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Antipsychotic polypharmacy reduction versus polypharmacy continuation for people with schizophrenia (Review)

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[Intervention Review]

Antipsychotic polypharmacy reduction versus polypharmacy continuation for people with schizophrenia

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ABSTRACT

Background

In clinical practice, different antipsychotics can be combined in the treatment of people with schizophrenia (polypharmacy). This strategy can aim at increasing efficacy, but might also increase the adverse effects due to drug–drug interactions. Reducing polypharmacy by withdrawing one or more antipsychotics may reduce this problem, but must be done carefully, in order to maintain efficacy.

Objectives

To examine the effects and safety of reducing antipsychotic polypharmacy compared to maintaining people with schizophrenia on the same number of antipsychotics.

Search methods

On 10 February 2021, we searched the Cochrane Schizophrenia Group's Study-Based Register of Trials, which is based on CENTRAL, CINAHL, ClinicalTrials.Gov, Embase, ISRCTN, MEDLINE, PsycINFO, PubMed and WHO ICTRP.

Selection criteria

We included randomised controlled trials (RCTs) that compared reduction in the number of antipsychotics to continuation of the current number of antipsychotics. We included adults with schizophrenia or related disorders who were receiving more than one antipsychotic and were stabilised on their current treatment.

Data collection and analysis

Two review authors independently screened all the identified references for inclusion, and all the full papers. We contacted study authors if we needed any further information. Two review authors independently extracted the data, assessed the risk of bias using RoB 2 and the

certainty of the evidence using the GRADE approach. The primary outcomes were: quality of life assessed as number of participants with clinically important change in quality of life; service use assessed as number of participants readmitted to hospital and adverse effects assessed with number of participants leaving the study early due to adverse effects.

Main results

We included five RCTs with 319 participants. Study duration ranged from three months to one year. All studies compared polypharmacy continuation with two antipsychotics to polypharmacy reduction to one antipsychotic.

We assessed the risk of bias of results as being of some concern or at high risk of bias.

A lower number of participants left the study early due to any reason in the polypharmacy continuation group (risk ratio (RR) 0.44, 95% confidence interval (CI) 0.29 to 0.68; I^2 = 0%; 5 RCTs, n = 319; low-certainty evidence), and a lower number of participants left the study early due to inefficacy (RR 0.21, 95% CI 0.07 to 0.65; I^2 = 0%; 3 RCTs, n = 201).

Polypharmacy continuation resulted in more severe negative symptoms (MD 3.30, 95% CI 1.51 to 5.09; 1 RCT, n = 35).

There was no clear difference between polypharmacy reduction and polypharmacy continuation on readmission to hospital, leaving the study early due to adverse effects, functioning, global state, general mental state and positive symptoms, number of participants with at least one adverse effect, weight gain and other specific adverse effects, mortality and cognition.

We assessed the certainty of the evidence as very low or low across measured outcomes.

No studies reported quality of life, days in hospital, relapse, depressive symptoms, behaviour and satisfaction with care.

Due to lack of data, it was not possible to perform some planned sensitivity analyses, including one controlling for increasing the dose of the remaining antipsychotic. As a result, we do not know if the observed results might be influenced by adjustment of dose of remaining antipsychotic compound.

Authors' conclusions

This review summarises the latest evidence on polypharmacy continuation compared with polypharmacy reduction. Our results show that polypharmacy continuation might be associated with a lower number of participants leaving the study early, especially due to inefficacy. However, the evidence is of low and very low certainty and the data analyses based on few study only, so that it is not possible to draw strong conclusions based on the results of the present review.

Further high-quality RCTs are needed to investigate this important topic.

PLAIN LANGUAGE SUMMARY

Reduction in the number of antipsychotics for people with schizophrenia

Key messages

– Reducing the number of antipsychotics may be associated with more participants leaving the study early, especially due to inefficacy.

- The low number of studies and participants do not allow us to make strong conclusions.

Introduction

Schizophrenia is a severe mental disorder. People with the illness struggle to differentiate between their own thoughts, beliefs and ideas versus reality. For example, they may be hearing voices in their head but it feels like someone is really talking to them. It is mainly treated with medications called antipsychotics. Often people with schizophrenia are offered treatment with more than one antipsychotic in order to achieve an effective treatment. Use of antipsychotics is connected with side effects, and the different antipsychotics could interact, making side effects worse.

What did we want to find out?

We wanted to find out if reducing the number of antipsychotics was better than keeping the same number of antipsychotics to improve:

– quality of life

– number of people readmitted to hospital

– number of people leaving the study early because of side effects

– a person's daily functioning

– relapse

– number of people leaving the study early for any reason

– number of people with at least one side effect.

What did we do?

We searched for studies that examined reducing the number of antipsychotics compared with keeping the same number of antipsychotics 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 five studies that involved 319 participants with schizophrenia. The studies lasted between three months and one year. They were conducted in Canada, Japan, Finland and two in the USA, and were all sponsored by public institutions.

We found that reducing the number of antipsychotics may increase the number of participants leaving the study early, especially because the treatment did not work as well.

We found no differences in terms of readmission to hospital, leaving the study early due to side effects, functioning and number of participants with at least one side effect, but we are very uncertain about the results.

We found no data about quality of life and relapses.

What are the limitations of the evidence?

We are not confident in the evidence because it is possible that the people in the studies were aware of which treatment they were getting. Not all of the studies provided data about everything that we were interested in. In addition, there were not enough studies to be certain about the results of our outcomes, and studies were small.

How up to date is this evidence?

The evidence is up to date to February 2021.

Summary of findings 1. Summary of findings table - Continuation compared to reduction of polypharmacy for people with schizophrenia

Continuation compared to reduction of polypharmacy for people with schizophrenia

Patient or population: people with schizophrenia
Setting:
Intervention: continuation
Comparison: reduction

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with reduction	Risk with continuation				
Quality of life: clinically important change - not reported	-	-	-	-	-	
Service use – readmission to hospital – total	108 per 1000	**81 per 1000** (27 to 241)	**RR 0.75** (0.25 to 2.24)	127 (1 RCT)	⊕⊖⊖⊖ Very low[a,b,c]	
Adverse effects – leaving the study early due to adverse effects – overall tolerability – total	11 per 1000	**49 per 1000** (9 to 276)	**RR 4.37** (0.77 to 24.88)	176 (3 RCTs)	⊕⊖⊖⊖ Very low[b,d]	
Functioning – mean endpoint score GAF (high = good) – total	The mean functioning – mean endpoint score GAF (high = good) – total was **0**	MD **0.66 higher** (5.89 lower to 7.21 higher)	-	12 (1 RCT)	⊕⊖⊖⊖ Very low[a,c,e]	
Global state: relapse/exacerbations of psychosis - not reported	-	-	-	-	-	
Leaving the study early due to any reason – overall acceptability (totals of time points combined)	327 per 1000	**144 per 1000** (95 to 222)	**RR 0.44** (0.29 to 0.68)	319 (5 RCTs)	⊕⊕⊖⊖ Low[f,g]	
Adverse effects: ≥ 1 adverse effect – total	0 per 1000	**0 per 1000** (0 to 0)	**RR 5.00** (0.28 to 88.53)	14 (1 RCT)	⊕⊖⊖⊖ Very low[c,e]	

***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; **MD:** mean difference; **RR:** risk ratio

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_431732298303949552.

[a] Downgraded one level for risk of bias: data were from one study at high risk of bias, with one domain at high risk of bias.
[b] Downgraded two levels for imprecision: optimal information size (OIS) criterion was not met, and 95% confidence intervals failed to exclude important benefit or important harm.
[c] Not possible to rate inconsistency (only one study included in analysis).
[d] Downgraded one level for risk of bias: one of three studies providing data (with 67% weight) was at high risk of bias due to one domain being at high risk of bias.
[e] Downgraded three levels for Imprecision: OIS criterion was not met (only one very small study), and 95% confidence intervals failed to exclude important benefit or important harm.
[f] Downgraded one level for risk of bias: two of five studies (about 80% weight) at overall high risk of bias, but just due to one domain.
[g] Downgraded one level for imprecision: OIS criterion was not met, but the 95% confidence intervals excluded no effect.

BACKGROUND

Antipsychotic drugs are effective for the acute treatment and relapse prevention of schizophrenia (Leucht 2012; Leucht 2013). However, they have important adverse effects such as movement disorders, weight gain and associated metabolic problems, which are likely to contribute to a well-documented excess mortality (Hjorthoj 2017). Controversial data suggest that antipsychotics are likely to be associated with brain volume loss in a dose-related manner (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). Therefore, the critical question the clinician must address is whether high dose and antipsychotic polypharmacy can be carefully reduced while 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). Evidently, there will always be a difficult trade-off, because if the dose is too low or if the antipsychotic is stopped, there could be a high risk for relapse that can have adverse consequences for patients (Leucht 2013). In the current Cochrane Review, we summarised all randomised controlled trials (RCTs) that compare reducing antipsychotic polypharmacy with remaining on the same number of antipsychotics. A companion review addresses the related question of reducing antipsychotic doses.

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 worldwide of long-term disability, with devastating impact for 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 rates that are highest among 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 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 disorder, weight gain, metabolic problems and sexual dysfunction (Leucht 2013); possible brain volume loss (Ho 2011); and increased risk of mortality (McGrath 2008).

Moreover, there are high rates of non-response, with 40% to 50% of people taking antipsychotics not reaching even a minimal response (Leucht 2017; Samara 2019), so that often clinicians try to combine several antipsychotics (polypharmacy) to increase efficacy (Gallego 2012). However, the exact rates of non-response are difficult to measure, because of the potential confounding derived from the poor adherence to medication.

One review of 147 studies found an overall prevalence of antipsychotic polypharmacy of approximately 20% (Gallego 2012).

Polypharmacy includes augmentation strategies, combining different antipsychotics because of their difference in targeted receptor sites (e.g. clozapine and amisulpride) or combining different antipsychotics in order to minimise adverse effects (e.g. clozapine and aripiprazole) (Hiemke 2018).

The intervention focus of this review is the reduction of the number of antipsychotics prescribed to the patient during the maintenance phase. We defined reducing antipsychotic polypharmacy as the process of withdrawing a person with schizophrenia from one or more of their prescribed antipsychotics. Reduction of polypharmacy can also mean that, even if the number of antipsychotics is reduced, this reduction is compensated by increasing the dose of the remaining compounds, so that the overall dose of antipsychotics received by the patient might not change. However, there is a difficult trade-off, because if the overall dose of antipsychotics becomes too low there is a risk for relapse (Leucht 2012).

How the intervention might work

On one side, specific combinations of antipsychotics may have beneficial therapeutic potential (Tiihonen 2019). On the other side, combinations of antipsychotic drugs can lead to drug–drug interactions resulting in unexpectedly high or low plasma levels, for example by the inhibition or induction of cytochrome P450 enzymes in the liver, which are responsible for the metabolism of most psychotropic drugs (Hiemke 2018). Under these circumstances, the drug–drug interactions, for example of haloperidol and olanzapine need to be monitored (Hiemke 2018).

This is a potentially dangerous situation and, if applied, plasma level monitoring should be performed, but such monitoring is expensive and not available in all settings (Hiemke 2018). Moreover, if two or more antipsychotics are combined, patients may receive overall too high doses. It has been shown, mainly for first-generation antipsychotics, that relatively low doses are needed to achieve at least 65% blockade of dopamine receptors that is thought to be sufficient for antipsychotic efficacy (Kapur 2000).

Reducing polypharmacy by withdrawing one or more antipsychotics should theoretically decrease the problems in terms of drug–drug interactions; it also has the potential to reduce the overall antipsychotic load and the adverse-effect burden for people with schizophrenia (Misawa 2011; Ray 2009; Uchida 2009). Reducing polypharmacy can also increase adherence and reduce treatment costs. However, there are potential harms; the risk is that patients need the drug combinations that they receive or that the overall dose becomes too low after withdrawal of one or several antipsychotics so that people relapse (Leucht 2012). The aim of this review was to examine the evidence and give information on potential benefits and pitfalls of this strategy.

Why it is important to do this review

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, weight gain and associated metabolic problems, which are likely to contribute to a well-documented excess mortality (Hjorthoj 2017). Controversial data suggest that antipsychotics could cause brain volume loss in a dose-related manner (Andreasen 2013; Ho 2011), even if it is difficult to differentiate this volume change from the one that could derive from the illness or other confounding factors such as cannabis use (van Haren 2013).

Due to various pressures, such as a risk for suicide or aggressive behaviour, but also shorter duration of hospitalisation and high rates of non-response (Samara 2016; Samara 2019), acutely ill patients are frequently treated with combinations of antipsychotics (Gallego 2012). However, guidelines recommend against combining antipsychotics, because this can lead to drug–drug interactions, and because there is limited evidence for the effectiveness of this strategy (Galling 2017). Therefore, whether polypharmacy can be carefully reduced during the maintenance phase remains unclear (Essock 2011). This review systematically summarises data from all relevant RCTs to provide high-quality evidence for the effects reducing antipsychotic polypharmacy compared to maintaining polypharmacy for people with schizophrenia who are stabilised on antipsychotic treatment. 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 addresses the related question of reducing antipsychotic doses (Bighelli 2021a).

OBJECTIVES

To examine the effects and safety of reducing antipsychotic polypharmacy compared to maintaining people with schizophrenia on the same number of antipsychotics.

To examine factors of reduction of polypharmacy such as the number of antipsychotics that are withdrawn and whether the reduction of polypharmacy was compensated by increasing the dose of the remaining antipsychotics.

METHODS

Criteria for considering studies for this review

Types of studies

We considered all relevant RCTs for inclusion. If a trial was described as 'double-blind' but randomisation was implied, we would have included such trials and examined 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 have remained in the analyses. If their inclusion resulted in important clinically significant but not necessarily statistically significant differences, we would not have added the data from these lower-quality studies to the results of the high-quality trials, but presented 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, and such studies had 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 (irrespectively of the diagnostic criteria used), who are receiving more than one antipsychotic and are stabilised on their current antipsychotic treatment, irrespective of age, gender, race or country. We accepted any definition of stability used in the individual studies. We excluded studies that compare antipsychotic polypharmacy with monotherapy for acutely ill people with schizophrenia.

If a study included participants with other diagnoses, we only included the study if participants with a diagnosis of schizophrenia or related disorders constituted at least 80% of the population.

We are interested in ensuring that information is relevant to the current care of people with schizophrenia. Therefore, we 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 primarily focused on people with particular problems (e.g. negative symptoms, treatment-resistant illnesses).

See Subgroup analysis and investigation of heterogeneity.

Types of interventions

1. Antipsychotic polypharmacy reduction

Any reduction in the number of antipsychotics (considering antipsychotics licensed in at least one country) from a starting point of at least two antipsychotics, irrespectively of which combinations participants were originally on, which antipsychotics were withdrawn, how many antipsychotics were withdrawn and how fast the withdrawal was undertaken.

2. Antipsychotic polypharmacy continuation

Continuation of the current number of antipsychotics.

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). Up to one year is the primary time point of interest.

Primary outcomes

1. Quality of life

1.1. Clinically important change in quality of life

Number of people 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 who were readmitted to hospital.

3. Adverse effects

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

Number of participants who discontinued their 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 neuroleptics 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 (GAF) or the Psychosocial Performance Scale.

4. Global state

4.1. Relapse/exacerbations of psychosis

We accepted any definitions of 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 who prematurely discontinued due to any reason.

5.2. Due to inefficacy – overall efficacy

Number of participants who 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 in negative symptom scale

We investigated the negative symptoms of schizophrenia according to the negative subscale of the PANSS or 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 Åsberg Depression Rating Scale or any other validated 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 effect/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. Due to natural causes

9.2.3. Due to suicide

10. Medication – mean antipsychotic dose at endpoint

We examined whether reduction of polypharmacy also led to a reduction of antipsychotic doses. We converted antipsychotic doses to olanzapine equivalents for this procedure (Gardner 2010).

11. Cognition

11.2. Mean endpoint or change score on cognition scale

We accepted any published rating scale.

Search methods for identification of studies

We applied no language restrictions within the search.

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:

Polypharmacy in Intervention Field 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 the methods from Cochrane (Lefebvre 2019), this register is compiled by systematic searches of major resources (Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, CINAHL, ISRCTN, PsycINFO, PubMed, World Health Organization (WHO) International Clinical Trials Registry Platform, ClinicalTrials.gov) 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, schizophrenia.cochrane.org/register-trials). There is no language, date, document type, or publication status limitations for inclusion of records into the register.

Searching other resources

1. Reference searching

We inspected references of 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 with a request for 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 at least one had conducted such studies.

Data collection and analysis

Selection of studies

After removing 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 (www.covidence.org/), which has been produced to improve the quality of the study selection and data extraction process, and remove duplicates. Where disputes arose, we acquired the full report for more detailed scrutiny. At least two review authors (of IBi, MS and AR, LB, IBa, SS, PC) independently obtained and inspected full reports of the abstracts meeting the review criteria. We resolved disagreements by discussion with another review author (SL). Where it was not possible to resolve disagreement 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, MS and AR, LB, IBa, SS, PC) independently extracted data from all included studies. We discussed any disagreements, eventually with another review author (SL), and, if necessary, we contacted authors of studies through an open-ended request to obtain missing information or for clarification. We documented information obtained from study authors in the Characteristics of included studies table.

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

For each included study, we extracted the following study characteristics, and provided them in the Characteristics of included studies table: methods, participants, interventions, outcomes and identification.

2. Management

2.1. Forms

We extracted data using the Covidence Software, after piloting the form with a sample of five studies (www.covidence.org/).

2.2. Scale-derived data

We included continuous data from rating scales only if:

- the psychometric properties of the measuring instrument were described in a peer-reviewed journal (Marshall 2000);
- the measuring instrument had not been written or modified by one of the trialists for that particular trial; and
- the instrument was a global assessment of an area of functioning, and not a subscore that had not been validated or shown to be reliable as a stand-alone instrument. However, there are exceptions; we included subscores from mental state scales that measured 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) that can be difficult to obtain in unstable and difficult-to-measure conditions such as schizophrenia. We decided primarily to use endpoint data, and only used change data if the endpoint data were not available.

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 check to relevant continuous data before inclusion.

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

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

For this calculation, we checked the original publication of the scales referenced in the studies, in order to understand if they could have a lowest possible score different from 0, and whether the adjustment described above was needed.

If the ratio obtained was lower than one, it strongly suggests that the data were skewed. If it was higher than one but less than two, there is suggestion that the data were skewed; if the ratio is larger than 2 it is less likely that they were skewed (Altman 1996).

Where there is suggestion of skewness (ratio less than 2), we excluded the relevant studies in a sensitivity analysis to check if they had an impact on the results (see Sensitivity analysis for further details).

Nevertheless, we reported skewed results in 'other data tables'.

We would have entered 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 would also have entered all relevant change data, as when continuous data are presented on a scale that includes a 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 continuous 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 a clinically significant response (Leucht 2005a; Leucht 2005b). If data based on these thresholds were unavailable, we used the primary cut-off presented by the original authors.

2.7. Direction of graphs

Where possible, we entered data so that the area to the right of the line of no effect indicated a favourable outcome for the intervention under investigation (reduction of polypharmacy). Where keeping to this made it impossible to avoid outcome titles with clumsy double-negatives (e.g. 'not unimproved'), we reported data where the right of the line indicated an unfavourable outcome and noted this in the graphs.

Assessment of risk of bias in included studies

Two review authors (of IBi, AR, LB, IBa, SS and PC) independently assessed risk of bias by using the RoB 2 tool (Sterne 2019), and referred to the criteria described in the *Cochrane Handbook for Systematic Reviews of Interventions* to assess trial quality (Higgins 2021). This set of criteria is based on the 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, some concerns, low) 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 the effect of assignment to the interventions at baseline, regardless of whether the interventions were received as intended (the intention-to-treat (ITT) effect) (Section 8.2.2; Higgins 2021).

We performed an evaluation with 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: due to any reason – overall acceptability;
- adverse effects/events: at least one adverse effect.

For cluster 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 use 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, we made the final rating by consensus, if necessary, with another review author (SL). Where studies provided inadequate details of randomisation and other characteristics, we attempted to contact 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 in included studies and in the risk of bias tables for analyses.

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 RRs 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

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

Unit of analysis issues

1. Cluster trials

Studies increasingly employ cluster randomisation (such as randomisation by clinician or practice), but analysis and pooling of clustered data poses problems. First, 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 has been incorporated into the analysis of primary studies, we would have presented 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 have presented data in a table, with a * symbol to indicate the presence of a probable unit of analysis error. We would have contacted the first authors of studies to obtain intraclass correlation coefficients (ICC) 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 assumed it to be 0.1 (Ukoumunne 1999).

If cluster studies were appropriately analysed and ICCs and relevant data documented in the report taken into account, synthesis with other studies would have been 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 washout 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 have presented the additional treatment arms in comparisons. If data were binary, we would have simply added these and combine within the 2 × 2 table.

If data were continuous, we would have combined them using the formula in Section 6.5.2.10 (Combining groups) of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). 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, but we accounted for attrition in the risk of bias assessment.

2. Binary

We presented data in an ITT analysis. If the original authors presented only the results of the per-protocol or completer population, we assumed that those participants lost to follow-up would not have had the outcome of interest if they had stayed in the study.

3. Continuous

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

There are various methods to account for participants who leave the trials early or are lost to follow-up. Some trials just present the results of study completers; other trials use the method of last observation carried forward (LOCF); while methods such as multiple imputation or mixed-effects models for repeated measurements (MMRM) have become more of a standard. While the 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, by preference we used the more sophisticated approaches (i.e. we would have preferred to use MMRM or multiple-imputation to LOCF), and we 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 studies did not report SDs, we tried 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 according to the rules described in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). When only the SEs were reported, we calculated SDs using the formula SD = SE × √(n). Section 6.5.2.3 of the *Cochrane Handbook for Systematic Reviews of Interventions* present detailed formulae for estimating SDs from P, t or F values; CIs; ranges or other statistics (Higgins 2021). 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 and thus to 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 are 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 (Section 10.10.2, *Cochrane Handbook for Systematic Reviews of Interventions*) (Higgins 2021). When there were substantial levels of heterogeneity in the primary outcomes, we explored reasons for 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 13 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2021). 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 were 10 studies or fewer, or where all studies were of 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).

Data synthesis

We understand that there is no closed argument for preference for 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 often seems 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: it puts added weight on small studies, which often are the most biased type. 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

Subgroup analyses were only conducted on the primary outcomes. We are aware that subgroup analyses are observational by nature and, therefore, consider the results to be exploratory and 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. We conducted subgroup analyses only for comparisons with at least 10 studies (Section 10.11.5.1, Higgins 2021).

1.1. Degree of antipsychotic polypharmacy reduction

We planned to perform subgroup analyses based on how many antipsychotics were withdrawn in the selected studies. The greater the number of drugs withdrawn, the higher the chances to have fewer adverse effects and better quality of life, but also the risk for major relapses leading to rehospitalisation should be higher.

1.2. Speed of antipsychotic polypharmacy reduction

Too fast a reduction of the number of antipsychotics may increase the risk for major relapses in terms of rehospitalisation. Therefore, we planned to categorise the studies into abrupt and gradual reduction.

1.3. Initial number of antipsychotics

Results may differ based upon whether participants were originally on two or more antipsychotics.

1.4. Severity of illness

It may be easier to reduce polypharmacy 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 polypharmacy reduction versus antipsychotic number maintenance for people with schizophrenia in general. In addition, however, we tried to report data on subgroups of people in the same clinical state, stage and with similar problems. The following groups appear to be especially pertinent.

1.5.1. Participants with first episode versus participants with multiple episodes

Up to 20% of first-episode participants may not have a second episode (Robinson 1999). Therefore, reducing polypharmacy may be particularly useful in this subgroup.

1.5.2. Participants in remission versus other participants

Reductions of polypharmacy may be more meaningful in participants in remission (if available according to Andreasen 2005), than in participants who are in a stable phase but not symptom free.

2. Investigation of heterogeneity

We reported if inconsistency was high. First, we investigated whether data had been entered correctly. Second, if data were correct, we inspected the graph visually and removed outlying studies successively to see if homogeneity was restored. Decisions 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 the difference between intervention and control (Higgins 2021). When unanticipated clinical or methodological heterogeneity was obvious, we simply stated hypotheses regarding these for future reviews or updates of this review. We do not anticipate undertaking analyses relating to these.

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 that were at overall high risk of bias for the primary outcome (see Assessment of risk of bias in included studies).

2. Imputed values

We planned to analyse the effects of excluding data from trials where we 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 planned to analyse the effects of excluding data from trials where there was a suggestion that data were skewed (mean/SD ratio lower than 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 planned to exclude these studies also from the main analysis, and present their data in 'Other data' tables.

6. Chinese studies

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

7. Reduction of polypharmacy is compensated by an increase in dose in the remaining antipsychotics

In some trials, reduction of polypharmacy may be compensated by the increase of the dose of the remaining antipsychotics. This procedure might still be superior to keeping the same number of antipsychotics due to fewer drug–drug interactions. We planned to carry out a sensitivity analysis excluding these trials.

Summary of findings and assessment of the certainty of the evidence

We used the GRADE approach to interpret findings (Higgins 2021); and used GRADEpro GDT to import data from Review Manager Web to create a summary of findings table for the comparison of polypharmacy reduction compared to polypharmacy continuation (GRADEpro GDT; Review Manager Web). 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 we rated as important to patient care and decision-making. The overall RoB 2 judgements were used to feed into the GRADE assessment. We selected the following main outcomes for inclusion 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: due to 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 we made comments in the footnotes to aid reader's understanding of the review where necessary.

Where one of predefined outcomes was not available, but data were available for a similar one, we rated this as a proxy of the predefined (e.g. for functioning, we reported mean endpoint score rather than clinically important change).

RESULTS

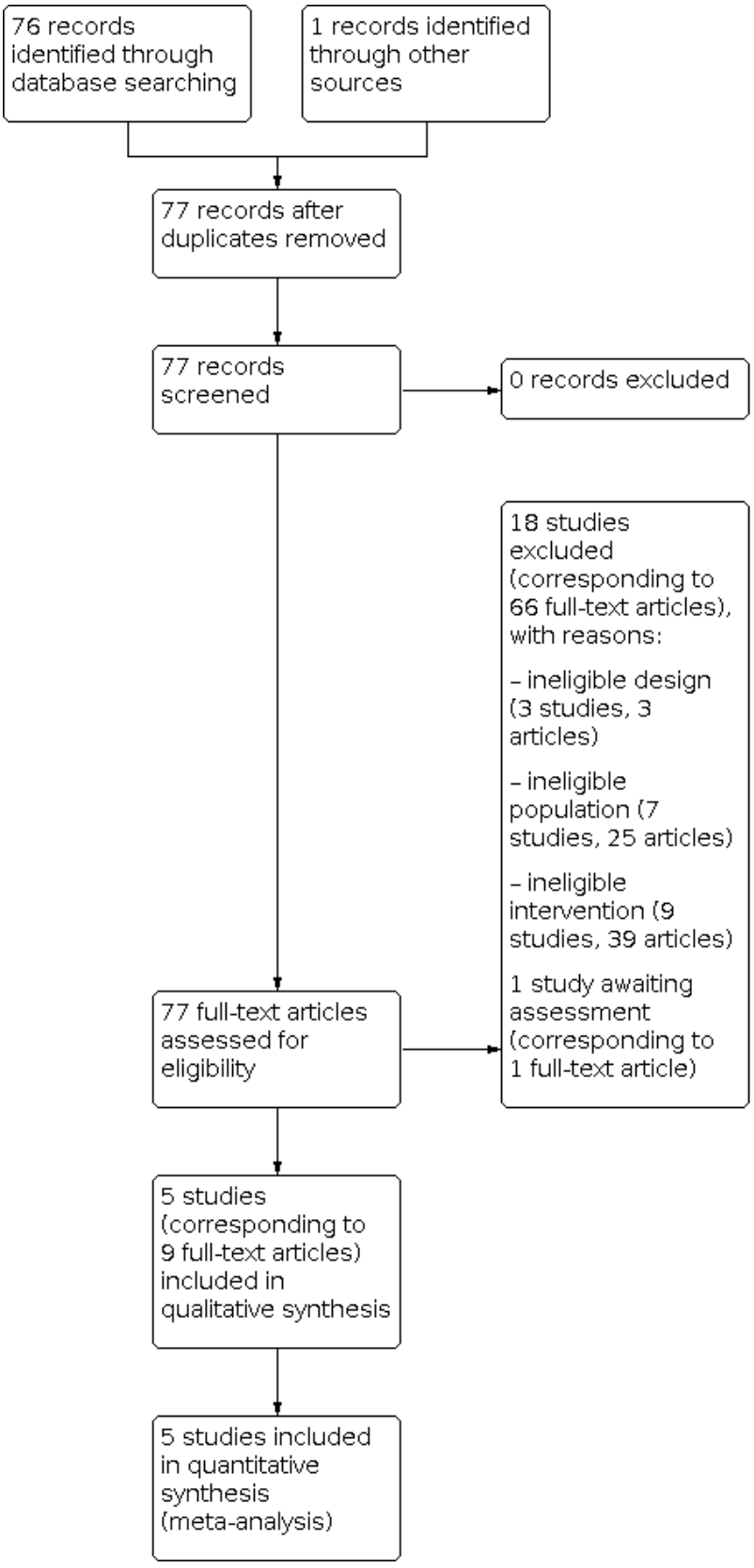
Description of studies

For detailed description of studies, see Characteristics of included studies, Characteristics of excluded studies and Characteristics of studies awaiting classification tables.

Results of the search

We searched the Cochrane Schizophrenia Group register of trials and identified 25 eligible studies (in 77 reports) for full-text screening (Figure 1). We excluded 18 studies (66 reports) and one study (one report) is awaiting classification. We included five studies (nine reports) in our review and in the quantitative synthesis (Borlido 2016; Constantine 2015; Essock 2011; Hori 2013; Repo-Tiihonen 2012). We found no ongoing studies.

Figure 1. Study flow diagram.



Included studies

Five studies (319 participants) met the inclusion criteria and were included in the review (Borlido 2016; Constantine 2015; Essock 2011; Hori 2013; Repo-Tiihonen 2012).

1. Design and duration

All were RCTs; one study had a cross-over design (Repo-Tiihonen 2012), and we used the data of the first phase.

Two studies had a duration of three months (Borlido 2016; Repo-Tiihonen 2012 (first phase)) and two lasted six months (Essock 2011; Hori 2013). The longest study had a duration of one year (Constantine 2015).

2. Participants

Two studies applied a diagnosis based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (Borlido 2016; Essock 2011), two studies based on Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision (DSM-IV-TR) (Constantine 2015; Hori 2013), and one study did not specify the criteria used for schizophrenia diagnosis (Repo-Tiihonen 2012). One study focused on treatment-resistant participants (Repo-Tiihonen 2012). The mean age of participants was about 45.3 years.

3. Size

The mean number of participants was 64. The smallest study included 14 participants (Repo-Tiihonen 2012), and the largest randomised 127 participants (Essock 2011).

4. Setting

One study included inpatients in a Department of Forensic Psychiatry (Repo-Tiihonen 2012), three studies included outpatients (Constantine 2015; Essock 2011; Hori 2013), and one study included both inpatients and outpatients (Borlido 2016).

5. Interventions

All studies compared the continuation of treatment with two antipsychotics with the reduction of the therapy to one antipsychotic. In most studies, the reduction to one antipsychotic was planned to happen within some weeks, one study did not provide details on the speed of polypharmacy reduction (Borlido 2016).

6. Outcomes

The included studies used different scales to measure the reported outcomes.

6.1. Outcome scales

6.1.1 Functioning

GAF is a clinician-rating of the impact of the severity of illness of the patient on daily life (APA 1987). It is a brief and easily administered scale measuring the impact on functioning on a numeric scale from 0 to 100, broken in 10 intervals, with a higher score indicated a better functioning.

One study used GAF (Repo-Tiihonen 2012).

6.1.2 Global state

The Clinical Global Impression (CGI) is a 7-point clinician-rated scale, comprising two subscales, one measuring global severity of illness (CGI-Severity or CGI-S) and one clinical improvement (CGI-Improvement or CGI-I) (Guy 1976). A lower score corresponds to lower severity of illness or more improvement (or less deterioration).

Two studies used CGI (Borlido 2016; Repo-Tiihonen 2012).

6.1.3 Mental state

The BPRS is a clinician-rated scale used to measure the severity of psychiatric symptoms, including psychotic symptoms (Overall 1962). The most frequently used version of the scale consists of 18-items encompassing positive, negative and affective symptoms. Each item is scored in a 7-point Likert scale from 1 "not present" to 7 "extreme 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 a higher severity of symptoms).

One study used the BPRS (Borlido 2016).

The PANSS was developed based on the BPRS scale (Kay 1986). It is a 30-item clinician-rated scale that covers positive, negative and general psychopathology symptoms of schizophrenia. Each item is scored in 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 a higher severity of symptoms).

There are three original subscales: positive symptoms, negative symptoms and general psychopathology. The positive symptoms and negative symptoms subscales are validated and often used measures of positive and negative symptoms respectively.

Two studies used PANSS (Essock 2011; Hori 2013).

6.1.4 Cognition

The Brief Assessment of Cognition in Schizophrenia – Japanese version (BACS-J) includes brief assessments of verbal memory, working memory, motor speed, verbal fluency, attention and executive function (Kaneda 2007). The composite score is obtained by averaging all z-scores of the six primary measures.

One study used BACS-J (Hori 2013).

7. Funding sources

All studies reported a public funding.

Excluded studies

We excluded 19 studies based on full-text assessment. The reasons for exclusion were:

- ineligible design (not randomised) (Corsini 1976; DosReis 2016; Sumic 2007);
- ineligible population – no diagnosis of schizophrenia (Verdoorn 2019); acute/agitated, participants with unstable schizophrenia (Greenspan 2004; Lin 2010; Lin 2013; Lin 2017; Stahl 2004; Veraksa 2016);

- ineligible intervention (no polypharmacy reduction) (Baandrup 2010; Fricchione 2012; Honer 2006; NCT02676375; Simpson 2006; Sukegawa 2008; Thompson 2008; Yamanouchi 2015; Yoon 2016).

Studies awaiting assessment

One study in abstract form is awaiting classification. It is unclear if the participants were in a stable phase and there were no usable data (Shakir 2017). We contacted the authors but received no reply.

Ongoing studies

We found no ongoing studies that matched our eligible criteria.

Risk of bias in included studies

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

Risk of bias of outcomes across all studies was 'some concerns' or 'high'. Allocation of participants was described as randomised, but without providing details on how the random sequence was generated. However, generally, there were no baseline differences to suggest problems with the randomisation process. Three studies were not double-blind, and this brought to some concerns or high risk of bias judgements in the domain "Deviations from intended interventions".

Across outcomes, risk of bias was rated as some concerns or high.

Readmission to hospital was at overall high risk of bias, but information was only from one open-label study, with deviations from intended interventions that differed between groups (Essock 2011).

Functioning measured with rating scales was at overall high risk of bias, but information was only from one study with problems of missing outcome data (Repo-Tiihonen 2012).

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Continuation compared to reduction of polypharmacy for people with schizophrenia

Five studies (319 participants) met the inclusion criteria and were included in the review (Borlido 2016; Constantine 2015; Essock 2011; Hori 2013; Repo-Tiihonen 2012). See Summary of findings 1 and forest plots.

Primary outcomes

1. Quality of life

1.1. Clinically important change in quality of life

No studies reported clinically important change in quality of life.

2. Service use

2.1. Readmission to hospital

One study lasting up to six months reported data about readmission to hospital. There was no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (RR 0.75, 95% CI 0.25 to 2.24; 1 RCT, n = 127; very low-certainty evidence; Analysis 1.1).

Since only one study reported data for this outcome, no sensitivity and subgroup analyses were performed.

3. Adverse effects

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

Results show a trend in favour of polypharmacy reduction in the number of participants leaving the study early due to adverse effects (RR 4.37, 95% CI 0.77 to 24.88; 3 RCTs, n = 176; I^2 = 0%, very low-certainty evidence), but the 95% CI did not exclude the possibility of no difference. Results were similar for the time point up to three months (RR 3.00, 95% CI 0.14 to 63.15; 2 RCTs, n = 49) and up to six months (RR 5.24, 95% CI 0.63 to 43.61; 1 RCT, n = 127). Test for subgroup difference revealed no difference between the time points (P = 0.77; Analysis 1.2).

Since fewer than 10 studies provided data for this outcome, no subgroup analyses were performed.

A sensitivity analysis excluding one study at high risk of bias (Essock 2011) did not substantially change the results (RR 3.00, 95% CI 0.14 to 63.15; Analysis 2.1). Excluding one study that did not specify operationalised criteria for diagnosis of schizophrenia (Repo-Tiihonen 2012) did not substantially change the results (RR 5.24, 95% CI 0.63 to 43.61; Analysis 2.2). A sensitivity analysis applying a fixed-effect instead of random-effects model did not change the results (RR 4.37, 95% CI 0.77 to 24.88; Analysis 2.3).

The other pr-planned sensitivity analyses could not be conducted (no study in this outcome had imputed values; check on skewed data does not apply to dichotomous outcomes; no Chinese studies included for this outcome; unclear if reduction of polypharmacy was compensated by an increase in dose of the remaining antipsychotic).

Secondary outcomes

1. Quality of life

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

No studies reported mean endpoint or change score on quality-of-life scale.

2. Service use

2.1. Days in hospital

There were no data for days in hospital.

3. Functioning

3.1. Clinically important change in functioning

There were no data for clinically important change in functioning.

3.2. Mean endpoint on functioning scale

One study lasting up to three months reported data on mean endpoint using the GAF scale. There was no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (MD 0.66, 95% CI −5.89 to 7.21; 1 RCT, n = 12; very low-certainty evidence; Analysis 1.3).

3.3. Mean change score on functioning scale

One study lasting up to three months reported data on mean change score using the GAF scale. There was no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (MD −0.77, 95% CI −2.75 to 1.21; 1 RCT, n = 12; Analysis 1.4).

4. Global state

4.1. Relapse/exacerbations of psychosis

No studies reported elapse/exacerbations of psychosis.

4.2. Clinically important change in global state (improvement)

One study lasting up to three months reported data on clinically important change in global state (improvement). There was no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (RR 1.11, 95% CI 0.58 to 2.14; 1 RCT, n = 28; Analysis 1.5).

4.3. Mean endpoint or change score on global state scale

4.3.1 Mean endpoint score

Two studies lasting up to three months reported data on mean endpoint score using the CGI-I. There was no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (MD 0.32, 95% CI −0.32 to 0.96; I^2 = 0%; 2 RCTs, n = 40; Analysis 1.6).

4.3.2 Mean change score using Clinical Global Impression – Improvement

One study lasting up to three months reported data about this outcome. It was not possible to estimate an effect size, because in one group (polypharmacy reduction) the mean change in CGI-I was 0 (1 RCT, n = 12; Analysis 1.7).

5. Leaving the study early

5.1. Due to any reason – overall acceptability

Participants who continued polypharmacy had a lower probability of leaving the study early in comparison with participants who reduced polypharmacy (RR 0.44, 95% CI 0.29 to 0.68; I^2 = 0%; 5 RCTs, n = 319; low-certainty evidence; Analysis 1.8).

Regarding different time points, at up to three months there was no evidence of a difference between continuation of polypharmacy and reduction to one antipsychotic (RR 0.71, 95% CI 0.13 to 3.81; 2 RCTs, n = 49). At up to six months and up to one year, there was a lower probability of leaving the study early due to any reason in the continuation group compared with the polypharmacy reduction group (up to six months: RR 0.48, 95% CI 0.27 to 0.87; I^2 = 0%; 3 RCTs, n = 270; up to one year: RR 0.41, 95% CI 0.23 to 0.73; 1 RCT, n = 104; Analysis 1.9). Test for subgroup found no differences between the subgroups (P = 0.80).

5.2. Due to inefficacy – overall efficacy

Participants who continued polypharmacy had a lower probability of leaving the study early for inefficacy in comparison with participants who reduced polypharmacy (RR 0.21, 95% CI 0.07 to 0.65; I^2 = 0%; 3 RCTs, n = 201; Analysis 1.10).

Regarding different time points, up to three months results show a trend in the direction of fewer participants leaving the study early due to inefficacy in the continuation group, but the CIs did not exclude the possibility of no difference (RR 0.26, 95% CI 0.03 to 2.14; 1 RCT, n = 25). At up to six months, results showed fewer participants leaving the study early for inefficacy in the continuation group compared with the polypharmacy group (RR 0.19, 95% CI 0.05 to 0.72; I^2 = 0%; 2 RCTs, n = 166). Test for subgroup difference revealed no evidence of a difference between the two time points (P = 0.81).

6. Mental state

6.1. General

6.1.1. Clinically important change in general mental state

No studies reported clinically important change in general mental state.

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

6.1.2.1 Mean endpoint score on Positive and Negative Syndrome Scale

One study presented data for PANSS Total scores at up to three and up to six months. There was no evidence of a difference between continuation and reduction of polypharmacy (up to three months: MD 0.86, 95% CI −5.29 to 7.01; 1 RCT, n = 105; up to six months: MD 3.22, 95% CI −1.48 to 7.92; I^2 = 0%; 2 RCTs, n = 130; Analysis 1.11). Test for subgroup differences no evidence of a difference between the two time points (P = 0.55).

6.1.2.2 Mean endpoint score on Brief Psychiatric Rating Scale

One study provided data for BPRS scores at up to three months. There was no evidence of a difference between continuation and reduction of polypharmacy (MD 0.80, 95% CI −5.30 to 6.90; 1 RCT, n = 35; Analysis 1.12).

6.1.2.3 Mean endpoint score Positive and Negative Syndrome Scale and Brief Psychiatric Rating Scale combined

When combining general mental state scales and across time points, there was no evidence of a difference between groups (SMD 0.16, 95% CI −0.14 to 0.47; I^2 = 0%; 3 RCTs, n = 167; Analysis 1.13).

6.2. Specific

6.2.1. Clinically important change in positive symptoms

No studies reported clinically important change in positive symptoms.

6.2.2. Mean endpoint or change score on positive symptom scale – Positive and Negative Syndrome Scale Positive

One study presented data for mean endpoint or change score on PANSS Positive scale at up to six months. There was no evidence of a difference between the continuation and reduction of polypharmacy (MD 1.40, 95% CI −1.14 to 3.94; 1 RCT, n = 35; Analysis 1.14).

6.2.3. Clinically important change in negative symptoms

No studies reported clinically important change in negative symptoms.

6.2.4. Mean endpoint or change score on in negative symptom scale – Positive and Negative Syndrome Scale Negative

One study lasting up to six months reported data on mean endpoint or change score on PANSS Negative scale. Participants in the reduction of polypharmacy group had lower negative symptoms scores measured with PANSS Negative subscales compared to the continuation group (MD 3.30, 95% CI 1.51 to 5.09; 1 RCT, n = 35; Analysis 1.15).

6.2.5. Clinically important change in depressive symptoms

No studies reported clinically important change in depressive symptoms.

6.2.6. Mean endpoint or change score on depressive symptom scale

No studies reported mean endpoint or change score on depressive symptom scale.

7. Behaviour

7.1. Clinically important change in behaviour (including aggression)

No studies reported clinically important change in behaviour (including aggression).

7.2. Mean endpoint or change score on behaviour scale

No studies reported mean endpoint or change score on behaviour scale.

8. Satisfaction with care

8.1. Clinically important change in satisfaction with care

No studies reported clinically important change in satisfaction with care.

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

No studies reported mean endpoint or change score on satisfaction with care scale.

9. Adverse effect/events

9.1. Adverse effects

9.1.1. At least one adverse effect

One study provided data for at least one adverse effect at up to three months. There was no evidence of a difference between continuation and reduction of polypharmacy (RR 5.00, 95% CI 0.28 to 88.53; 1 RCT, n = 14; very low-certainty evidence; Analysis 1.16).

9.1.2. Weight gain: clinically important change

No studies reported clinically important change in weight.

9.1.2.1 Weight gain – mean body mass index change

One study with duration up to six months reported data on mean body mass index (BMI) change. There was a trend in the direction of a lower BMI in the reduction of polypharmacy group in comparison with the continued polypharmacy group. However, the CIs did not exclude the possibility of no difference between groups (MD 0.78, 95% CI −0.03 to 1.59; 1 RCT, n = 127; Analysis 1.17).

9.1.2.2 Weight gain – endpoint mean weight (kg)

One study reported data about weight at up to three and up to six months. At both timepoints, there was no evidence of a difference between groups (up to three months: MD 3.45, 95% CI −4.08 to 10.98; 1 RCT, n = 104; up to six months: MD 5.94, 95% CI −2.12 to 14.00; 1 RCT, n = 94; Analysis 1.18). Test for subgroup difference revealed no difference between the two time points (P = 0.66).

9.1.3. Incidence of various specific adverse effects

9.1.3.1 Tardive dyskinesia

There was no evidence of a difference in tardive dyskinesia between groups at up to six months (RR 0.93, 95% CI 0.38 to 2.26; 1 RCT, n = 127; Analysis 1.19).

9.1.3.2 At least one extrapyramidal adverse effect

There was no evidence of a difference in participants with at least one extrapyramidal adverse effect at up to six months between groups (RR 1.05, 95% CI 0.51 to 2.16; 1 RCT, n = 127; Analysis 1.20).

9.2. Event: mortality

9.2.1. Overall mortality

One study reported data on overall mortality at up to three months. In both groups, the number of mortality events was 0, therefore an effect size could not be estimated (1 RCT, n = 14; Analysis 1.21).

9.2.2. Due to natural causes

One study reported data on mortality due to natural causes at up to three months. In both groups, the number of mortality events was 0, therefore an effect size could not be estimated (1 RCT, n = 14; Analysis 1.22).

9.2.3. Due to suicide

One study reported data on mortality due to suicide at up to three months. In both groups the number of mortality events was 0, therefore an effect size could not be estimated (1 RCT, n = 14; Analysis 1.23).

10. Medication – mean antipsychotic dose at endpoint

One study reported antipsychotic dose at endpoint at up to six months. After converting the antipsychotic dose to olanzapine equivalents (Gardner 2010), there was no evidence of a difference in doses between continuation and reduction of polypharmacy (MD 2.71, 95% CI −1.60 to 7.02; 1 RCT, n = 35; Analysis 1.24).

11. Cognition

11.1. Clinically important change in cognition

No study reported clinically important change in cognition.

11.2. Mean endpoint or change score on cognition scale

One study reported data on cognition at up to six months. There was no evidence of a difference between continuation and reduction of polypharmacy (MD 0.11, 95% CI −0.22 to 0.44; 1 RCT, n = 35; Analysis 1.25).

Publication bias

All analyses included fewer than 10 studies, so a funnel plot was not created.

DISCUSSION

Summary of main results

We identified five studies with 319 participants who were eligible for inclusion in this review.

Our results showed that, based on low- and very low-certainty evidence, reducing the number of antipsychotics compared to continuing the treatment on multiple antipsychotics has an effect in terms of a higher number of participants leaving the study early, and leaving the study early due to inefficacy. The risk of bias for 'leaving the study early due to any reason' was between 'some concerns' and 'high'.

Reducing the number of antipsychotics was associated with a reduction in negative symptoms (based on only one RCT and 35 participants).

Polypharmacy reduction might be associated with a reduction in the number of participants leaving the study early due to adverse effects, but CIs did not exclude the possibility of no difference.

Polypharmacy reduction might be associated with a reduction in BMI and weight gain, but data from only one study failed to exclude the possibility of no difference.

Polypharmacy reduction might be associated with a reduction in antipsychotic dose, but data from only one study failed to exclude the possibility of no difference.

The data showed no difference between continuation and reduction of polypharmacy regarding the primary outcomes of readmission to hospital and number of participants leaving the study early due to adverse effects.

We were unable to find any data about the primary outcome of quality of life.

In summary, more participants dropped out in general with polypharmacy reduction, and this was mainly due to inefficacy; fewer participants may have dropped out due to adverse effects, in comparison to continuing the treatment with two antipsychotics. Reducing antipsychotic polypharmacy may on one side reduce efficacy, but on the other side reduce the burden connected to adverse effects.

Overall completeness and applicability of evidence

Previous reviews were limited in scope (Tani 2013), investigating assertive or educational interventions directed at clinicians to encourage them to reduce polypharmacy and not focusing on the outcome at the patient level, or in outcomes examined (Matsui 2019).

This review is the first to consider a broad and comprehensive range of outcome measures, applying a comprehensive search and attempting to analyse time points separately.

The findings of this review were limited by the small number of studies and participants; data on many outcomes were based on one study only, and for other outcomes there were no data.

It is likely that our analyses were underpowered and failed to identify possible differences between polypharmacy reduction and continuation. This might be true in particular for the outcomes leaving the study early due to adverse effects, BMI and weight gain, where there was a trend in the direction of a benefit with antipsychotic polypharmacy reduction, but the CIs did not exclude the possibility of no difference between the two intervention strategies.

Moreover, all the identified studies examined reduction from two antipsychotics to one antipsychotic, so that our findings cannot be generalised to situations in which people are receiving three or more drugs.

The certainty of the evidence was mainly very low, indicating that further research is very likely to have an important impact on our confidence in the estimate of effect.

Quality of the evidence

Using GRADE, we assessed the certainty of the evidence to be very low for all the outcomes, with the exception of leaving the study early due to any reason (low certainty).

We evaluated the certainty of the evidence for service use – readmission to hospital as very low. The only study contributing data had a high risk of bias in one domain and a low number of participants. Moreover, CIs did not exclude important benefit or important harm. Therefore, we downgraded one level for risk of bias and two levels for imprecision.

We evaluated the certainty of the evidence for leaving the study early due to adverse effects as very low. One study contributing data had a high risk of bias, information was available for a small number of participants and CIs included both no effect and appreciable benefit for polypharmacy reduction. Therefore, we downgraded one level for risk of bias and two levels for imprecision.

We evaluated the certainty of the evidence for functioning as very low. The only study contributing data had a high risk of bias in one domain and an extremely low number of participants. Moreover, CIs did not exclude important benefit or important harm. Therefore, we downgraded one level for risk of bias and three levels for imprecision.

We evaluated the certainty of the evidence for leaving the study early due to any reason as low. Some studies contributing data had a high risk of bias, and information was available for a small number of participants. Therefore, we downgraded one level for risk of bias and one level for imprecision.

We evaluated the certainty of the evidence for number of participants with at least one adverse effect as very low. The only study contributing data had an extremely low number of participants. Therefore, we downgraded three levels for imprecision.

Potential biases in the review process

We documented and justified modifications to our published protocol in the Differences between protocol and review section (Bighelli 2021b).

The present review has some limitations.

The overall risk of bias for the outcomes investigated and reported in the included studies was of some concerns or high.

Due to a lack of information, we could not perform the preplanned subgroup analyses, and only some of the sensitivity analyses (which were underpowered). Therefore, we could not draw conclusion on possible effect moderators such as degree and speed at which polypharmacy reduction was performed or participants' severity of illness.

Another limitation was that it was not possible to investigate whether reduction in the number of antipsychotics was compensated by increasing the doses of the remaining drugs, since only one study reported mean antipsychotic dose at endpoint.

The effect of dose reduction on multiple outcomes is investigated by a companion review (Bighelli 2021a).

Agreements and disagreements with other studies or reviews

We found one review that compared switching to antipsychotic monotherapy versus staying on antipsychotic polypharmacy in schizophrenia (Matsui 2019). It included six RCTs involving 341 participants. We included five of these studies. The sixth study compared switching to monotherapy with adding aripiprazole, and not with continuing the previous therapy; therefore, we excluded it as it did not fulfil the inclusion criteria of the present review.

Readmission to hospital

Our results are consistent with Matsui 2019, which also found no difference between polypharmacy reduction and continuation for readmission to hospital. Matsui 2019 also provided data on relapse, finding no difference between groups.

Leaving the study early due to adverse effects

Our results are consistent with Matsui 2019, which also found a trend in favour of polypharmacy reduction in number of participants leaving the study early due to adverse effects.

Leaving the study early due to any reason

Our results are consistent with Matsui 2019, which also found in favour of polypharmacy continuation in number of participants leaving the study early due to any reason.

Leaving the study early due to any inefficacy

Our results are partially consistent with Matsui 2019, which found a trend in favour of polypharmacy continuation in number of participants leaving the study early due to inefficacy, while our results show a clear benefit for polypharmacy continuation on this outcome.

Mental state – mean endpoint or change score on general mental state scale

Our results are consistent with Matsui 2019, which also found no substantial difference between polypharmacy continuation and polypharmacy reduction on overall and positive symptoms of schizophrenia. Concerning negative symptoms, Matsui and colleagues found no difference, whereas the present review found an appreciable benefit for polypharmacy reduction, based on only one study.

Cognition – change score Brief Assessment of Cognition in Schizophrenia – Japanese version

Our results are consistent with Matsui 2019, which also found no substantial difference between polypharmacy continuation and polypharmacy reduction on cognition scores.

Matsui 2019 did not report results on other outcomes.

AUTHORS' CONCLUSIONS

Implications for practice

Our patients' representatives collaborators identified the investigation of the possibility to reduce the number of antipsychotics administered to people with schizophrenia as a relevant topic for clinical practice. Unfortunately, results of the present review could only provide underpowered information, based on low- to very low-certainty evidence, so that it is not possible to draw strong conclusions based on the current data.

Some patients may be willing to remain on a well-established combination of antipsychotics, that may work for their individual case. A relationship of trust with the treating clinician remains fundamental to find the optimal individualised therapy.

Implications for research

Future studies should examine the reduction from more than two antipsychotic agents in addition to reducing from two to one antipsychotic.

An individual participant data (IPD) meta-analysis could help to clarify the role of the different potential moderators, such as degree and speed of antipsychotic polypharmacy reduction, initial number of antipsychotics, agents that are withdrawn, severity of illness and other patient characteristics.

A companion review is currently investigating the role of dose reduction on several outcomes (Bighelli 2021b).

In parallel, further research should be conducted on the possible ways to implement polypharmacy reduction, since this remains unclear (Bighelli 2016; Tani 2013).

The topic of polypharmacy reduction, together with antipsychotic dose reduction, will be the focus of a Cochrane living systematic review, currently planned by the same team of review authors. (Living systematic reviews offer a new approach to review updating in which the review is continually updated, incorporating relevant new evidence as it becomes available.)

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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): Anne Lawson, Copy Edit Support, Cochrane.
- Information Specialist (search strategy and search results): Farhad Shokraneh, Systematic Review Consultants.
- Peer-reviewers* (provided comments and recommended an editorial decision): Puti Retasya Novira, The University of Melbourne, Budi Gittanaya Anindyanari, The 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]*

Borlido 2016

Study characteristics	
Methods	Study design: randomised controlled trial
	Study grouping: parallel group
	Additional medication allowed: yes
	Compliance measured: yes
	Duration in weeks: 12
	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: no information

Borlido 2016 *(Continued)*

	Number of sites: 1 academic site
Participants	Diagnosis: schizophrenia or schizoaffective disorder Diagnostic criteria: DSM-IV Current clinical state: no information Definition of stability: participants taking 2 antipsychotic drugs for ≥ 30 days Inclusion criteria: male or female outpatients or inpatients aged ≥ 18 years, with schizophrenia or schizoaffective disorder treated with 2 antipsychotic drugs for ≥ 30 days Exclusion criteria: history of depot antipsychotic treatment within 6 months unless the depot antipsychotic was considered the main antipsychotic drug, prescribing history reviewed by a pharmacist; prospective participants with evidence of ongoing cross-titration of antipsychotic medication as part of switching agents; use of prescribed antipsychotics on an as-needed basis Setting: inpatient and outpatient n = 35 Gender: 24 men, 11 women Median age: 47.5 years Continuation arm Participants total: 17, men: 10, women: 7 Median age: 48 years Baseline BPRS 35.7 (SD 9.3) Median duration of illness: 25 years Duration current episode: NA Median weight at baseline: 85 kg Height: NA BMI: NA Median time in study: 73 days Reduction arm Participants total: 18, men: 14, women: 4 Median age: 47 years Baseline BPRS: 32.9 (SD 9.2) Median duration of illness: 28 years Duration current episode: NA Median weight at baseline: 85 kg Height: NA BMI: NA Median time in study: 60 days
Interventions	1. Continuation. n = 17

Borlido 2016 *(Continued)*

	Antipsychotics used: lozapine, quetiapine, olanzapine, risperidone, haloperidol, pipotiazine palmitate, loxapine Mean dose: 241.02 (SD 127.72) mg (not specified in the study, but probably chlorpromazine equivalents). Description dose scheme: continuation of regular regimen of prescribed primary antipsychotic and fixed dose of secondary antipsychotic. The treating physician identified the primary antipsychotic, except for clozapine and depot antipsychotics in which case it was assumed that they represented the primary antipsychotic. 2. Reduction. n = 18 Antipsychotics used: clozapine, quetiapine, olanzapine, risperidone, flupentixol decanoate, haloperidol decanoate, fluphenazine decanoate, haloperidol, zuclopenthixol decanoate, perphenazine, methotrimeprazine, loxapine Mean dose: 328.74 (SD 201.94) mg (not specified in the study, but probably chlorpromazine equivalents). Description dose scheme: continuation of primary antipsychotic and placebo. The treating physician identified the primary antipsychotic, except for clozapine and depot antipsychotics in which case it was assumed that they represented the primary antipsychotic. Initial number of antipsychotics: 2 Degree of antipsychotic polypharmacy reduction: 1 antipsychotic Speed of antipsychotic polypharmacy reduction: no information Reduction of polypharmacy compensated by an increase in dose in the remaining antipsychotics: yes (quote: "the present investigation permitted treating physicians to increase the dose of the primary antipsychotic in such circumstances, although, in fact, they seldom did so.")
Outcomes	Adverse effects – leaving the study early due to adverse effects – overall tolerability (< 3 months) Global state – clinically important change in global state (improvement) (< 3 months) Global state: mean endpoint score CGI-I (< 3 months) Leaving the study early due to any reason – overall acceptability (< 3 months) Leaving the study early due to inefficacy – overall efficacy (< 3 months) Mental state – general: mean endpoint score on BPRS total (< 3 months)
Identification	Sponsorship source: Canadian Psychiatric Research Foundation (CPRF) now referred to as Healthy Minds Country: Canada Trial registration ID: NCT00493233 Number of countries: 1
Notes	Authors offered to share additional data, but then did not reply to specific request.

Constantine 2015

Study characteristics

Constantine 2015 *(Continued)*

Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes Compliance measured: no Duration in weeks: 52 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: m-ITT Number of sites: 7
Participants	Diagnosis: schizophrenia or schizoaffective disorder Diagnostic criteria: DSM-IV-TR Current clinical state: chronically ill Definition of stability: recruits stable on this medication regimen, as indicated by the lack of a psychiatric hospitalisation or emergency department visit in the previous 90 days, and the treating physician's certification that there were no plans to change the antipsychotic regimen. Inclusion criteria: people with schizophrenia or schizoaffective disorder (DSM-IV-TR) who had been receiving 2 antipsychotic medications for ≥ 90 days. Recruits were stable on this medication regimen, as indicated by the lack of a psychiatric hospitalisation or emergency department visit in the previous 90 days, and the treating physician's certification that there were no plans to change the antipsychotic regimen. Aged 18–64 years, enrolled in Florida's Medicaid programme, and with a stable residence or case manager (or both) who could contact the participant during the study. Exclusion criteria: incarceration, legal incompetence, co-occurring developmental disability, pregnancy, general medical condition that in the opinion of the treating physician made it unsafe for the patient to participate in the study, or having had ≥ 2 unsuccessful trials of antipsychotic monotherapy or clozapine of sufficient durations and doses as defined by the Florida Medicaid Drug Therapy Management Program (2011) guidelines for adults within the prior 3 years. Setting: outpatient n = 104 Gender: 42 men, 48 women (participants with gender given) Mean age: 45.5 years Continuation arm Participants total: 52, men: 21, women: 26 Mean age: 47.0 (SD 11.1) years PANSS baseline: 66.6 (SD 19.7) Duration of illness: NA Weight at baseline: NA Height: NA

Constantine 2015 *(Continued)*

	BMI: 31.3 (SD 7.3) Mean time in study: NA Reduction arm Participants total: 52, men: 21, women: 22 Mean age: 43.9 (SD 9.6) years PANSS baseline: 71.3 (SD 18.6) years Duration of illness: NA Weight at baseline: NA Height: NA BMI: 33.6 (SD 7.4) Mean time in study: NA
Interventions	1. Continuation. n = 52 Antipsychotics used: clozapine, long-acting injectables and others Mean dose: 41.2 (SD 18.5) (olanzapine equivalent daily doses) Description dose scheme: participants remained on the 2 antipsychotic medications they were currently receiving but treating clinicians had flexibility with dosing. 2. Reduction. n = 52 Antipsychotics used: clozapine, long-acting injectables and others Mean dose: 32.9 (SD 10.7) (olanzapine equivalent daily doses) Description dose scheme: switch participants were required to switch from the 2 antipsychotics they were currently receiving to 1 of the 2 within 60 days of baseline assessments. Physicians were free to choose which of the 2 antipsychotics to continue and at what dose, except that participants currently on treatment with an injectable antipsychotic or those receiving clozapine were required to remain on these medications. Initial number of antipsychotics: 2 Degree of antipsychotic polypharmacy reduction: 1 antipsychotic Speed of antipsychotic polypharmacy reduction: gradual (within 60 days) Reduction of polypharmacy compensated by an increase in dose in the remaining antipsychotics: no (quote: "physicians were free to augment treatment of both switch and stay participants with psychotherapeutic medications other than antipsychotics").
Outcomes	Leaving the study early due to any reason – overall acceptability (< 6 months) Leaving the study early due to any reason – overall acceptability (< 12 months)
Identification	Sponsorship source: Florida Agency for Health Care Administration Country: USA Trial registration ID: NA
Notes	Authors contacted to request additional data, but received no reply.

Essock 2011

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes Compliance measured: yes *(from study authors)* Duration in weeks: 26 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 Number of sites: 19
Participants	Diagnosis: schizophrenia or schizoaffective disorder Diagnostic criteria: DSM-IV Current clinical state: partial remission Definition of stability: participants were currently taking 2 prescribed antipsychotic medications, documented by a plasma level > 0 for each antipsychotic. No psychiatric hospitalisation or use of crisis services in the 3 months prior to study entry. Inclusion criteria: aged ≥ 18 years with a diagnosis of schizophrenia or schizoaffective disorder (according to the SCID-P) and were currently taking 2 prescribed antipsychotic medications, documented by a plasma level > 0 for each antipsychotic. Additional inclusion criteria were persistent psychopathology or significant adverse effects; willingness to consider a change in antipsychotic medication; continuing access to medications without financial burden; and ≥ 1 clinical visit every 3 months for the past 6 months. Exclusion criteria: symptoms or adverse effects so severe that a medication change was indicated immediately; having an exacerbation of psychiatric symptoms within the past 3 months resulting in significant intervention, such as having spent ≥ 1 nights in psychiatric hospitalisation or having received services from a crisis intervention programme or psychiatric emergency department; living in a skilled nursing facility as a result of a physical condition or disability; having pending criminal charges; currently pregnant or breastfeeding; and currently receiving ≥ 3 antipsychotic medications for ongoing daily administration. Setting: outpatients (from study authors) n = 127 Gender: 84 men, 43 women Age: 47 years (from study authors) Continuation arm Participants total: 62, men: 34, women: 28 Mean age: 46.17 years (from study authors)

Essock 2011 *(Continued)*

	PANSS baseline: 72.4 (SD 14.3) Duration of illness: NA Weight at baseline: 91.98 kg (from study authors) Height: 170.4 cm (from study authors) BMI: 31.9 Mean time in study: NA Reduction arm Participants total: 65, men: 50, women: 15 Mean age: 47.80 years (from study authors) PANSS baseline: 70.9 (SD 14.5) Duration if illness: NA Weight at baseline: 91.89 kg (from study authors) Height: 171.7 cm (from study authors) BMI: 31.4 Mean time in study: NA
Interventions	1. Continuation. n = 62 Antipsychotics used: risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole Mean dose: 325.8 (SD 184.4) (mg chlorpromazine equivalents), corresponding to olanzapine 10.85 mg equivalents Description dose scheme: participants continued taking medication prescribed at study entry: 1. either long-acting injectable haloperidol or fluphenazine, OR 2. 2 antipsychotic medications which may have included a combination of the following: risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole or conventional (typical) antipsychotic medications. From study authors: for 6 months, unless clinically contraindicated. Dosing could be adjusted by clinical judgement. Use of concomitant psychotropic medications other than antipsychotics not restricted. 2. Reduction. n = 65 Antipsychotics used: risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole Mean dose: 387.8 (SD 296.7) (mg chlorpromazine equivalents), corresponding to olanzapine 12.8 mg equivalents. Description dose scheme: participants changed medications from medication prescribed at study entry, either: 1. long-acting injectable risperidone, OR 2. 1 of the 2 antipsychotic medications prescribed at baseline which may have included: risperidone, olanzapine, ziprasidone, quetiapine, aripiprazole, or conventional (typical) antipsychotic medications. From study authors: for 6 months, unless clinically contraindicated, dosing could be adjusted by clinical judgement. Use of concomitant psychotropic medications other than antipsychotics not restricted. Participant and physician decided together which of the 2 antipsychotics to discontinue. Study protocol specified that the antipsychotic chosen to be discontinued be stopped within 30 days. Initial number of antipsychotic: 2 Degree of antipsychotic polypharmacy reduction: 1 antipsychotic Speed of antipsychotic polypharmacy reduction: gradual (within 30 days)

Essock 2011 *(Continued)*

	Reduction of polypharmacy compensated by an increase in dose in the remaining antipsychotics: medication dosing not constrained by study protocol; instead, prescribers used their clinical judgement to adjust dosages as best for participants within the assigned treatment condition.
Outcomes	Service use – readmission to hospital (< 6 months) Adverse effects – leaving the study early due to adverse effects – overall tolerability (< 6 months) Leaving the study early due to any reason – overall acceptability (< 6 months) Leaving the study early due to inefficacy – overall efficacy (< 6 months) Mental state – general: mean endpoint score on PANSS Total (< 3 months) Mental state – general: mean endpoint score on PANSS Total (< 6 months) Adverse effects – weight gain – mean BMI change (< 6 months) Adverse effects – weight gain – mean weight (kg) (< 3 months) Adverse effects – weight gain – mean weight (kg) (< 6 months) Adverse effects – specific: tardive dyskinesia (< 6 months) Adverse effects – specific: ≥ 1 EPS (< 6 months)
Identification	**Sponsorship source:** supported by NIMH grant MH59312 (to Dr Essock) and by NIMH contract MH900001 (to Dr Stroup) **Country:** USA **Trial registration ID:** NCT00044655
Notes	Authors contacted, and provided additional data (see above for details).

Hori 2013

Study characteristics	
Methods	Study design: randomised controlled trial Study grouping: parallel group Additional medication allowed: yes Compliance measured: no Duration in weeks: 24 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: completer analysis Number of sites: 1 (academic)
Participants	Diagnosis term: schizophrenia

Hori 2013 *(Continued)*

Diagnostic criteria: DSM-IV-TR

Current clinical state: chronically ill, partial remission

Definition of stability: chronic illness without acute exacerbation; continuing a stable dose of both antipsychotics ≥ 3 months

Inclusion criteria: outpatients with schizophrenia diagnosed using DSM-IV-TR at University of Occupational and Environmental Health in Japan; aged 20–60 years; presence of chronic illness without acute exacerbation; continuing a stable dose of both antipsychotics ≥ 3 months.

Exclusion criteria: comorbid central nervous system disorder; severe psychotic symptoms; meeting DSM-IV criteria for alcohol or other substance dependence; meeting DMS-IV criteria for mental retardation; taking antidepressants; treatment with electroconvulsive therapy in 6 months preceding study; inability to understand study protocol.

Setting: outpatient

n = 39

Gender: 19 men, 16 women (participants with gender given)

Age: 36.4 years

Continuation arm

Participants total: 19, men: 10, women: 8

Mean age: 36.1 years

PANSS baseline: 69.1 (SD 14.1)

Duration of illness: 12.6

Duration of current episode in days: NA

Weight at baseline: NA

Height: NA

BMI: NA

Mean time in study: NA

Reduction arm

Participants total: 20, men: 9, women: 8

Mean age: 36.6 years

PANSS baseline: 65.3 (SD 8.8)

Duration of illness: 11.9

Duration of current episode in days: NA

Weight at baseline: NA

Height: NA

BMI: NA

Mean time in study: NA

Interventions	1. Continuation. n = 19

Hori 2013 *(Continued)*

	Antipsychotics used: first-generation antipsychotics, olanzapine, risperidone, quetiapine, aripiprazole, blonanserin and others Mean dose: 635.0 (SD 204.2) (mg/day chlorpromazine equivalents), corresponding to olanzapine equivalents 20.96 mg/day. Description dose scheme: participants continued with their assigned medication regimen for 24 weeks unless treatment was clinically contraindicated. 2. Reduction. n = 20 Antipsychotics used: first-generation antipsychotics, olanzapine, risperidone, quetiapine, aripiprazole, blonanserin and others Mean dose: 617.9 (SD 186.0) (mg/day chlorpromazine equivalents), corresponding to olanzapine equivalents 20.39 mg/day. Description dose scheme: with participants administered a first-generation and a second-generation antipsychotic drug, the first-generation antipsychotic drug was tapered off. With participants administered 2 second-generation antipsychotic drugs, the drug with smaller amount (chlorpromazine-equivalent) was tapered off. Tapering off within 12 weeks. Initial number of antipsychotics: 2 Degree of antipsychotic polypharmacy reduction: 1 antipsychotic Speed of antipsychotic polypharmacy reduction: gradual (within 12 weeks) Reduction of polypharmacy compensated by an increase in dose in the remaining antipsychotics: yes. Doses of antipsychotic drug in switching group were allowed to change flexibly, depending on the clinical symptoms.
Outcomes	Leaving the study early due to any reason – overall acceptability (< 6 months) Leaving the study early due to inefficacy – overall efficacy (< 6 months) Mental state – general: mean endpoint score on PANSS Total (< 6 months) Mental state – specific: mean endpoint score on PANSS Positive (< 6 months) Mental state – specific: mean endpoint score on PANSS Negative (< 6 months) Medication – mean antipsychotic dose at endpoint (< 6 months) Cognition – BACS-J change score (higher scores = better outcome) (< 6 months)
Identification	Sponsorship source: Ministry of Education, Culture, Sports, Science and Technology Japan (No. 24791246) Country: Japan Trial registration ID: NA
Notes	Authors contacted and declared themselves available in sharing additional data, but then did not reply to specific request.

Repo-Tiihonen 2012

Study characteristics	
Methods	Study design: randomised controlled trial

Repo-Tiihonen 2012 *(Continued)*

	Study grouping: cross-over (only first phase used) Description study phases: randomised in 2 groups. In group A, olanzapine was gradually changed to placebo over 8 weeks and group B received olanzapine add-on. Olanzapine and placebo were dispensed in similar gelatine capsules that were formulated for this trial. After the 8-week period, the 2 groups crossed over and treatments repeated Additional medication allowed: yes (benzodiazepines) Compliance measured: no information Duration in weeks: 12 Number of study arms: 2 Number of drugs used: 2 Randomisation assumed from double-blind: no Type of blinding: double-blind Type of data analysis for overall efficacy: m-ITT Number of sites: 1 academic site
Participants	Diagnosis: schizophrenia Diagnostic criteria: NA Current clinical state: chronically ill, treatment resistant Definition of stability: unchanged psychotropic medication during the last 2 months Inclusion criteria: aged ≥ 18 years; competence to understand the meaning of study and give informed consent; insufficient response to clozapine–olanzapine therapy; unchanged psychotropic medication during last 2 months; no concurrent pregnancy. Insufficient response to medication considered when the GAF 12 was < 25 and, on clinical treatment-resistance reported by each participant's own physician. Exclusion criteria: NA Setting: inpatients (forensic psychiatry hospital) n = 14 Gender: 11 men, 1 woman (participants with gender given) Mean age: 47.58 years Continuation arm Participants total: 7, men: 4; women 3 Mean age: 50 years PANSS baseline: NA Duration of illness: NA Weight at baseline: NA Height: NA BMI: NA Mean time in study: NA Reduction arm

Repo-Tiihonen 2012 *(Continued)*

	Participants total: 7, men: 7 Mean age: 44.14 years PANSS baseline: NA Duration of illness: NA Weight at baseline: NA Height: NA BMI: NA Mean time in study: NA
Interventions	1. Continuation. n = 7 Antipsychotics used: olanzapine, clozapine. Dose: NA Description dose scheme: in addition to clozapine, participants received their normal dose of olanzapine (same as on hospital ward) for 12 weeks 2. Reduction. n = 7 Antipsychotics used: olanzapine, clozapine Dose: NA Description dose scheme: in addition to clozapine, participants received a decreasing dose of olanzapine for 4 weeks, then placebo for 8 weeks Initial number of antipsychotics: 2 Degree of antipsychotic polypharmacy reduction: 1 antipsychotic Speed of antipsychotic polypharmacy reduction: gradual (olanzapine gradually changed to placebo over 8 weeks) Reduction of polypharmacy compensated by an increase in dose in the remaining antipsychotics: unclear
Outcomes	Adverse effects – leaving the study early due to adverse effects – overall tolerability (< 3 months) Global state: mean endpoint score CGI-I (< 3 months) Global state: mean change score CGI-I (< 3 months) Leaving the study early due to any reason – overall acceptability (< 3 months) Adverse events: overall mortality (< 3 months) Adverse events – mortality due to natural causes (< 3 months) Adverse events – mortality due to suicide (< 3 months)
Identification	**Sponsorship source:** annual EVO Financing (special government subsidies from the Ministry of Health and Welfare, Finland) **Country:** Finland **Trial registration ID:** NCT00918021

Repo-Tiihonen 2012 *(Continued)*

Notes	Authors contacted, and replied they do not have additional data.

BPRS: Brief Psychiatric Rating Scale; BMI: body mass index; CGI-I: Clinical Global Impression – Improvement; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition; DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision; GAF: Global Assessment of Functioning; ITT: intention to treat; mITT: modified intention to treat; n: number of participants; NA: not available; SCID-P: Structured Clinical Interview for DSM-IV Axis I Disorders-Patient Edition; SD: standard deviation.

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

Study	Reason for exclusion
Baandrup 2010	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction (educational intervention for practitioners)
Corsini 1976	Design: not randomised
DosReis 2016	Design: not randomised
Fricchione 2012	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction
Greenspan 2004	Design: randomised Participants: not stable schizophrenia (acute exacerbation, agitated)
Honer 2006	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction (dose augmentation)
Lin 2010	Design: randomised Population: not stable schizophrenia (acute exacerbation)
Lin 2013	Design: randomised Population: not stable schizophrenia
Lin 2017	Design: randomised Population: not stable schizophrenia (acute exacerbation)
NCT02676375	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction
Simpson 2006	Design: randomised Participants: people with stable schizophrenia

Study	Reason for exclusion
	Intervention: no polypharmacy reduction (comparison of different doses)
Stahl 2004	Design: randomised Population: not stable schizophrenia (acute exacerbation)
Sukegawa 2008	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction (combined dose reduction and polypharmacy reduction)
Sumic 2007	Design: not randomised
Thompson 2008	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction
Veraksa 2016	Design: randomised Population: not 80% schizophrenia, not stable schizophrenia
Verdoorn 2019	Design: randomised Population: no schizophrenia
Yamanouchi 2015	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction (combined dose reduction and polypharmacy reduction)
Yoon 2016	Design: randomised Participants: people with stable schizophrenia Intervention: no polypharmacy reduction (switching to another antipsychotic)

Characteristics of studies awaiting classification *[ordered by study ID]*

Shakir 2017

Methods	Randomised open-label trial
Participants	Diagnosed with schizophrenia; treatment with a typical and atypical antipsychotics
Interventions	50% of participants were tapered to 1 antipsychotic 50% received their usual treatment regimen
Outcomes	Relapse, movement disorder, weight, quality of life
Notes	Only abstract available. We contacted the authors but received no reply.

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

	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 At < 6 months						
Essock 2011	~	✗	✓	✓	✓	✗

Risk of bias for analysis 1.2 Adverse effects – leaving the study early due to adverse effects – overall tolerability

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 At < 3 months						
Borlido 2016	~	~	✓	✓	✓	~
Repo-Tiihonen 2012	~	✓	✓	✓	✓	~
Subgroup 1.2.2 At < 6 months						
Essock 2011	~	✗	✓	✓	✓	✗

Risk of bias for analysis 1.3 Functioning – mean endpoint score using Global Assessment of Functioning (high = good)

	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 At < 3 months						
Repo-Tiihonen 2012	~	✓	✗	✓	✓	✗

Risk of bias for analysis 1.4 Functioning – mean change score using Global Assessment of Functioning (high = good)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 At < 3 months						
Repo-Tiihonen 2012	~	✓	✗	✓	✓	✗

Risk of bias for analysis 1.8 Leaving the study early due to any reason – overall acceptability (totals of time points combined)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Borlido 2016	~	~	✓	✓	✓	~
Constantine 2015	~	✗	✓	✓	✓	✗
Essock 2011	~	✗	✓	✓	✓	✗
Hori 2013	~	~	✓	✓	✓	~
Repo-Tiihonen 2012	~	✓	✓	✓	✓	~

Risk of bias for analysis 1.9 Leaving the study early due to any reason – overall acceptability (subtotals only)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.9.1 At < 3 months						
Borlido 2016	~	~	✓	✓	✓	~
Repo-Tiihonen 2012	~	✓	✓	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.9.2 At < 6 months						
Constantine 2015	~	✗	✓	✓	✓	✗
Essock 2011	~	✗	✓	✓	✓	✗
Hori 2013	~	~	✓	✓	✓	~
Subgroup 1.9.3 At < 1 year						
Constantine 2015	~	✗	✓	✓	✓	✗

Risk of bias for analysis 1.16 Adverse effects: ≥ 1 adverse effect

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.16.1 At < 3 months						
Repo-Tiihonen 2012	~	✓	✓	✓	✓	~

Risk of bias for analysis 2.1 Excluding high risk of bias studies

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 At < 3 months						
Borlido 2016	~	~	✓	✓	✓	~
Repo-Tiihonen 2012	~	✓	✓	✓	✓	~

Risk of bias for analysis 2.2 Excluding non-operationalised diagnosis criteria

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.2.1 At < 3 months						
Borlido 2016	~	~	✓	✓	✓	~
Subgroup 2.2.2 At < 6 months						
Essock 2011	~	✗	✓	✓	✓	✗

Risk of bias for analysis 2.3 Fixed-effect vs random-effects

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.3.1 At < 3 months						
Borlido 2016	~	~	✓	✓	✓	~
Repo-Tiihonen 2012	~	✓	✓	✓	✓	~
Subgroup 2.3.2 At < 6 months						
Essock 2011	~	✗	✓	✓	✓	✗

DATA AND ANALYSES

Comparison 1. Polypharmacy continuation versus polypharmacy reduction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Service use – readmission to hospital	1	127	Risk Ratio (IV, Random, 95% CI)	0.75 [0.25, 2.24]
1.1.1 At < 6 months	1	127	Risk Ratio (IV, Random, 95% CI)	0.75 [0.25, 2.24]

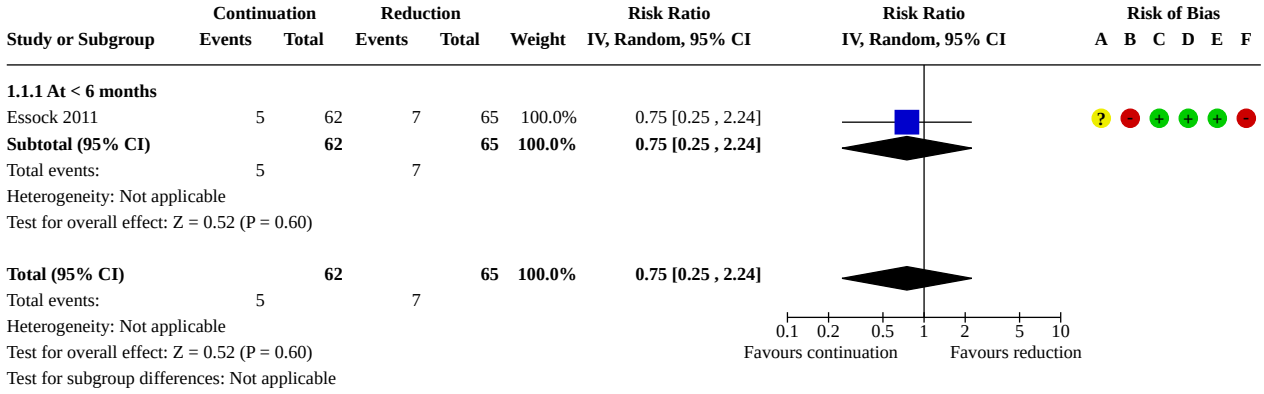
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.2 Adverse effects – leaving the study early due to adverse effects – overall tolerability	3	176	Risk Ratio (IV, Random, 95% CI)	4.37 [0.77, 24.88]
1.2.1 At < 3 months	2	49	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 63.15]
1.2.2 At < 6 months	1	127	Risk Ratio (IV, Random, 95% CI)	5.24 [0.63, 43.61]
1.3 Functioning – mean endpoint score using Global Assessment of Functioning (high = good)	1	12	Mean Difference (IV, Random, 95% CI)	0.66 [-5.89, 7.21]
1.3.1 At < 3 months	1	12	Mean Difference (IV, Random, 95% CI)	0.66 [-5.89, 7.21]
1.4 Functioning – mean change score using Global Assessment of Functioning (high = good)	1	12	Mean Difference (IV, Random, 95% CI)	-0.77 [-2.75, 1.21]
1.4.1 At < 3 months	1	12	Mean Difference (IV, Random, 95% CI)	-0.77 [-2.75, 1.21]
1.5 Global state – clinically important change in global state (improvement)	1	28	Risk Ratio (IV, Random, 95% CI)	1.11 [0.58, 2.14]
1.5.1 At < 3 months	1	28	Risk Ratio (IV, Random, 95% CI)	1.11 [0.58, 2.14]
1.6 Global state: mean endpoint score using Clinical Global Impression – Improvement (high = poor)	2	40	Mean Difference (IV, Random, 95% CI)	0.32 [-0.32, 0.96]
1.6.1 At < 3 months	2	40	Mean Difference (IV, Random, 95% CI)	0.32 [-0.32, 0.96]
1.7 Global state: mean change score Clinical Global Impression – Improvement (high = poor)	1	12	Mean Difference (IV, Random, 95% CI)	Not estimable
1.7.1 At < 3 months	1	12	Mean Difference (IV, Random, 95% CI)	Not estimable
1.8 Leaving the study early due to any reason – overall acceptability (totals of time points combined)	5	319	Risk Ratio (IV, Random, 95% CI)	0.44 [0.29, 0.68]
1.9 Leaving the study early due to any reason – overall acceptability (subtotals only)	5		Risk Ratio (IV, Random, 95% CI)	Subtotals only
1.9.1 At < 3 months	2	49	Risk Ratio (IV, Random, 95% CI)	0.71 [0.13, 3.81]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.2 At < 6 months	3	270	Risk Ratio (IV, Random, 95% CI)	0.48 [0.27, 0.87]
1.9.3 At < 1 year	1	104	Risk Ratio (IV, Random, 95% CI)	0.41 [0.23, 0.73]
1.10 Leaving the study early due to inefficacy – overall efficacy	3	201	Risk Ratio (IV, Random, 95% CI)	0.21 [0.07, 0.65]
1.10.1 At < 3 months	1	35	Risk Ratio (IV, Random, 95% CI)	0.26 [0.03, 2.14]
1.10.2 At < 6 months	2	166	Risk Ratio (IV, Random, 95% CI)	0.19 [0.05, 0.72]
1.11 Mental state – general: mean endpoint score on Positive and Negative Syndrome Scale Total (high = poor)	2		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.11.1 At < 3 months	1	105	Mean Difference (IV, Random, 95% CI)	0.86 [-5.29, 7.01]
1.11.2 At < 6 months	2	130	Mean Difference (IV, Random, 95% CI)	3.22 [-1.48, 7.92]
1.12 Mental state – general: mean endpoint score on Brief Psychiatric Rating Scale Total (high = poor)	1	35	Mean Difference (IV, Random, 95% CI)	0.80 [-5.30, 6.90]
1.12.1 At < 3 months	1	35	Mean Difference (IV, Random, 95% CI)	0.80 [-5.30, 6.90]
1.13 Mental state – general: mean endpoint score on Positive and Negative Syndrome Scale Total and Brief Psychiatric Rating Scale Total combined (high = poor) (time points combined)	3	167	Std. Mean Difference (IV, Random, 95% CI)	0.16 [-0.14, 0.47]
1.14 Mental state – specific: mean endpoint score on Positive and Negative Syndrome Scale Positive (high = poor)	1	35	Mean Difference (IV, Random, 95% CI)	1.40 [-1.14, 3.94]
1.14.1 At < 6 months	1	35	Mean Difference (IV, Random, 95% CI)	1.40 [-1.14, 3.94]
1.15 Mental state – specific: mean endpoint score on Positive and Negative Syndrome Scale Negative (high = poor)	1	35	Mean Difference (IV, Random, 95% CI)	3.30 [1.51, 5.09]
1.15.1 At < 6 months	1	35	Mean Difference (IV, Random, 95% CI)	3.30 [1.51, 5.09]
1.16 Adverse effects: ≥ 1 adverse effect	1	14	Risk Ratio (IV, Random, 95% CI)	5.00 [0.28, 88.53]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.16.1 At < 3 months	1	14	Risk Ratio (IV, Random, 95% CI)	5.00 [0.28, 88.53]
1.17 Adverse effects – weight gain – mean body mass index change	1	127	Mean Difference (IV, Random, 95% CI)	0.78 [-0.03, 1.59]
1.17.1 At < 6 months	1	127	Mean Difference (IV, Random, 95% CI)	0.78 [-0.03, 1.59]
1.18 Adverse effects – weight gain – endpoint mean weight (kg)	1		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.18.1 At < 3 months	1	104	Mean Difference (IV, Random, 95% CI)	3.45 [-4.08, 10.98]
1.18.2 At < 6 months	1	94	Mean Difference (IV, Random, 95% CI)	5.94 [-2.12, 14.00]
1.19 Adverse effects – specific: tardive dyskinesia	1	127	Risk Ratio (IV, Random, 95% CI)	0.93 [0.38, 2.26]
1.19.1 At < 6 months	1	127	Risk Ratio (IV, Random, 95% CI)	0.93 [0.38, 2.26]
1.20 Adverse effects – specific: ≥ 1 extrapyramidal adverse effect	1	127	Risk Ratio (IV, Random, 95% CI)	1.05 [0.51, 2.16]
1.20.1 At < 6 months	1	127	Risk Ratio (IV, Random, 95% CI)	1.05 [0.51, 2.16]
1.21 Adverse events: overall mortality	1	14	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.21.1 At < 3 months	1	14	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.22 Adverse events – mortality due to natural causes	1	14	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.22.1 At < 3 months	1	14	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.23 Adverse events – mortality due to suicide	1	14	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.23.1 At < 3 months	1	14	Risk Ratio (IV, Random, 95% CI)	Not estimable
1.24 Medication – mean antipsychotic dose at endpoint (olanzapine equivalents)	1	35	Mean Difference (IV, Random, 95% CI)	2.71 [-1.60, 7.02]
1.24.1 At < 6 months	1	35	Mean Difference (IV, Random, 95% CI)	2.71 [-1.60, 7.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.25 Cognition – change score using Brief Assessment of Cognition in Schizophrenia – Japanese version (high = good)	1	35	Mean Difference (IV, Random, 95% CI)	0.11 [-0.22, 0.44]
1.25.1 At < 6 months	1	35	Mean Difference (IV, Random, 95% CI)	0.11 [-0.22, 0.44]

Analysis 1.1. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 1: Service use – readmission to hospital

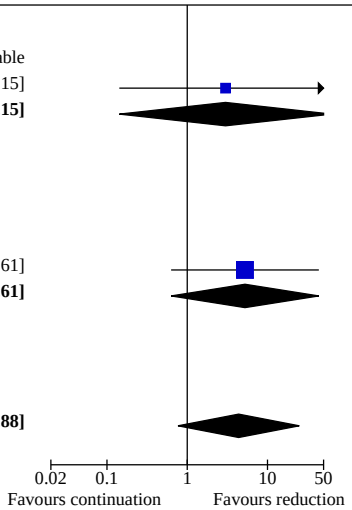


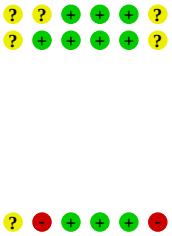
Risk of bias legend

(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: Polypharmacy continuation versus polypharmacy reduction, Outcome 2: Adverse effects – leaving the study early due to adverse effects – overall tolerability

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
1.2.1 At < 3 months						
Borlido 2016	0	17	0	18		Not estimable
Repo-Tiihonen 2012	1	7	0	7	32.6%	3.00 [0.14 , 63.15]
Subtotal (95% CI)		**24**		**25**	**32.6%**	**3.00 [0.14 , 63.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
1.2.2 At < 6 months						
Essock 2011	5	62	1	65	67.4%	5.24 [0.63 , 43.61]
Subtotal (95% CI)		**62**		**65**	**67.4%**	**5.24 [0.63 , 43.61]**
Total events:	5		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)		**86**		**90**	**100.0%**	**4.37 [0.77 , 24.88]**
Total events:	6		1			
Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.66 (P = 0.10)						
Test for subgroup differences: Chi² = 0.09, df = 1 (P = 0.77), I² = 0%						

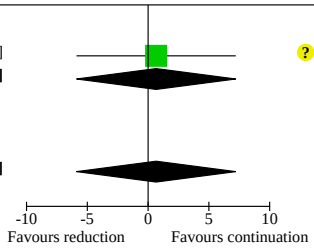




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 3: Functioning – mean endpoint score using Global Assessment of Functioning (high = good)

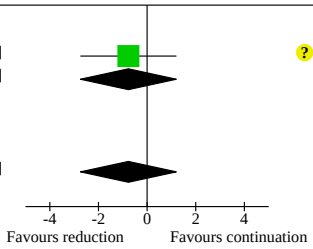
Study or Subgroup	Continuation Mean	Continuation SD	Continuation Total	Reduction Mean	Reduction SD	Reduction Total	Weight	Mean Difference IV, Random, 95% CI
1.3.1 At < 3 months								
Repo-Tiihonen 2012	18.8	7.09	5	18.14	2.79	7	100.0%	0.66 [-5.89 , 7.21]
Subtotal (95% CI)			**5**			**7**	**100.0%**	**0.66 [-5.89 , 7.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
Total (95% CI)			**5**			**7**	**100.0%**	**0.66 [-5.89 , 7.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.20 (P = 0.84)								
Test for subgroup differences: Not applicable								

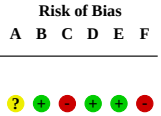


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 4: Functioning – mean change score using Global Assessment of Functioning (high = good)

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.4.1 At < 3 months								
Repo-Tiihonen 2012	-0.2	1.79	5	0.57	1.62	7	100.0%	-0.77 [-2.75 , 1.21]
Subtotal (95% CI)			**5**			**7**	**100.0%**	**-0.77 [-2.75 , 1.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.76 (P = 0.44)								
Total (95% CI)			**5**			**7**	**100.0%**	**-0.77 [-2.75 , 1.21]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.76 (P = 0.44)								
Test for subgroup differences: Not applicable								

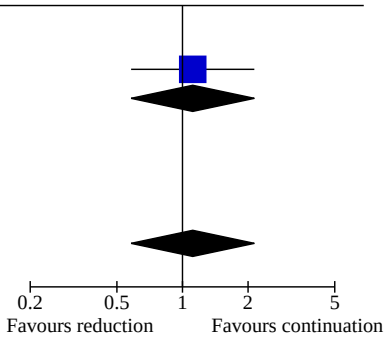




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

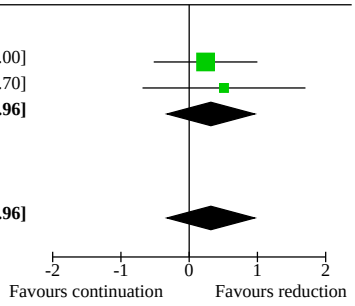
Analysis 1.5. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 5: Global state – clinically important change in global state (improvement)

Study or Subgroup	Continuation Events	Total	Reduction Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.5.1 At < 3 months						
Borlido 2016	9	15	7	13	100.0%	1.11 [0.58 , 2.14]
Subtotal (95% CI)		**15**		**13**	**100.0%**	**1.11 [0.58 , 2.14]**
Total events:	9		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Total (95% CI)		**15**		**13**	**100.0%**	**1.11 [0.58 , 2.14]**
Total events:	9		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
Test for subgroup differences: Not applicable						



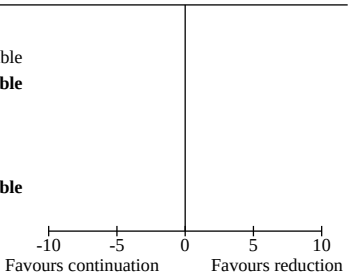
Analysis 1.6. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 6: Global state: mean endpoint score using Clinical Global Impression – Improvement (high = poor)

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.6.1 At < 3 months								
Borlido 2016	3.93	1.1	15	3.69	0.95	13	71.2%	0.24 [-0.52 , 1.00]
Repo-Tiihonen 2012	5.8	1.1	5	5.29	0.95	7	28.8%	0.51 [-0.68 , 1.70]
Subtotal (95% CI)			**20**			**20**	**100.0%**	**0.32 [-0.32 , 0.96]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Total (95% CI)			**20**			**20**	**100.0%**	**0.32 [-0.32 , 0.96]**
Heterogeneity: Tau² = 0.00; Chi² = 0.14, df = 1 (P = 0.71); I² = 0%								
Test for overall effect: Z = 0.97 (P = 0.33)								
Test for subgroup differences: Not applicable								



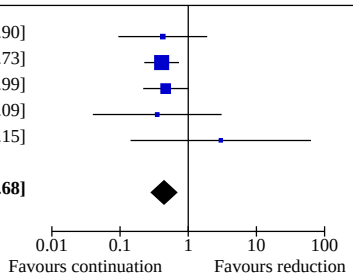
Analysis 1.7. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 7: Global state: mean change score Clinical Global Impression – Improvement (high = poor)

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.7.1 At < 3 months								
Repo-Tiihonen 2012	0.2	0.45	5	0	0	7		Not estimable
Subtotal (95% CI)			**5**			**7**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Total (95% CI)			**5**			**7**		**Not estimable**
Heterogeneity: Not applicable								
Test for overall effect: Not applicable								
Test for subgroup differences: Not applicable								



Analysis 1.8. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 8: Leaving the study early due to any reason – overall acceptability (totals of time points combined)

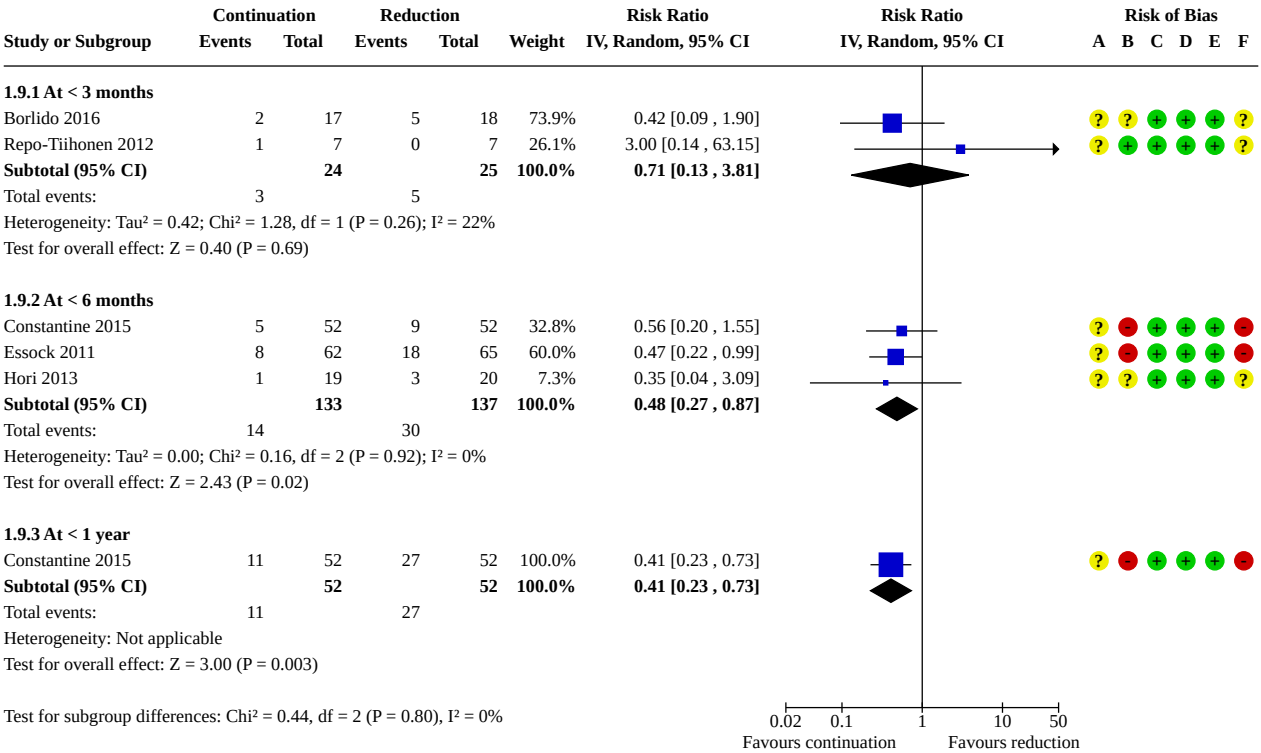
Study or Subgroup	Continuation Events	Total	Reduction Events	Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A	B	C	D	E	F
Borlido 2016	2	17	5	18	8.2%	0.42 [0.09 , 1.90]	?	?	+	+	+	?
Constantine 2015	11	52	27	52	53.7%	0.41 [0.23 , 0.73]	?	-	+	+	+	-
Essock 2011	8	62	18	65	32.2%	0.47 [0.22 , 0.99]	?	-	+	+	+	-
Hori 2013	1	19	3	20	3.9%	0.35 [0.04 , 3.09]	?	?	+	+	+	?
Repo-Tiihonen 2012	1	7	0	7	2.0%	3.00 [0.14 , 63.15]	?	+	+	+	+	?
Total (95% CI)		**157**		**162**	**100.0%**	**0.44 [0.29 , 0.68]**						
Total events:	23		53									
Heterogeneity: Tau² = 0.00; Chi² = 1.66, df = 4 (P = 0.80); I² = 0%												
Test for overall effect: Z = 3.73 (P = 0.0002)												
Test for subgroup differences: Not applicable												



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 1.9. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 9: Leaving the study early due to any reason – overall acceptability (subtotals only)

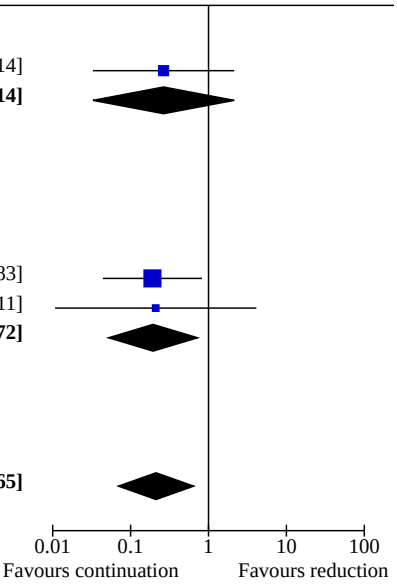


Risk of bias legend

(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

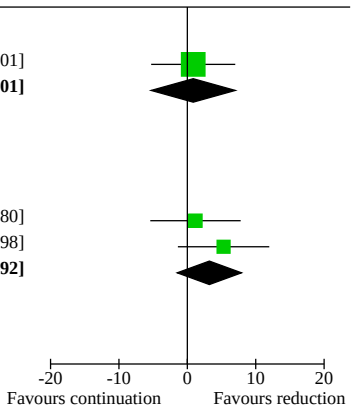
Analysis 1.10. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 10: Leaving the study early due to inefficacy – overall efficacy

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
1.10.1 At < 3 months						
Borlido 2016	1	17	4	18	28.4%	0.26 [0.03 , 2.14]
Subtotal (95% CI)		**17**		**18**	**28.4%**	**0.26 [0.03 , 2.14]**
Total events:	1		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.25 (P = 0.21)						
1.10.2 At < 6 months						
Essock 2011	2	62	11	65	57.6%	0.19 [0.04 , 0.83]
Hori 2013	0	19	2	20	14.0%	0.21 [0.01 , 4.11]
Subtotal (95% CI)		**81**		**85**	**71.6%**	**0.19 [0.05 , 0.72]**
Total events:	2		13			
Heterogeneity: Tau² = 0.00; Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 2.44 (P = 0.01)						
Total (95% CI)		**98**		**103**	**100.0%**	**0.21 [0.07 , 0.65]**
Total events:	3		17			
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 2 (P = 0.97); I² = 0%						
Test for overall effect: Z = 2.73 (P = 0.006)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						



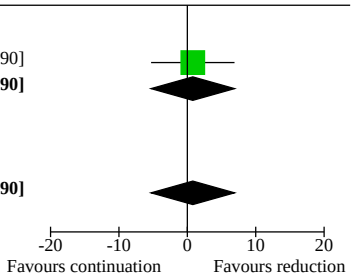
Analysis 1.11. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 11: Mental state – general: mean endpoint score on Positive and Negative Syndrome Scale Total (high = poor)

Study or Subgroup	Continuation Mean	Continuation SD	Continuation Total	Reduction Mean	Reduction SD	Reduction Total	Weight	Mean Difference IV, Random, 95% CI
1.11.1 At < 3 months								
Essock 2011	69.94	15.47	52	69.08	16.66	53	100.0%	0.86 [-5.29 , 7.01]
Subtotal (95% CI)			**52**			**53**	**100.0%**	**0.86 [-5.29 , 7.01]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.27 (P = 0.78)								
1.11.2 At < 6 months								
Essock 2011	70.85	16.2	48	69.66	16.65	47	50.6%	1.19 [-5.42 , 7.80]
Hori 2013	68.4	12.6	18	63.1	6.9	17	49.4%	5.30 [-1.38 , 11.98]
Subtotal (95% CI)			**66**			**64**	**100.0%**	**3.22 [-1.48 , 7.92]**
Heterogeneity: Tau² = 0.00; Chi² = 0.73, df = 1 (P = 0.39); I² = 0%								
Test for overall effect: Z = 1.34 (P = 0.18)								
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%								



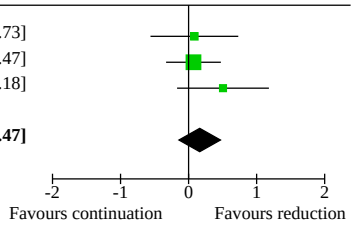
Analysis 1.12. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 12: Mental state – general: mean endpoint score on Brief Psychiatric Rating Scale Total (high = poor)

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.12.1 At < 3 months								
Borlido 2016	32	9.2	17	31.2	9.2	18	100.0%	0.80 [-5.30 , 6.90]
Subtotal (95% CI)			**17**			**18**	**100.0%**	**0.80 [-5.30 , 6.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
Total (95% CI)			**17**			**18**	**100.0%**	**0.80 [-5.30 , 6.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.26 (P = 0.80)								
Test for subgroup differences: Not applicable								



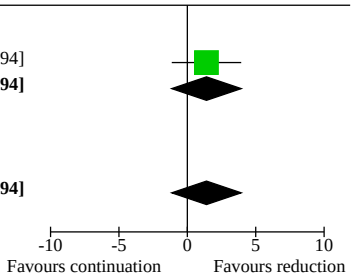
Analysis 1.13. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 13: Mental state – general: mean endpoint score on Positive and Negative Syndrome Scale Total and Brief Psychiatric Rating Scale Total combined (high = poor) (time points combined)

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Borlido 2016	32	9.2	19	31.2	9.2	18	22.3%	0.09 [-0.56 , 0.73]
Essock 2011	70.85	16.2	48	69.66	16.65	47	57.3%	0.07 [-0.33 , 0.47]
Hori 2013	68.4	12.6	18	63.1	6.9	17	20.4%	0.51 [-0.17 , 1.18]
Total (95% CI)			**85**			**82**	**100.0%**	**0.16 [-0.14 , 0.47]**
Heterogeneity: Tau² = 0.00; Chi² = 1.24, df = 2 (P = 0.54); I² = 0%								
Test for overall effect: Z = 1.05 (P = 0.29)								
Test for subgroup differences: Not applicable								



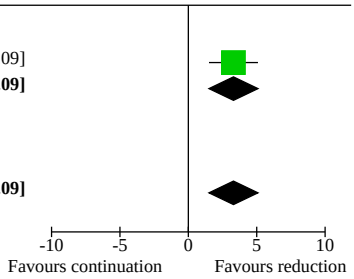
Analysis 1.14. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 14: Mental state – specific: mean endpoint score on Positive and Negative Syndrome Scale Positive (high = poor)

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.14.1 At < 6 months								
Hori 2013	17.3	4.4	18	15.9	3.2	17	100.0%	1.40 [-1.14 , 3.94]
Subtotal (95% CI)			**18**			**17**	**100.0%**	**1.40 [-1.14 , 3.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Total (95% CI)			**18**			**17**	**100.0%**	**1.40 [-1.14 , 3.94]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Not applicable								



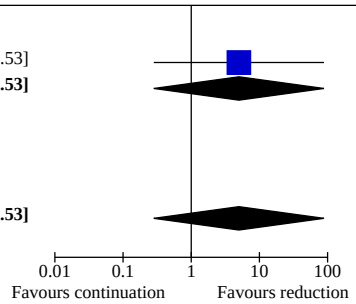
Analysis 1.15. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 15: Mental state – specific: mean endpoint score on Positive and Negative Syndrome Scale Negative (high = poor)

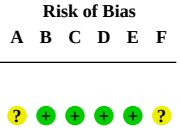
Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.15.1 At < 6 months								
Hori 2013	20.6	2.7	18	17.3	2.7	17	100.0%	3.30 [1.51 , 5.09]
Subtotal (95% CI)			**18**			**17**	**100.0%**	**3.30 [1.51 , 5.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.61 (P = 0.0003)								
Total (95% CI)			**18**			**17**	**100.0%**	**3.30 [1.51 , 5.09]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.61 (P = 0.0003)								
Test for subgroup differences: Not applicable								



Analysis 1.16. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 16: Adverse effects: ≥ 1 adverse effect

Study or Subgroup	Continuation Events	Total	Reduction Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.16.1 At < 3 months						
Repo-Tiihonen 2012	2	7	0	7	100.0%	5.00 [0.28 , 88.53]
Subtotal (95% CI)		**7**		**7**	**100.0%**	**5.00 [0.28 , 88.53]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Total (95% CI)		**7**		**7**	**100.0%**	**5.00 [0.28 , 88.53]**
Total events:	2		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.10 (P = 0.27)						
Test for subgroup differences: Not applicable						

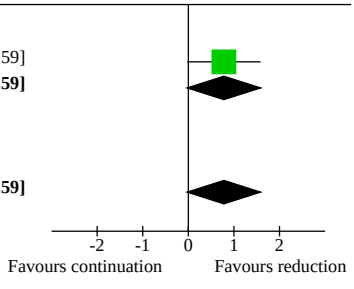




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

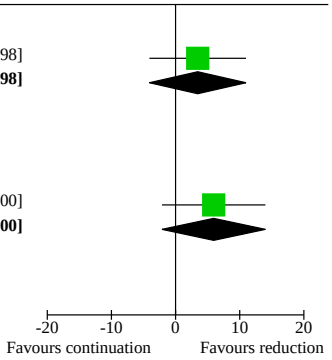
Analysis 1.17. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 17: Adverse effects – weight gain – mean body mass index change

Study or Subgroup	Continuation Mean	SD	Total	Reduction Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
1.17.1 At < 6 months								
Essock 2011	0.28	2.31	62	-0.5	2.32	65	100.0%	0.78 [-0.03 , 1.59]
Subtotal (95% CI)			**62**			**65**	**100.0%**	**0.78 [-0.03 , 1.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
Total (95% CI)			**62**			**65**	**100.0%**	**0.78 [-0.03 , 1.59]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.90 (P = 0.06)								
Test for subgroup differences: Not applicable								



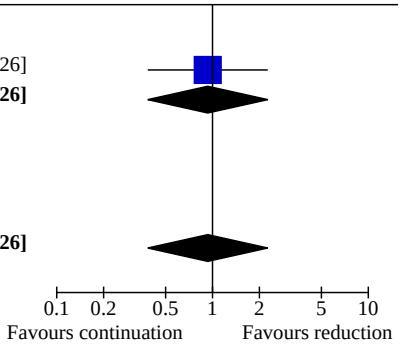
Analysis 1.18. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 18: Adverse effects – weight gain – endpoint mean weight (kg)

Study or Subgroup	Continuation Mean [kg]	SD [kg]	Total	Reduction Mean [kg]	SD [kg]	Total	Weight	Mean Difference IV, Random, 95% CI [kg]
1.18.1 At < 3 months								
Essock 2011	94.07	21.3	52	90.62	17.7	52	100.0%	3.45 [-4.08 , 10.98]
Subtotal (95% CI)			**52**			**52**	**100.0%**	**3.45 [-4.08 , 10.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.90 (P = 0.37)								
1.18.2 At < 6 months								
Essock 2011	95.16	22.22	48	89.22	17.46	46	100.0%	5.94 [-2.12 , 14.00]
Subtotal (95% CI)			**48**			**46**	**100.0%**	**5.94 [-2.12 , 14.00]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.44 (P = 0.15)								
Test for subgroup differences: Chi² = 0.20, df = 1 (P = 0.66), I² = 0%								



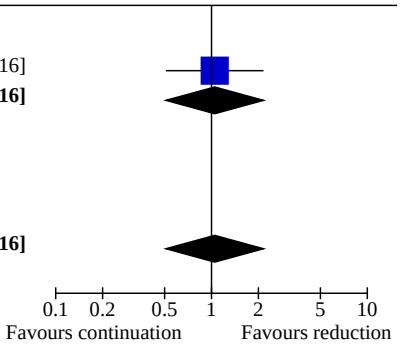
Analysis 1.19. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 19: Adverse effects – specific: tardive dyskinesia

Study or Subgroup	Continuation Events	Total	Reduction Events	Total	Weight	Risk Ratio IV, Random, 95% CI
1.19.1 At < 6 months						
Essock 2011	8	62	9	65	100.0%	0.93 [0.38 , 2.26]
Subtotal (95% CI)		**62**		**65**	**100.0%**	**0.93 [0.38 , 2.26]**
Total events:	8		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
Total (95% CI)		**62**		**65**	**100.0%**	**0.93 [0.38 , 2.26]**
Total events:	8		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Not applicable						



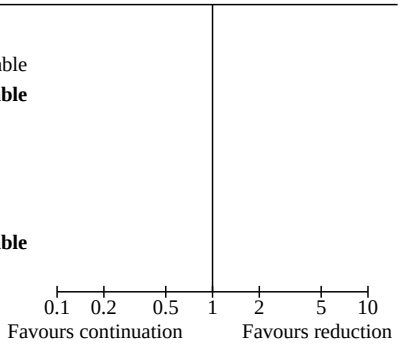
Analysis 1.20. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 20: Adverse effects – specific: ≥ 1 extrapyramidal adverse effect

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
1.20.1 At < 6 months						
Essock 2011	12	62	12	65	100.0%	1.05 [0.51 , 2.16]
Subtotal (95% CI)		**62**		**65**	**100.0%**	**1.05 [0.51 , 2.16]**
Total events:	12		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
Total (95% CI)		**62**		**65**	**100.0%**	**1.05 [0.51 , 2.16]**
Total events:	12		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.13 (P = 0.90)						
Test for subgroup differences: Not applicable						



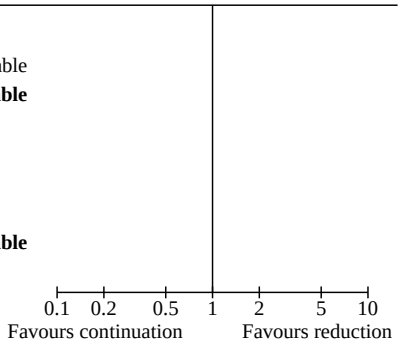
Analysis 1.21. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 21: Adverse events: overall mortality

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
1.21.1 At < 3 months						
Repo-Tiihonen 2012	0	7	0	7		Not estimable
Subtotal (95% CI)		**7**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**7**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



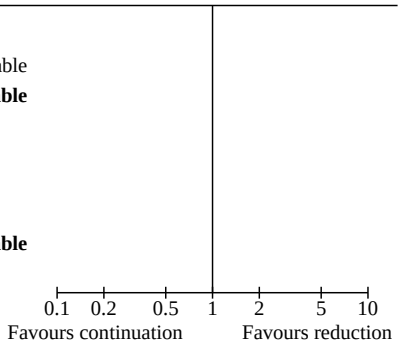
Analysis 1.22. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 22: Adverse events – mortality due to natural causes

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
1.22.1 At < 3 months						
Repo-Tiihonen 2012	0	7	0	7		Not estimable
Subtotal (95% CI)		**7**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**7**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



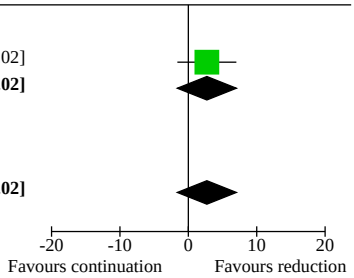
Analysis 1.23. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 23: Adverse events – mortality due to suicide

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
1.23.1 At < 3 months						
Repo-Tiihonen 2012	0	7	0	7		Not estimable
Subtotal (95% CI)		**7**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**7**		**7**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



Analysis 1.24. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 24: Medication – mean antipsychotic dose at endpoint (olanzapine equivalents)

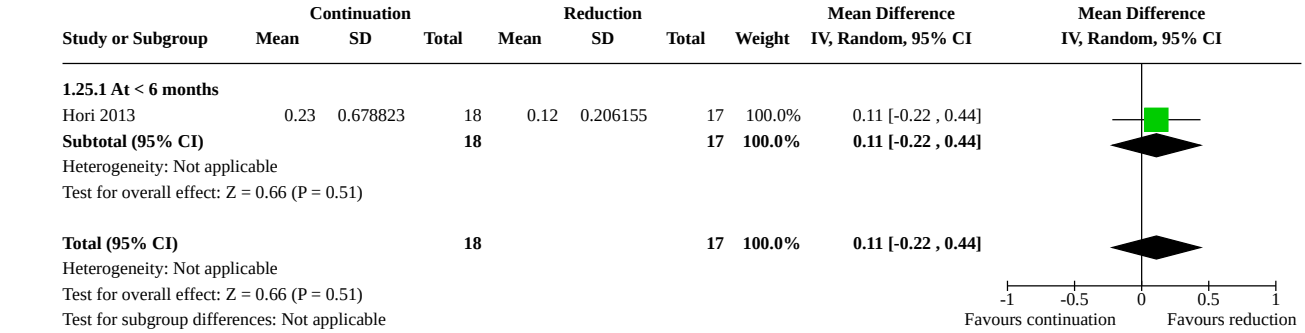
Study or Subgroup	Continuation Mean	Continuation SD	Continuation Total	Reduction Mean	Reduction SD	Reduction Total	Weight	Mean Difference IV, Random, 95% CI
1.24.1 At < 6 months								
Hori 2013 (1)	20.96	6.75	18	18.25	6.27	17	100.0%	2.71 [-1.60 , 7.02]
Subtotal (95% CI)			**18**			**17**	**100.0%**	**2.71 [-1.60 , 7.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.23 (P = 0.22)								
Total (95% CI)			**18**			**17**	**100.0%**	**2.71 [-1.60 , 7.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.23 (P = 0.22)								
Test for subgroup differences: Not applicable								



Footnotes

(1) Doses were converted from chlorpromazine equivalents to olanzapine equivalents (Gardner 2010).

Analysis 1.25. Comparison 1: Polypharmacy continuation versus polypharmacy reduction, Outcome 25: Cognition – change score using Brief Assessment of Cognition in Schizophrenia – Japanese version (high = good)

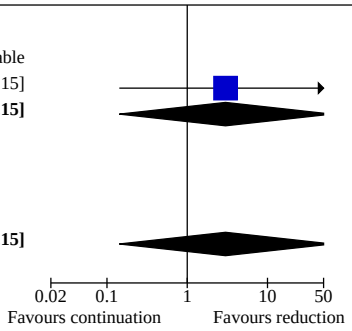


Comparison 2. Sensitivity analyses – adverse effects – leaving the study early due to adverse effects – overall tolerability

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 Excluding high risk of bias studies	2	49	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 63.15]
2.1.1 At < 3 months	2	49	Risk Ratio (IV, Random, 95% CI)	3.00 [0.14, 63.15]
2.2 Excluding non-operationalised diagnosis criteria	2	162	Risk Ratio (IV, Random, 95% CI)	5.24 [0.63, 43.61]
2.2.1 At < 3 months	1	35	Risk Ratio (IV, Random, 95% CI)	Not estimable
2.2.2 At < 6 months	1	127	Risk Ratio (IV, Random, 95% CI)	5.24 [0.63, 43.61]
2.3 Fixed-effect vs random-effects	3	176	Risk Ratio (IV, Fixed, 95% CI)	4.37 [0.77, 24.88]
2.3.1 At < 3 months	2	49	Risk Ratio (IV, Fixed, 95% CI)	3.00 [0.14, 63.15]
2.3.2 At < 6 months	1	127	Risk Ratio (IV, Fixed, 95% CI)	5.24 [0.63, 43.61]

Analysis 2.1. Comparison 2: Sensitivity analyses – adverse effects – leaving the study early due to adverse effects – overall tolerability, Outcome 1: Excluding high risk of bias studies

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI
2.1.1 At < 3 months						
Borlido 2016 (1)	0	17	0	18		Not estimable
Repo-Tiihonen 2012	1	7	0	7	100.0%	3.00 [0.14 , 63.15]
Subtotal (95% CI)		**24**		**25**	**100.0%**	**3.00 [0.14 , 63.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**24**		**25**	**100.0%**	**3.00 [0.14 , 63.15]**
Total events:	1		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Not applicable						



Footnotes

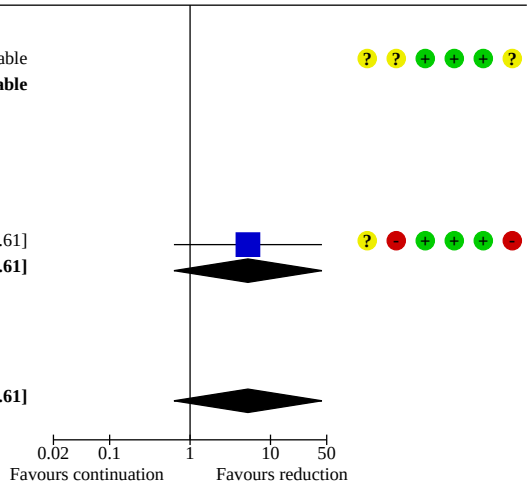
(1) Essock 2011 was at high risk of bias for this outcome, therefore it was excluded from this sensitivity analysis.

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 2.2. Comparison 2: Sensitivity analyses – adverse effects – leaving the study early due to adverse effects – overall tolerability, Outcome 2: Excluding non-operationalised diagnosis criteria

Study or Subgroup	Continuation Events	Continuation Total	Reduction Events	Reduction Total	Weight	Risk Ratio IV, Random, 95% CI	Risk of Bias A B C D E F
2.2.1 At < 3 months							
Borlido 2016 (1)	0	17	0	18		Not estimable	? ? + + + ?
Subtotal (95% CI)		**17**		**18**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
2.2.2 At < 6 months							
Essock 2011	5	62	1	65	100.0%	5.24 [0.63 , 43.61]	? - + + + -
Subtotal (95% CI)		**62**		**65**	**100.0%**	**5.24 [0.63 , 43.61]**	
Total events:	5		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.53 (P = 0.13)							
Total (95% CI)		**79**		**83**	**100.0%**	**5.24 [0.63 , 43.61]**	
Total events:	5		1				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.53 (P = 0.13)							
Test for subgroup differences: Not applicable							



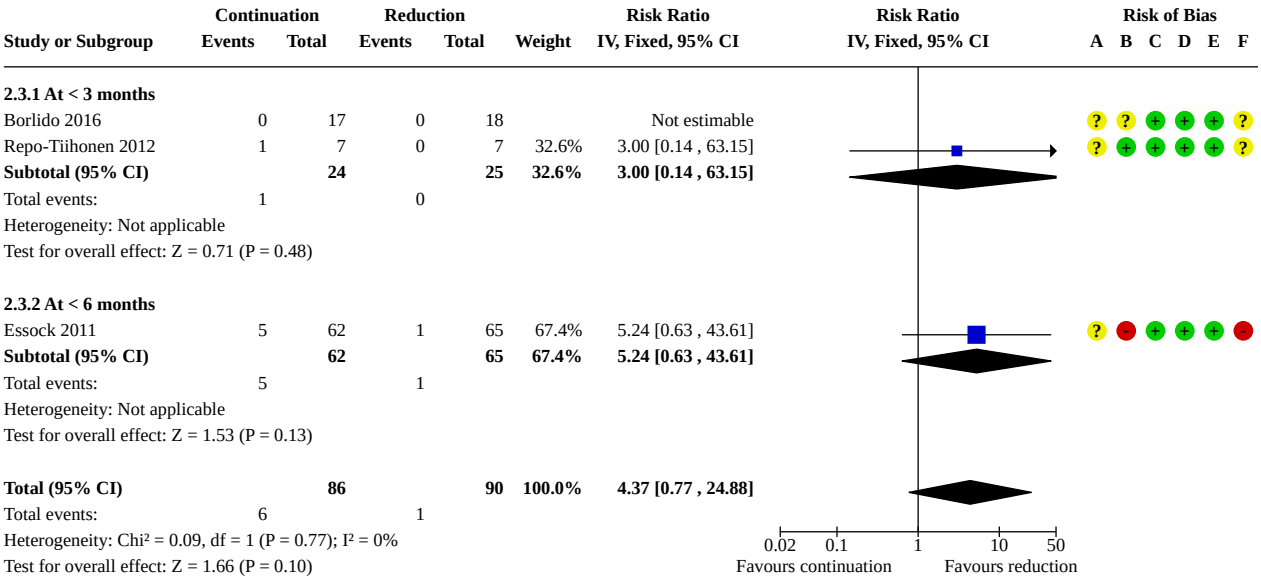
Footnotes

(1) Repo Tiihonen 2012 did not specify manualised criteria for diagnosis of schizophrenia and was excluded from this analysis.

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 2.3. Comparison 2: Sensitivity analyses – adverse effects – leaving the study early due to adverse effects – overall tolerability, Outcome 3: Fixed-effect vs random-effects



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

HISTORY

Protocol first published: Issue 4, 2021

CONTRIBUTIONS OF AUTHORS

IBi: conception and design of the review; search and selection of studies for inclusion; collection of data; assessment of the risk of bias in the included studies; analysis of data; assessment of certainty of evidence; interpretation of data; and writing of the review.

AR: search and selection of studies for inclusion; collection of data; assessment of the risk of bias in the included studies; analysis of data; assessment of certainty of evidence; interpretation of data, and writing of the review.

SSi: search and selection of studies for inclusion; collection of data; assessment of the risk of bias in the included studies; analysis of data; assessment of certainty of evidence; interpretation of data, and writing of the review.

MS: conception and design of the review; writing of the review.

WPH: conception and 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 is of May 2022 deceased. 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; collection of data; and assessment of the risk of bias in the included studies.

IBa: search and selection of studies for inclusion; collection of data; and assessment of the risk of bias in the included studies.

LB: search and selection of studies for inclusion; collection of data; and assessment of the risk of bias in the included studies.

SL: conception and design of the review; co-ordination of the review; interpretation of data; and writing of the review.

DECLARATIONS OF INTEREST

IB: is the Deputy Co-ordinating editor of Schizophrenia Group. She was not involved in the editorial process of the present review.

AR: is an editor of Schizophrenia Group. He was not involved in the editorial process of the present review.

SSi: is an editor of Schizophrenia Group. He was not involved in the editorial process of the present review.

MS: is an editor of Schizophrenia Group. She was not involved in the editorial process of the present review. She works as a psychiatrist in a private practice.

WPH: none.

SSa: none. Author deceased; declarations of interest provided before the author died.

EA: from 2019 to 2022, EA has been a consultant, a speaker or received research grants from Allergan, Angelini, Doc Generici, FB-Health, Janssen, Lundbeck, Otsuka, Fidia, Recordati; he is currently the President of the Italian Society of Psychopathology.

PC: none.

IBa: none.

LB: none.

SL: from 2019 to 2022, SL has received honoraria for service as a consultant or adviser (or both) or for lectures from Angelini, Boehringer 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 Schizophrenia Group. He was not involved in the editorial process of the present review.

SOURCES OF SUPPORT

Internal sources

- Freistaat Bayern, Germany

  The employer of IB, SSi, SL
- National Institute for Health and Care Research (NIHR), UK

  provided funding for Cochrane Schizophrenia Group

External sources

- Bundesministerium für Bildung und Forschung, Germany

  Project n. 01KG1807
- POC Sicilia 2014-20 – Avviso 37/2020, Other

  Project n. G67C20000210002

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We planned to search Chinese databases, but this was not possible. For technical reasons, Chinese databases could not be systematically searched in the Cochrane Schizophrenia Group's Study-based Register of Trials only until 2016. Therefore, to be systematic, we excluded records found in Chinese databases.

We added cognition as an outcome for systematic appraisal.

We extracted the time point less than three months in addition to the preplanned times, where available. We presented analyses at both time points and combined them. For the combined analyses, data from studies providing information for more than one time point were kept only for one time point (the closest to 12 months), in order to avoid double counting.

For analyses of dichotomous outcomes, the number of participants randomised was the denominator.

Strategy of dealing with skewed data was adapted to the new template protocol adopted by the Schizophrenia Group.

Forest plots were created so that an effect favouring polypharmacy continuation was indicated in the area on the left, and favouring polypharmacy reduction on the right. The direction is the opposite for continuous outcomes measured on a scale where higher scores correspond to a better outcome. The labels in the forest plots make interpretation clear.

RoB 2 results were presented in risk of bias tables, after characteristics of studies section, and in the forest plots, following indications of "RoB2 starter pack", version January 2022. Accordingly, we did not create risk of bias graph and summary figures.

RoB 2 judgements were performed for the predefined outcomes at the primary time point of 12 months, or, when not available, the closest one.

Summary of findings tables included the predefined outcomes at the total level (merging time points) or, when no totals were possible, at the closest to 12 months.

For functioning, we used continuous data for RoB 2 ratings and the summary of finding table, because the preplanned dichotomous outcome were not available.

We planned to conduct subgroup analyses for analyses with at least 10 studies, according to the *Cochrane Handbook for Systematic Reviews of Interventions* (Section 10.11.5.1).

INDEX TERMS

Medical Subject Headings (MeSH)

*Antipsychotic Agents [adverse effects]; Polypharmacy; *Schizophrenia [drug therapy]; Weight Gain

MeSH check words

Adult; Humans