0.39 [0.22 , 0.71]
Total (95% CI)		**286**		**597**	**100.0%**	**0.39 [0.25 , 0.61]**
Total events:	20		111			
Heterogeneity: Tau² = 0.00; Chi² = 0.01, df = 1 (P = 0.93); I² = 0%						
Test for overall effect: Z = 4.09 (P < 0.0001)						
Test for subgroup differences: Not applicable						

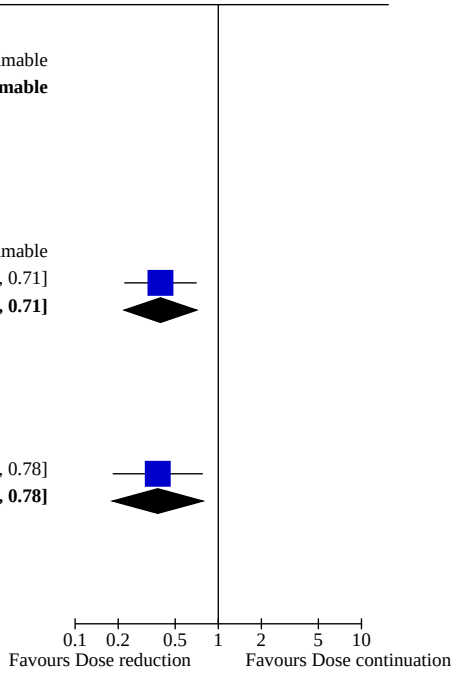


Footnotes
(1) <1 year; weight gain ≥7%
(2) <6 months; weight gain ≥7%

Analysis 1.86. Comparison 1: Dose reduction versus dose maintenance , Outcome 86: Adverse effects - number of participants with clinically important weight gain (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.86.1 < 3 months						
Huhn 2020 (1)	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.86.2 < 6 months						
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (2)	12	144	68	322	100.0%	0.39 [0.22 , 0.71]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.39 [0.22 , 0.71]**
Total events:	12		68			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.13 (P = 0.002)						
1.86.3 < 1 year						
Fleischhacker 2014 (3)	8	131	43	266	100.0%	0.38 [0.18 , 0.78]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.38 [0.18 , 0.78]**
Total events:	8		43			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.63 (P = 0.009)						

Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.93), I² = 0%



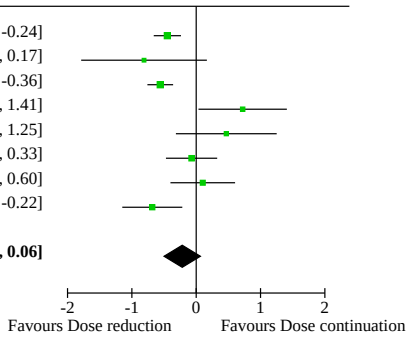
Footnotes

(1) <3 monhts; weight gain ≥7%
(2) <6 months; weight gain ≥7%
(3) <1 year; weight gain ≥7%

Analysis 1.87. Comparison 1: Dose reduction versus dose maintenance , Outcome 87: Adverse effects - mean endpoint/change weight (kg, %, BMI) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	-1.6	7.4	131	1	4.8	266	18.3%	-0.45 [-0.66 , -0.24]
Huhn 2020 (2)	-0.7	1.89	10	0.88	1.81	8	5.9%	-0.81 [-1.79 , 0.17]
Kane 2010 (3)	-0.95	4.09	144	1.3	3.99	322	18.5%	-0.56 [-0.76 , -0.36]
Ozawa 2019 (1)	0.4	2.2	17	-2.1	4.2	18	9.2%	0.72 [0.04 , 1.41]
Remington 2011 (4)	-1.7	2.07	14	-2.7	2.07	12	7.9%	0.47 [-0.32 , 1.25]
Rouillon 2008 (3)	0.12	4.1	49	0.4	3.6	48	14.5%	-0.07 [-0.47 , 0.33]
Takeuchi 2014 (1)	-0.3	2.7	31	-0.6	3.1	30	12.4%	0.10 [-0.40 , 0.60]
Zhou 2018 (5)	23.7	3.7	37	26.9	5.4	38	13.1%	-0.68 [-1.15 , -0.22]
Total (95% CI)			**433**			**742**	**100.0%**	**-0.22 [-0.50 , 0.06]**

Heterogeneity: Tau² = 0.10; Chi² = 26.07, df = 7 (P = 0.0005); I² = 73%
Test for overall effect: Z = 1.51 (P = 0.13)
Test for subgroup differences: Not applicable



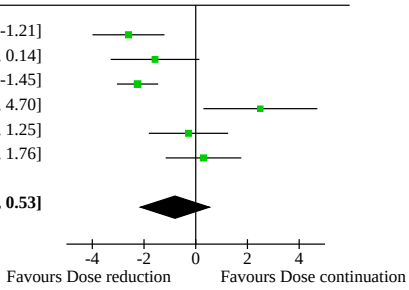
Footnotes

(1) kg; change; < 1 year
(2) kg; endpoint; < 6 months; change was used post-hoc due to baseline imbalance
(3) kg; change; < 6 months
(4) %; change; <6 months ; imputed SD
(5) kg/m2; endpoint; <1 year

Analysis 1.88. Comparison 1: Dose reduction versus dose maintenance , Outcome 88: Adverse effects - mean endpoint/change weight (kg) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Fleischhacker 2014 (1)	-1.6	7.4	131	1	4.8	266	17.3%	-2.60 [-3.99 , -1.21]
Huhn 2020 (2)	-0.7	1.89	10	0.875	1.81	8	15.8%	-1.57 [-3.29 , 0.14]
Kane 2010 (3)	-0.95	4.09	144	1.3	3.99	322	19.8%	-2.25 [-3.05 , -1.45]
Ozawa 2019 (1)	0.4	2.2	17	-2.1	4.2	18	13.5%	2.50 [0.30 , 4.70]
Rouillon 2008 (3)	0.12	4.1	49	0.4	3.6	48	16.6%	-0.28 [-1.81 , 1.25]
Takeuchi 2014 (1)	-0.3	2.7	31	-0.6	3.1	30	17.0%	0.30 [-1.16 , 1.76]
Total (95% CI)			**382**			**692**	**100.0%**	**-0.80 [-2.14 , 0.53]**

Heterogeneity: Tau² = 2.16; Chi² = 26.53, df = 5 (P < 0.0001); I² = 81%
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable

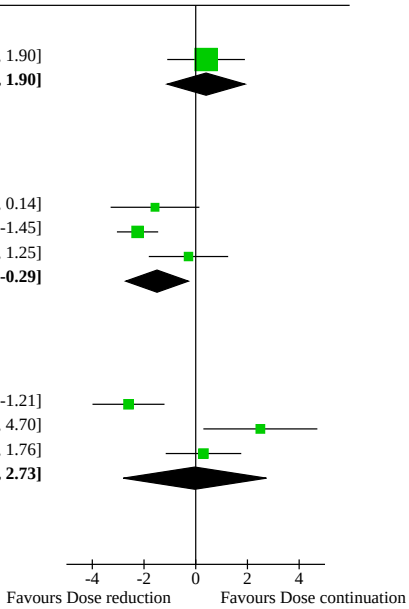


Footnotes
(1) kg; change; < 1 year
(2) kg; endpoint; < 6 months; change was used post-hoc due to baseline imbalance
(3) kg; change; < 6 months

Analysis 1.89. Comparison 1: Dose reduction versus dose maintenance , Outcome 89: Adverse effects - mean endpoint/change weight (kg) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.89.1 < 3 months								
Huhn 2020 (1)	0.4	1.84	10	0	1.41	8	100.0%	0.40 [-1.10 , 1.90]
Subtotal (95% CI)			**10**			**8**	**100.0%**	**0.40 [-1.10 , 1.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
1.89.2 < 6 months								
Huhn 2020 (2)	-0.7	1.89	10	0.875	1.81	8	26.2%	-1.57 [-3.29 , 0.14]
Kane 2010 (3)	-0.95	4.09	144	1.3	3.99	322	44.6%	-2.25 [-3.05 , -1.45]
Rouillon 2008 (3)	0.12	4.1	49	0.4	3.6	48	29.3%	-0.28 [-1.81 , 1.25]
Subtotal (95% CI)			**203**			**378**	**100.0%**	**-1.50 [-2.71 , -0.29]**
Heterogeneity: Tau² = 0.69; Chi² = 5.06, df = 2 (P = 0.08); I² = 60%								
Test for overall effect: Z = 2.42 (P = 0.02)								
1.89.3 < 1 year								
Fleischhacker 2014 (4)	-1.6	7.4	131	1	4.8	266	34.8%	-2.60 [-3.99 , -1.21]
Ozawa 2019 (5)	0.4	2.2	17	-2.1	4.2	18	30.7%	2.50 [0.30 , 4.70]
Takeuchi 2014 (4)	-0.3	2.7	31	-0.6	3.1	30	34.5%	0.30 [-1.16 , 1.76]
Subtotal (95% CI)			**179**			**314**	**100.0%**	**-0.03 [-2.80 , 2.73]**
Heterogeneity: Tau² = 5.22; Chi² = 16.98, df = 2 (P = 0.0002); I² = 88%								
Test for overall effect: Z = 0.02 (P = 0.98)								

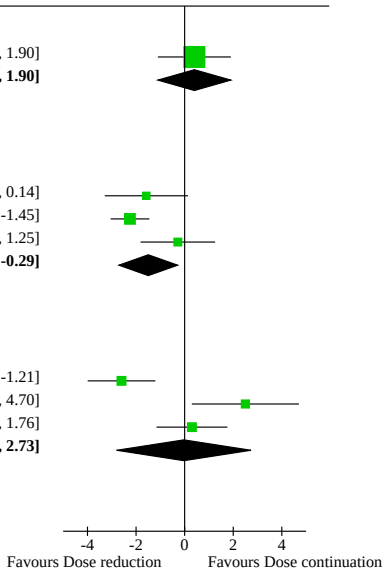
Test for subgroup differences: Chi² = 3.94, df = 2 (P = 0.14), I² = 49.3%



Footnotes
(1) kg; change; <3 months; change was used post-hoc due to baseline imbalance
(2) kg; endpoint; < 6 months; change was used post-hoc due to baseline imbalance
(3) kg; change; < 6 months
(4) kg; change; < 1 year
(5) kg; change; > 1 year

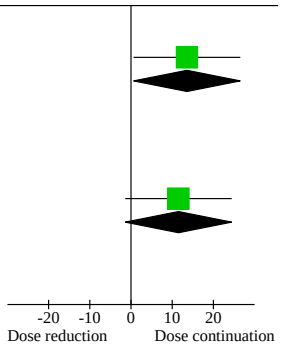
Analysis 1.90. Comparison 1: Dose reduction versus dose maintenance , Outcome 90: Adverse effects - mean change weight (kg)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.90.1 < 3 months								
Huhn 2020	0.4	1.837873167	10	0	1.414213562	8	100.0%	0.40 [-1.10 , 1.90]
Subtotal (95% CI)			**10**			**8**	**100.0%**	**0.40 [-1.10 , 1.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
1.90.2 < 6 months								
Huhn 2020	-0.7	1.888562063	10	0.875	1.807721534	8	26.2%	-1.57 [-3.29 , 0.14]
Kane 2010	-0.95	4.09	144	1.3	3.99	322	44.5%	-2.25 [-3.05 , -1.45]
Rouillon 2008	0.12	4.1	49	0.4	3.6	48	29.3%	-0.28 [-1.81 , 1.25]
Subtotal (95% CI)			**203**			**378**	**100.0%**	**-1.50 [-2.71 , -0.29]**
Heterogeneity: Tau² = 0.69; Chi² = 5.06, df = 2 (P = 0.08); I² = 60%								
Test for overall effect: Z = 2.42 (P = 0.02)								
1.90.3 < 1 year								
Fleischhacker 2014	-1.6	7.4	131	1	4.8	266	34.8%	-2.60 [-3.99 , -1.21]
Ozawa 2019	0.4	2.2	17	-2.1	4.2	18	30.7%	2.50 [0.30 , 4.70]
Takeuchi 2014	-0.3	2.7	31	-0.6	3.1	30	34.5%	0.30 [-1.16 , 1.76]
Subtotal (95% CI)			**179**			**314**	**100.0%**	**-0.03 [-2.80 , 2.73]**
Heterogeneity: Tau² = 5.22; Chi² = 16.98, df = 2 (P = 0.0002); I² = 88%								
Test for overall effect: Z = 0.02 (P = 0.98)								
Test for subgroup differences: Chi² = 3.94, df = 2 (P = 0.14), I² = 49.3%								



Analysis 1.91. Comparison 1: Dose reduction versus dose maintenance , Outcome 91: Adverse effects - mean weight endpoint (kg)

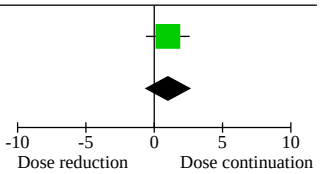
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.91.1 < 3 months								
Huhn 2020	90.45454545	12.39648044	11	76.875	15.42203896	8	100.0%	13.58 [0.62 , 26.54]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**13.58 [0.62 , 26.54]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.05 (P = 0.04)								
1.91.2 < 6 months								
Huhn 2020	89.27272727	11.02806338	11	77.75	16.10456901	8	100.0%	11.52 [-1.40 , 24.45]
Subtotal (95% CI)			**11**			**8**	**100.0%**	**11.52 [-1.40 , 24.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.75 (P = 0.08)								
Test for subgroup differences: Chi² = 0.05, df = 1 (P = 0.83), I² = 0%								



Analysis 1.92. Comparison 1: Dose reduction versus dose maintenance , Outcome 92: Adverse effects - weight change in % from baseline to endpoint

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Remington 2011 (1)	-1.7	2.07	14	-2.7	2.07	12	100.0%	1.00 [-0.60 , 2.60]
Total (95% CI)			**14**			**12**	**100.0%**	**1.00 [-0.60 , 2.60]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.23 (P = 0.22)
Test for subgroup differences: Not applicable

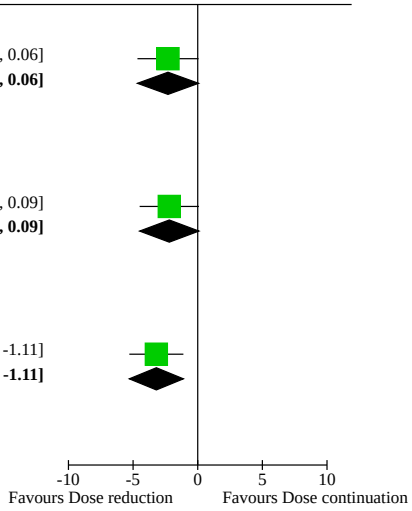


Footnotes
(1) imputed SD from Huhn et al

Analysis 1.93. Comparison 1: Dose reduction versus dose maintenance , Outcome 93: Adverse effects - mean endpoint BMI (kg/m^2)

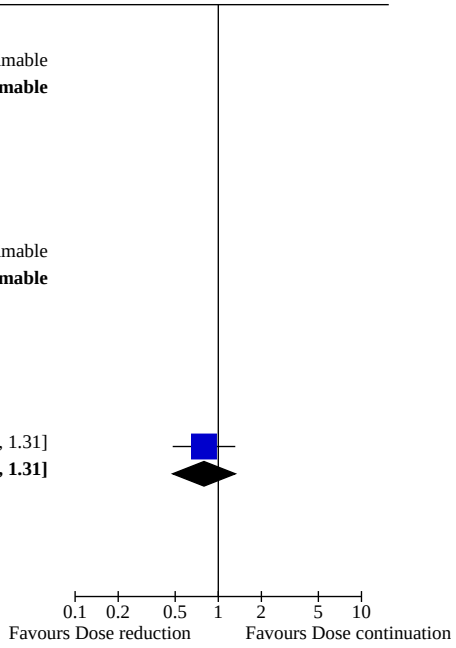
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.93.1 < 3 months								
Zhou 2018	24.8	4.7	37	27.1	5.7	38	100.0%	-2.30 [-4.66 , 0.06]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-2.30 [-4.66 , 0.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.91 (P = 0.06)								
1.93.2 < 6 months								
Zhou 2018	24.6	4.6	37	26.8	5.5	38	100.0%	-2.20 [-4.49 , 0.09]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-2.20 [-4.49 , 0.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.88 (P = 0.06)								
1.93.3 < 1 year								
Zhou 2018	23.7	3.7	37	26.9	5.4	38	100.0%	-3.20 [-5.29 , -1.11]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-3.20 [-5.29 , -1.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.00 (P = 0.003)								

Test for subgroup differences: Chi² = 0.50, df = 2 (P = 0.78), I² = 0%



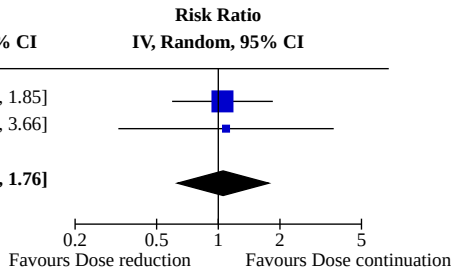
Analysis 1.94. Comparison 1: Dose reduction versus dose maintenance , Outcome 94: Adverse effects - specific: number of participants that needed antiparkinsonian medication

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.94.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.94.2 < 6 months						
Huhn 2020	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.94.3 < 1 year						
Fleischhacker 2014	18	131	46	266	100.0%	0.79 [0.48 , 1.31]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.79 [0.48 , 1.31]**
Total events:	18		46			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.90 (P = 0.37)						



Analysis 1.95. Comparison 1: Dose reduction versus dose maintenance , Outcome 95: Adverse effects - specific: number of participants with at least 1 extrapyramidal symptom (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014 (1)	16	131	31	266	82.1%	1.05 [0.60 , 1.85]
Huhn 2020 (2)	4	11	3	9	17.9%	1.09 [0.33 , 3.66]
Total (95% CI)		**142**		**275**	**100.0%**	**1.06 [0.63 , 1.76]**
Total events:	20		34			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.21 (P = 0.84)						
Test for subgroup differences: Not applicable						



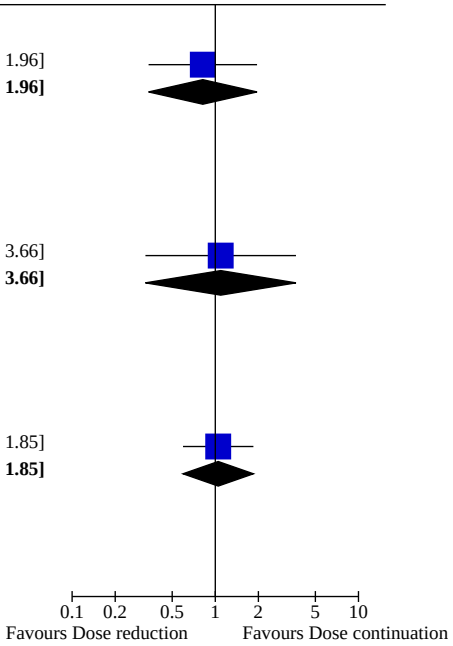
Footnotes

(1) <1 year

(2) <6 months; At least 1 in at least one of the UKU items dystonia, rigidity, hypokinesia, hyperkinesia, tremor and akathisia

Analysis 1.96. Comparison 1: Dose reduction versus dose maintenance , Outcome 96: Adverse effects - specific: number of participants with at least 1 extrapyramidal symptom (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.96.1 < 3 months						
Huhn 2020 (1)	5	11	5	9	100.0%	0.82 [0.34 , 1.96]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.82 [0.34 , 1.96]**
Total events:	5		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.45 (P = 0.65)						
1.96.2 < 6 months						
Huhn 2020 (2)	4	11	3	9	100.0%	1.09 [0.33 , 3.66]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**1.09 [0.33 , 3.66]**
Total events:	4		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.14 (P = 0.89)						
1.96.3 < 1 year						
Fleischhacker 2014 (3)	16	131	31	266	100.0%	1.05 [0.60 , 1.85]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**1.05 [0.60 , 1.85]**
Total events:	16		31			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.87)						
Test for subgroup differences: Chi² = 0.25, df = 2 (P = 0.88), I² = 0%						



Footnotes

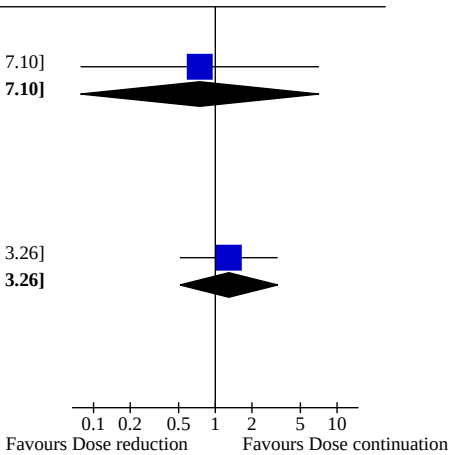
(1) <3 months; At least 1 in at least one of the UKU items dystonia, rigidity, hypokinesia, hyperkinesia, tremor and akathisia

(2) <6 months; At least 1 in at least one of the UKU items dystonia, rigidity, hypokinesia, hyperkinesia, tremor and akathisia

(3) <1 year

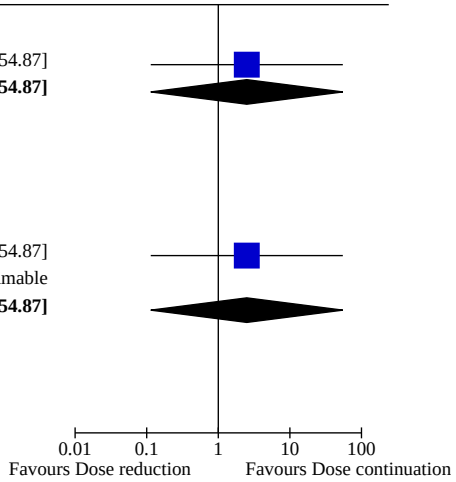
Analysis 1.97. Comparison 1: Dose reduction versus dose maintenance , Outcome 97: Adverse effects - specific: number of participants with parkinsonism

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.97.1 < 6 months						
Kane 2010	1	144	3	322	100.0%	0.75 [0.08 , 7.10]
Subtotal (95% CI)		**144**		**322**	**100.0%**	**0.75 [0.08 , 7.10]**
Total events:	1		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
1.97.2 < 1 year						
Fleischhacker 2014	7	131	11	266	100.0%	1.29 [0.51 , 3.26]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**1.29 [0.51 , 3.26]**
Total events:	7		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%						



Analysis 1.98. Comparison 1: Dose reduction versus dose maintenance , Outcome 98: Adverse effects - specific: number of participants with rigidity

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.98.1 < 3 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.98.2 < 6 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Kane 2010	0	144	0	322		Not estimable
Subtotal (95% CI)		**155**		**331**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						

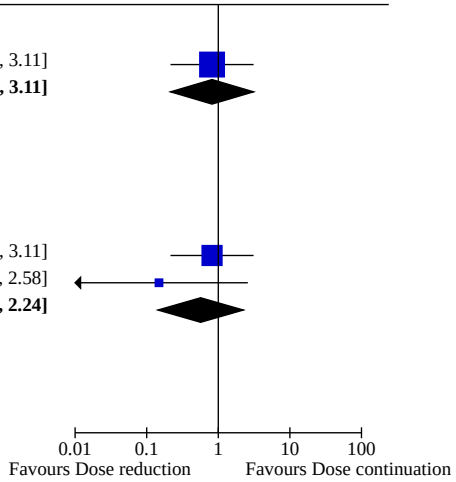


Footnotes

(1) As per the corresponding item in UKU (LOCF)

Analysis 1.99. Comparison 1: Dose reduction versus dose maintenance , Outcome 99: Adverse effects - specific: number of participants with tremors

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.99.1 < 3 months						
Huhn 2020 (1)	3	11	3	9	100.0%	0.82 [0.22 , 3.11]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.82 [0.22 , 3.11]**
Total events:	3		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.29 (P = 0.77)						
1.99.2 < 6 months						
Huhn 2020 (1)	3	11	3	9	78.5%	0.82 [0.22 , 3.11]
Kane 2010	0	144	7	322	21.5%	0.15 [0.01 , 2.58]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.57 [0.14 , 2.24]**
Total events:	3		10			
Heterogeneity: Tau² = 0.16; Chi² = 1.13, df = 1 (P = 0.29); I² = 11%						
Test for overall effect: Z = 0.81 (P = 0.42)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						



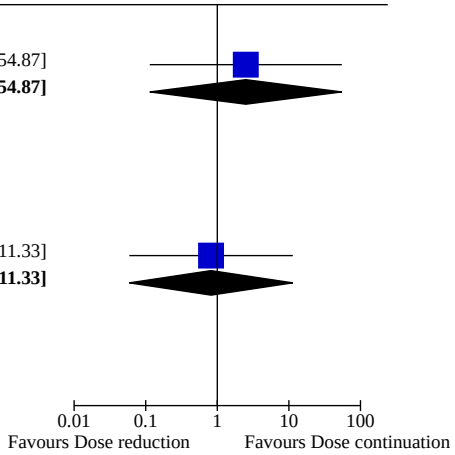
Footnotes

(1) As defined per UKU item "tremor" (LOCF)

Analysis 1.100. Comparison 1: Dose reduction versus dose maintenance , Outcome 100: Adverse effects - specific: number of participants with dystonia

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.100.1 < 3 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.100.2 < 6 months						
Huhn 2020 (1)	1	11	1	9	100.0%	0.82 [0.06 , 11.33]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.82 [0.06 , 11.33]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						

Test for subgroup differences: Chi² = 0.29, df = 1 (P = 0.59), I² = 0%



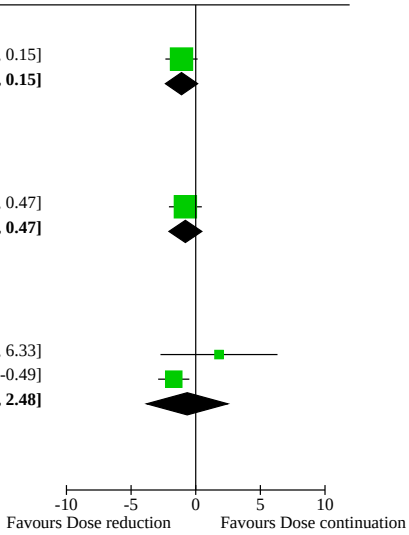
Footnotes

(1) As defined per the corresponding item in UKU (LOCF)

Analysis 1.101. Comparison 1: Dose reduction versus dose maintenance , Outcome 101: Adverse effects - mean endpoint SAS (high = poor)

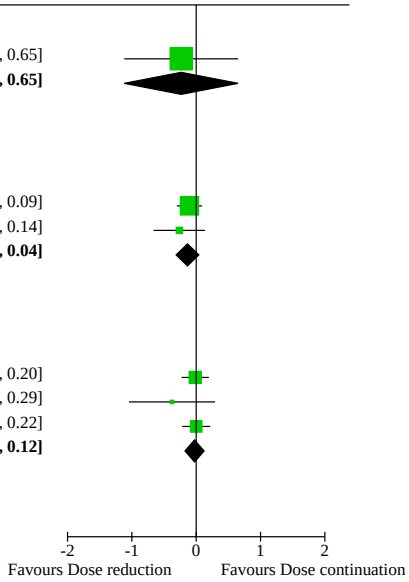
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.101.1 < 3 months								
Zhou 2018	5.2	3.2	37	6.3	2.2	38	100.0%	-1.10 [-2.35 , 0.15]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-1.10 [-2.35 , 0.15]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.73 (P = 0.08)								
1.101.2 < 6 months								
Zhou 2018	5.1	3	37	5.9	2.6	38	100.0%	-0.80 [-2.07 , 0.47]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-0.80 [-2.07 , 0.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.23 (P = 0.22)								
1.101.3 < 1 year								
Ozawa 2019	7.4	7.6	17	5.6	5.9	18	29.8%	1.80 [-2.73 , 6.33]
Zhou 2018	4.9	2.9	37	6.6	2.4	38	70.2%	-1.70 [-2.91 , -0.49]
Subtotal (95% CI)			**54**			**56**	**100.0%**	**-0.66 [-3.79 , 2.48]**
Heterogeneity: Tau² = 3.27; Chi² = 2.15, df = 1 (P = 0.14); I² = 53%								
Test for overall effect: Z = 0.41 (P = 0.68)								

Test for subgroup differences: Chi² = 0.14, df = 2 (P = 0.93), I² = 0%



Analysis 1.102. Comparison 1: Dose reduction versus dose maintenance , Outcome 102: Adverse effects - mean change SAS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.102.1 < 3 months								
Volavka 2000 (1)	-0.1	1.8	9	0.3	1.5	11	100.0%	-0.23 [-1.12 , 0.65]
Subtotal (95% CI)			**9**			**11**	**100.0%**	**-0.23 [-1.12 , 0.65]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.52 (P = 0.60)								
1.102.2 < 6 months								
Kane 2010	-0.35	2.2	144	-0.14	1.9	322	80.5%	-0.10 [-0.30 , 0.09]
Rouillon 2008	-0.2	1.4	49	0.3	2.3	48	19.5%	-0.26 [-0.66 , 0.14]
Subtotal (95% CI)			**193**			**370**	**100.0%**	**-0.14 [-0.31 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 0.47, df = 1 (P = 0.49); I² = 0%								
Test for overall effect: Z = 1.50 (P = 0.13)								
1.102.3 < 1 year								
Fleischhacker 2014	-0.09	1.4	128	-0.07	1.3	260	49.2%	-0.01 [-0.23 , 0.20]
Ozawa 2019	-0.6	1.3	17	-0.1	1.3	18	4.9%	-0.38 [-1.05 , 0.29]
Wang 2010	-0.3	2	211	-0.3	1.7	129	45.9%	0.00 [-0.22 , 0.22]
Subtotal (95% CI)			**356**			**407**	**100.0%**	**-0.03 [-0.17 , 0.12]**
Heterogeneity: Tau² = 0.00; Chi² = 1.11, df = 2 (P = 0.57); I² = 0%								
Test for overall effect: Z = 0.34 (P = 0.73)								
Test for subgroup differences: Chi² = 0.99, df = 2 (P = 0.61), I² = 0%								

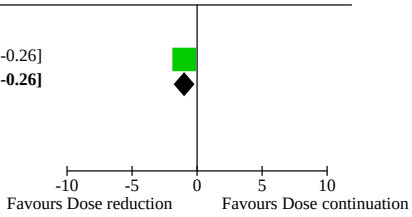


Footnotes

(1) minus transformed it was reported as improvement

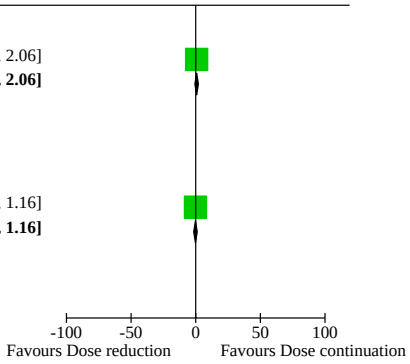
Analysis 1.103. Comparison 1: Dose reduction versus dose maintenance , Outcome 103: Adverse effects - mean change DIEPSS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.103.1 < 1 year								
Takeuchi 2014	-0.9	1.7	31	0.1	1.2	30	100.0%	-1.00 [-1.74 , -0.26]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-1.00 [-1.74 , -0.26]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.66 (P = 0.008)								



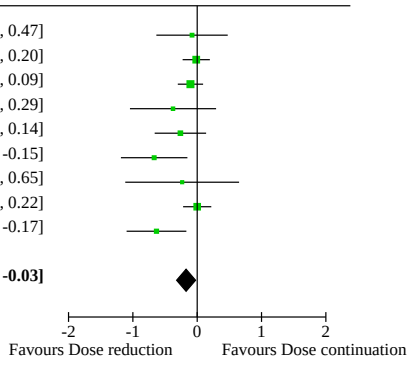
Analysis 1.104. Comparison 1: Dose reduction versus dose maintenance , Outcome 104: Adverse effects - mean endpoint MPRC parkinsonian scale (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.104.1 < 6 months								
Carpenter 1999	2.9	2.6	25	2.2	2.3	25	100.0%	0.70 [-0.66 , 2.06]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**0.70 [-0.66 , 2.06]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.01 (P = 0.31)								
1.104.2 < 1 year								
Carpenter 1999	2	2.6	25	2.2	2.3	25	100.0%	-0.20 [-1.56 , 1.16]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**-0.20 [-1.56 , 1.16]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.29 (P = 0.77)								
Test for subgroup differences: Chi² = 0.84, df = 1 (P = 0.36), I² = 0%								



Analysis 1.105. Comparison 1: Dose reduction versus dose maintenance , Outcome 105: Adverse effects - mean endpoint/change EPS scales (SAS, DIEPSS, MPRC parkinsonian) (high = poor) (combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Carpenter 1999 (1)	2	2.6	25	2.2	2.3	25	5.9%	-0.08 [-0.63 , 0.47]
Fleischhacker 2014 (2)	-0.09	1.4	128	-0.07	1.3	260	20.8%	-0.01 [-0.23 , 0.20]
Kane 2010 (3)	-0.35	2.2	144	-0.14	1.9	322	22.1%	-0.10 [-0.30 , 0.09]
Ozawa 2019 (4)	-0.6	1.3	17	-0.1	1.3	18	4.3%	-0.38 [-1.05 , 0.29]
Rouillon 2008 (3)	-0.2	1.4	49	0.3	2.3	48	9.9%	-0.26 [-0.66 , 0.14]
Takeuchi 2014 (5)	-0.9	1.7	31	0.1	1.2	30	6.6%	-0.67 [-1.19 , -0.15]
Volavka 2000 (6)	-0.1	1.8	9	0.3	1.5	11	2.6%	-0.23 [-1.12 , 0.65]
Wang 2010 (2)	-0.3	2	211	-0.3	1.7	129	20.1%	0.00 [-0.22 , 0.22]
Zhou 2018 (7)	4.9	2.9	37	6.6	2.4	38	7.9%	-0.63 [-1.10 , -0.17]
Total (95% CI)			**651**			**881**	**100.0%**	**-0.17 [-0.32 , -0.03]**
Heterogeneity: Tau² = 0.02; Chi² = 12.25, df = 8 (P = 0.14); I² = 35%								
Test for overall effect: Z = 2.30 (P = 0.02)								
Test for subgroup differences: Not applicable								

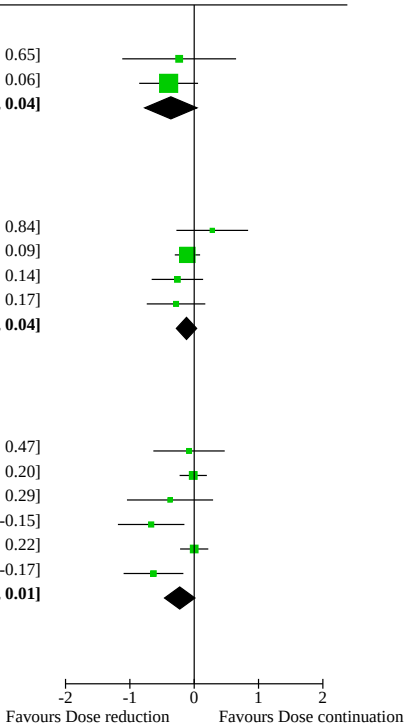


Footnotes

(1) MRPC; change; <1 year
(2) SAS; change; <1 year
(3) SAS; change; < 6 months
(4) SAS; change; <1 year; change score was used post-hoc since most of the studies reported change score scores (SMD) and there was important baseline imbalance
(5) DIEPSS; change; < 1 year
(6) SAS; change; <3 months; mimus transformed it was reported as improvemnt
(7) SAS; endpoint; <1 year

Analysis 1.106. Comparison 1: Dose reduction versus dose maintenance , Outcome 106: Adverse effects - mean endpoint/change EPS scales (SAS, DIEPSS, MPRC parkinsonian) (high = poor) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.106.1 < 3 months								
Volavka 2000 (1)	-0.1	1.8	9	0.3	1.5	11	21.1%	-0.23 [-1.12 , 0.65]
Zhou 2018 (2)	5.2	3.2	37	6.3	2.2	38	78.9%	-0.40 [-0.85 , 0.06]
Subtotal (95% CI)			**46**			**49**	**100.0%**	**-0.36 [-0.77 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 0.10, df = 1 (P = 0.75); I² = 0%								
Test for overall effect: Z = 1.75 (P = 0.08)								
1.106.2 < 6 months								
Carpenter 1999	2.9	2.6	25	2.2	2.3	25	8.0%	0.28 [-0.28 , 0.84]
Kane 2010 (3)	-0.35	2.2	144	-0.14	1.9	322	64.4%	-0.10 [-0.30 , 0.09]
Rouillon 2008 (3)	-0.2	1.4	49	0.3	2.3	48	15.6%	-0.26 [-0.66 , 0.14]
Zhou 2018 (4)	5.1	3	37	5.9	2.6	38	12.0%	-0.28 [-0.74 , 0.17]
Subtotal (95% CI)			**255**			**433**	**100.0%**	**-0.12 [-0.28 , 0.04]**
Heterogeneity: Tau² = 0.00; Chi² = 2.98, df = 3 (P = 0.40); I² = 0%								
Test for overall effect: Z = 1.49 (P = 0.14)								
1.106.3 < 1 year								
Carpenter 1999 (5)	2	2.6	25	2.2	2.3	25	11.7%	-0.08 [-0.63 , 0.47]
Fleischhacker 2014 (6)	-0.09	1.4	128	-0.07	1.3	260	26.2%	-0.01 [-0.23 , 0.20]
Ozawa 2019 (7)	-0.6	1.3	17	-0.1	1.3	18	9.0%	-0.38 [-1.05 , 0.29]
Takeuchi 2014 (8)	-0.9	1.7	31	0.1	1.2	30	12.8%	-0.67 [-1.19 , -0.15]
Wang 2010 (6)	-0.3	2	211	-0.3	1.7	129	25.8%	0.00 [-0.22 , 0.22]
Zhou 2018 (9)	4.9	2.9	37	6.6	2.4	38	14.5%	-0.63 [-1.10 , -0.17]
Subtotal (95% CI)			**449**			**500**	**100.0%**	**-0.22 [-0.46 , 0.01]**
Heterogeneity: Tau² = 0.04; Chi² = 11.70, df = 5 (P = 0.04); I² = 57%								
Test for overall effect: Z = 1.87 (P = 0.06)								
Test for subgroup differences: Chi² = 1.46, df = 2 (P = 0.48), I² = 0%								

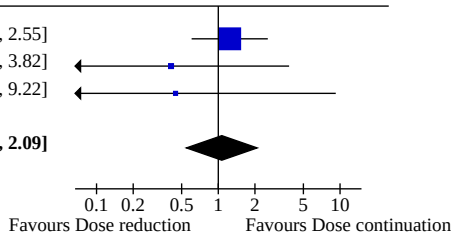


Footnotes

(1) SAS; change; <3 months; minus transformed it was reported as improvement
(2) SAS; endpoint; <3 months
(3) SAS; change; < 6 months
(4) SAS; endpoint; <6 months
(5) MRPC; change; <1 year
(6) SAS; change; <1 year
(7) SAS; endpoint; <1 year; change used post-hoc because of important baseline imbalance (and most of the studies used change scores in SMDs)
(8) DIEPSS; change; < 1 year
(9) SAS; endpoint; <1 year

Analysis 1.107. Comparison 1: Dose reduction versus dose maintenance , Outcome 107: Adverse effects - specific: number of participants with akathisia (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014 (1)	11	131	18	266	86.2%	1.24 [0.60 , 2.55]
Huhn 2020 (2)	1	11	2	9	9.0%	0.41 [0.04 , 3.82]
Kane 2010 (3)	0	144	2	322	4.9%	0.45 [0.02 , 9.22]
Total (95% CI)		**286**		**597**	**100.0%**	**1.07 [0.55 , 2.09]**
Total events:	12		22			
Heterogeneity: Tau² = 0.00; Chi² = 1.20, df = 2 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.19 (P = 0.85)						
Test for subgroup differences: Not applicable						

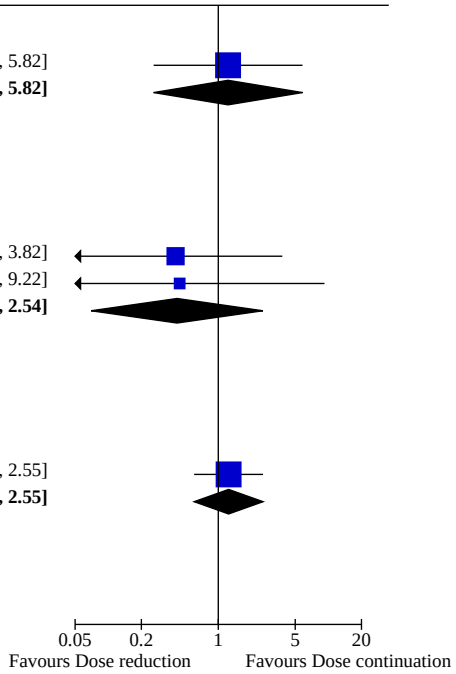


Footnotes

(1) <1 year
(2) <6 months; As per the corresponding item in UKU (LOCF)
(3) <6 months

Analysis 1.108. Comparison 1: Dose reduction versus dose maintenance , Outcome 108: Adverse effects - specific: number of participants with akathisia (separated time points)

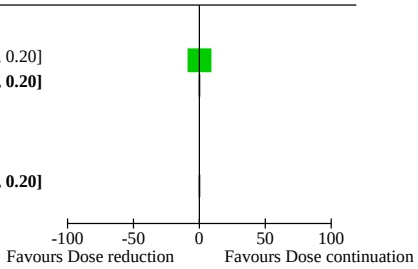
Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.108.1 < 3 months						
Huhn 2020 (1)	3	11	2	9	100.0%	1.23 [0.26 , 5.82]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**1.23 [0.26 , 5.82]**
Total events:	3		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
1.108.2 < 6 months						
Huhn 2020 (1)	1	11	2	9	64.8%	0.41 [0.04 , 3.82]
Kane 2010	0	144	2	322	35.2%	0.45 [0.02 , 9.22]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.42 [0.07 , 2.54]**
Total events:	1		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.96); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
1.108.3 < 1 year						
Fleischhacker 2014	11	131	18	266	100.0%	1.24 [0.60 , 2.55]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**1.24 [0.60 , 2.55]**
Total events:	11		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Chi² = 1.22, df = 2 (P = 0.54), I² = 0%						



Footnotes
(1) As per the corresponding item in UKU (LOCF)

Analysis 1.109. Comparison 1: Dose reduction versus dose maintenance , Outcome 109: Adverse effects - mean endpoint BARS (high = poor)

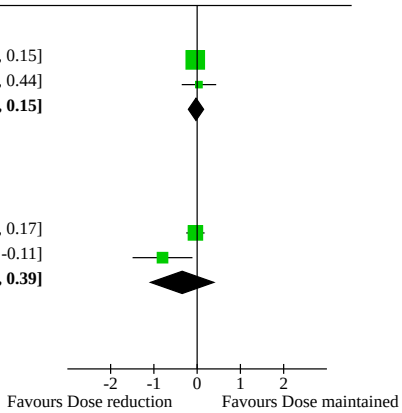
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.109.1 < 1 year								
Ozawa 2019 (1)	0.1	0.2	17	0	0.04	18	100.0%	0.10 [0.00 , 0.20]
Subtotal (95% CI)			**17**			**18**	**100.0%**	**0.10 [0.00 , 0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.02 (P = 0.04)								
Total (95% CI)			**17**			**18**	**100.0%**	**0.10 [0.00 , 0.20]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.02 (P = 0.04)								
Test for subgroup differences: Not applicable								



Footnotes
(1) BARS global, SD to 0.04

Analysis 1.110. Comparison 1: Dose reduction versus dose maintenance , Outcome 110: Adverse effects - mean change BARS (high = poor)

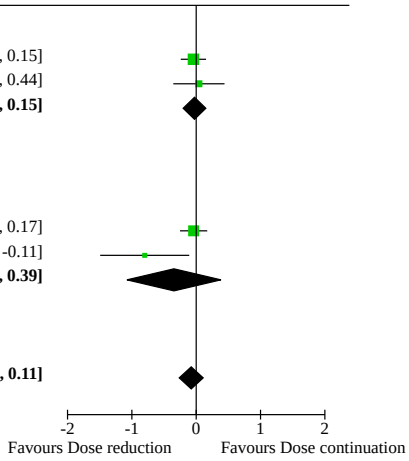
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.110.1 < 6 months								
Kane 2010	-0.05	0.56	144	-0.03	0.41	322	80.4%	-0.04 [-0.24 , 0.15]
Rouillon 2008	0.02	1.2	49	-0.04	1.6	48	19.6%	0.04 [-0.36 , 0.44]
Subtotal (95% CI)			**193**			**370**	**100.0%**	**-0.03 [-0.20 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.77)								
1.110.2 < 1 year								
Fleischhacker 2014	-0.03	0.5	128	-0.01	0.5	260	59.8%	-0.04 [-0.25 , 0.17]
Ozawa 2019 (1)	-0.4	0.7	17	0	0.04	18	40.2%	-0.80 [-1.49 , -0.11]
Subtotal (95% CI)			**145**			**278**	**100.0%**	**-0.35 [-1.08 , 0.39]**
Heterogeneity: Tau² = 0.22; Chi² = 4.24, df = 1 (P = 0.04); I² = 76%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%								



Footnotes
(1) BARS global; SD to 0.04

Analysis 1.111. Comparison 1: Dose reduction versus dose maintenance , Outcome 111: Adverse effects - mean endpoint/change BARS (high = poor) (separated and combined time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.111.1 < 6 months								
Kane 2010 (1)	-0.05	0.56	144	-0.03	0.41	322	39.7%	-0.04 [-0.24 , 0.15]
Rouillon 2008 (2)	0.02	1.2	49	-0.04	1.6	48	16.7%	0.04 [-0.36 , 0.44]
Subtotal (95% CI)			**193**			**370**	**56.4%**	**-0.03 [-0.20 , 0.15]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.30 (P = 0.77)								
1.111.2 < 1 year								
Fleischhacker 2014 (3)	-0.03	0.5	128	-0.01	0.5	260	37.0%	-0.04 [-0.25 , 0.17]
Ozawa 2019 (4)	-0.4	0.7	17	0	0.04	18	6.6%	-0.80 [-1.49 , -0.11]
Subtotal (95% CI)			**145**			**278**	**43.6%**	**-0.35 [-1.08 , 0.39]**
Heterogeneity: Tau² = 0.22; Chi² = 4.24, df = 1 (P = 0.04); I² = 76%								
Test for overall effect: Z = 0.93 (P = 0.35)								
Total (95% CI)			**338**			**648**	**100.0%**	**-0.08 [-0.26 , 0.11]**
Heterogeneity: Tau² = 0.01; Chi² = 4.71, df = 3 (P = 0.19); I² = 36%								
Test for overall effect: Z = 0.82 (P = 0.41)								
Test for subgroup differences: Chi² = 0.69, df = 1 (P = 0.41), I² = 0%								

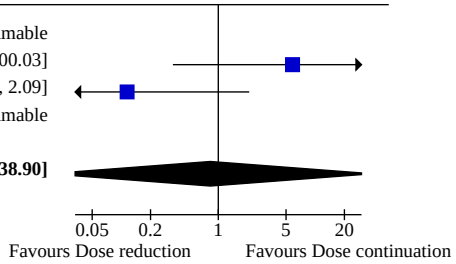


Footnotes
(1) BARS global; change
(2) unclear if it was BARS global or total; change
(3) BARS globa; change
(4) BARS global; SD to 0.04; change scores were used because of baseline imbalance and change scores were used in other studies (SMD)

Analysis 1.112. Comparison 1: Dose reduction versus dose maintenance , Outcome 112: Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Cookson 1987 (1)	0	9	0	9		Not estimable
Huhn 2020 (2)	3	11	0	9	50.3%	5.83 [0.34 , 100.03]
Kane 1983 (3)	0	62	4	64	49.7%	0.11 [0.01 , 2.09]
Kane 2010 (4)	0	144	0	322		Not estimable
Total (95% CI)		**226**		**404**	**100.0%**	**0.83 [0.02 , 38.90]**
Total events:	3		4			

Heterogeneity: Tau² = 5.57; Chi² = 3.60, df = 1 (P = 0.06); I² = 72%
Test for overall effect: Z = 0.10 (P = 0.92)
Test for subgroup differences: Not applicable

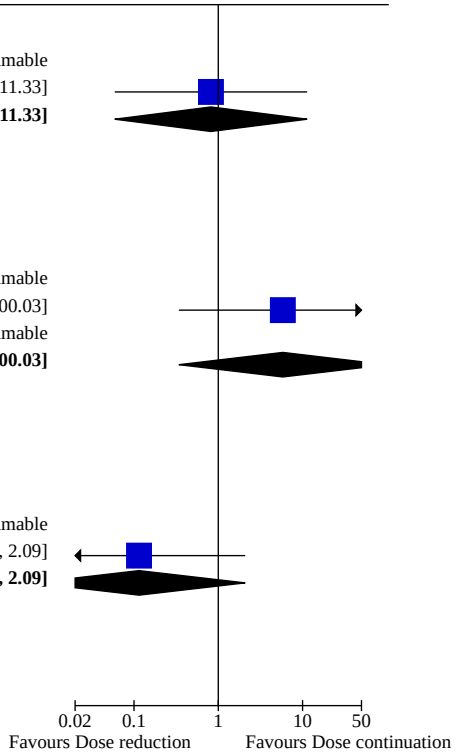


Footnotes

(1) <1 year
(2) <6 months; Defined as hyperkinesia in UKU (LOCF)
(3) <1 year
(4) <6 months

Analysis 1.113. Comparison 1: Dose reduction versus dose maintenance , Outcome 113: Adverse effects - specific: number of participants with dyskinesia (including tardive dyskinesia) (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.113.1 < 3 months						
Cookson 1987 (1)	0	9	0	9		Not estimable
Huhn 2020 (2)	1	11	1	9	100.0%	0.82 [0.06 , 11.33]
Subtotal (95% CI)		**20**		**18**	**100.0%**	**0.82 [0.06 , 11.33]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.113.2 < 6 months						
Cookson 1987 (3)	0	9	0	9		Not estimable
Huhn 2020 (4)	3	11	0	9	100.0%	5.83 [0.34 , 100.03]
Kane 2010 (3)	0	144	0	322		Not estimable
Subtotal (95% CI)		**164**		**340**	**100.0%**	**5.83 [0.34 , 100.03]**
Total events:	3		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.22 (P = 0.22)						
1.113.3 < 1 year						
Cookson 1987 (5)	0	9	0	9		Not estimable
Kane 1983 (6)	0	62	4	64	100.0%	0.11 [0.01 , 2.09]
Subtotal (95% CI)		**71**		**73**	**100.0%**	**0.11 [0.01 , 2.09]**
Total events:	0		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.46 (P = 0.14)						
Test for subgroup differences: Chi² = 3.60, df = 2 (P = 0.17), I² = 44.4%						

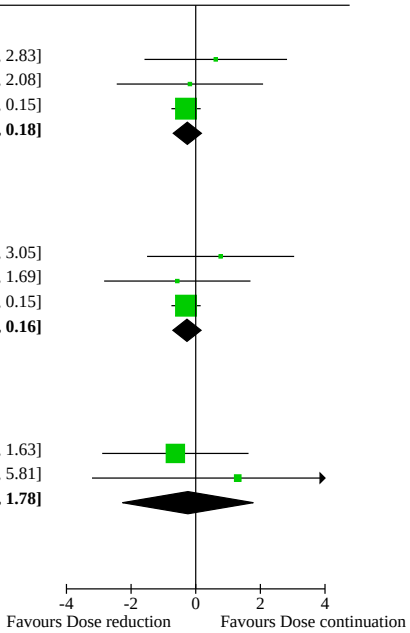


Footnotes

(1) <3 months
(2) <3 months; Defined as hyperkinesia in UKU (LOCF)
(3) <6 months
(4) <6 months; Defined as hyperkinesia in UKU (LOCF)
(5) <1 year
(6) <1 year

Analysis 1.114. Comparison 1: Dose reduction versus dose maintenance , Outcome 114: Adverse effects - mean endpoint AIMS (high = poor)

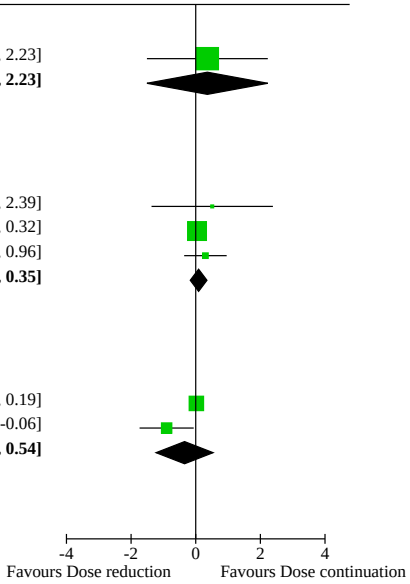
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.114.1 < 3 months								
Huhn 2020	1.73	3.23	11	1.11	1.69	9	3.9%	0.62 [-1.59 , 2.83]
Johnson 1987 (1)	1.5	4.43	28	1.68	4.43	31	3.7%	-0.18 [-2.44 , 2.08]
Remington 2011 (2)	0	0.004	14	0.3	0.8	12	92.4%	-0.30 [-0.75 , 0.15]
Subtotal (95% CI)			**53**			**52**	**100.0%**	**-0.26 [-0.69 , 0.18]**
Heterogeneity: Tau² = 0.00; Chi² = 0.65, df = 2 (P = 0.72); I² = 0%								
Test for overall effect: Z = 1.17 (P = 0.24)								
1.114.2 < 6 months								
Huhn 2020	1.55	3.53	11	0.78	1.39	9	3.7%	0.77 [-1.51 , 3.05]
Johnson 1987 (1)	1.91	4.43	28	2.48	4.43	31	3.7%	-0.57 [-2.83 , 1.69]
Remington 2011 (3)	0	0.004	14	0.3	0.8	12	92.6%	-0.30 [-0.75 , 0.15]
Subtotal (95% CI)			**53**			**52**	**100.0%**	**-0.27 [-0.71 , 0.16]**
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 2 (P = 0.64); I² = 0%								
Test for overall effect: Z = 1.22 (P = 0.22)								
1.114.3 < 1 year								
Johnson 1987 (1)	1.16	4.43	28	1.79	4.43	31	79.9%	-0.63 [-2.89 , 1.63]
Ozawa 2019	7.5	7.7	17	6.2	5.7	18	20.1%	1.30 [-3.21 , 5.81]
Subtotal (95% CI)			**45**			**49**	**100.0%**	**-0.24 [-2.26 , 1.78]**
Heterogeneity: Tau² = 0.00; Chi² = 0.56, df = 1 (P = 0.45); I² = 0%								
Test for overall effect: Z = 0.23 (P = 0.82)								
Test for subgroup differences: Chi² = 0.00, df = 2 (P = 1.00), I² = 0%								



Footnotes
(1) imputed SD
(2) SD to 0.004
(3) SD to 0.004

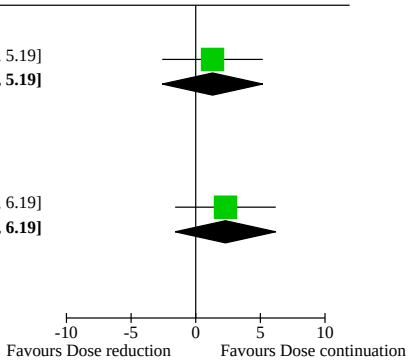
Analysis 1.115. Comparison 1: Dose reduction versus dose maintenance , Outcome 115: Adverse effects - mean change AIMS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.115.1 < 3 months								
Huhn 2020	1.36	2.46	11	1	1.8	9	100.0%	0.36 [-1.51 , 2.23]
Subtotal (95% CI)			**11**			**9**	**100.0%**	**0.36 [-1.51 , 2.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.38 (P = 0.71)								
1.115.2 < 6 months								
Huhn 2020	1.18	2.71	11	0.67	1.5	9	1.9%	0.51 [-1.37 , 2.39]
Kane 2010	-0.14	1.54	144	-0.18	1.2	322	82.7%	0.04 [-0.24 , 0.32]
Rouillon 2008	-0.1	1.6	49	-0.4	1.7	48	15.4%	0.30 [-0.36 , 0.96]
Subtotal (95% CI)			**204**			**379**	**100.0%**	**0.09 [-0.17 , 0.35]**
Heterogeneity: Tau² = 0.00; Chi² = 0.70, df = 2 (P = 0.70); I² = 0%								
Test for overall effect: Z = 0.68 (P = 0.50)								
1.115.3 < 1 year								
Fleischhacker 2014	-0.06	0.8	128	-0.08	0.8	260	60.3%	0.02 [-0.15 , 0.19]
Ozawa 2019	-0.7	1.4	17	0.2	1.1	18	39.7%	-0.90 [-1.74 , -0.06]
Subtotal (95% CI)			**145**			**278**	**100.0%**	**-0.34 [-1.23 , 0.54]**
Heterogeneity: Tau² = 0.33; Chi² = 4.46, df = 1 (P = 0.03); I² = 78%								
Test for overall effect: Z = 0.77 (P = 0.44)								
Test for subgroup differences: Chi² = 0.96, df = 2 (P = 0.62), I² = 0%								



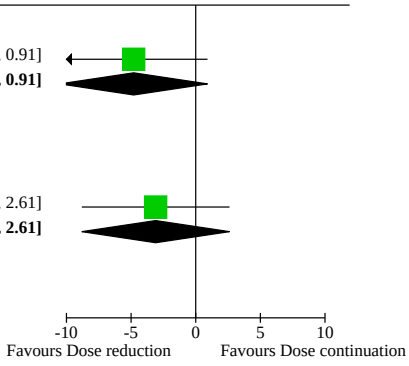
Analysis 1.116. Comparison 1: Dose reduction versus dose maintenance , Outcome 116: Adverse effects - mean endpoint MPRC dyskinesia scale (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.116.1 < 6 months								
Carpenter 1999	4.2	7.5	25	2.9	6.5	25	100.0%	1.30 [-2.59 , 5.19]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**1.30 [-2.59 , 5.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.65 (P = 0.51)								
1.116.2 < 12 months								
Carpenter 1999	5.2	7.5	25	2.9	6.5	25	100.0%	2.30 [-1.59 , 6.19]
Subtotal (95% CI)			**25**			**25**	**100.0%**	**2.30 [-1.59 , 6.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.16 (P = 0.25)								
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%								



Analysis 1.117. Comparison 1: Dose reduction versus dose maintenance , Outcome 117: Adverse effects - specific: mean endpoint abbreviated RTDRS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.117.1 < 3 months								
Branchey 1981 (1)	4	6.67	10	8.8	6.67	11	100.0%	-4.80 [-10.51 , 0.91]
Subtotal (95% CI)			**10**			**11**	**100.0%**	**-4.80 [-10.51 , 0.91]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.65 (P = 0.10)								
1.117.2 < 6 months								
Branchey 1981 (1)	6.4	6.67	10	9.5	6.67	11	100.0%	-3.10 [-8.81 , 2.61]
Subtotal (95% CI)			**10**			**11**	**100.0%**	**-3.10 [-8.81 , 2.61]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.06 (P = 0.29)								
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%								



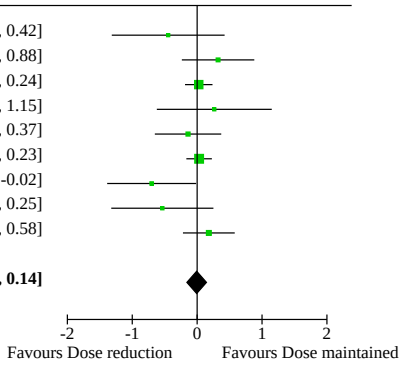
Footnotes

(1) imputed SD from Altamura et al 1990

Analysis 1.118. Comparison 1: Dose reduction versus dose maintenance , Outcome 118: Adverse effects - mean endpoint/change dyskinesia scales (AIMS, MRCP dyskinesia, RTDRS) (high = poor) (combined time points)

	Dose reduction			Dose continuation				Std. Mean Difference	Std. Mean Difference
Study or Subgroup	**Mean**	**SD**	**Total**	**Mean**	**SD**	**Total**	**Weight**	**IV, Random, 95% CI**	**IV, Random, 95% CI**
Branchey 1981 (1)	6.4	6.67	10	9.5	6.67	11	2.9%	-0.45 [-1.32 , 0.42]	
Carpenter 1999 (2)	5.2	7.5	25	2.9	6.5	25	6.6%	0.32 [-0.24 , 0.88]	
Fleischhacker 2014 (3)	-0.06	0.8	128	-0.08	0.8	260	29.0%	0.02 [-0.19 , 0.24]	
Huhn 2020 (4)	1.55	3.53	11	0.78	1.39	9	2.8%	0.26 [-0.62 , 1.15]	
Johnson 1987 (5)	1.16	4.43	28	1.79	4.43	31	7.7%	-0.14 [-0.65 , 0.37]	
Kane 2010 (6)	-0.14	1.54	144	-0.18	1.2	322	31.5%	0.03 [-0.17 , 0.23]	
Ozawa 2019 (7)	-0.7	1.4	17	0.2	1.1	18	4.5%	-0.70 [-1.39 , -0.02]	
Remington 2011 (8)	0	0.004	14	0.3	0.8	12	3.5%	-0.54 [-1.32 , 0.25]	
Rouillon 2008 (6)	-0.1	1.6	49	-0.4	1.7	48	11.8%	0.18 [-0.22 , 0.58]	
Total (95% CI)			**426**			**736**	**100.0%**	**-0.01 [-0.16 , 0.14]**	

Heterogeneity: Tau² = 0.01; Chi² = 9.65, df = 8 (P = 0.29); I² = 17%
Test for overall effect: Z = 0.09 (P = 0.93)
Test for subgroup differences: Not applicable

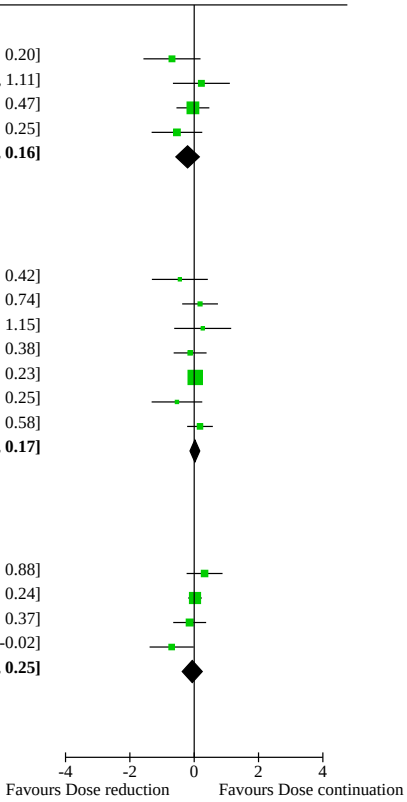


Footnotes

(1) RTDSR; endpoint; <6 months; imputed from Altamura et al 1990
(2) MRPC dyskinesia; endpoint; < 1 year
(3) AIMS; change; <1 year
(4) AIMS; endpoint; <6 months
(5) AIMS; endpoint; <1 year; imputed SD
(6) AIMS; change; <6 months
(7) AIMS; change; < 1 year; change scores were used post-hoc since there was baseline imbalance and chabge scores were used in most of the studies
(8) AIMS; endpoint; <6 months; sd to 0.004

Analysis 1.119. Comparison 1: Dose reduction versus dose maintenance , Outcome 119: Adverse effects - mean endpoint/change dyskinesia scales (AIMS, MRCP dyskinesia, RTDRS) (high = poor) (separated time points)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.119.1 < 3 months								
Branchey 1981 (1)	4	6.67	10	8.8	6.67	11	16.4%	-0.69 [-1.58 , 0.20]
Huhn 2020 (2)	1.73	3.23	11	1.11	1.69	9	16.5%	0.22 [-0.66 , 1.11]
Johnson 1987 (3)	1.5	4.43	28	1.68	4.43	31	46.5%	-0.04 [-0.55 , 0.47]
Remington 2011 (4)	0	0.004	14	0.3	0.8	12	20.6%	-0.54 [-1.32 , 0.25]
Subtotal (95% CI)			**63**			**63**	**100.0%**	**-0.21 [-0.57 , 0.16]**
Heterogeneity: Tau² = 0.01; Chi² = 3.13, df = 3 (P = 0.37); I² = 4%								
Test for overall effect: Z = 1.11 (P = 0.27)								
1.119.2 < 6 months								
Branchey 1981 (5)	6.4	6.67	10	9.5	6.67	11	3.0%	-0.45 [-1.32 , 0.42]
Carpenter 1999 (6)	4.2	7.5	25	2.9	6.5	25	7.5%	0.18 [-0.37 , 0.74]
Huhn 2020 (7)	1.55	3.53	11	0.78	1.39	9	2.9%	0.26 [-0.62 , 1.15]
Johnson 1987 (8)	1.91	4.43	28	2.48	4.43	31	8.8%	-0.13 [-0.64 , 0.38]
Kane 2010 (9)	-0.14	1.54	144	-0.18	1.2	322	59.6%	0.03 [-0.17 , 0.23]
Remington 2011 (10)	0	0.004	14	0.3	0.8	12	3.7%	-0.54 [-1.32 , 0.25]
Rouillon 2008 (9)	-0.1	1.6	49	-0.4	1.7	48	14.5%	0.18 [-0.22 , 0.58]
Subtotal (95% CI)			**281**			**458**	**100.0%**	**0.02 [-0.13 , 0.17]**
Heterogeneity: Tau² = 0.00; Chi² = 4.59, df = 6 (P = 0.60); I² = 0%								
Test for overall effect: Z = 0.27 (P = 0.79)								
1.119.3 < 1 year								
Carpenter 1999 (11)	5.2	7.5	25	2.9	6.5	25	19.7%	0.32 [-0.24 , 0.88]
Fleischhacker 2014 (12)	-0.06	0.8	128	-0.08	0.8	260	43.4%	0.02 [-0.19 , 0.24]
Johnson 1987 (13)	1.16	4.43	28	1.79	4.43	31	22.0%	-0.14 [-0.65 , 0.37]
Ozawa 2019 (14)	-0.7	1.4	17	0.2	1.1	18	14.9%	-0.70 [-1.39 , -0.02]
Subtotal (95% CI)			**198**			**334**	**100.0%**	**-0.06 [-0.37 , 0.25]**
Heterogeneity: Tau² = 0.05; Chi² = 5.62, df = 3 (P = 0.13); I² = 47%								
Test for overall effect: Z = 0.38 (P = 0.70)								
Test for subgroup differences: Chi² = 1.34, df = 2 (P = 0.51), I² = 0%								

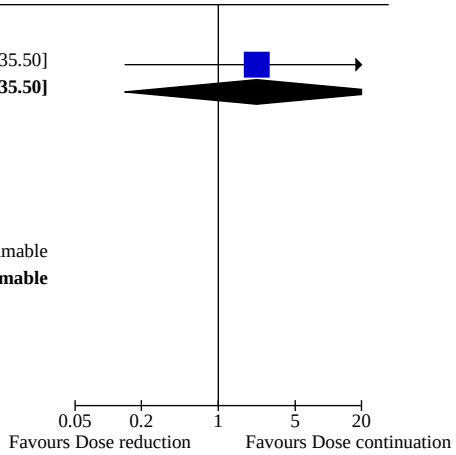


Footnotes

(1) RTDSR; endpoint; <3 months; imputed from Altamura et al 1990
(2) AIMS; endpoint; <3 months
(3) AIMS; endpoint; <3 months; imputed sd
(4) AIMS; endpoint; <3 months; SD to 0.004
(5) RTDSR; endpoint; <6 months; imputed from Altamura et al 1990
(6) MRPC dyskinesia; endpoint; <6 months
(7) AIMS; endpoint; <6 months
(8) AIMS; endpoint; <6 months; imputed SD
(9) AIMS; change; <6 months
(10) AIMS; endpoint; <6 months; sd to 0.004
(11) MRPC dyskinesia; endpoint; < 1 year
(12) AIMS; change; <1 year
(13) AIMS; endpoint; <1 year; imputed SD
(14) AIMS; change; < 1 year; change scores were used post-hoc since there is baseline imbalance and most studies used change score (SMD)

Analysis 1.120. Comparison 1: Dose reduction versus dose maintenance , Outcome 120: Adverse effects - specific: number of participants with QTc prolongation

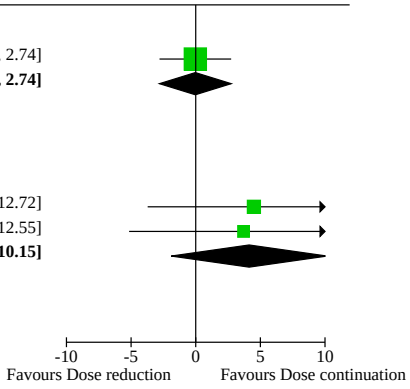
Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.120.1 < 6 months						
Kane 2010 (1)	1	144	1	322	100.0%	2.24 [0.14 , 35.50]
Subtotal (95% CI)		**144**		**322**	**100.0%**	**2.24 [0.14 , 35.50]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.57 (P = 0.57)						
1.120.2 < 1 year						
Fleischhacker 2014	0	131	0	266		Not estimable
Subtotal (95% CI)		**131**		**266**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Footnotes
(1) Calclulated with Fredericias's formula; >= 450/470(M/F)

Analysis 1.121. Comparison 1: Dose reduction versus dose maintenance , Outcome 121: Adverse effects - mean change QTc interval (milliseconds)

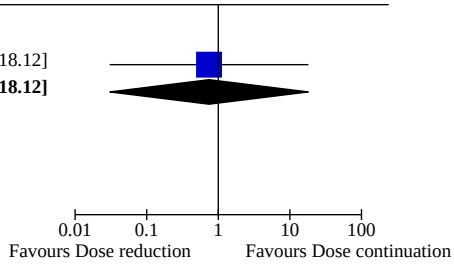
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.121.1 < 6 months								
Kane 2010 (1)	0.49	14.09	142	0.52	13.88	321	100.0%	-0.03 [-2.80 , 2.74]
Subtotal (95% CI)			**142**			**321**	**100.0%**	**-0.03 [-2.80 , 2.74]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.02 (P = 0.98)								
1.121.2 < 1 year								
Ozawa 2019	0.2	11.8	17	-4.3	13	18	53.7%	4.50 [-3.72 , 12.72]
Takeuchi 2014	2.1	16	22	-1.6	14.5	24	46.3%	3.70 [-5.15 , 12.55]
Subtotal (95% CI)			**39**			**42**	**100.0%**	**4.13 [-1.89 , 10.15]**
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.02$, df = 1 (P = 0.90); $I^2 = 0\%$								
Test for overall effect: Z = 1.34 (P = 0.18)								
Test for subgroup differences: $Chi^2 = 1.51$, df = 1 (P = 0.22), $I^2 = 33.9\%$								



Footnotes
(1) Calculated with Fredericia's Formula

Analysis 1.122. Comparison 1: Dose reduction versus dose maintenance , Outcome 122: Adverse effects - specific: number of participants with arrhythmia

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.122.1 < 6 months						
Kane 2010 (1)	0	144	1	322	100.0%	0.74 [0.03 , 18.12]
Subtotal (95% CI)		**144**		**322**	**100.0%**	**0.74 [0.03 , 18.12]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						

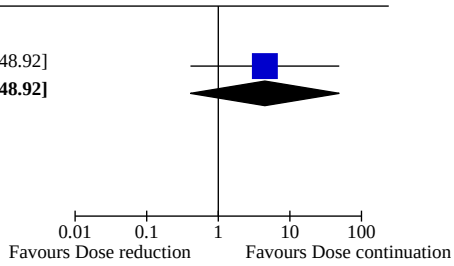


Footnotes

(1) Consider the highes value among atrial, ventricular and sinus arrhythmia

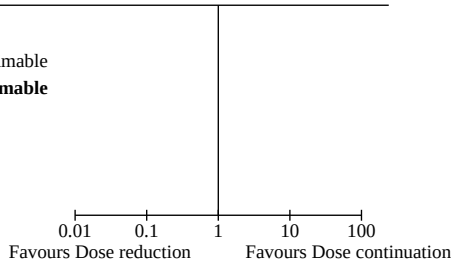
Analysis 1.123. Comparison 1: Dose reduction versus dose maintenance , Outcome 123: Adverse effects - specific: number of participants with hypotension

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.123.1 < 6 months						
Kane 2010	2	144	1	322	100.0%	4.47 [0.41 , 48.92]
Subtotal (95% CI)		**144**		**322**	**100.0%**	**4.47 [0.41 , 48.92]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.23 (P = 0.22)						



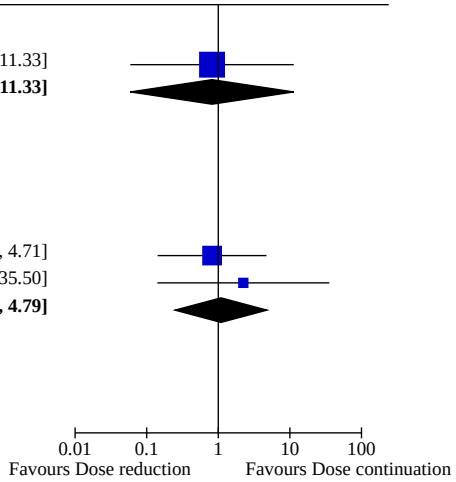
Analysis 1.124. Comparison 1: Dose reduction versus dose maintenance , Outcome 124: Adverse effects - specific: number of participants with bradycardia

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.124.1 < 6 months						
Kane 2010	0	144	0	322		Not estimable
Subtotal (95% CI)		**144**		**322**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						



Analysis 1.125. Comparison 1: Dose reduction versus dose maintenance , Outcome 125: Adverse effects - specific: number of participants with tachycardia

Study or Subgroup	Dose reudction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.125.1 < 3 months						
Huhn 2020 (1)	1	11	1	9	100.0%	0.82 [0.06 , 11.33]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.82 [0.06 , 11.33]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.15 (P = 0.88)						
1.125.2 < 6 months						
Huhn 2020 (1)	2	11	2	9	71.4%	0.82 [0.14 , 4.71]
Kane 2010	1	144	1	322	28.6%	2.24 [0.14 , 35.50]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**1.09 [0.25 , 4.79]**
Total events:	3		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.91)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.85), I² = 0%						

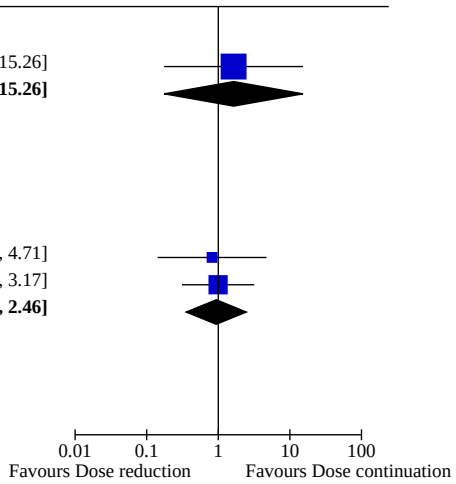


Footnotes

(1) Defined as per UKU item palpitations/tachycardia

Analysis 1.126. Comparison 1: Dose reduction versus dose maintenance , Outcome 126: Adverse effects - specific: number of participants with dizziness

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.126.1 < 3 months						
Huhn 2020 (1)	2	11	1	9	100.0%	1.64 [0.18 , 15.26]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**1.64 [0.18 , 15.26]**
Total events:	2		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.43 (P = 0.67)						
1.126.2 < 6 months						
Huhn 2020 (1)	2	11	2	9	30.6%	0.82 [0.14 , 4.71]
Kane 2010	4	144	9	322	69.4%	0.99 [0.31 , 3.17]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.94 [0.36 , 2.46]**
Total events:	6		11			
Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 1 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.13 (P = 0.89)						
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.65), I² = 0%						

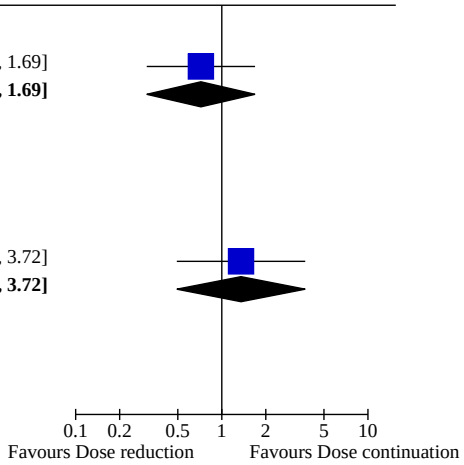


Footnotes

(1) As defined per UKU "orthostatic dizziness"

Analysis 1.127. Comparison 1: Dose reduction versus dose maintenance , Outcome 127: Adverse effects - specific: number of participants with increased prolactin

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
1.127.1 < 6 months						
Kane 2010 (1)	6	66	23	182	100.0%	0.72 [0.31 , 1.69]
Subtotal (95% CI)		**66**		**182**	**100.0%**	**0.72 [0.31 , 1.69]**
Total events:	6		23			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.127.2 < 1 year						
Fleischhacker 2014	6	131	9	266	100.0%	1.35 [0.49 , 3.72]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**1.35 [0.49 , 3.72]**
Total events:	6		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Chi² = 0.88, df = 1 (P = 0.35), I² = 0%						

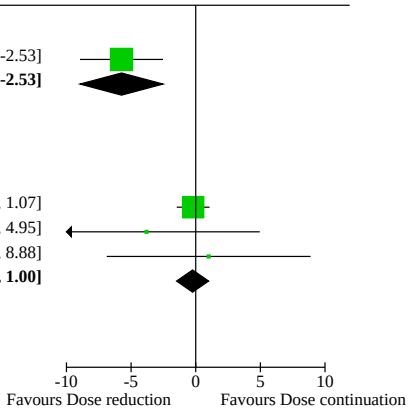


Footnotes

(1) Denominator = Total number of at risk patients with the lab test

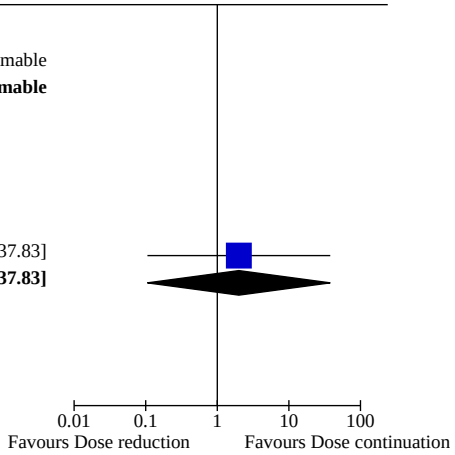
Analysis 1.128. Comparison 1: Dose reduction versus dose maintenance , Outcome 128: Adverse effects - mean change prolactin levels (ng/mL)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.128.1 < 6 months								
Kane 2010	-7.53	15.24	144	-1.79	18.59	322	100.0%	-5.74 [-8.95 , -2.53]
Subtotal (95% CI)			**144**			**322**	**100.0%**	**-5.74 [-8.95 , -2.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.50 (P = 0.0005)								
1.128.2 < 1 year								
Fleischhacker 2014	0.43	3.66	57	0.63	5.4	159	95.5%	-0.20 [-1.47 , 1.07]
Ozawa 2019	-6.8	12.3	17	-3	14.1	18	2.0%	-3.80 [-12.55 , 4.95]
Takeuchi 2014	-2.8	9.6	31	-3.8	19.9	30	2.5%	1.00 [-6.88 , 8.88]
Subtotal (95% CI)			**105**			**207**	**100.0%**	**-0.24 [-1.48 , 1.00]**
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 2 (P = 0.69); I² = 0%								
Test for overall effect: Z = 0.38 (P = 0.70)								
Test for subgroup differences: Chi² = 9.79, df = 1 (P = 0.002), I² = 89.8%								



Analysis 1.129. Comparison 1: Dose reduction versus dose maintenance , Outcome 129: Adverse effects - specific: number of participants (women) with amenorrhoea

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.129.1 < 3 months						
Huhn 2020 (1)	0	5	0	3		Not estimable
Subtotal (95% CI)		**5**		**3**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.129.2 < 6 months						
Huhn 2020 (1)	1	5	0	3	100.0%	2.00 [0.11 , 37.83]
Subtotal (95% CI)		**5**		**3**	**100.0%**	**2.00 [0.11 , 37.83]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Not applicable						

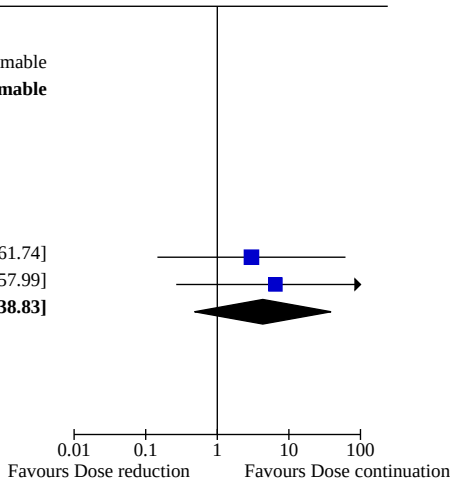


Footnotes

(1) Defined as per UKU item (using the number of women as denominator)

Analysis 1.130. Comparison 1: Dose reduction versus dose maintenance , Outcome 130: Adverse effects - specific: number of participants (men) with erectile dysfunction

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.130.1 < 3 months						
Huhn 2020 (1)	0	6	0	6		Not estimable
Subtotal (95% CI)		**6**		**6**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.130.2 < 6 months						
Huhn 2020 (1)	1	6	0	6	52.7%	3.00 [0.15 , 61.74]
Kane 2010	1	96	0	209	47.3%	6.49 [0.27 , 157.99]
Subtotal (95% CI)		**102**		**215**	**100.0%**	**4.32 [0.48 , 38.83]**
Total events:	2		0			
Heterogeneity: Tau² = 0.00; Chi² = 0.12, df = 1 (P = 0.73); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
Test for subgroup differences: Not applicable						

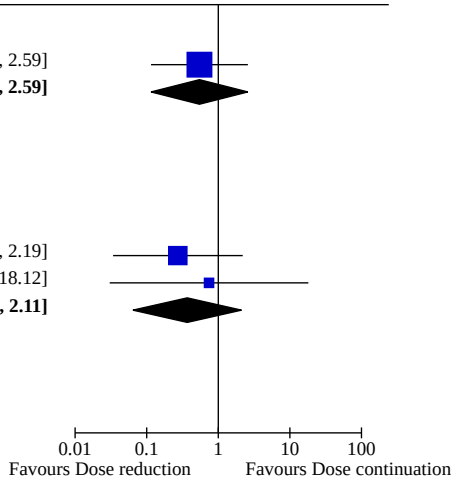


Footnotes

(1) Defined as per UKU (using the number of men participants as denominator)

Analysis 1.131. Comparison 1: Dose reduction versus dose maintenance , Outcome 131: Adverse effects - specific: number of participants with libido decreased

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.131.1 < 3 months						
Huhn 2020 (1)	2	11	3	9	100.0%	0.55 [0.11 , 2.59]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.55 [0.11 , 2.59]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.131.2 < 6 months						
Huhn 2020 (1)	1	11	3	9	70.1%	0.27 [0.03 , 2.19]
Kane 2010 (2)	0	144	1	322	29.9%	0.74 [0.03 , 18.12]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.37 [0.06 , 2.11]**
Total events:	1		4			
Heterogeneity: Tau² = 0.00; Chi² = 0.26, df = 1 (P = 0.61); I² = 0%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Chi² = 0.11, df = 1 (P = 0.74), I² = 0%						



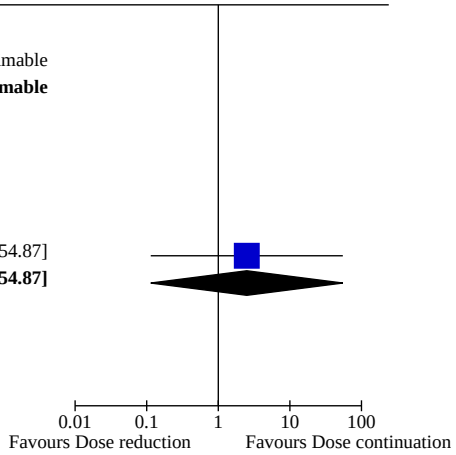
Footnotes

(1) Defined as diminished sexual drive in UKU

(2) Consider the highest value of the outcomes "Libido decreased" and "Loss of libido"

Analysis 1.132. Comparison 1: Dose reduction versus dose maintenance , Outcome 132: Adverse effects - specific: number of participants with libido increased

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.132.1 < 3 months						
Huhn 2020 (1)	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.132.2 < 6 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
Test for subgroup differences: Not applicable						

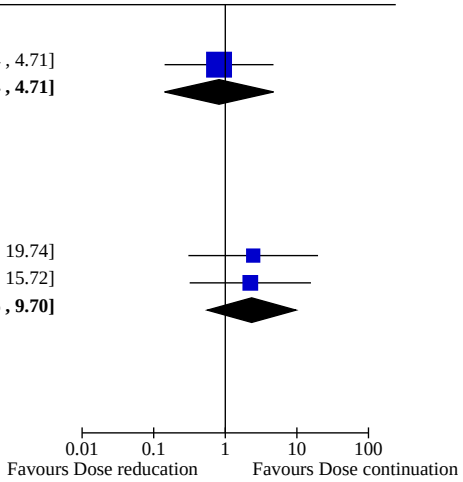


Footnotes

(1) Defined as increased sexual drive in UKU

Analysis 1.133. Comparison 1: Dose reduction versus dose maintenance , Outcome 133: Adverse effects - specific: number of participants with sedation

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.133.1 < 3 months						
Huhn 2020 (1)	2	11	2	9	100.0%	0.82 [0.14 , 4.71]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.82 [0.14 , 4.71]**
Total events:	2		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.22 (P = 0.82)						
1.133.2 < 6 months						
Huhn 2020 (2)	3	11	1	9	46.7%	2.45 [0.31 , 19.74]
Kane 2010	2	144	2	322	53.3%	2.24 [0.32 , 15.72]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**2.34 [0.56 , 9.70]**
Total events:	5		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Chi² = 0.83, df = 1 (P = 0.36), I² = 0%						

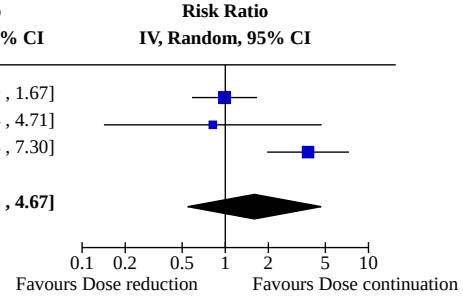


Footnotes

(1) (1) As per "sleepiness/sedation" in UKU (LOCF)
(2) As per "sleepiness/sedation" in UKU (LOCF)

Analysis 1.134. Comparison 1: Dose reduction versus dose maintenance , Outcome 134: Adverse effects - specific: number of participants with insomnia (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014 (1)	18	131	37	266	40.8%	0.99 [0.59 , 1.67]
Huhn 2020 (2)	2	11	2	9	20.5%	0.82 [0.14 , 4.71]
Kane 2010 (3)	22	144	13	322	38.7%	3.78 [1.96 , 7.30]
Total (95% CI)		**286**		**597**	**100.0%**	**1.60 [0.55 , 4.67]**
Total events:	42		52			
Heterogeneity: Tau² = 0.66; Chi² = 10.43, df = 2 (P = 0.005); I² = 81%						
Test for overall effect: Z = 0.86 (P = 0.39)						
Test for subgroup differences: Not applicable						

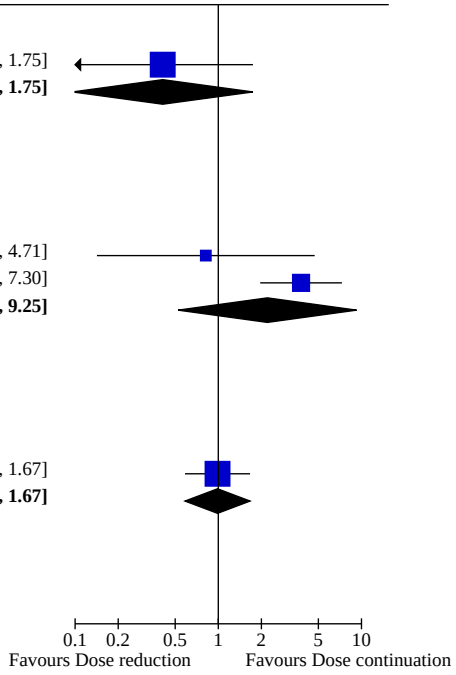


Footnotes

(1) <1 year
(2) as per "reduced duration of sleep" in UKU (LOCF); <6 months
(3) 6 months

Analysis 1.135. Comparison 1: Dose reduction versus dose maintenance , Outcome 135: Adverse effects - specific: number of participants with insomnia (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.135.1 < 3 months						
Huhn 2020 (1)	2	11	4	9	100.0%	0.41 [0.10 , 1.75]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.41 [0.10 , 1.75]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.21 (P = 0.23)						
1.135.2 < 6 months						
Huhn 2020 (2)	2	11	2	9	35.4%	0.82 [0.14 , 4.71]
Kane 2010	22	144	13	322	64.6%	3.78 [1.96 , 7.30]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**2.20 [0.52 , 9.25]**
Total events:	24		15			
Heterogeneity: Tau² = 0.72; Chi² = 2.58, df = 1 (P = 0.11); I² = 61%						
Test for overall effect: Z = 1.08 (P = 0.28)						
1.135.3 < 1 year						
Fleischhacker 2014	18	131	37	266	100.0%	0.99 [0.59 , 1.67]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.99 [0.59 , 1.67]**
Total events:	18		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 2.61, df = 2 (P = 0.27), I² = 23.5%						

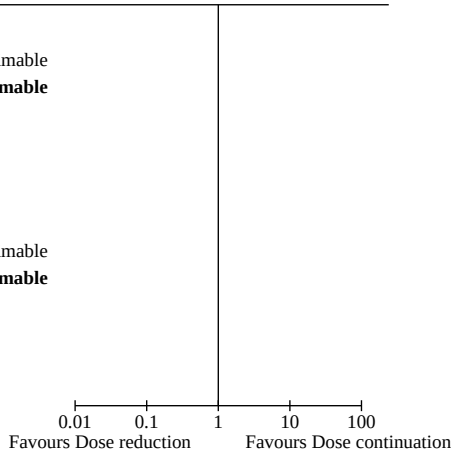


Footnotes

(1) (1) as per "reduced duration of sleep" in UKU (LOCF)
(2) as per "reduced duration of sleep" in UKU (LOCF)

Analysis 1.136. Comparison 1: Dose reduction versus dose maintenance , Outcome 136: Adverse effects - specific: number of participants with epileptic seizures

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.136.1 < 3 months						
Huhn 2020 (1)	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.136.2 < 6 months						
Huhn 2020 (1)	0	11	0	9		Not estimable
Subtotal (95% CI)		**11**		**9**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

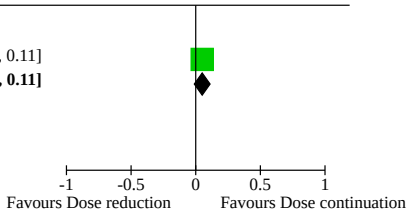


Footnotes

(1) Defined as per the coresponding UKU item

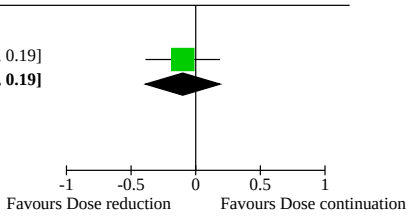
Analysis 1.137. Comparison 1: Dose reduction versus dose maintenance , Outcome 137: Adverse effects - mean change CGI-SS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.137.1 < 1 year								
Fleischhacker 2014	0.06	0.35	131	0.01	0.09	266	100.0%	0.05 [-0.01 , 0.11]
Subtotal (95% CI)			**131**			**266**	**100.0%**	**0.05 [-0.01 , 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.61 (P = 0.11)								



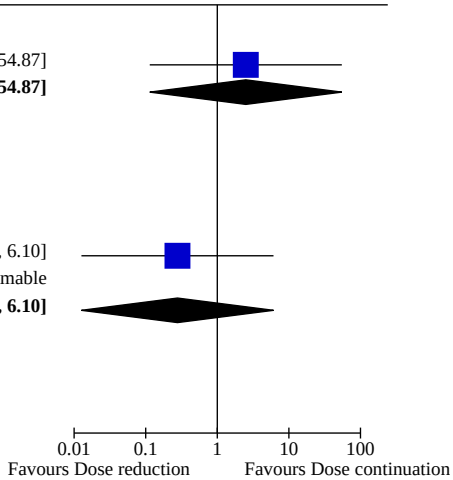
Analysis 1.138. Comparison 1: Dose reduction versus dose maintenance , Outcome 138: Adverse effects - mean change CSSRS (high = poor)

Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.138.1 < 1 year								
Fleischhacker 2014	0	0.04	31	0.1	1.3	78	100.0%	-0.10 [-0.39 , 0.19]
Subtotal (95% CI)			**31**			**78**	**100.0%**	**-0.10 [-0.39 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.68 (P = 0.50)								



Analysis 1.139. Comparison 1: Dose reduction versus dose maintenance , Outcome 139: Adverse effects - specific: number of participants with blurred vision

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.139.1 < 3 months						
Huhn 2020 (1)	1	11	0	9	100.0%	2.50 [0.11 , 54.87]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**2.50 [0.11 , 54.87]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.58 (P = 0.56)						
1.139.2 < 6 months						
Huhn 2020 (1)	0	11	1	9	100.0%	0.28 [0.01 , 6.10]
Kane 2010	0	144	0	322		Not estimable
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.28 [0.01 , 6.10]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.81 (P = 0.42)						
Test for subgroup differences: Chi² = 0.97, df = 1 (P = 0.32), I² = 0%						

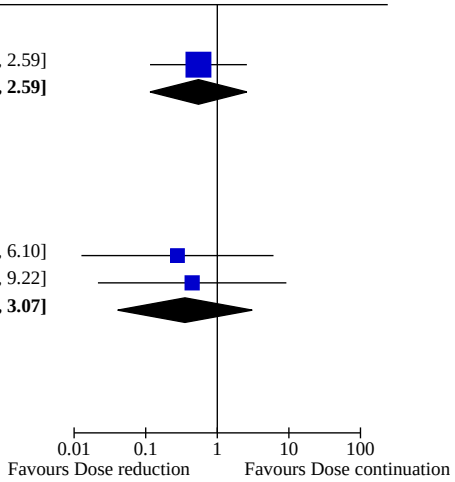


Footnotes

(1) Defined as per UKU item "Accomondation disturbances"

Analysis 1.140. Comparison 1: Dose reduction versus dose maintenance , Outcome 140: Adverse effects - specific: number of participants with constipation

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.140.1 < 3 months						
Huhn 2020 (1)	2	11	3	9	100.0%	0.55 [0.11 , 2.59]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.55 [0.11 , 2.59]**
Total events:	2		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.76 (P = 0.45)						
1.140.2 < 6 months						
Huhn 2020 (1)	0	11	1	9	49.0%	0.28 [0.01 , 6.10]
Kane 2010	0	144	2	322	51.0%	0.45 [0.02 , 9.22]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.35 [0.04 , 3.07]**
Total events:	0		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.05, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.94 (P = 0.35)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						

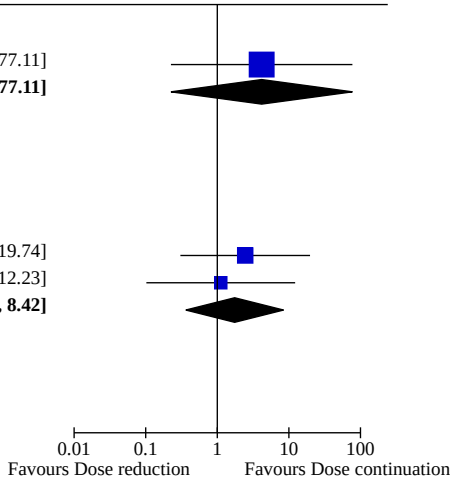


Footnotes

(1) Defined as per the UKU item "constipation"

Analysis 1.141. Comparison 1: Dose reduction versus dose maintenance , Outcome 141: Adverse effects - specific: number of participants with dry mouth

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.141.1 < 3 months						
Huhn 2020 (1)	2	11	0	9	100.0%	4.17 [0.23 , 77.11]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**4.17 [0.23 , 77.11]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.96 (P = 0.34)						
1.141.2 < 6 months						
Huhn 2020 (1)	3	11	1	9	56.8%	2.45 [0.31 , 19.74]
Kane 2010	1	144	2	322	43.2%	1.12 [0.10 , 12.23]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**1.75 [0.36 , 8.42]**
Total events:	4		3			
Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.70 (P = 0.49)						
Test for subgroup differences: Chi² = 0.26, df = 1 (P = 0.61), I² = 0%						

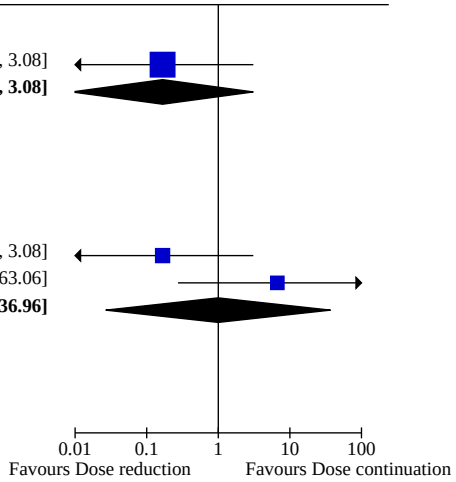


Footnotes

(1) Defined as decreased salivation in UKU

Analysis 1.142. Comparison 1: Dose reduction versus dose maintenance , Outcome 142: Adverse effects - specific: number of participants with hypersalivation

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.142.1 < 3 months						
Huhn 2020 (1)	0	11	2	9	100.0%	0.17 [0.01 , 3.08]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.17 [0.01 , 3.08]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.142.2 < 6 months						
Huhn 2020 (1)	0	11	2	9	51.6%	0.17 [0.01 , 3.08]
Kane 2010	1	144	0	322	48.4%	6.68 [0.27 , 163.06]
Subtotal (95% CI)		**155**		**331**	**100.0%**	**0.99 [0.03 , 36.96]**
Total events:	1		2			
Heterogeneity: Tau² = 4.38; Chi² = 2.80, df = 1 (P = 0.09); I² = 64%						
Test for overall effect: Z = 0.00 (P = 1.00)						
Test for subgroup differences: Chi² = 0.57, df = 1 (P = 0.45), I² = 0%						

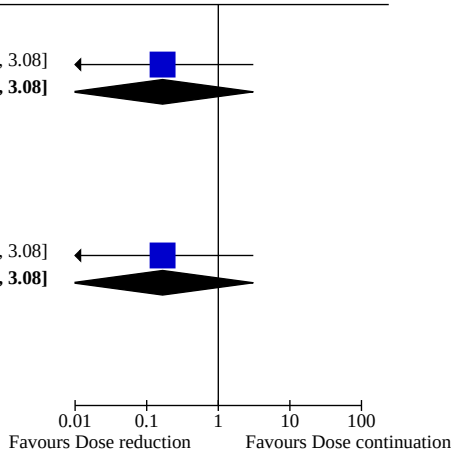


Footnotes

(1) Defined as per UKU increased salivaiton

Analysis 1.143. Comparison 1: Dose reduction versus dose maintenance , Outcome 143: Adverse effects - specific: number of participants with urinary retention

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.143.1 < 3 months						
Huhn 2020 (1)	0	11	2	9	100.0%	0.17 [0.01 , 3.08]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.17 [0.01 , 3.08]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
1.143.2 < 6 months						
Huhn 2020 (1)	0	11	2	9	100.0%	0.17 [0.01 , 3.08]
Subtotal (95% CI)		**11**		**9**	**100.0%**	**0.17 [0.01 , 3.08]**
Total events:	0		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.20 (P = 0.23)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 1.00), I² = 0%						

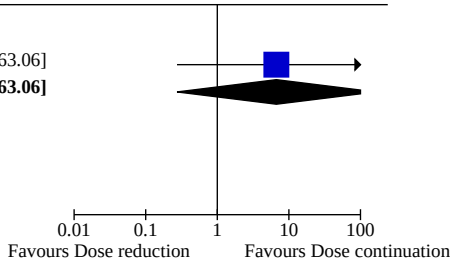


Footnotes

(1) Defined as per UKU item "micturion disturbances"

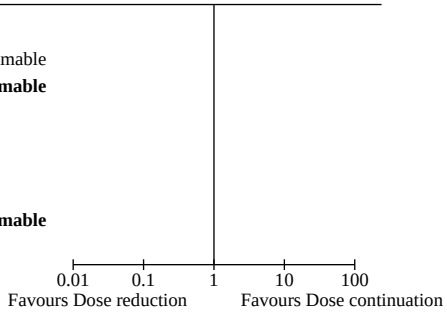
Analysis 1.144. Comparison 1: Dose reduction versus dose maintenance , Outcome 144: Adverse effects - specific: number of participants with leukopenia

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.144.1 < 6 months						
Kane 2010	1	144	0	322	100.0%	6.68 [0.27 , 163.06]
Subtotal (95% CI)		**144**		**322**	**100.0%**	**6.68 [0.27 , 163.06]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.17 (P = 0.24)						
Test for subgroup differences: Not applicable						



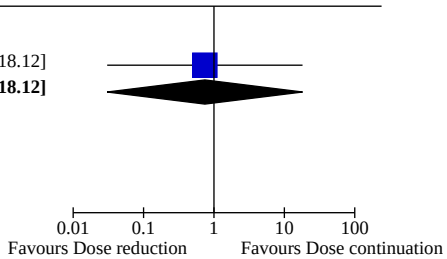
Analysis 1.145. Comparison 1: Dose reduction versus dose maintenance , Outcome 145: Adverse effects - specific: number of participants with neutropenia

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.145.1 < 6 months						
Kane 2010	0	144	0	322		Not estimable
Subtotal (95% CI)		**144**		**322**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**144**		**322**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 1.146. Comparison 1: Dose reduction versus dose maintenance , Outcome 146: Adverse effects - specific: number of participants with thrombosis

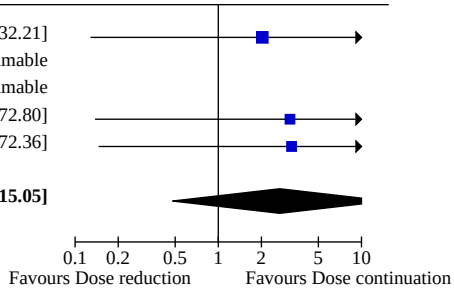
Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
1.146.1 < 6 months						
Kane 2010	0	144	1	322	100.0%	0.74 [0.03 , 18.12]
Subtotal (95% CI)		**144**		**322**	**100.0%**	**0.74 [0.03 , 18.12]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.18 (P = 0.86)						



Analysis 1.147. Comparison 1: Dose reduction versus dose maintenance , Outcome 147: Adverse effect - mortality: overall mortality (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014	1	131	1	266	38.9%	2.03 [0.13 , 32.21]
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Ozawa 2019	1	17	0	18	30.2%	3.17 [0.14 , 72.80]
Volavka 2000	1	11	0	12	30.9%	3.25 [0.15 , 72.36]
Total (95% CI)		**314**		**627**	**100.0%**	**2.69 [0.48 , 15.05]**
Total events:	3		1			

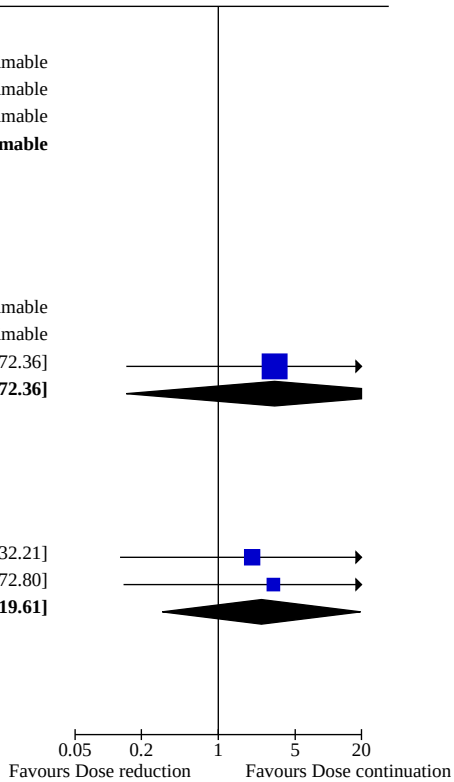
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%
Test for overall effect: Z = 1.12 (P = 0.26)
Test for subgroup differences: Not applicable



Analysis 1.148. Comparison 1: Dose reduction versus dose maintenance , Outcome 148: Adverse effect - mortality: overall mortality (separated time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.148.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Volavka 2000	0	11	0	12		Not estimable
Subtotal (95% CI)		**166**		**343**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.148.2 < 6 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Volavka 2000	1	11	0	12	100.0%	3.25 [0.15 , 72.36]
Subtotal (95% CI)		**166**		**343**	**100.0%**	**3.25 [0.15 , 72.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.148.3 < 1 year						
Fleischhacker 2014	1	131	1	266	56.3%	2.03 [0.13 , 32.21]
Ozawa 2019	1	17	0	18	43.7%	3.17 [0.14 , 72.80]
Subtotal (95% CI)		**148**		**284**	**100.0%**	**2.47 [0.31 , 19.61]**
Total events:	2		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.85 (P = 0.39)						

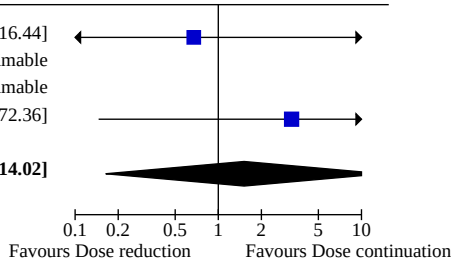
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%



Analysis 1.149. Comparison 1: Dose reduction versus dose maintenance , Outcome 149: Adverse effect - mortality: mortality due to natural causes (combined time points)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
Fleischhacker 2014	0	131	1	266	48.6%	0.67 [0.03 , 16.44]
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Volavka 2000	1	11	0	12	51.4%	3.25 [0.15 , 72.36]
Total (95% CI)		**297**		**609**	**100.0%**	**1.51 [0.16 , 14.02]**
Total events:	1		1			

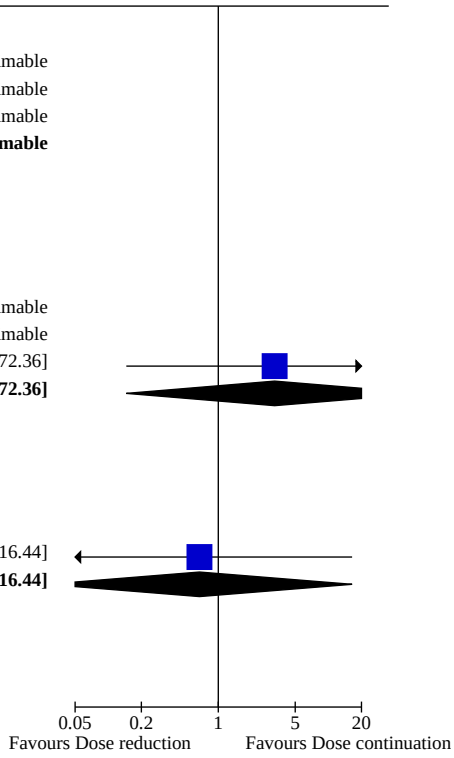
Heterogeneity: Tau² = 0.00; Chi² = 0.48, df = 1 (P = 0.49); I² = 0%
Test for overall effect: Z = 0.37 (P = 0.71)
Test for subgroup differences: Not applicable



Analysis 1.150. Comparison 1: Dose reduction versus dose maintenance , Outcome 150: Adverse effect - mortality: mortality due to natural causes (separated time points)

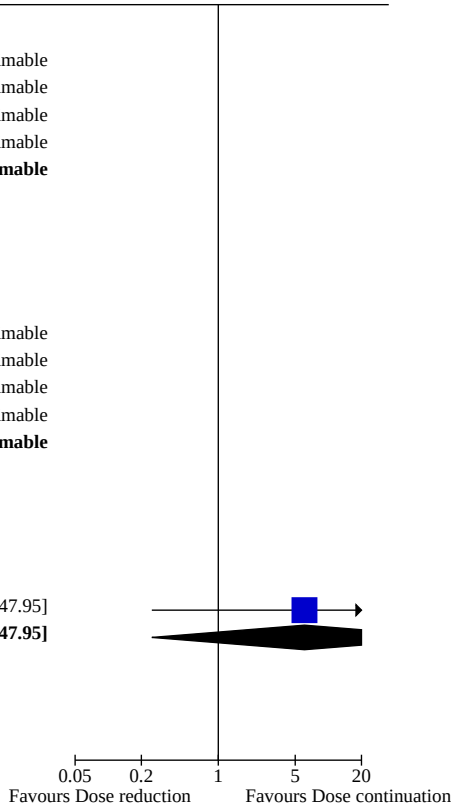
Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.150.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Volavka 2000	0	11	0	12		Not estimable
Subtotal (95% CI)		**166**		**343**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.150.2 < 6 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Volavka 2000	1	11	0	12	100.0%	3.25 [0.15 , 72.36]
Subtotal (95% CI)		**166**		**343**	**100.0%**	**3.25 [0.15 , 72.36]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.74 (P = 0.46)						
1.150.3 < 1 year						
Fleischhacker 2014	0	131	1	266	100.0%	0.67 [0.03 , 16.44]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**0.67 [0.03 , 16.44]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.24 (P = 0.81)						

Test for subgroup differences: Chi² = 0.48, df = 1 (P = 0.49), I² = 0%



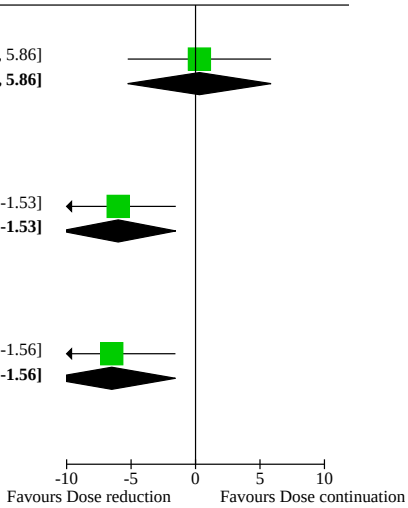
Analysis 1.151. Comparison 1: Dose reduction versus dose maintenance , Outcome 151: Adverse effect - mortality: mortality due to suicide

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.151.1 < 3 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Rouillon 2008	0	49	0	48		Not estimable
Volavka 2000	0	11	0	12		Not estimable
Subtotal (95% CI)		**215**		**391**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.151.2 < 6 months						
Huhn 2020	0	11	0	9		Not estimable
Kane 2010	0	144	0	322		Not estimable
Rouillon 2008	0	49	0	48		Not estimable
Volavka 2000	0	11	0	12		Not estimable
Subtotal (95% CI)		**215**		**391**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.151.3 < 1 year						
Fleischhacker 2014	1	131	0	266	100.0%	6.07 [0.25 , 147.95]
Subtotal (95% CI)		**131**		**266**	**100.0%**	**6.07 [0.25 , 147.95]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.11 (P = 0.27)						
Test for subgroup differences: Not applicable						



Analysis 1.152. Comparison 1: Dose reduction versus dose maintenance , Outcome 152: Cognition - mean endpoint MCCB total (high = poor)

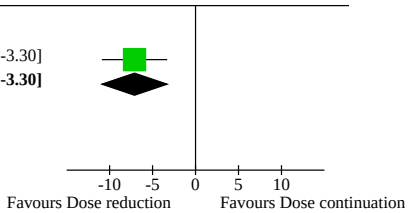
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.152.1 < 3 months								
Zhou 2018 (1)	-34.6	13	37	-34.9	11.5	38	100.0%	0.30 [-5.26 , 5.86]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**0.30 [-5.26 , 5.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.92)								
1.152.2 < 6 months								
Zhou 2018 (2)	-38.8	8.1	37	-32.8	11.4	38	100.0%	-6.00 [-10.47 , -1.53]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-6.00 [-10.47 , -1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.63 (P = 0.008)								
1.152.3 < 1 year								
Zhou 2018 (3)	-42.2	10.2	37	-35.7	11.6	38	100.0%	-6.50 [-11.44 , -1.56]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-6.50 [-11.44 , -1.56]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.58 (P = 0.010)								



Footnotes
(1) minust transformed
(2) minus trasnformed
(3) minus transformed

Analysis 1.153. Comparison 1: Dose reduction versus dose maintenance , Outcome 153: Cognition - mean change RBANS (high = poor)

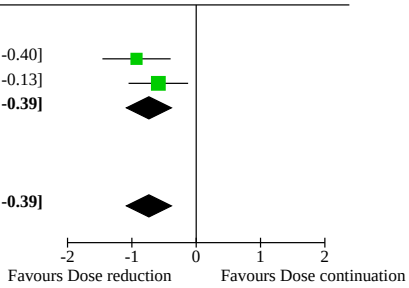
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.153.1 < 1 year								
Takeuchi 2014 (1)	-7	7.1	31	0.1	8	30	100.0%	-7.10 [-10.90 , -3.30]
Subtotal (95% CI)			**31**			**30**	**100.0%**	**-7.10 [-10.90 , -3.30]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.66 (P = 0.0003)								



Footnotes
(1) minus transformed

Analysis 1.154. Comparison 1: Dose reduction versus dose maintenance , Outcome 154: Cognition - mean endpoint/change overall cognition (MCCB, RBANS) (high = poor) (combined time points)

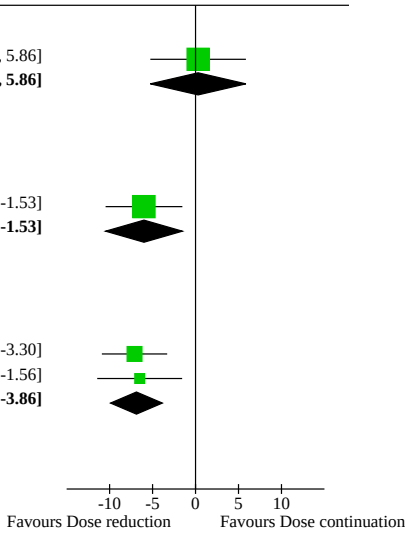
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
1.154.1 < 1 year								
Takeuchi 2014 (1)	-7	7.1	31	0.1	8	30	43.3%	-0.93 [-1.46 , -0.40]
Zhou 2018 (2)	-42.2	10.2	37	-35.7	11.6	38	56.7%	-0.59 [-1.05 , -0.13]
Subtotal (95% CI)			**68**			**68**	**100.0%**	**-0.74 [-1.08 , -0.39]**
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 4.13 (P < 0.0001)								
Total (95% CI)			**68**			**68**	**100.0%**	**-0.74 [-1.08 , -0.39]**
Heterogeneity: Tau² = 0.00; Chi² = 0.89, df = 1 (P = 0.34); I² = 0%								
Test for overall effect: Z = 4.13 (P < 0.0001)								
Test for subgroup differences: Not applicable								



Footnotes
(1) RBANS; change; minus transformed
(2) MCCB; endpoint; minus transformed

Analysis 1.155. Comparison 1: Dose reduction versus dose maintenance , Outcome 155: Cognition - mean endpoint/change overall cognition (MCCB, RBANS) (high = poor) (separated time points)

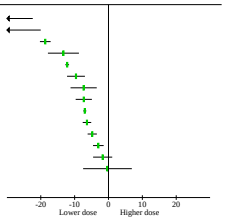
Study or Subgroup	Dose reduction Mean	SD	Total	Dose continuation Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.155.1 < 3 months								
Zhou 2018 (1)	-34.6	13	37	-34.9	11.5	38	100.0%	0.30 [-5.26 , 5.86]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**0.30 [-5.26 , 5.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.11 (P = 0.92)								
1.155.2 < 6 months								
Zhou 2018 (2)	-38.8	8.1	37	-32.8	11.4	38	100.0%	-6.00 [-10.47 , -1.53]
Subtotal (95% CI)			**37**			**38**	**100.0%**	**-6.00 [-10.47 , -1.53]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.63 (P = 0.008)								
1.155.3 < 1 year								
Takeuchi 2014 (3)	-7	7.1	31	0.1	8	30	62.8%	-7.10 [-10.90 , -3.30]
Zhou 2018 (4)	-42.2	10.2	37	-35.7	11.6	38	37.2%	-6.50 [-11.44 , -1.56]
Subtotal (95% CI)			**68**			**68**	**100.0%**	**-6.88 [-9.89 , -3.86]**
Heterogeneity: Tau² = 0.00; Chi² = 0.04, df = 1 (P = 0.85); I² = 0%								
Test for overall effect: Z = 4.47 (P < 0.00001)								
Test for subgroup differences: Chi² = 5.03, df = 2 (P = 0.08), I² = 60.2%								



Footnotes
(1) minust transformed; MCCB; endpoint
(2) minus trasnformed; MCCB endpoint
(3) minus transformed; RBANS; change
(4) minus transformed; MCCB; endpoint

Analysis 1.156. Comparison 1: Dose reduction versus dose maintenance , Outcome 156: Medication – mean antipsychotic dose at endpoint (olanzapine equivalents mg/d) (combined time points)

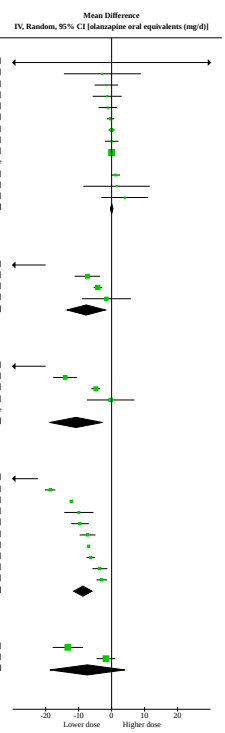
Study or Subgroup	Dose reduction: Mean [olanzapine oral equivalents (mg/d)]	Dose reduction: SD [olanzapine oral equivalents (mg/d)]	Dose reduction: Total	Dose continuation: Mean [olanzapine oral equivalents (mg/d)]	Dose continuation: SD [olanzapine oral equivalents (mg/d)]	Dose continuation: Total	Mean Difference: IV, Random, 95% CI [olanzapine oral equivalents (mg/d)]
Cookson 1987 (1)	60.21	55.5	9	169.93	121.64	9	-109.72 [-197.07 , -22.37]
Volavka 2000 (2)	38.8	12.6	11	74.6	24.6	12	-35.80 [-51.59 , -20.01]
Kane 1983 (3)	2.08	0.65	62	20.75	6.41	64	-18.67 [-20.25 , -17.09]
Schooler 1997 (4)	7.17	6.43	59	20.48	15.72	52	-13.31 [-17.89 , -8.73]
Fleischhacker 2014 (5)	1.13	0.007	131	13.33	4.6	266	-12.20 [-12.75 , -11.65]
Ozawa 2019 (6)	5.5	1.8	17	15.1	5.4	18	-9.60 [-12.24 , -6.96]
Hogarty 1995 (7)	8.33	6	38	15.67	11	41	-7.34 [-11.21 , -3.47]
Takeuchi 2014 (8)	7.1	1.96	31	14.4	6.4	30	-7.30 [-9.69 , -4.91]
Wang 2010 (9)	7	1.3	152	14	2	96	-7.00 [-7.45 , -6.55]
Zhou 2018 (10)	10.14	1.88	33	16.5	3.12	32	-6.36 [-7.62 , -5.10]
Rouillon 2008 (11)	13.3	3.9	46	18.1	2.6	44	-4.80 [-6.16 , -3.44]
Johnson 1987 (12)	6	2.06	28	9	3.9	31	-3.00 [-4.57 , -1.43]
Wunderink 2007 (13)	8.03	7.86	57	9.75	7.77	61	-1.72 [-4.54 , 1.10]
Huhn 2020 (14)	9.72	7.02	11	10.02	8.99	9	-0.30 [-7.49 , 6.89]
Kane 2010 (15)	1.61	0	144	14.3	4.3	322	Not estimable



Footnotes
(1) < 1 year; Coverted from flupenthixole decanoate biweekly administration, data provided for the individual patient
(2) < 6 months; Converted from haloperidol oral, same dose fo 12 weeks, given te period 3 is dose maintenance
(3) < 1 year; The range allowed was used to estimate the mean and SD. Fluphenazine depot was converted to olanzapine equivalents.
(4) > 1 year; Fluphenazine depot was converted to oalnzapine equivalents
(5) < 1 year; The depot dose was first transformed to oral equivalents and then to olanzapine oral equivalents.
(6) < 1 year; Combination of oral olanzapine and risperidone
(7) < 3 months; Converted from Fluphenazine decanoate, used the number of randomised
(8) < 1 year; Pooling olanzapine and risperidone doses (olanzapine equivalents)
(9) < 1 year; Original drug was risperidone
(10) < 1 year; Pooling olanzapine and risperidone doses (olanzapine equivalents).
(11) < 6 months;
(12) < 1 year; The dose range was used to estimate SD. Flupenthixol biweekly to olanzapine equivalents.
(13) > 1 year; Pooling the 5 most frequently used antipsychotics risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol (olanzapine equivalents)
(14) < 6 months; Dose of antipsychotics were added for each patients and converted to olanzapine equivalents (Gardner et al and DDD method for perazine)
(15) < 6 months

Analysis 1.157. Comparison 1: Dose reduction versus dose maintenance , Outcome 157: Medication – mean antipsychotic dose at endpoint (olanzapine equivalents mg/d) (separated time points)

Study or Subgroup	Dose reduction: Mean [olanzapine oral equivalents (mg/d)]	Dose reduction: SD [olanzapine oral equivalents (mg/d)]	Dose reduction: Total	Dose continuation: Mean [olanzapine oral equivalents (mg/d)]	Dose continuation: SD [olanzapine oral equivalents (mg/d)]	Dose continuation: Total	Weight	Mean Difference: IV, Random, 95% CI [olanzapine oral equivalents (mg/d)]
1.157.1 Baseline								
Cookson 1987 (1)	120.93	110.86	9	169.93	121.64	9	0.0%	-49.00 [-156.52 , 58.52]
Volavka 2000 (2)	65.8	10.6	11	68.6	17.4	12	0.1%	-2.80 [-14.47 , 8.87]
Ozawa 2019 (3)	13.5	5.3	17	15.1	5.4	18	1.2%	-1.60 [-5.15 , 1.95]
Hogarty 1995 (4)	14.33	8.89	38	15.67	11	41	0.8%	-1.34 [-5.74 , 3.06]
Takeuchi 2014 (5)	13.23	4.55	31	14.4	6.4	30	1.9%	-1.17 [-3.96 , 1.62]
Rouillon 2008 (6)	17.6	2.8	49	17.9	2.7	48	12.6%	-0.30 [-1.39 , 0.79]
Fleischhacker 2014 (7)	12.9	4.4	131	12.9	4.4	266	17.8%	0.00 [-0.92 , 0.92]
Kane 1983 (8)	20.48	5.84	62	20.48	5.84	64	3.6%	0.00 [-2.04 , 2.04]
Wang 2010 (9)	13.33	3	211	13.33	2	129	53.3%	0.00 [-0.53 , 0.53]
Caffey 1964 (10)	13.6	0	89	13.6	0	88		Not estimable
Zhou 2018 (5)	17.7	2.9	37	16.5	3.1	38	8.2%	1.20 [-0.16 , 2.56]
Branchey 1981 (11)	23.4	14.75	31	21.91	14.62	11	0.1%	1.49 [-8.59 , 11.57]
Huhn 2020 (12)	14.16	7.05	11	10.2	8.81	9	0.3%	3.96 [-3.15 , 11.07]
Subtotal (95% CI)			**727**			**763**	**100.0%**	**0.02 [-0.37 , 0.41]**
Heterogeneity: Tau² = 0.00; Chi² = 7.39, df = 11 (P = 0.77); I² = 0%								
Test for overall effect: Z = 0.09 (P = 0.93)								
1.157.2 < 3 months								
Volavka 2000 (2)	38.8	12.6	11	74.6	24.6	12	9.9%	-35.80 [-51.59 , -20.01]
Hogarty 1995 (13)	8.33	6	38	15.67	11	41	31.4%	-7.34 [-11.21 , -3.47]
Rouillon 2008	13.9	3.4	46	18.1	2.6	45	35.8%	-4.20 [-5.44 , -2.96]
Huhn 2020 (12)	9.57	6.67	11	11.13	9.59	9	22.9%	-1.56 [-8.96 , 5.84]
Subtotal (95% CI)			**106**			**107**	**100.0%**	**-7.71 [-13.53 , -1.89]**
Heterogeneity: Tau² = 24.25; Chi² = 17.98, df = 3 (P = 0.0004); I² = 83%								
Test for overall effect: Z = 2.59 (P = 0.009)								
1.157.3 < 6 months								
Volavka 2000 (14)	38.8	12.6	11	74.6	24.6	12	14.1%	-35.80 [-51.59 , -20.01]
Schooler 1997 (15)	10.67	10.21	106	24.75	16.06	105	29.6%	-14.08 [-17.72 , -10.44]
Rouillon 2008	13.3	3.9	46	18.1	2.6	44	31.2%	-4.80 [-6.16 , -3.44]
Huhn 2020 (12)	9.72	7.02	11	10.02	8.99	9	25.1%	-0.30 [-7.49 , 6.89]
Kane 2010	1.61	0	144	14.3	4.3	322		Not estimable
Subtotal (95% CI)			**318**			**492**	**100.0%**	**-10.79 [-18.78 , -2.81]**
Heterogeneity: Tau² = 52.73; Chi² = 38.05, df = 3 (P < 0.00001); I² = 92%								
Test for overall effect: Z = 2.65 (P = 0.008)								
1.157.4 < 1 year								
Cookson 1987 (16)	60.21	55.5	9	169.93	121.64	9	0.1%	-109.72 [-197.07 , -22.37]
Kane 1983 (8)	2.08	0.65	62	20.75	6.41	64	11.4%	-18.67 [-20.25 , -17.09]
Fleischhacker 2014 (17)	1.13	0.007	131	13.33	4.6	266	11.8%	-12.20 [-12.75 , -11.65]
Schooler 1997 (18)	13.51	14.7	88	23.45	15.73	93	9.1%	-9.94 [-14.37 , -5.51]
Ozawa 2019 (3)	5.5	1.8	17	15.1	5.4	18	10.7%	-9.60 [-12.24 , -6.96]
Takeuchi 2014 (5)	7.1	1.96	31	14.4	6.4	30	10.9%	-7.30 [-9.69 , -4.91]
Wang 2010 (9)	7	1.3	152	14	2	96	11.8%	-7.00 [-7.45 , -6.55]
Zhou 2018 (19)	10.14	1.88	33	16.5	3.12	32	11.6%	-6.36 [-7.62 , -5.10]
Wunderink 2007 (20)	6.58	6.59	58	10.12	5.87	60	11.0%	-3.54 [-5.79 , -1.29]
Johnson 1987 (21)	6	2.06	28	9	3.9	31	11.4%	-3.00 [-4.57 , -1.43]
Subtotal (95% CI)			**609**			**699**	**100.0%**	**-8.72 [-11.52 , -5.92]**
Heterogeneity: Tau² = 17.19; Chi² = 451.32, df = 9 (P < 0.00001); I² = 98%								
Test for overall effect: Z = 6.11 (P < 0.00001)								
1.157.5 > 1 year								
Schooler 1997 (22)	7.17	6.43	59	20.48	15.72	52	48.7%	-13.31 [-17.89 , -8.73]
Wunderink 2007 (23)	8.03	7.86	57	9.75	7.77	61	51.3%	-1.72 [-4.54 , 1.10]
Subtotal (95% CI)			**116**			**113**	**100.0%**	**-7.37 [-18.72 , 3.99]**
Heterogeneity: Tau² = 63.40; Chi² = 17.85, df = 1 (P < 0.0001); I² = 94%								
Test for overall effect: Z = 1.27 (P = 0.20)								



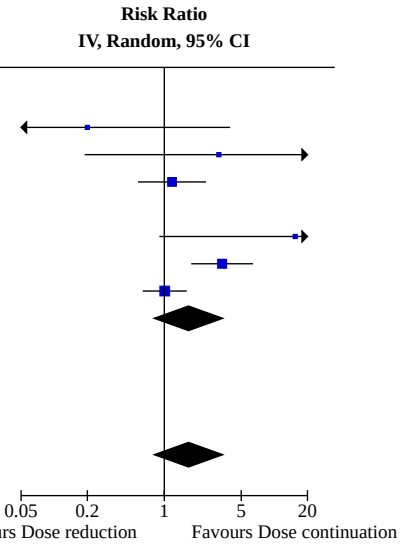
Footnotes
(1) Coverted from flupenthixole decanoate biweekly administration, data provided for the individual patient. For the dose reduction group provided data have been doubled to report pre-randomisation doses
(2) Converted from haloperidol oral
(3) Combination of oral olanzapine and risperidone
(4) Converted from Fluphenazine decanoate
(5) Pooling olanzapine and risperidone doses (olanzapine equivalents)
(6) Available as olanzapine oral
(7) The mean dose for both arms was used at randomization, from oral aripiprazole to olanzapine equivalents
(8) The range allowed was used to estimate the mean and SD. Fluphenazine depot to olanzapine equivalents.
(9) Original drug was risperidone
(10) This is the average dose fo the whole sample. Original drugs are chlorpromazine and thioridazine (depot)
(11) Original drug was loxapine
(12) Dose of antipsychotics were added for each patients and converted to olanzapine equivalents (Gardner et al and DDD method for perazine)
(13) Converted from Fluphenazine decanoate, used the number of randomised
(14) Converted from haloperidol oral, same dose fo 12 weeks, given te period 3 is dose maintenance
(15) Converted from fluphenazine depot to olanzapine equivalents
(16) Coverted from flupenthixole decanoate biweekly administration, data provided for the individual patient
(17) The depot dose was first transformed to oral equivalents and then to olanzapine oral equivalents.
(18) Fluphenazine depot to olanzapine equivalents
(19) Pooling olanzapine and risperidone doses (olanzapine equivalents).
(20) Pooling the 5 most frequently used antipsychotics risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol (olanzapine equivalents) - some patients could have counted twice - not sure if to use
(21) The dose range was used to estimate SD. Flupenthixol biweekly to olanzapine equivalents.
(22) Fluphenazine depot was converted to oaltzapine equivalents
(23) Pooling the 5 most frequently used antipsychotics risperidone, olanzapine, quetiapine, clozapine, zuclopenthixol (olanzapine equivalents) - some patients could have counted twice

Comparison 2. Sensitivity analyses - service use - rehospitalisation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Excluding studies at high risk of bias (Remington 2011 and Rouillon 2008 excluded)	7	1301	Risk Ratio (IV, Random, 95% CI)	1.66 [0.81, 3.39]
2.1.1 Combined time points	7	1301	Risk Ratio (IV, Random, 95% CI)	1.66 [0.81, 3.39]
2.2 Fixed-effect	9	1433	Risk Ratio (IV, Fixed, 95% CI)	1.46 [1.08, 1.98]
2.2.1 Combined time points	9	1433	Risk Ratio (IV, Fixed, 95% CI)	1.46 [1.08, 1.98]

Analysis 2.1. Comparison 2: Sensitivity analyses - service use - rehospitalisation, Outcome 1: Excluding studies at high risk of bias (Remington 2011 and Rouillon 2008 excluded)

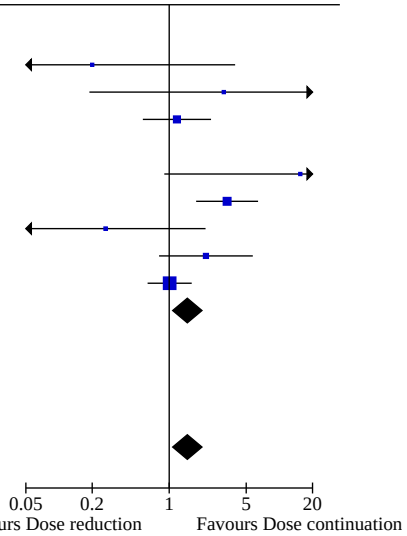
Study or Subgroup	Dose reduction Events	Dose reduction Total	Dose continuation Events	Dose continuation Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 Combined time points						
Carpenter 1999 (1)	0	25	2	25	4.9%	0.20 [0.01 , 3.97]
Faraone 1989 (2)	4	22	0	7	5.5%	3.13 [0.19 , 51.93]
Fleischhacker 2014 (3)	11	131	19	266	26.1%	1.18 [0.58 , 2.40]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 1983 (3)	7	62	0	64	5.4%	15.48 [0.90 , 265.33]
Kane 2010 (2)	21	144	14	322	27.4%	3.35 [1.76 , 6.41]
Schooler 1997 (4)	27	106	27	107	30.7%	1.01 [0.64 , 1.60]
Subtotal (95% CI)		**501**		**800**	**100.0%**	**1.66 [0.81 , 3.39]**
Total events:	70		62			
Heterogeneity: Tau² = 0.38; Chi² = 13.80, df = 5 (P = 0.02); I² = 64%						
Test for overall effect: Z = 1.39 (P = 0.17)						
Total (95% CI)		**501**		**800**	**100.0%**	**1.66 [0.81 , 3.39]**
Total events:	70		62			
Heterogeneity: Tau² = 0.38; Chi² = 13.80, df = 5 (P = 0.02); I² = 64%						
Test for overall effect: Z = 1.39 (P = 0.17)						
Test for subgroup differences: Not applicable						



Footnotes

(1) <1 year
(2) < 6 months
(3) < 1 year
(4) > 1 year

Analysis 2.2. Comparison 2: Sensitivity analyses - service use - rehospitalisation, Outcome 2: Fixed-effect



Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
2.2.1 Combined time points						
Carpenter 1999 (1)	0	25	2	25	1.0%	0.20 [0.01 , 3.97]
Faraone 1989 (2)	4	22	0	7	1.2%	3.13 [0.19 , 51.93]
Fleischhacker 2014 (1)	11	131	19	266	18.4%	1.18 [0.58 , 2.40]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 1983 (1)	7	62	0	64	1.2%	15.48 [0.90 , 265.33]
Kane 2010 (2)	21	144	14	322	22.3%	3.35 [1.76 , 6.41]
Remington 2011 (2)	1	17	4	18	2.1%	0.26 [0.03 , 2.14]
Rouillon 2008 (2)	11	49	5	48	9.7%	2.16 [0.81 , 5.74]
Schooler 1997 (3)	27	106	27	107	44.0%	1.01 [0.64 , 1.60]
Subtotal (95% CI)		**567**		**866**	**100.0%**	**1.46 [1.08 , 1.98]**
Total events:	82		71			
Heterogeneity: Chi² = 16.98, df = 7 (P = 0.02); I² = 59%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Total (95% CI)		**567**		**866**	**100.0%**	**1.46 [1.08 , 1.98]**
Total events:	82		71			
Heterogeneity: Chi² = 16.98, df = 7 (P = 0.02); I² = 59%						
Test for overall effect: Z = 2.43 (P = 0.02)						
Test for subgroup differences: Not applicable						

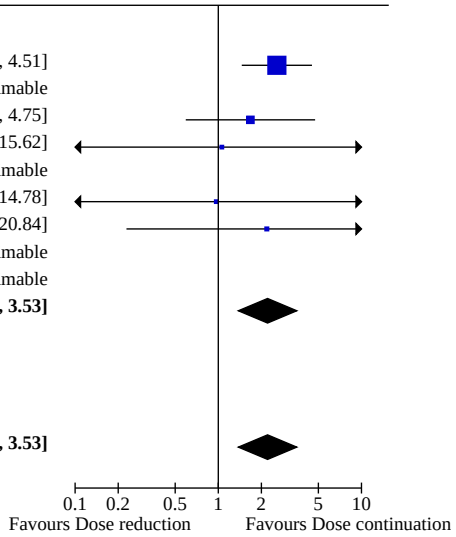
Footnotes
(1) < 1 year
(2) < 6 months
(3) > 1 year

Comparison 3. Sensitivity analyses - adverse effects - leaving the study early due to adverse effects - overall tolerability

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Excluding studies at overall high risk of bias (Rouillon 2008 excluded)	9	1243	Risk Ratio (IV, Random, 95% CI)	2.21 [1.38, 3.53]
3.1.1 Combined time points	9	1243	Risk Ratio (IV, Random, 95% CI)	2.21 [1.38, 3.53]
3.2 Excluding studies that did not use operationalised criteria to diagnose schizophrenia (Volavka 2000 excluded)	9	1317	Risk Ratio (IV, Random, 95% CI)	2.20 [1.37, 3.52]
3.2.1 Combined time points	9	1317	Risk Ratio (IV, Random, 95% CI)	2.20 [1.37, 3.52]
3.3 Excluding studies conducted in mainland China (Zhou 2018 excluded)	9	1265	Risk Ratio (IV, Random, 95% CI)	2.20 [1.39, 3.49]
3.3.1 Combined time points	9	1265	Risk Ratio (IV, Random, 95% CI)	2.20 [1.39, 3.49]
3.4 Fixed-effect	10	1340	Risk Ratio (IV, Fixed, 95% CI)	2.20 [1.39, 3.49]
3.4.1 Combined time points	10	1340	Risk Ratio (IV, Fixed, 95% CI)	2.20 [1.39, 3.49]

Analysis 3.1. Comparison 3: Sensitivity analyses - adverse effects - leaving the study early due to adverse effects - overall tolerability, Outcome 1: Excluding studies at overall high risk of bias (Rouillon 2008 excluded)

Study or Subgroup	Dose reduction Events	Dose reduction Total	Dose continuation Events	Dose continuation Total	Weight	Risk Ratio IV, Random, 95% CI
3.1.1 Combined time points						
Fleischhacker 2014 (1)	24	131	19	266	69.3%	2.56 [1.46 , 4.51]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (2)	6	144	8	322	20.4%	1.68 [0.59 , 4.75]
Ozawa 2019 (1)	1	17	1	18	3.0%	1.06 [0.07 , 15.62]
Remington 2011 (2)	0	17	0	18		Not estimable
Takeuchi 2014 (1)	1	31	1	30	3.0%	0.97 [0.06 , 14.78]
Volavka 2000 (2)	2	11	1	12	4.3%	2.18 [0.23 , 20.84]
Wunderink 2007 (1)	0	68	0	63		Not estimable
Zhou 2018 (1)	0	37	0	38		Not estimable
Subtotal (95% CI)		**467**		**776**	**100.0%**	**2.21 [1.38 , 3.53]**
Total events:	34		30			
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 4 (P = 0.88); I² = 0%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Total (95% CI)		**467**		**776**	**100.0%**	**2.21 [1.38 , 3.53]**
Total events:	34		30			
Heterogeneity: Tau² = 0.00; Chi² = 1.18, df = 4 (P = 0.88); I² = 0%						
Test for overall effect: Z = 3.31 (P = 0.0009)						
Test for subgroup differences: Not applicable						



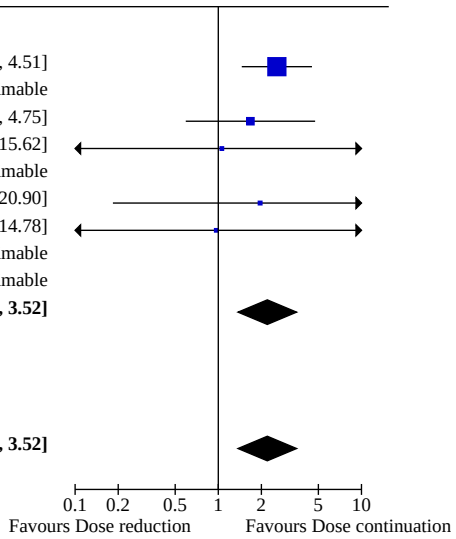
Footnotes

(1) < 1 year

(2) < 6 months

Analysis 3.2. Comparison 3: Sensitivity analyses - adverse effects - leaving the study early due to adverse effects - overall tolerability, Outcome 2: Excluding studies that did not use operationalised criteria to diagnose schizophrenia (Volavka 2000 excluded)

Study or Subgroup	Dose reduction Events	Dose reduction Total	Dose continuation Events	Dose continuation Total	Weight	Risk Ratio IV, Random, 95% CI
3.2.1 Combined time points						
Fleischhacker 2014 (1)	24	131	19	266	69.5%	2.56 [1.46 , 4.51]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (3)	6	144	8	322	20.5%	1.68 [0.59 , 4.75]
Ozawa 2019 (4)	1	17	1	18	3.1%	1.06 [0.07 , 15.62]
Remington 2011 (5)	0	17	0	18		Not estimable
Rouillon 2008 (5)	2	49	1	48	4.0%	1.96 [0.18 , 20.90]
Takeuchi 2014 (6)	1	31	1	30	3.0%	0.97 [0.06 , 14.78]
Wunderink 2007 (6)	0	68	0	63		Not estimable
Zhou 2018 (1)	0	37	0	38		Not estimable
Subtotal (95% CI)		**505**		**812**	**100.0%**	**2.20 [1.37 , 3.52]**
Total events:	34		30			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 4 (P = 0.88); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
Total (95% CI)		**505**		**812**	**100.0%**	**2.20 [1.37 , 3.52]**
Total events:	34		30			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 4 (P = 0.88); I² = 0%						
Test for overall effect: Z = 3.28 (P = 0.001)						
Test for subgroup differences: Not applicable						

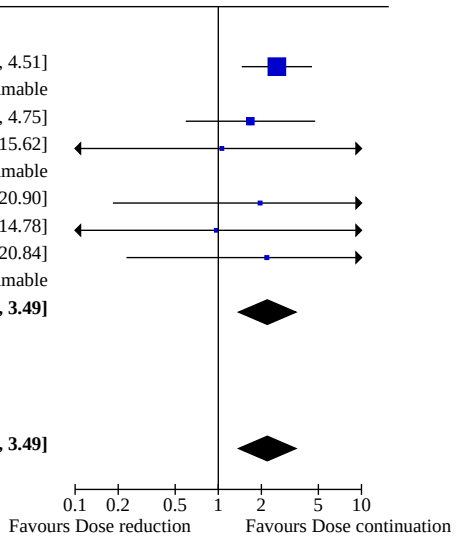


Footnotes

(1) < 1 year (DSM-IV-TR)
(2) < 6 months (ICD-10)
(3) < 6 months (DSM-IV)
(4) < 1 year (DSM-IV, DSM-5)
(5) < 6 months (DSM-IV)
(6) < 1 year (DSM-IV)

Analysis 3.3. Comparison 3: Sensitivity analyses - adverse effects - leaving the study early due to adverse effects - overall tolerability, Outcome 3: Excluding studies conducted in mainland China (Zhou 2018 excluded)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
3.3.1 Combined time points						
Fleischhacker 2014 (1)	24	131	19	266	66.6%	2.56 [1.46 , 4.51]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (2)	6	144	8	322	19.6%	1.68 [0.59 , 4.75]
Ozawa 2019 (1)	1	17	1	18	2.9%	1.06 [0.07 , 15.62]
Remington 2011 (2)	0	17	0	18		Not estimable
Rouillon 2008 (2)	2	49	1	48	3.8%	1.96 [0.18 , 20.90]
Takeuchi 2014 (1)	1	31	1	30	2.9%	0.97 [0.06 , 14.78]
Volavka 2000 (2)	2	11	1	12	4.2%	2.18 [0.23 , 20.84]
Wunderink 2007 (1)	0	68	0	63		Not estimable
Subtotal (95% CI)		**479**		**786**	**100.0%**	**2.20 [1.39 , 3.49]**
Total events:	36		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Total (95% CI)		**479**		**786**	**100.0%**	**2.20 [1.39 , 3.49]**
Total events:	36		31			
Heterogeneity: Tau² = 0.00; Chi² = 1.19, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Test for subgroup differences: Not applicable						



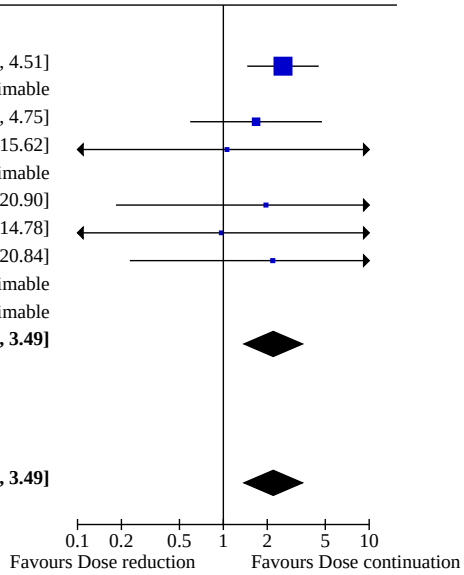
Footnotes

(1) < 1 year

(2) < 6 months

Analysis 3.4. Comparison 3: Sensitivity analyses - adverse effects - leaving the study early due to adverse effects - overall tolerability, Outcome 4: Fixed-effect

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.4.1 Combined time points						
Fleischhacker 2014 (1)	24	131	19	266	66.6%	2.56 [1.46 , 4.51]
Huhn 2020 (2)	0	11	0	9		Not estimable
Kane 2010 (2)	6	144	8	322	19.6%	1.68 [0.59 , 4.75]
Ozawa 2019 (1)	1	17	1	18	2.9%	1.06 [0.07 , 15.62]
Remington 2011 (2)	0	17	0	18		Not estimable
Rouillon 2008 (2)	2	49	1	48	3.8%	1.96 [0.18 , 20.90]
Takeuchi 2014 (1)	1	31	1	30	2.9%	0.97 [0.06 , 14.78]
Volavka 2000 (2)	2	11	1	12	4.2%	2.18 [0.23 , 20.84]
Wunderink 2007 (1)	0	68	0	63		Not estimable
Zhou 2018 (1)	0	37	0	38		Not estimable
Subtotal (95% CI)		**516**		**824**	**100.0%**	**2.20 [1.39 , 3.49]**
Total events:	36		31			
Heterogeneity: Chi² = 1.19, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Total (95% CI)		**516**		**824**	**100.0%**	**2.20 [1.39 , 3.49]**
Total events:	36		31			
Heterogeneity: Chi² = 1.19, df = 5 (P = 0.95); I² = 0%						
Test for overall effect: Z = 3.35 (P = 0.0008)						
Test for subgroup differences: Not applicable						



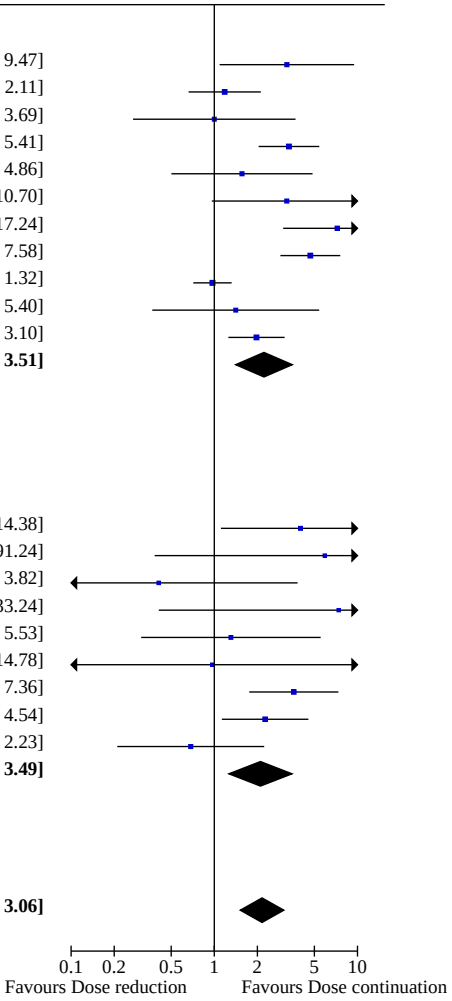
Footnotes
(1) < 1 year
(2) < 6 months

Comparison 4. Subgroup analysis - global state - number of participants with relapse/exacerbations of psychosis (post hoc)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 Speed of dose reduction (abrupt vs gradual)	20	2481	Risk Ratio (IV, Random, 95% CI)	2.16 [1.52, 3.06]
4.1.1 Abrupt	11	1660	Risk Ratio (IV, Random, 95% CI)	2.22 [1.41, 3.51]
4.1.2 Gradual	9	821	Risk Ratio (IV, Random, 95% CI)	2.10 [1.26, 3.49]

Analysis 4.1. Comparison 4: Subgroup analysis - global state - number of participants with relapse/ exacerbations of psychosis (post hoc), Outcome 1: Speed of dose reduction (abrupt vs gradual)

Study or Subgroup	Dose reduction Events	Total	Dose continuation Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.1.1 Abrupt						
Caffey 1964 (1)	13	89	4	88	4.9%	3.21 [1.09 , 9.47]
Carpenter 1999 (2)	13	25	11	25	7.4%	1.18 [0.66 , 2.11]
Cookson 1987 (2)	3	9	3	9	4.1%	1.00 [0.27 , 3.69]
Fleischhacker 2014 (2)	36	131	22	266	7.9%	3.32 [2.04 , 5.41]
Hogarty 1988 (2)	7	37	4	33	4.7%	1.56 [0.50 , 4.86]
Johnson 1987 (2)	9	29	3	31	4.4%	3.21 [0.96 , 10.70]
Kane 1983 (2)	35	62	5	64	5.9%	7.23 [3.03 , 17.24]
Kane 2010 (3)	44	144	21	322	7.9%	4.69 [2.90 , 7.58]
Lonowski 1978 (3)	19	25	18	23	8.7%	0.97 [0.71 , 1.32]
Remington 2011 (3)	4	17	3	18	3.9%	1.41 [0.37 , 5.40]
Schooler 1997 (4)	41	106	21	107	8.1%	1.97 [1.25 , 3.10]
Subtotal (95% CI)		**674**		**986**	**68.1%**	**2.22 [1.41 , 3.51]**
Total events:	224		115			
Heterogeneity: Tau² = 0.42; Chi² = 51.31, df = 10 (P < 0.00001); I² = 81%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
4.1.2 Gradual						
Branchey 1981 (5)	16	22	2	11	4.2%	4.00 [1.11 , 14.38]
Faraone 1989 (1)	8	22	0	7	1.4%	5.91 [0.38 , 91.24]
Huhn 2020 (3)	1	11	2	9	2.0%	0.41 [0.04 , 3.82]
Ozawa 2019 (6)	3	17	0	18	1.3%	7.39 [0.41 , 133.24]
Rouillon 2008 (7)	4	49	3	48	3.6%	1.31 [0.31 , 5.53]
Takeuchi 2014 (2)	1	31	1	30	1.4%	0.97 [0.06 , 14.78]
Wang 2010 (2)	47	211	8	129	6.7%	3.59 [1.75 , 7.36]
Wunderink 2007 (2)	22	68	9	63	6.8%	2.26 [1.13 , 4.54]
Zhou 2018 (2)	4	37	6	38	4.5%	0.68 [0.21 , 2.23]
Subtotal (95% CI)		**468**		**353**	**31.9%**	**2.10 [1.26 , 3.49]**
Total events:	106		31			
Heterogeneity: Tau² = 0.14; Chi² = 10.59, df = 8 (P = 0.23); I² = 24%						
Test for overall effect: Z = 2.86 (P = 0.004)						
Total (95% CI)		**1142**		**1339**	**100.0%**	**2.16 [1.52 , 3.06]**
Total events:	330		146			
Heterogeneity: Tau² = 0.34; Chi² = 62.50, df = 19 (P < 0.00001); I² = 70%						
Test for overall effect: Z = 4.29 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%						



Footnotes

(1) < 6 months; relapse by clinical judgement
(2) < 1 year; scale defined relapse
(3) < 6 months; scale defined relapse
(4) < 1 year; clinical worsening needing rescue medication
(5) < 1 year; severe or persistent (> 1 week) clinical worsening
(6) < 1 year; dropouts due to clinical worsening
(7) < 6 months; hospitalisation

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

AR: search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; GRADE assessment; interpretation of data; writing of the review

SSi: design of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; GRADE assessment; interpretation of data; writing of the review

IBi: conception of the review; design of the review; search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies; analysis of data; GRADE assessment; interpretation of data; writing of the review

MS: conception of the review

WPH: conception of the review; design of the review; interpretation of data with patient perspective; writing of the review

SSa: interpretation of data; co-ordination of the review. The author was deceased in May 2022. No substantive changes have been made to the review beyond his contribution.

EA: interpretation of data; co-ordination of the review

PC: search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies

IBa: search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies

LB: search and selection of studies for inclusion in the review; collection of data for the review; assessment of the risk of bias in the included studies

SL: conception of the review; design of the review; co-ordination of the review; interpretation of data; writing of the review

DECLARATIONS OF INTEREST

AR is an editor of the Cochrane Schizophrenia Group. He was not involved in the editorial process of the current review.

SSi is an editor of the Cochrane Schizophrenia Group. He was not involved in the editorial process of the current review.

IB is the Deputy Co-ordinating Editor of the Cochrane Schizophrenia Group. She was not involved in the editorial process of the current review.

MS is an editor of the Cochrane Schizophrenia Group. She was not involved in the editorial process of the current review. She works as a psychiatrist in private practice.

WPH: none

SSa: none. Author deceased; declarations of interest if provided before the author died.

EA: In the past 3 years, EA has been a consultant or speaker or received research grants from Allergan, Angelini, Doc Generici, FB-Health, Janssen, Lundbeck, Otsuka, Fidia, Recordati; I am currently the President of the Italian Society of Psychopathology.

PC: none

IBa: none

LB: none

SL: In the past 3 years, SL has received honoraria for service as a consultant or adviser and/or for lectures from Angelini, Böhringer Ingelheim, Geodon & Richter, Janssen, Johnson & Johnson, Lundbeck, LTS Lohmann, MSD, Otsuka, Recordati, Sanofi-Aventis, Sandoz, Sunovion, TEVA, ROVI, and EISAI. SL is an editor of the Cochrane Schizophrenia Group. He was not involved in the editorial process of the current review.

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Internal sources

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  The employer of most of the authors
- National Institute for Health and Care Research (NIHR), UK

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  Project n. 01KG1807
- POC Sicilia 2014-20 – Avviso 37/2020, Italy

  Project n. G67C20000210002

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned to search Chinese databases; however, this was not possible.

We decided primarily to use endpoint data, and only use change data if endpoint data were not available. Nevertheless, we used post hoc change scores in a few cases when there was a substantial baseline imbalance that could have influenced the results (e.g. weight gain in one study (Huhn 2020), and scales for extrapyramidal symptoms in another study (Ozawa 2019)); such changes are noted in the forest plots with footnotes.

Cognition was added as an outcome of the review and systematically appraised in all of the included studies.

Where available, we extracted data for the less than three months time point in addition to the pre-planned time points. Analyses were presented both at different time points and by merging the time points. For these merged analyses, data from studies providing information for more than one time point were kept only for one time point (the closest to 12 months) to avoid double-counting.

For analyses of dichotomous outcomes, we post hoc assumed that participants leaving the study early did not have the outcome. We consider that another assumption would have overestimated the risk. Moreover, this assumption is frequently used, such as in a previous meta-analysis of our group (Leucht 2021). In contrast, in the protocol we stated that we would assume participants leaving the study early to have the same rates of events as participants who completed the study.

We adapted the strategy of dealing with skewed data to the new template protocol adopted by the Cochrane Schizophrenia Group.

We presented RoB 2 results in risk of bias tables in the Characteristics of included studies section and in the forest plots, following indications of Risk of Bias 2 Starter Pack. Accordingly, we did not create risk of bias graph and risk of bias summary figures.

We performed RoB 2 judgements for the predefined outcomes at the primary time point of 12 months, or when not available, the closest one.

When data were not available for the predefined outcomes that would have been rated with RoB 2, we rated RoB 2 for their proxy outcomes.

We created summary of findings tables for the predefined outcomes at the total level (merging time points) or at the closest to 12 months when totals were not possible.

We used continuous data for RoB 2 ratings and summary of findings tables for functioning and quality of life because the pre-planned dichotomous outcomes were unavailable.

We specified that funnel plot analyses were considered for the outcomes of the summary of findings tables when at least 10 effect estimates were available.

We conducted subgroup analyses for analyses with at least 10 studies, according to Section 10.11.5.1 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2022).

We performed a post hoc meta-regression with the endpoint dose and speed of dose reduction for the outcome of relapse/acute exacerbation.

INDEX TERMS

Medical Subject Headings (MeSH)

*Antipsychotic Agents [adverse effects]; Drug Tapering; *Drug-Related Side Effects and Adverse Reactions; Quality of Life; Recurrence; *Schizophrenia [drug therapy]

MeSH check words

Adult; Humans