TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Mode of antipsychotic administration

Introduction

Studies have shown that about 80% of patients relapse to psychosis within 5 years of initial treatment. This is often due to lack of adherence to antipsychotic medications. Long-acting injectable antipsychotics are a treatment option for patients who are not adhering to treatment or who do not remember to take their oral preparations.

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 rated as having less than 50% of items checked 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 of staff of NeuRA (Neuroscience Research Australia).

Results

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

All antipsychotics

- Moderate to high quality evidence shows long-acting injectable second-generation antipsychotics are more effective than placebo injections for *symptom improvement*, with no differences when compared to oral antipsychotics. There were more extrapyramidal side effects with long-acting injectable second-generation antipsychotics than with placebo or oral antipsychotics (any type), and more weight gain with active injectables than placebo.
- Moderate to high quality evidence finds small effects of fewer relapses, longer time to relapse and fewer hospital days with long-acting injectable vs. oral second-generation

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antipsychotics. There was a large effect of lower *hospitalisation* rates in people on long-acting injectable antipsychotics, even though people on injectable antipsychotics had more severe and chronic illnesses. This effect was most robustly found in studies with; publication year ≥2010, academic sponsorship, large databases, retrospective databases, no need for informed consent, adjustment for differences in baseline patient characteristics, intent-to-treat analyses, higher quality, follow-up duration 6 to 12 months, and second-generation, long-acting injectable antipsychotics.

- High quality evidence finds no differences in rates of at least one *adverse event* between long-acting injectable antipsychotics and oral antipsychotics, although there was more extrapyramidal symptoms and low-density lipoprotein cholesterol change and less prolactin change with injectables. Moderate to high quality evidence also finds more anxiety and moderate to low quality evidence finds more akinesia with long-acting injectable antipsychotics.

Individual antipsychotics

- Moderate to high quality evidence finds no differences between long-acting injectable and oral risperidone in response or relapse and no differences in adverse effects, apart from a small effect of less hyperprolactinemia with long-acting injectable risperidone.
- Moderate to high quality evidence finds no differences between long-acting injectable and oral olanzapine in response or relapse apart from a small effect of more dropouts due to inefficacy with long-acting injectable olanzapine. There were no differences in adverse effects.
- Moderate to low quality evidence finds a small effect of fewer relapses with long-acting injectable fluphenazine compared to oral fluphenazine, and no differences in adverse effects.
- Moderate to high quality evidence finds no differences between long-acting injectable and oral aripiprazole in response, relapse or adverse effects.
- Moderate quality evidence finds no differences between long-acting injectable and oral haloperidol in response, relapse or adverse effects.

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Fusar-Poli P, Kempton MJ, Rosenheck RA

Efficacy and safety of second-generation long-acting injections in schizophrenia: a meta-analysis of randomized-controlled trials

International Clinical Psychopharmacology 2013; 28: 57-66

View review abstract online

Comparison	**Long-acting injectable second-generation antipsychotics vs. placebo injections or oral antipsychotics.**
Summary of evidence	**High quality evidence (large sample, consistent, precise, direct) shows long-acting injectable second-generation antipsychotics are more effective than placebo injections for symptom improvement. Moderate to high quality evidence finds no differences when compared to oral antipsychotics.** **There were greater risks of extrapyramidal side effects with long-acting injectable second-generation antipsychotics than with placebo or oral antipsychotics, and more weight gain with injectables than oral antipsychotics.**

Symptoms

A small to medium-sized improvement in symptoms with long-acting injectable second-generation antipsychotics over placebo;

6 RCTs, N = 2,627, g = 0.336, 95%CI 0.246 to 0.426, $p < 0.001$

No differences were found when compared to oral antipsychotics;

7 RCTs, N = 3,686, g = 0.072, 95%CI -0.072 to 0.217, p = 0.326

Sensitivity analyses on all RCTs found a significant effect of the type of antipsychotic; paliperidon was associated with the largest effect size, risperidone with the lowest, and olanzapine with the intermediate.

Smaller PANSS improvements were found in studies with a longer follow-up period.

There were no moderating effects of year of publication, proportion of males, or age.

Risks	There were more extrapyramidal side effects with long-acting injectable second-generation antipsychotics than with placebo or oral antipsychotics. There was a greater risk of weight gain with long-acting injectable second-generation antipsychotics compared to placebo, but not when compared to oral antipsychotics. There were no significant differences in any adverse event, or rates of insomnia, QT prolongation, or pain in the injection site.

Consistency in results	Authors report consistent results for placebo comparison, but inconsistent results for oral comparison.
Precision in results	Precise
Directness of results	Direct

Kishimoto T, Hagi K, Nitta M, Leucht S, Olfson M, Kane JM, Correll CU

Effectiveness of Long-Acting Injectable vs Oral Antipsychotics in Patients With Schizophrenia: A Meta-analysis of Prospective and Retrospective Cohort Studies

Schizophrenia Bulletin 2018; 44: 603-19

View review abstract online

Comparison	**Long-acting injectable antipsychotics vs. oral antipsychotics.** **Studies had follow-up ≥6 months.**
Summary of evidence	**Moderate to high quality (large samples, inconsistent, precise, direct) finds a large effect of lower hospitalisation rates with long-acting injectable vs. oral antipsychotics. This effect was most robustly found in studies with; publication year ≥2010, academic sponsorship, large databases, retrospective databases, no need for informed consent, adjustment for differences in baseline patient characteristics, intent-to-treat analyses, higher quality, follow-up duration 6 to 12 months, and second-generation long-acting injectable antipsychotics.** **There were no differences in the number of hospital days.**

Hospitalisation

A large effect of lower hospitalisation rates with long-acting injectable antipsychotics;

15 studies, RR = 0.85, person-years = 68,009, 95%CI 0.78 to 0.93, $p < 0.001$, $I^2 = 95\%$, $p < 0.001$

Rate = the number of hospitalisations divided by person-years at risk

A trend effect of lower hospitalisation risk with long-acting injectable antipsychotics;

33 studies, N = 51,733, RR = 0.92, 95%CI 0.84 to 1.00, $p = 0.06$, $I^2 = 85\%$, $p < 0.001$

Risk = the number of patients with ≥1 hospitalisation divided by the number of patients at risk

There were no significant differences in the number of hospital days;

11 studies, N = 21,328, $g = -0.05$, 95%CI -0.16 to 0.06, $p = 0.39$, $I^2 = 85\%$, $p < 0.001$

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Illness severity and chronicity were greater in people taking long-acting injectable antipsychotics. Lower rates of hospitalisation with long-acting injectable antipsychotics were most robustly found in studies with publication year ≥2010, studies having academic sponsorship, large database studies, retrospective database studies, studies with no need for informed consent, studies adjusting for differences in baseline patient characteristics, studies with intent-to-treat analyses, higher quality studies, studies with follow-up duration 6 to 12 months, and studies of second-generation long-acting injectable antipsychotics. Adjusting for potential publication bias found similar results.

Risks	There were fewer all-cause discontinuations with long-acting injectables.
Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Kishimoto T, Robenzadeh A, Leucht C, Leucht S, Watanabe K, Mimura M, Borenstein M, Kane JM, Correll CU

Long-Acting Injectable vs. Oral Antipsychotics for Relapse Prevention in Schizophrenia: A Meta-Analysis of Randomized Trials

Schizophrenia Bulletin 2014; 40(1): 192-213

View review abstract online

Comparison	**Long-acting injectable antipsychotics vs. oral antipsychotics.**
Summary of evidence	**Moderate to high quality (large sample, inconsistent, precise, direct) suggests no differences in relapse rates or discontinuation due to adverse events between people receiving long-acting injectable antipsychotics or oral antipsychotics.**
Relapse	
No significant differences in relapse rates; 21 RCTs, N = 4,950, RR = 0.93, 95%CI 0.80 to 1.08, $p = 0.35$, $I^2 = 58\%$, $p = 0.0005$	
Risks	There were no significant differences in the number of discontinuations due to adverse events.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Kishimoto T, Nitta M, Borenstein M, Kane JM, Correll CU

Long-Acting Injectable versus Oral Antipsychotics in Schizophrenia: A Systematic Review and Meta-Analysis of Mirror-Image studies

The Journal of Clinical Psychiatry 2013; 74(10): 957-965

View review abstract online

Comparison	**Long-acting injectable antipsychotics vs. oral antipsychotics.** **Mirror-image studies compared periods of oral then injectable antipsychotic treatment in the same patients.**
Summary of evidence	**Moderate to high quality evidence from mirror-image studies (large sample, inconsistent, precise, direct) finds fewer hospitalisations with long-acting injectable antipsychotics.**

Hospitalisations

A medium-sized effect showed fewer hospitalisations with long-acting injectable antipsychotics;

16 studies, N = 4,066, RR = 0.43, 95%CI 0.35 to 0.53, $p < 0.0001$, $I^2 = 87.6\%$, $p < 0.001$

Results were similar in studies of first-generation antipsychotics, risperidone, older or newer studies, those with large or small samples, studies from the U.S. or Europe, studies sponsored or not sponsored by industry, and studies that included or did not include dropouts in their analyses.

Consistency in results	Inconsistent
Precision in results	Precise
Directness of results	Direct

Lafeuille M, Dean J, Carter V, Duh MS, Fastenau J, Dirani R, Lefebvre P

Systematic review of long-acting injectables versus oral atypical antipsychotics on hospitalization in schizophrenia

Current Medical Research and Opinion 2014; 30(8): 1643-1655

View review abstract online

Comparison	**Long-acting injectable antipsychotics vs. second-generation oral antipsychotics.**
Summary of evidence	**Moderate quality evidence (large samples, appears inconsistent, imprecise, direct) finds fewer hospitalisations with long-acting injectable antipsychotics over second-generation antipsychotics.**
Hospitalisation	
There were fewer hospitalisations with long-acting injectable antipsychotics; 58 studies, N = 28,032, 56.2% vs. 35.5%, *p* = 0.023 Adjusting for age, sex, treatment resistance, and study scale increased this effect. *A trend effect of fewer hospitalisations with long-acting injectable antipsychotics was found at follow-up (≥6 months);* 47 studies, N = 100,711, estimate: -8.6, 95%CI -18.1 to 1.0, *p* = 0.077 Adjusted for age, sex, treatment resistance, study design (randomised or observational), study scale, baseline hospitalisation rates, study setting, and type of metrics.	
Consistency in results	No measure of consistency is reported; forest plots appear inconsistent.
Precision in results	Imprecise
Directness of results	Direct

Misawa F, Kishimoto T, Hagi K, Kane JM, Correll CU

Safety and tolerability of long-acting injectable versus oral antipsychotics: A meta-analysis of randomized controlled studies comparing the same antipsychotics

Schizophrenia Research 2016; 2-3: 220-230

View review abstract online

Comparison	**Long-acting injectable antipsychotics vs. oral antipsychotics.**
Summary of evidence	**High quality evidence (large samples, consistent, precise, direct) suggests no differences in serious adverse effects or rates of at least one adverse event, although there was more low-density lipoprotein cholesterol change and less prolactin change with long-acting injectable antipsychotics.** **Moderate to high quality evidence (imprecise) suggests more anxiety with second generation long-acting injectable antipsychotics, with no differences in treatment discontinuation due to adverse events or in death rates.** **Moderate to low quality evidence (small sample) finds more akinesia with long-acting injectable antipsychotics.**

Adverse events

16 RCTs, N = 4,902

There were significant differences in only 4 of 119 individual adverse events, with long-acting injectable antipsychotics associated with more;

Low-density lipoprotein cholesterol change: 4 RCTs, N = 1,950, SMD = 0.096, 95%CI 0.006 to 0.186, $p = 0.037$, I^2 p-value = 0.577

Anxiety: 7 RCTs (all assessing second generation long-acting injectable antipsychotics), N = 3,409, RR = 1.495, 95%CI 1.132 to 1.975, $p = 0.005$, I^2 p-value = 0.902

Akinesia: 1 RCT, N = 51, RR = 20.542, 95%CI 1.249 to 337.941, $p = 0.034$

Long-acting injectable antipsychotics were associated with less;

Prolactin change: 8 RCTs, N = 2,868, SMD = -0.152, 95%CI -0.262 to -0.043, $p = 0.006$, I^2 p-value = 0.080

There were no significant differences in;

Treatment discontinuation due to adverse events: 14 RCTs, N = 3,570, RR = 1.163, 95%CI 0.887 to 1.524, $p = 0.275$, $I^2 = 0\%$, $p = 0.486$

Serious adverse events: 6 RCTs, N = 1,848, RR = 0.907, 95%CI 0.662 to 1.242, $p = 0.542$, I^2 =

11%, $p = 0.343$ At least one adverse event: 7 RCTs, N = 2,686, RR = 1.026, 95%CI = 0.984 to 1.071, $p = 0.231$, $I^2 = 3.4\%$, $p = 0.400$ All-cause death: 14 RCTs, N = 4,127, RR = 0.613, 95%CI 0.177 to 2.128, $p = 0.441$, $I^2 = 0\%$, $p = 0.746$ In subgroup analysis, first generation long-acting injectable antipsychotics showed a trend effect toward a higher risk of treatment discontinuation due to adverse events than first generation oral antipsychotics. Authors report that imputing missing studies due to possible publication bias did not change the lack of difference regarding the primary outcome, treatment discontinuation due to adverse events.	
Consistency in results	Consistent
Precision in results	Precise, apart from akinesia, anxiety, treatment discontinuation and all-cause death.
Directness of results	Direct

Ostuzzi G, Bighelli I, So R, Furukawa TA, Barbui C

Does formulation matter? A systematic review and meta-analysis of oral versus long-acting antipsychotic studies

Schizophrenia Research 2017; 183: 10-21

View review abstract online

Comparison 1	**Long-acting injectable risperidone vs. oral risperidone.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency or imprecision, direct) finds no differences in response or relapse, and no differences in adverse effects, apart from a small effect of less hyperprolactinemia with long-acting injectable risperidone.**
Response and relapse	
No significant differences in; Response: 4 RCTs, N = 970, RR = 1.02, 95%CI 0.97 to 1.07, $p > 0.05$, $I^2 = 0\%$ Relapse: 2 RCTs, N = 291, RR = 0.45, 95%CI 0.05 to 3.82, $p > 0.05$, $I^2 = 84\%$ Dropouts due to inefficacy: 5 RCTs, N = 1,056, RR = 1.08, 95%CI 0.43 to 2.71, $p > 0.05$, $I^2 = 44\%$	

Adverse effects	
A small effect of less hyperprolactinemia with long-acting injectable risperidone; 5 RCTs, N = 891, RR = 0.81, 95%CI 0.68 to 0.98, $p < 0.05$, $I^2 = 32\%$ *No significant differences in;* Dropouts for adverse events: 5 RCTs, N = 1,056, RR = 1.01, 95%CI 0.67 to 1.53, $p > 0.05$, $I^2 = 0\%$ Extrapyramidal symptoms: 5 RCTs, N = 891, RR = 0.66, 95%CI 0.37 to 1.18, $p > 0.05$, $I^2 = 70\%$ Weight gain: 5 RCTs, N = 920, RR = 1.01, 95%CI 0.73 to 1.41, $p > 0.05$, $I^2 = 0\%$	
Consistency in results	Consistent, apart from relapse and extrapyramidal symptoms.
Precision in results	Imprecise, apart from response and hyperprolactinemia.
Directness of results	Direct
Comparison 2	**Long-acting injectable olanzapine vs. oral olanzapine.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) finds no differences in response or relapse apart from a small effect of more dropouts due to inefficacy with long-acting injectable olanzapine. There were no differences in adverse effects.**
Response and relapse	
A small effect of more dropouts due to inefficacy with long-acting injectable olanzapine; 2 RCTs, N = 1,445, RR = 1.52, 95%CI 1.12 to 2.07, $p < 0.05$, $I^2 = 0\%$ *No significant differences in;* Response: 2 RCTs, N = 1,445, RR = 1.01, 95%CI 0.96 to 1.07, $p > 0.05$, $I^2 = 0\%$ Relapse: 2 RCTs, N = 1,445, RR = 1.28, 95%CI 0.88 to 1.85, $p > 0.05$, $I^2 = 41\%$	
Adverse effects	
No significant differences in; Dropouts for adverse events: 2 RCTs, N = 1,445, RR = 1.13, 95%CI 0.73 to 1.74, $p > 0.05$, $I^2 = 0\%$ Extrapyramidal symptoms: 2 RCTs, N = 1,445, RR = 1.53, 95%CI 0.99 to 2.36, $p > 0.05$, $I^2 = 28\%$ Hyperprolactinemia: 2 RCTs, N = 1,202, RR = 1.07, 95%CI 0.90 to 1.27, $p < 0.05$, $I^2 = 0\%$ Weight gain: 2 RCTs, N = 1,445, RR = 1.02, 95%CI 0.80 to 1.30, $p > 0.05$, $I^2 = 0\%$	
Consistency in results	Consistent

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Precision in results	Imprecise, apart from response and hyperprolactinemia.
Directness of results	Direct
Comparison 3	**Long-acting injectable aripiprazole vs. oral aripiprazole.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) finds no differences in response, relapse or adverse effects.**
Response and relapse	
No significant differences in; Response: 2 RCTs, N = 986, RR = 0.98, 95%CI 0.93 to 1.04, $p > 0.05$, $I^2 = 9\%$ Relapse: 2 RCTs, N = 986, RR = 1.03, 95%CI 0.66 to 1.60, $p > 0.05$, $I^2 = 0\%$ Dropouts for inefficacy: 2 RCTs, N = 986, RR = 0.93, 95%CI 0.61 to 1.42, $p > 0.05$, $I^2 = 0\%$	
Adverse effects	
No significant differences in; Dropouts for adverse events: 2 RCTs, N = 986, RR = 0.93, 95%CI 0.80 to 1.30, $p > 0.05$, $I^2 = 0\%$ Extrapyramidal symptoms: 2 RCTs, N = 818, RR = 1.11, 95%CI 0.85 to 1.46, $p > 0.05$, $I^2 = 0\%$ Hyperprolactinemia: 2 RCTs, N = 659, RR = 6.25, 95%CI 0.33 to 120.01, $p > 0.05$, $I^2 = 0\%$ Weight gain: 2 RCTs, N = 847, RR = 0.85, 95%CI 0.64 to 1.14, $p > 0.05$, $I^2 = 5\%$	
Consistency in results	Consistent
Precision in results	Imprecise, apart from response.
Directness of results	Direct
Comparison 4	**Long-acting injectable zuclopenthixol vs. oral zuclopenthixol.**
Summary of evidence	**Low quality evidence (small sample, imprecise, direct) is unable to determine differences in response and adverse effects.**
Response	
No differences in dropouts for inefficacy; 1 RCT, N = 46, RR = 0.77, 95%CI 0.05 to 11.56, $p > 0.05$	
Adverse effects	

There were no dropouts due to adverse events in both groups.	
Consistency in results	N/A – 1 study
Precision in results	Imprecise
Directness of results	Direct
Comparison 5	**Long-acting injectable fluphenazine vs. oral fluphenazine.**
Summary of evidence	**Moderate to low quality evidence (small to large samples, some inconsistency, imprecise, direct) finds a small effect of fewer relapses with long-acting injectable fluphenazine, and no differences in adverse effects.**
Response and relapse	
A small effect of fewer relapses with long-acting injectable fluphenazine; 2 RCTs, N = 156, RR = 0.63, 95%CI 0.43 to 0.92, $p < 0.05$, $I^2 = 0\%$ *No significant differences in dropouts for inefficacy;* 4 RCTs, N = 469, RR = 0.85, 95%CI 0.61 to 1.18, $p > 0.05$, $I^2 = 0\%$	
Adverse effects	
No significant differences in; Dropouts for adverse events: 5 RCTs, N = 574, RR = 2.62, 95%CI 0.65 to 10.57, $p > 0.05$, $I^2 = 60\%$ Extrapyramidal symptoms: 2 RCTs, N = 122, RR = 4.43, 95%CI 0.08 to 260.31, $p > 0.05$, $I^2 = 88\%$ Weight gain: 1 RCT, N = 82, RR = 6.69, 95%CI 0.28 to 158.85, $p > 0.05$	
Consistency in results	Consistent, apart from dropouts for adverse events and extrapyramidal symptoms.
Precision in results	Imprecise
Directness of results	Direct
Comparison 5	**Long-acting injectable haloperidol vs. oral haloperidol.**
Summary of evidence	**Moderate quality evidence (medium-sized samples, consistent where applicable, imprecise, direct) finds no differences in response, relapse or adverse effects.**
Response and relapse	
No significant differences in;	

Response: 1 RCT, N = 288, RR = 1.03, 95%CI 0.91 to 1.15, $p > 0.05$ Relapse: 2 RCTs, N = 310, RR = 1.00, 95%CI 0.41 to 2.42, $p > 0.05$, $I^2 = 0\%$ Dropouts for inefficacy: 1 RCT, N = 288, RR = 2.00, 95%CI 0.51 to 7.84, $p > 0.05$
Adverse effects
No significant differences in; Dropouts for adverse events: 1 RCT, N = 288, RR = 1.33, 95%CI 0.47 to 3.75, $p > 0.05$ Extrapyramidal symptoms: 2 RCTs, N = 305, RR = 1.11, 95%CI 0.68 to 1.80, $p > 0.05$, $I^2 = 0\%$ Weight gain: 1 RCT, N = 283, RR = 0.50, 95%CI 0.25 to 1.00, $p > 0.05$

Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct

Park SC, Choi MY, Choi J, Park E, Tchoe HJ, Suh JK, Kim YH, Won SH, Chung YC, Bae KY, Lee SK, Park CM, Lee SH

Comparative efficacy and safety of long-Acting injectable and oral second-generation antipsychotics for the treatment of schizophrenia: A systematic review and meta-Analysis

Clinical Psychopharmacology and Neuroscience 2018; 16: 361-75

View review abstract online

Comparison	**Pre-post analysis of long-acting injectable vs. oral second-generation antipsychotics.**
Summary of evidence	**Moderate to high quality evidence (large samples, some inconsistency, precise, direct) finds fewer relapses and hospital days with long-acting injectable second-generation antipsychotics, however there was more extrapyramidal and prolactin-related side effects.**
Symptoms	
No significant differences between groups on PANSS total scores (both groups improved); 9 RCTs, N not reported, SMD = -0.05; 95%CI -0.12 to 0.12, $p > 0.05$, I^2 not reported	

Relapse and non-compliance	
A small, significant effect of fewer relapses with injectables; 6 RCTs, N = 2,886, RR = 0.85, 95%CI 0.74 to 0.99, $p < 0.05$, I^2 not reported *The group treated with injectables had significantly longer time to relapse;* 2 RCTs, N = 1,003, SMD = 0.42, 95%CI 0.29 to 0.54, $p < 0.05$, $I^2 = 90\%$	
Hospitalisation	
No significant difference between groups in hospitalisation rates; 4 RCTs, N = 1,518, RR = 0.83, 95%CI, 0.62 to 1.11, $p > 0.05$, $I^2 = 29\%$ *The mean hospital days was significantly shorter with injectables;* 2 RCTs, N = 1,444, SMD = -0.11, 95%CI -0.22 to -0.01, $p < 0.05$, I^2 not reported	
Remission	
No significant difference between groups in remission rates; 5 RCTs, N = 2,161, RR = 1.07, 95%CI 0.99 to 1.15, $p > 0.05$, $I^2 = 70\%$. *The remission rate was significantly greater with injectables in studies lasting ≥1 year;* RR = 1.42, 95%CI 1.18 to 1.71, $p < 0.05$	
Risks	There were more extrapyramidal and prolactin-related side effects with injectables. There were no significant differences in akathisia, insomnia, and weight gain.
Consistency in results	Some inconsistency
Precision in results	Precise
Directness of results	Direct

Explanation of acronyms

CI = confidence interval, *g* = Hedges' *g* standardised mean difference, I^2 = the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance), N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), RCT = randomised controlled trials, RR = relative risk or rate ratio, SMD = standardised mean difference, vs. = versus

Explanation of technical terms

* Bias has the potential to affect reviews of both RCT and observational studies. Forms of bias include; reporting bias – selective reporting of results; publication bias - trials that are not formally published tend to show less effect than published trials, further if there are statistically significant differences between groups in a trial, these trial results tend to get published before those of trials without significant differences; language bias – only including English language reports; funding bias - source of funding for the primary research with selective reporting of results within primary studies; outcome variable selection bias; database bias - including reports from some databases and not others; citation bias - preferential citation of authors. Trials can also be subject to bias when evaluators are not blind to treatment condition and selection bias of participants if trial samples are small[11].

† Different effect measures are reported by different reviews.

Prevalence refers to how many existing cases there are at a particular point in time. Incidence refers to how many new cases there are per population in a specified time period. Incidence is usually reported as the number of new cases per 100,000 people per year. Alternatively some studies present the number of new cases that have accumulated over several years against a person-years denominator. This denominator is the sum of individual units of time that the persons in the population are at risk of becoming a case. It takes into account the size of the underlying population sample and its age structure over the duration of observation.

Reliability and validity refers to how accurate the instrument is. Sensitivity is the proportion of actual positives that are correctly identified (100% sensitivity = correct identification of all actual positives) and specificity is the proportion of negatives that are correctly identified (100% specificity = not identifying anyone as positive if they are truly not).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 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.

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Correlation coefficients (eg, r) indicate the strength of association or relationship between variables. They can provide an indirect 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, which 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.

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