TECHNICAL COMMENTARY

Treatments for first-episode psychosis

NeuRA Discover. Conquer. Cure.

SCHIZOPHRENIA LIBRARY

Introduction

People with a first episode of psychosis may experience distressing symptoms such as unusual beliefs or abnormal behaviour (positive symptoms) and/or withdrawal or loss of interest in work or school (negative symptoms). A first episode of psychosis may be distinct from a first episode of schizophrenia, which has significantly more stringent requirements for diagnosis.

Early intervention paradigms for schizophrenia and psychosis are often combined into multi-element programs comprising both pharmaceutical and psychosocial therapies or enriched therapies that are tailored to individuals' needs. Consequently, this table presents the evidence for interventions utilising either, or both antipsychotic medications and/or cognitive or behavioural therapies for treating early psychosis and preventing relapse.

The conclusions presented here are based on group data, and as such individual treatment programs need to be tailored by trained clinicians. Individual response to treatment can vary in terms of both symptoms and adverse effects.

Method

We have included only systematic reviews (systematic literature search, detailed methodology with inclusion/exclusion criteria) published in full text, in English, from the year 2000 that report results separately for people with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder or first episode schizophrenia. Reviews were identified by searching the databases MEDLINE, EMBASE, CINAHL, Current Contents, PsycINFO and the Cochrane library. Hand searching reference lists of identified reviews was also conducted. When multiple copies of reviews were found, only the most recent version was included. Reviews with pooled data are prioritised for inclusion.

Review reporting assessment was guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist which describes a preferred way to present a meta-analysis[1]. Reviews were assigned a low, medium or high possibility of reporting bias* depending on how many items were checked. Reviews reporting less than 50% of items have been excluded from the library. The PRISMA flow diagram is a suggested way of providing information about studies included and excluded with reasons for exclusion. Where no flow diagram has been presented by individual reviews, but identified studies have been described in the text, reviews have been checked for this item. Note that early reviews may have been guided by less stringent reporting checklists than the PRISMA, and that some reviews may have been limited by journal guidelines.

Evidence was graded using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group approach where high quality evidence such as that gained from randomised controlled trials (RCTs) may be downgraded to moderate or low if review and study quality is limited, if there is inconsistency in results, indirect comparisons, imprecise or sparse data and high probability of reporting bias. It may also be downgraded if risks associated with the intervention or other matter under review are high. Conversely, low quality evidence such as that gained from observational studies may be upgraded if effect sizes are large or if there is a dose dependent response. We have also taken into account sample size and whether results are consistent, precise and direct with low associated risks (see end of table for an explanation of these terms)[2]. The resulting table represents an objective summary of the available evidence, although the conclusions are solely the opinion

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

of staff of NeuRA (Neuroscience Research Australia).

Results

We found eight reviews that met our inclusion criteria[3-10].

Symptoms and functioning

- Moderate to high quality evidence finds small effects of greater improvements in symptoms, functioning and quality of life, and more remission and recovery with targetted early intervention services that include both pharmaceutical and psychosocial components.
- Moderate quality evidence finds antipsychotics in general are associated with an 81% response rate when measured as 20% reduction in symptoms, and a 52% response rate when measured as 50% reduction in symptoms.
- High quality evidence finds a small effect of greater improvement in overall symptoms with olanzapine than with haloperidol, while moderate to high quality evidence also finds greater improvement in negative symptoms with olanzapine.
- Moderate to high quality evidence finds a small to medium-sized effect of greater improvement in overall symptoms with amisulpride than with haloperidol.
- Moderate to high quality evidence finds a small effect of greater improvement in overall symptoms with risperidone than with haloperidol.
- Moderate quality evidence finds a small effect of greater improvement in overall symptoms with amisulpride than with quetiapine.
- Moderate quality evidence finds a small effect of greater improvement in negative symptoms with olanzapine than with risperidone.
- Moderate quality evidence finds a small effect of greater improvement in positive symptoms with olanzapine than with quetiapine.
- Moderate quality evidence finds a medium-sized effect of greater improvement in positive and negative symptoms with quetiapine than with haloperidol.
- Moderate quality evidence finds a small effect of greater improvement in positive symptoms with risperidone than with quetiapine.
- Moderate quality evidence finds a small effect of greater improvement in overall symptoms with ziprasidone than with haloperidol.
- Moderate to low quality evidence suggests chlorpromazine, haloperidol, risperidone, and olanzapine are more effective than placebo from the first week of treatment, and are most effective in the first two weeks of treatment.

Relapse prevention

- Moderate to high quality evidence finds small effects of fewer relapses and hospitalisations with targetted early intervention services.
- Moderate quality evidence finds relapse and rehospitalisation rates were higher after discontinuation rather than maintenance of antipsychotics in people in remission following a first-episode of psychosis. Relapse rates were highest in studies with a short follow-up (<1 year), a non-targeted or non-intermittent discontinuation strategy, a lower relapse threshold, a smaller sample size, and in samples of patients with drug or alcohol dependency.
- Moderate to high quality evidence finds second-generation antipsychotics are more effective for reducing relapse than first-

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

generation antipsychotics, although this finding was inconsistent in individual drug comparisons.

- Moderate to low quality evidence finds first-generation antipsychotics did not significantly reduce rate of relapse over placebo.

All-cause discontinuation

- Moderate to high quality evidence finds less all-cause discontinuation with targeted early intervention services.
- Moderate to low quality evidence finds a medium-sized effect of less all-cause discontinuation with aripiprazole than with haloperidol.
- Moderate quality evidence finds a medium-sized effect of less all-cause discontinuation with quetiapine than with haloperidol.
- Moderate to high quality evidence finds a small effect of less all-cause discontinuation with risperidone than with haloperidol.
- Moderate to low quality evidence finds a small effect of less all-cause discontinuation with olanzapine than with haloperidol.

Side effects

- Olanzapine was associated with at least one use of drugs to treat parkinsonian symptoms. Quetiapine was associated with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine. Molindone resulted in less weight gain than risperidone, haloperidol, and olanzapine and less increase in prolactin release than risperidone.

Agid O, Kapur S, Arenovich T, Zipursky RB

Delayed-Onset Hypothesis of Antipsychotic Action. A HypothesisTested and Rejected

Archives of General Psychiatry 2003; 60: 1228-1235

View review abstract online

Comparison	**Chlorpromazine, haloperidol, risperidone, or olanzapine vs. placebo in patients with schizophrenia or schizoaffective disorder during the first 4 weeks of antipsychotic drug treatment.**
Summary of evidence	**Moderate to low quality evidence (large sample, unable to assess consistency or precision, indirect) suggests chlorpromazine, haloperidol, risperidone, and olanzapine are more effective than placebo from the first week of treatment, and are most effective in the first two weeks of treatment.**
Symptoms **Measured by BPRS or PANSS**	
Significant improvement over 4 weeks in mean total scores in the treatment group (42 RCTs N = 7,450, $p < 0.001$), but not the placebo group ($p = 0.22$). Mean weekly total scores in the medication group were significantly better than placebo from the first week of treatment ($p < 0.05$). Clinical improvement was greatest earlier on in treatment, with improvement in the first 2 weeks being significantly greater than as observed in weeks 3 and 4 ($p < 0.001$). These findings were similar using only positive symptoms scores, and no differences were reported when analyzing each antipsychotic separately.	
Consistency in results‡	No measure of consistency is reported.
Precision in results§	No measure of precision is reported.
Directness of results‖	Indirect (mixed antipsychotic classes combined).

Alvarez-Jimenez M, Parker AG, Hetrick SE, McGorry PD, Gleeson JF

Preventing the Second Episode: A Systematic Review and Meta-analysis of Psychosocial and Pharmacological Trials in First-Episode Psychosis

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Schizophrenia Bulletin 2011; 37(3): 619-30 View review abstract online	
Comparison 1	**First generation antipsychotic (FGA) medications (various) vs. placebo.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, inconsistent, imprecise, direct) suggests first generation antipsychotics did not significantly reduce rate of relapse over placebo.**
Relapse prevention	
3 RCTs compared FGA with placebo (over 1-2 years). Medications assessed included (but were not limited to) fluphenazine, pimozine, and flupenthixol decanoate. *Non-significant (trend) benefit of FGA over placebo for reducing relapse rates;* N = 166, OR = 5.17, 95%CI 0.87 to 30.63, p = 0.07, I^2 = 50%, p = 0.14	
Consistency in results	Inconsistent – heterogeneity statistically non-significant but of moderate magnitude.
Precision in results	Imprecise
Directness of results	Direct
Comparison 2	**Second generation antipsychotics (SGA) vs. first generation antipsychotics (FGA).**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, consistent, imprecise, direct) suggests second generation antipsychotics may be more effective for reducing relapse than first generation antipsychotics, although this finding was not consistent in individual drug comparisons. There was no difference between first and second generation antipsychotics for rates of discontinuation due to adverse effects.**
Relapse prevention	
4 RCTs compared SGA with FGA (over 1-2 years). SGA medications included risperidone, amizulpride, olanzapine, clozapine, quetiapine, ziprasidone. FGA medication included haloperidol and chlorpromazine. *Overall effect favoured SGAs over FGAs for reducing relapse, however subgroup analyses show no significant difference between specific antipsychotics;* Overall SGAs vs FGAs: N = 1,055, OR = 1.47, 95%CI 1.07 to 2.01, p = 0.02, NNT = 10, I^2 = 0%, p =	

0.53 Subgroup - risperidone vs haloperidol: N = 551, OR = 1.54, 95%CI 0.98 to 2.42, p = 0.06, I^2 = 11%, p = 0.29 Subgroup - clozapine vs chlorpromazine: N = 143, OR = 0.81, 95%CI 0.24 to 2.78, p = 0.74, I^2 = NA, 1 study only Subgroup - haloperidol vs various SGAs: N = 361, OR = 1.38, 95%CI 0.71 to 2.69, p = 0.34, I^2 = NA, 1 study only 4 RCTs reported on discontinuation of medication due to adverse events *No significant difference between SGA and FGA for rate of discontinuation;* Overall SGA vs FGA: OR = 1.23, 95%CI 0.72 to 2.09, p = 0.44 Risperidone vs haloperidol: OR = 1.50, 95%CI 0.99 to 2.27, p = 0.06	
Consistency in results	Consistent
Precision in results	Imprecise
Directness of results	Direct
Comparison 3	**First generation antipsychotics vs. other FGAs for reducing relapse rate.**
Summary of evidence	**Low quality evidence (1 very small RCT, imprecise, direct) is unable to assess differences in relapse prevention.**
Relapse prevention	
1 RCT compared pimozine with flupenthixol (over 1 year) *No significant difference between FGAs for relapse rate;* N = 26, OR = 1.00, 95%CI 0.19 to 5.29, p = 1.00	
Consistency in results	N/A – one trial
Precision in results	Imprecise
Directness of results	Direct
Comparison 4	**Medication maintenance vs. guided discontinuation of antipsychotics (various) for reducing relapse rate.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized sample, imprecise, direct) suggests maintenance of medication may be more effective for reducing rate of relapse than discontinuation.**

Relapse prevention	
1 RCT compared medication maintenance with guided discontinuation, where dosage was gradually tapered until suspended. Medications included risperidone, olanzapine, quetiapine, clozapine and zuclopenthixol. *Relapse rate was reduced significantly more by maintenance of treatment than discontinuation of treatment;* N = 128, OR = 2.91, 95%CI 1.33 to 6.37, $p < 0.01$ *There was no difference in number of days confined to bed between those who maintain or discontinue medication;* WMD = -23.31 days, 95%CO -65.71 to -25.09, $p = 0.38$	
Consistency in results	N/A – one trial
Precision in results	Imprecise for relapse rate, unable to assess bed days
Directness of results	Direct

Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, Craig TJ, Nordentoft M, Srihari VH, Guloksuz S, Hui CLM, Chen EYH, Valencia M, Juarez F, Robinson DG, Schooler NR, Brunette MF, Mueser KT, Rosenheck RA, Marcy P, Addington J, Estroff SE, Robinson J, Penn D, Severe JB, Kane JM

Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression

JAMA Psychiatry 2018; 75: 555-65

View review abstract online

Comparison	**Integrated early intervention services specifically designed for people with early-phase psychosis (pharmaceutical plus psychosocial therapies such as case management, psychotherapy, supported employment and education, and family support) vs. treatment as usual. Mean trial duration = 16.2 months (range 9-24 months).**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, indirect) finds small effects of fewer**

	relapses and hospitalisations, more remission and recovery, greater improvements in symptoms, functioning and quality of life, and less all-cause treatment discontinuation with early intervention services. These effects were similar across most time points (6, 9-12, and 18-24 months). There were few moderating variables. Studies including fidelity monitoring had fewer hospitalisations than those without fidelity monitoring. Larger study sample size was associated with lower hospitalisation risk. Younger age, male sex, higher baseline symptom severity and more patients with schizophrenia were each associated with greater improvements in total symptoms.
Hospitalisation and relapse	
A small, significant effects of fewer hospitalisations and relapses with early intervention services; At least one hospitalisation: 10 RCTs, N = 2,105, RR = 0.74, 95%CI 0.61 to 0.90, $p = 0.003$, $I^2 = 47\%$, $p = 0.047$ Number of hospitalisations: 8 RCTs, N = 1,412, SMD = -0.17, 95%CI -0.31 to -0.03, $p = 0.018$, $I^2 = 35\%$, $p = 0.157$ Duration of hospitalisation: 6 RCTs, N = 1,107, SMD = -0.17, 95%CI -0.28 to -0.05, $p = 0.006$, $I^2 = 0\%$, $p = 0.470$ Relapse: 7 RCTs, N = 1,275, RR = 0.71, 95%CI 0.53 to 0.93, $p = 0.014$, $I^2 = 37\%$, $p = 0.143$ In subgroup analyses, the only significant between-subgroup difference was that studies including fidelity monitoring had fewer hospitalisations vs. treatment as usual than those without fidelity monitoring (RR = 0.88 vs. 0.50, $p = 0.001$). Meta-regression showed larger study sample size was associated with lower hospitalisation risk (coefficient = 0.001, $p = 0.002$). There were no moderating effects of region, blinding, type of psychosocial component (family therapy, crisis response, social skills, vocational), number of sites, duration of treatment, number of treatment components, ratio of number of visits in intervention vs. control groups, study risk of bias, diagnosis, baseline symptoms and functioning, age, gender, duration of treated or untreated psychosis, prior antipsychotic treatment, attrition rates.	
Symptoms	
Small, significant effects of greater improvements in symptoms with early intervention services; Total symptoms: 8 RCTs, N = 1,179, SMD = -0.32, 95%CI -0.47 to -0.17, $p < 0.001$, $I^2 = 32\%$, $p = 0.175$ General symptoms: 8 RCTs, N = 1,118, SMD = -0.30, 95%CI -0.47 to -0.13, $p < 0.001$, $I^2 = 40\%$, $p = 0.111$ Positive symptoms: 10 RCTs, N = 1,532, SMD = -0.22, 95%CI -0.32 to -0.11, $p < 0.001$, $I^2 = 0.5\%$, $p = 0.433$	

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Negative symptoms: 10 RCTs, N = 1,532, SMD = -0.28, 95%CI -0.42 to -0.14, $p < 0.001$, $I^2 = 38\%$, $p = 0.102$ Depressive symptoms: 5 RCTs, N = 874, SMD = -0.19, 95%CI -0.35 to -0.03, $p = 0.017$, $I^2 = 18\%$, $p = 0.301$ Meta-regressions showed moderating effects of younger age, male sex, higher baseline symptom severity and the percentage of patients with schizophrenia vs. other psychoses were each associated with greater improvements in total symptoms with early intervention services. There were no moderating effects on total symptoms in other subgroup or meta-regression analyses (see the hospitalisation section for a full list of variables assessed).	
Remission and recovery	
Small, significant effects of more remission and recovery with early intervention services; Remission: 7 RCTs, N = 1,229, RR = 1.29, 95%CI 1.07 to 1.55, $p = 0.007$, $I^2 = 69\%$, $p = 0.004$ Recovery: 3 RCTs, N = 640, RR = 1.24, 95%CI 1.03 to 1.50, $p = 0.022$, $I^2 = 0\%$, $p = 0.689$	
Functioning and quality of life	
Small, significant effects of greater improvements in functioning and quality of life with early intervention services; Overall functioning: 7 RCTs, N = 1,005, SMD = 0.21, 95%CI 0.08 to 0.34, $p < 0.001$, $I^2 = 0\%$, $p = 0.590$ Involvement in school or work: 6 RCTs, N = 1,743, RR = 1.13, 95%CI 1.03 to 1.24, $p = 0.01$, $I^2 = 0\%$, $p = 0.659$ Quality of life: 4 RCTs, N = 505, SMD = 0.23, 95%CI 0.004 to 0.46, $p = 0.046$, $I^2 = 34\%$, $p = 0.208$ There were no moderating variables.	
Risks	*There was less all-cause treatment discontinuation with early intervention services;* 10 RCTs, N = 2,173, RR = 0.70, 95%CI 0.61 to 0.80, $p < 0.001$, $I^2 = 0.4\%$, $p = 0.434$
Consistency in results	Consistent, apart from remission and at least one hospitalisation.
Precision in results	Precise
Directness of results	Indirect (mixed interventions combined).

Kishi T, Ikuta T, Matsui Y, Inada K, Matsuda Y, Mishima K, Iwata N

Effect of discontinuation v. maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis

Psychological Medicine 2019; 49: 772-9

View review abstract online

Comparison	**Discontinuating antipsychotics abruptly vs. gradual tapering off over ~3 months after remittance of a first-episode of psychosis.** **Mean study duration was 18.6 months.**
Summary of evidence	**Moderate to high quality evidence (medium to large sample, consistent, some imprecision, direct) finds gradual tapering off antipsychotics over 3 months after remittance of a first-episode of psychosis results in fewer relapses for up to 2 years than abrupt discontinuation. However, tapering results in more adverse effects.**
Relapse	
10 RCTs, N = 776 *The maintenance group experienced significantly fewer relapses at all time points except 1 month;* 1 month: 6 RCTs, N unclear, RR = 0.55, 95%CI 0.21 to 1.41, $p = 0.21$, $I^2 = 0\%$, $p = 0.46$ 2 months: 6 RCTs, N unclear, RR = 0.49, 95%CI 0.29 to 0.85, $p = 0.01$, $I^2 = 0\%$, $p = 0.49$ 3 months: 6 RCTs, N unclear, RR = 0.46, 95%CI 0.30 to 0.70, $p = 0.0002$, $I^2 = 0\%$, $p = 0.84$ 6 months: 6 RCTs, N unclear, RR = 0.55, 95%CI 0.42 to 0.72, $p < 0.00001$, $I^2 = 0\%$, $p = 0.51$ 9 months: 6 RCTs, N unclear, RR = 0.48, 95%CI 0.32 to 0.62, $p = 0.0002$, $I^2 = 44\%$, $p = 0.11$ 12 months: 10 RCTs, N = 739, RR = 0.47, 95%CI 0.35 to 0.70, $p < 0.00001$, $I^2 = 31\%$, $p = 0.16$ 18-24 months: 4 RCTs, N unclear, RR = 0.57, 95%CI 0.41 to 0.80, $p = 0.001$, $I^2 = 43\%$, $p = 0.16$ Authors report there was significant publication bias for the 12-month outcome There were no moderating effects of study size, publication year, study duration, sex, age, duration of illness, or antipsychotic dose at baseline.	
Risks	The maintenance group was associated with higher discontinuation due to adverse events.
Consistency in results	Consistent
Precision in results	Precise, apart from 1 and 2 months.

Directness of results	Direct

Oliver D, Davies C, Crossland G, Lim S, Gifford G, McGuire P, Fusar-Poli P

Can We Reduce the Duration of Untreated Psychosis? A Systematic Review and Meta-Analysis of Controlled Interventional Studies

Schizophrenia bulletin 2018; 44: 1362-72

View review abstract online

Comparison	**First episode psychosis services, clinical high risk services, community interventions, healthcare professional training, or multifocus interventions vs. control conditions.**
Summary of evidence	**Moderate to high quality evidence (large samples, mostly consistent, precise, indirect) finds no differences in the duration of untreated psychosis between various early intervention services and controls conditions.**

Duration of untreated psychosis

There were no differences between groups;

16 studies, N = 1,964, g = -0.12, 95%CI -0.25 to 0.01, $p > 0.05$, I^2 = 66%, $p < 0.001$

Subgroup analysis of intervention type showed only clinical high-risk services significantly reduced the duration of untreated psychosis compared to treatment as usual, but this was based on only one trial. Meta-regression showed that defining the duration of untreated psychosis *onset* as the onset of frank psychotic positive symptoms or by using the PANSS was associated with a significantly greater decrease in duration of untreated psychosis compared to other onset definitions.

There were no moderating effects of age, marital status, length of interventions, quality of studies, publication year, continent, healthcare system type, study design, definition of duration of untreated psychosis, or length of duration of untreated psychosis in the control groups.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Indirect (mixed interventions combined).

Thompson A, Winsper C, Marwaha S, Haynes J, Alvarez-Jimenez M, Hetrick S,

Realpe A, Vail L, Dawson S, Sullivan SA

Maintenance antipsychotic treatment versus discontinuation strategies following remission from first episode psychosis: Systematic review

BJPsych Open 2018; 4: 215-25

View review abstract online

Comparison	**Maintenance vs. discontinuaton of antipsychotics following remission from a first-episode of psychosis.**
Summary of evidence	**Moderate quality evidence (large samples, inconsistent, unable to assess precision, direct) suggests relapse and rehospitalisation rates were higher after discontinuation of antipsychotics in people in remission following a first-episode of psychosis. Relapse rates were higher in studies with a short follow-up (<1 year) a non-targeted or non-intermittent discontinuation strategy, a lower relapse threshold, a smaller sample size, and in samples of patients with drug or alcohol dependency.**
Relapse and hospitalisation	
Relapse rates were higher in the discontinuation group; 7 RCTs, N = 520, RD = 0.26, 95%CI 0.18 to 0.34, $p < 0.05$, $I^2 = 51.2\%$, $p = 0.056$ Discontinuation = 53%, Maintenance = 19% *Hospitalisations were higher in the discontinuation group;* 5 RCTs, N = 372, RD = 0.12, 95%CI 0.05 to 0.20, $p = 0.002$, $I^2 = 60\%$, $p = 0.042$ Discontinuation = 22%, Maintenance = 11% Subgroup analyses showed relapse rates were higher in studies with a shorter follow-up period (<1 year), a non-targeted or non-intermittent discontinuation strategy, a lower relapse threshold, a smaller sample size, and in samples with patients with drug or alcohol dependency.	
Consistency in results	Inconsistent
Precision in results	Unable to assess; RDs not standardised
Directness of results	Direct

Zhu Y, Krause M, Huhn M, Rothe P, Schneider-Thoma J, Chaimani A, Li C, Davis J

M, Leucht S

Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses

The Lancet Psychiatry 2017; 4: 694-705

View review abstract online

Comparison	**Comparison of haloperidol, risperidone, olanzapine, quetiapine, ziprasidone, zuclopenthixol, molindone, flupenthixol, pimozide, aripiprazole, amisulpride, and sertindole. Mean duration of treatment was 8 weeks.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) finds a small effect of greater improvement in overall symptoms with olanzapine than with haloperidol, while moderate to high quality evidence (inconsistent) also finds greater improvement in negative symptoms with olanzapine.** **Moderate to high quality evidence (medium-sized sample, consistent, precise, direct) finds a small to medium-sized effect of greater improvement in overall symptoms with amisulpride than with haloperidol.** **Moderate to high quality evidence (large sample, consistent, precise, indirect) finds a small effect of greater improvement in overall symptoms with risperidone than with haloperidol.** **Moderate quality evidence (medium-sized sample, consistent, precise, indirect) finds a small effect of greater improvement in overall symptoms with amisulpride than with quetiapine.** **Moderate quality evidence (large sample, inconsistent, precise, indirect) finds a small effect of greater improvement in negative symptoms with olanzapine than with risperidone.** **Moderate quality evidence (unclear sample size, inconsistent, precise, direct) finds a small effect of greater improvement in positive symptoms with olanzapine than with quetiapine.** **Moderate quality evidence (unclear sample size, inconsistent, precise, direct) finds a medium-sized effect of greater improvement in positive and negative symptoms with quetiapine than with haloperidol.** **Moderate quality evidence (unclear sample, inconsistent, precise, direct) finds a small effect of greater improvement in**

	positive symptoms with risperidone than with quetiapine. **Moderate quality evidence (medium-sized sample, consistent, precise, indirect) finds a small effect of greater improvement in overall symptoms with ziprasidone than with haloperidol.** **Moderate to low quality evidence (unclear sample, consistent, imprecise, indirect) finds a medium-sized effect of less discontinuation with aripiprazole than with haloperidol.** **Moderate quality evidence (unclear sample, consistent, imprecise, direct) finds a medium-sized effect of less discontinuation with quetiapine than with haloperidol.** **Moderate to high quality evidence (large sample, consitent, imprecise, direct) finds a small effect of less discontinuation with risperidone than with haloperidol.** **Moderate to low quality evidence (unclear sample, consistent, imprecise, indirect) finds a small effect of less discontinuation with olanzapine than with haloperidol.** **Authors conclude that olanzapine was associated with at least one use of drugs to treat parkinsonian symptoms. Quetiapine was associated with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine. Molindone resulted in less weight gain than risperidone, haloperidol, and olanzapine and less increase in prolactin release than risperidone.**
Symptoms	
Amisulpride vs. haloperidol *A small to medium-sized effect of greater improvement in overall symptoms with amisulpride than with haloperidol;* Overall symptoms pairwise meta-analysis: 1 RCT, N = 207, SMD = -0.33, 95%CI -0.60 to -0.06, $p < 0.05$ Overall symptoms network meta-analysis: SMD = -0.37, 95%CI -0.61 to -0.14, $p < 0.05$ Amisulpride vs. quetiapine *A small effect of greater improvement in overall symptoms with amisulpride than with quetiapine in the network meta-analysis but not the pairwise meta-analysis;* Overall symptoms pairwise meta-analysis: 1 RCT, N = 208, SMD = -0.21, 95%CI -0.48 to 0.06, $p > 0.05$ Overall symptoms network meta-analysis: SMD = -0.25, 95%CI -0.50 to -0.01, $p < 0.05$ Olanzapine vs. haloperidol *A small effect of greater improvement in overall and negative symptoms with olanzapine than with*	

haloperidol;

Overall symptoms pairwise meta-analysis: 5 RCTs, N = 711, SMD = -0.29, 95%CI -0.50 to -0.09, $p < 0.05$

Overall symptoms network meta-analysis: SMD = -0.25, 95%CI -0.39 to -0.12, $p < 0.05$

Negative symptoms pairwise meta-analysis: 3 RCTs, N = 711, SMD = -0.34, 95%CI -0.53 to -0.15, $p < 0.05$

Negative symptoms network meta-analysis: SMD = -0.31, 95%CI -0.48 to -0.13, $p < 0.05$

Olanzapine vs. risperidone

A small effect of greater improvement in negative symptoms with olanzapine than with risperidone in the network meta-analysis but not the pairwise meta-analysis;

Negative symptoms pairwise meta-analysis: 3 RCTs, N = 550, SMD = -0.13, 95%CI -0.08 to 0.34, $p > 0.05$

Negative symptoms network meta-analysis: SMD = -0.20, 95%CI -0.37 to -0.03, $p < 0.05$

Olanzapine vs. quetiapine

A small effect of greater improvement in positive symptoms with olanzapine than with quetiapine in the pairwise meta-analysis but not the network meta-analysis;

Positive symptoms pairwise meta-analysis: 1 RCT, N = unclear, SMD = -0.36, 95%CI -0.65 to -0.06, $p < 0.05$

Positive symptoms network meta-analysis: SMD = -0.13, 95%CI -0.49 to 0.24, $p > 0.05$

Quetiapine vs. haloperidol

A medium-sized effect of greater improvement in positive and negative symptoms with quetiapine than with haloperidol in the pairwise meta-analyses but not the network meta-analyses;

Positive symptoms pairwise meta-analysis: 1 RCT, N = unclear, SMD = -0.65, 95%CI -1.12 to -0.17, $p < 0.05$

Positive symptoms network meta-analysis: SMD = -0.12, 95%CI -0.50 to 0.27, $p > 0.05$

Negative symptoms pairwise meta-analysis: 1 RCT, N = unclear, SMD = -0.63, 95%CI -1.11 to -0.16, $p < 0.05$

Negative symptoms network meta-analysis: SMD = -0.16, 95%CI -0.44 to 0.13, $p > 0.05$

Risperidone vs. haloperidol

A small effect of greater improvement in overall symptoms with risperidone than with haloperidol in the network meta-analysis but not the pairwise meta-analysis;

Overall symptoms pairwise meta-analysis: 6 RCTs, N = 693, SMD = -0.10, 95%CI -0.25 to 0.06, $p > 0.05$

Overall symptoms network meta-analysis: SMD = -0.14, 95%CI -0.27 to -0.01, $p < 0.05$

Risperidone vs. quetiapine

A small effect of greater improvement in positive symptoms with risperidone than with quetiapine in the pairwise meta-analysis but not the network meta-analysis; Positive symptoms pairwise meta-analysis: 1 RCT, N = unclear, SMD = -0.33, 95%CI -0.62 to -0.03, $p < 0.05$ Positive symptoms network meta-analysis: SMD = -0.09, 95%CI -0.45 to 0.27, $p > 0.05$ <u>Ziprasidone vs. haloperidol</u> *A small effect of greater improvement in overall symptoms with ziprasidone than with haloperidol in the network meta-analysis but not the pairwise meta-analysis;* Overall symptoms pairwise meta-analysis: 2 RCTs, N = 226, SMD = -0.25, 95%CI -0.52 to 0.01, $p > 0.05$ Overall symptoms network meta-analysis: SMD = -0.25, 95%CI -0.48 to -0.01, $p < 0.05$ There were no other significant differences between treatments.
All cause discontinuation
<u>Aripiprazole vs. haloperidol</u> *A medium-sized effect of less discontinuation with aripiprazole than with haloperidol;* Network meta-analysis: OR = 2.53, 95%CI 1.31 to 4.92, $p < 0.05$ <u>Quetiapine vs. haloperidol</u> *A medium-sized effect of less discontinuation with quetiapine than with haloperidol;* Pairwise meta-analysis: 1 RCT, N = unclear, OR = 2.23, 95%CI 1.16 to 4.28, $p < 0.05$ Network meta-analysis: OR = 2.23, 95%CI 1.16 to 4.28, $p < 0.05$ <u>Risperidone vs. haloperidol</u> *A small effect of less discontinuation with risperidone than with haloperidol;* Pairwise meta-analysis: 6 RCTs, N = 693, OR = 1.69, 95%CI 1.17 to 2.43, $p < 0.05$ Network meta-analysis: OR = 1.88, 95%CI 1.34 to 2.65, $p < 0.05$ <u>Olanzapine vs. haloperidol</u> *A small effect of less discontinuation with olanzapine than with haloperidol in the network meta-analysis but not the pairwise meta-analysis;* Pairwise meta-analysis: 3 RCTs, N = unclear, OR = 2.17, 95%CI 0.94 to 5.02, $p > 0.05$ Network meta-analysis: OR = 1.83, 95%CI 1.23 to 2.74, $p < 0.05$ There were no other significant differences between treatments.
Risks — Olanzapine was associated with less frequent use of drugs to treat parkinsonian symptoms than haloperidol, zuclopenthixol, and risperidone, and quetiapine was associated with less use of drugs to

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

	treat parkinsonian symptoms than haloperidol and zuclopenthixol. Molindone was associated with significantly less weight gain than olanzapine, haloperidol, and risperidone, and haloperidol was superior to olanzapine. Quetiapine was associated with less akathisia than haloperidol, aripiprazole, risperidone, and olanzapine, and olanzapine with less than haloperidol, aripiprazole and risperidone. Quetiapine was associated with less sedation than risperidone and aripiprazole. Molindone, aripiprazole, olanzapine, and haloperidol were associated with lower increases in prolactin release than risperidone, as were molindone and olanzapine than haloperidol.
Consistency in results	Authors report the results were consistent for overall symptoms and all-cause discontinuation, but there was some inconsistency for positive symptoms, negative symptoms, and sedation.
Precision in results	Precise for SMDs, imprecise for ORs.
Directness of results	Direct for pairwise meta-analyses, indirect for network meta-analyses.

Zhu Y, Li C, Huhn M, Rothe P, Krause M, Bighelli I, Schneider-Thoma J, Leucht S

How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis

European Neuropsychopharmacology 2017; 27: 835-44

View review abstract online

Comparison	**Pre-post analysis of response rate after treatment with antipsychotics (haloperidol, risperidone, olanzapine, quetiapine, clozapine, ziprasidone, zuclopenthixol, amisulpride, chlorpromazine, and molindone).** **Median trial duration = 12 weeks.**
Summary of evidence	**Moderate quality evidence (large sample, unable to assess consistency, precise, indirect) suggests antipsychotics are associated with an 81% response rate measured as a 20% reduction in symptoms, and a 52% response rate measured as a**

	50% reduction in symptoms.
Symptoms **Measured by BPRS or PANSS**	
20% reduction from baseline on PANSS/BPRS: 17 RCTs, N = 3,156, 81%, 95%CI 77% to 85% 50% reduction from baseline on PANSS/BPRS: 17 RCTs, N = 3,156, 52%, 95%CI 47% to 57% Subgroup analyses showed a slightly higher response rates in open-label than blinded studies (48.0% vs. 57.2%, *p* = 0.055). There were also higher response rates in drug naïve patients than in patients with some exposure to medication (65.8% vs. 46.7%, *p* = 0.004). Meta-regressions showed female patients had higher response rates than males (β = -2.53, *p* < 0.0001). Patients with more severe symptoms at baseline had higher response rates than patients with mild symptoms (β = 0.02, *p* = 0.02). Patients with shorter illness duration had higher response rates than those with longer illness duration (β = -0.43, *p* = 0.047). Older patients had higher response rates than younger patients(β = 0.12, *p* = 0.04). There was no associations between trial duration or medication dosage and response rates.	
Consistency in results	No measure of consistency is reported.
Precision in results	Precise
Directness of results	Indirect (mixed antipsychotic classes combined).

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CI = Confidence Interval, *d* = Cohen's *d* and *g* = Hedges' *g* = standardised mean differences, FEP = first episode psychosis, FGA = First generation antipsychotic, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), MD = mean difference, N = number of participants, NS = non-significant, OR = odds ratio, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, Q_w = test for within group differences (heterogeneity in study results within a group of studies – measure of study consistency), Q_B = test for between group differences (heterogeneity between groups of studies for an outcome of interest), *r* = coefficient, RD = risk difference, RR = relative risk, SMD = standardised mean difference, vs. = versus, SGA = Second generation antipsychotic, vs. = versus, WMD = weighted mean difference, χ^2 = Chi-square test for heterogeneity between groups.

Margarete Ainsworth Building, Barker Street, Randwick NSW 2031. Phone: 02 9399 1000. Email: info@neura.edu.au

Explanation of technical terms

† Different effect measures are reported by different reviews.

Weighted mean difference scores refer to mean differences between treatment and comparison groups after treatment (or occasionally pre to post treatment) and in a randomised trial there is an assumption that both groups are comparable on this measure prior to treatment. Standardised mean differences are divided by the pooled standard deviation (or the standard deviation of one group when groups are homogenous) which allows results from different scales to be combined and compared. Each study's mean difference is then given a weighting depending on the size of the sample and the variability in the data. 0.2 represents a small effect, 0.5 a moderate effect, and 0.8 and over represents a large effect[11].

Odds ratio (OR) or relative risk (RR) refers to the probability of a reduction (< 1) or an increase (> 1) in a particular outcome in a treatment group, or a group exposed to a risk factor, relative to the comparison group. For example, a RR of 0.75 translates to a reduction in risk of an outcome of 25% relative to those not receiving the treatment or not exposed to the risk factor. Conversely, a RR of 1.25 translates to an increased risk of 25% relative to those not receiving treatment or not having been exposed to a risk factor. A RR or OR of 1.00 means there is no difference between groups. A medium effect is considered if RR > 2 or < 0.5 and a large effect if RR > 5 or < 0.2[12]. lnOR stands for logarithmic OR where a lnOR of 0 shows no difference between groups. Hazard ratios measure the effect of an explanatory variable on the hazard or risk of an event.

Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They are an indication of prediction, but do not confirm causality due to possible and often unforseen confounding variables. An r of 0.10 represents a weak association, 0.25 a medium association and 0.40 and over represents a strong association. Unstandardised (*b*) regression coefficients indicate the average change in the dependent variable associated with a 1 unit change in the independent variable, statistically controlling for the other independent variables. Standardised regression coefficients represent the change being in units of standard deviations to allow comparison across different scales.

---

‡ Inconsistency refers to differing estimates of effect across studies (i.e. heterogeneity or variability in results) that is not explained by subgroup analyses and therefore reduces confidence in the effect estimate. I^2 is the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance) - 0% to 40%: heterogeneity might not be important, 30% to 60%: may represent moderate heterogeneity, 50% to 90%: may represent considerable heterogeneity and over this is considerable heterogeneity. I^2 can be calculated from Q (chi-square) for the test of heterogeneity with the following formula[11];

$$I^2 = \left(\frac{Q - df}{Q}\right) \times 100\%$$

---

§ Imprecision refers to wide confidence intervals indicating a lack of confidence in the effect estimate. Based on GRADE recommendations, a result for continuous data (standardised mean differences, not

weighted mean differences) is considered imprecise if the upper or lower confidence limit crosses an effect size of 0.5 in either direction, and for binary and correlation data, an effect size of 0.25. GRADE also recommends downgrading the evidence when sample size is smaller than 300 (for binary data) and 400 (for continuous data), although for some topics, these criteria should be relaxed[13].

‖ Indirectness of comparison occurs when a comparison of intervention A versus B is not available but A was compared with C and B was compared with C that allows indirect comparisons of the magnitude of effect of A versus B. Indirectness of population, comparator and/or outcome can also occur when the available evidence regarding a particular population, intervention, comparator, or outcome is not available and is therefore inferred from available evidence. These inferred treatment effect sizes are of lower quality than those gained from head-to-head comparisons of A and B.

References

1. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMAGroup (2009): Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *British Medical Journal* 151: 264-9.
2. GRADEWorkingGroup (2004): Grading quality of evidence and strength of recommendations. *British Medical Journal* 328: 1490.
3. Alvarez-Jimenez M, Parker, A.G., Hetrick, S.E., McGorry, P.D., and Gleeson, J.F. (2009): Preventing the Second Episode: A Systematic Review and Meta-analysis of Psychosocial and Pharmacological Trials in First-Episode psychosis. *Schizophrenia Bulletin* doi:10.1093/schbul/sbp129.
4. Agid O, Kapur S, Arenovich T, Zipursky RB (2003): Delayed-onset hypothesis of antipsychotic action: a hypothesis tested and rejected. *Archives of General Psychiatry* 60: 1228-35.
5. Zhu Y, Krause M, Huhn M, Rothe P, Schneider-Thoma J, Chaimani A*, et al.* (2017): Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. *The Lancet Psychiatry* 4: 694-705.
6. Zhu Y, Li C, Huhn M, Rothe P, Krause M, Bighelli I*, et al.* (2017): How well do patients with a first episode of schizophrenia respond to antipsychotics: A systematic review and meta-analysis. *European Neuropsychopharmacology* 27: 835-44.
7. Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M*, et al.* (2018): Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis, and meta-regression. *JAMA Psychiatry* 75: 555-65.
8. Oliver D, Davies C, Crossland G, Lim S, Gifford G, McGuire P*, et al.* (2018): Can We Reduce the Duration of Untreated Psychosis? A Systematic Review and Meta-Analysis of Controlled Interventional Studies. *Schizophrenia bulletin* 44: 1362-72.
9. Thompson A, Winsper C, Marwaha S, Haynes J, Alvarez-Jimenez M, Hetrick S*, et al.* (2018): Maintenance antipsychotic treatment versus discontinuation strategies following remission from first episode psychosis: Systematic review. *BJPsych Open* 4: 215-25.
10. Kishi T, Ikuta T, Matsui Y, Inada K, Matsuda Y, Mishima K*, et al.* (2019): Effect of discontinuation v. maintenance of antipsychotic medication on relapse rates in patients with remitted/stable first-episode psychosis: a meta-analysis. *Psychological Medicine* 49: 772-9.
11. CochraneCollaboration (2008): Cochrane Handbook for Systematic Reviews of Interventions. Accessed 24/06/2011.
12. Rosenthal JA (1996): Qualitative Descriptors of Strength of Association and Effect Size. *Journal of Social Service Research* 21: 37-59.
13. GRADEpro (2008): [Computer program]. Jan Brozek, Andrew Oxman, Holger Schünemann. *Version 32 for Windows*