TECHNICAL COMMENTARY

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SCHIZOPHRENIA LIBRARY

Treatments for aggression and agitation

Introduction

Agitation and/or aggression are sometimes observed during a psychiatric emergency such as in onset of acute psychosis. Agitation typically includes irritability and restlessness, motor or verbal hyperactivity, uncooperativeness, and occasionally aggressive gestures or behaviour. This can pose a risk both to the individual, as well as the attending health care professionals, and so is important to manage this behaviour and prevent potential harm. A number of pharmacological therapies have been tested for quickly alleviating agitated or aggressive behaviour in people with schizophrenia.

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 seven systematic reviews that met inclusion criteria[3-9].

- Moderate quality evidence finds a small to medium-sized effect of less hostility with second-generation antipsychotics than with first-generation antipsychotics, particularly when given in high doses (>500mg chlorpromazine equivalent).
- For particular antipsychotics, moderate to high quality evidence finds haloperidol was more effective than placebo for sedation, agitation, and mental state in the short term,

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but haloperidol induced more extrapyramidal symptoms. There were small benefits of aripiprazole over placebo for agitation and needing fewer additional injections, with no differences in side effects.

- Moderate to high quality evidence finds haloperidol had similar benefit to aripiprazole for aggression, but less need for an additional injection. Aripiprazole had less overall side effects than haloperidol.
- Moderate quality evidence finds olanzapine was more beneficial than haloperidol for sedation, agitation and adverse effects, particularly extrapyramidal symptoms. There was also less agitation and better global state with olanzapine compared to aripiprazole, although there was more somnolence with olanzapine.
- Moderate quality evidence finds haloperidol was more effective than risperidone for sedation and aggression but resulted in more akathisia. Ziprasidone had similar benefit to haloperidol for sedation and aggression but had fewer side effects. Droperidol resulted in less need for an additional injection than haloperidol.
- Moderate to low quality evidence suggests a medium-sized benefit of 5-10mg of aerosol loxapine for reducing agitation compared to inhaled placebo.
- For combination therapies, moderate to low quality evidence finds people receiving adjunctive benzodiazepines were more likely to be sedated for up to one hour, but were not less aggressive after one hour, than those on antipsychotics alone. Parkinsonism was lower and somnolence was higher with benzodiazepines. Haloperidol plus promethazine was more effective than haloperidol alone for sedation and resulted in fewer overall adverse effects, particularly dystonia. Risperidone plus clonazepam resulted in more overall adverse effects than haloperidol, particularly extrapyramidal symptoms, with no differences in sedation or agitation.

Citrome L

Aerosolised antipsychotic assuages agitation: inhaled loxapine for agitation associated with schizophrenia or bipolar disorder

International J Clinical Practice 2011; 65(3): 330-340

View review abstract online

Citrome L

Inhaled loxapine for agitation revisited: focus on effect sizes from 2 Phase III randomised controlled trials in persons with schizophrenia or bipolar disorder

International J Clinical Practice 2012; 66(3): 318-325

View review abstract online

Comparison	**Efficacy of inhaled loxapine (5 or 10mg) vs. inhaled placebo.**
Summary of evidence	**Moderate to low quality evidence (small to medium-sized samples, unable to assess consistency or precision, direct) suggests a medium-sized effect of 5-10mg of aerosol loxapine for reducing agitation.**
1 RCT (N = 129) found that loxapine 10mg was significantly superior to placebo by 20 minutes post-dose for reducing PANSS-excitation scores ($p < 0.05$), but ta 5mg dose had only a trend effect by 45 minutes ($p = 0.051$). 1 RCT (N = 344) reported a significant effect of both 5mg and 10mg doses of loxapine for reduced PANSS-excitation and CGI scores compared to placebo at 10 minutes ($p = < 0.05$, d not reported). At 2 hours, both doses showed a medium, significant effect (PANSS: 5mg $d = 0.45$; 10mg $d = 0.60$, CGI: 5mg $d = 0.45$; 10mg $d = 0.63$).	
Risks	Dose-response effects were observed for mild throat irritation and moderate sedation.
Consistency in results‡	No measure of consistency is reported.
Precision in results§	No measure of precision is reported.
Directness of results‖	Direct

Faay MDM, Czobor P, Sommer IEC

Efficacy of typical and atypical antipsychotic medication on hostility in patients with psychosis-spectrum disorders: a review and meta-analysis

Neuropsychopharmacology 2018; 43: 2340-9

View review abstract online

Comparison	**First-generation antipsychotics (mostly haloperidol) vs. second-generation antipsychotics (risperidone, clozapine, olanzapine, quetiapine, ziprasidone or amisulpride) for at least 4 weeks.**
Summary of evidence	**Moderate quality evidence (large sample, inconsistent, unable to assess imprecision, direct) suggests a small to medium-sized effect of less hostility with second-generation antipsychotics, particularly in high doses (>500mg chlorpromazine equivalent).**

Hostility

A small effect of reduced hostility with second generation antipsychotics;

10 RCTs, N = 6,799, $g = 0.260$, CI not reported, $p = 0.025$, $I^2 = 93\%$

Subgroup analyses showed a medium-sized effect of high-dose second-generation antipsychotics (>500mg chlorpromazine equivalent, $g = 0.567$) and no effect of low-dose second-generation antipsychotics (<500mg; $g = 0.023$). Double-blind studies had a slightly larger effect than open label studies ($g = 0.280$ vs. $g = 0.136$). The effect was similar in sponsored and non-sponsored studies ($g = 0.262$ vs. $g = 0.248$).

Risks	Not reported
Consistency in results	Inconsistent
Precision in results	Unable to assess; no CIs reported.
Directness of results	Direct antipsychotic class.

Ostinelli EG, Brooke-Powney MJ, Li X, Adams CE

Haloperidol for psychosis-induced aggression or agitation (rapid tranquillisation)

Cochrane Database of Systematic Reviews 2017; 7: CD009377

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View review abstract online	
Comparison	**Efficacy of haloperidol for reducing agitation or aggression compared to placebo or other antipsychotics, and compared to benzodiazepines and other agents, in patients with acute psychotic symptoms (majority with schizophrenia).**
Summary of evidence	**Moderate to high quality evidence (medium to large samples, mostly consistent and precise, direct) suggests haloperidol was effective for sedation, reducing agitation, and improving short term mental state, but induced extrapyramidal symptoms compared to placebo. Compared to aripiprazole, haloperidol had equal benefit for aggression, but less need for an additional injection. Aripiprazole had less side effects.** **Moderate quality evidence (small to medium-sized samples, consistent, mostly imprecise, direct) shows that olanzapine had benefits over haloperidol for sedation, agitation and adverse effects particularly extrapyramidal symptoms. Droperidol had benefit over haloperidol for less need for additional injection. Ziprasidone showed equivalent benefits to haloperidol for sedation/aggression but had fewer side effects. Haloperidol was more effective than risperidone for sedation and aggression but had more akathisia.** **Moderate to low quality evidence (small to medium-sized samples, mostly imprecise and inconsistent or unable to assess, direct) suggests haloperidol plus promethazine may be more beneficial than haloperidol alone for sedation and results in fewer overall adverse effects, particularly dystonia. However, risperidone plus clonazepam results in more overall adverse effects than haloperidol, particularly extrapyramidal symptoms.** **Any benefit of haloperidol for sedation, agitation or aggression over chlorpromazine, quetiapine, loxapine, perphenazine, thiothixene, benzodiazepines, other agents or other combination therapies is unclear due to small samples.**
Haloperidol vs. placebo	
Significant, small to medium-sized benefits of haloperidol for: Sedation (asleep at 2 hours): 2 RCTs, N = 220, RR = 0.88, 95%CI 0.82 to 0.95, p = 0.00073, Q = 4.17, p = 0.04, I^2 = 76% Less need for repeat doses: 4 RCTs, N = 660, R = 0.51, 95%CI 0.42 to 0.62, p < 0.0001, Q = 3.57, p = 0.31, I^2 = 16% Less need for benzodiazapines: 4 RCTs, N = 660, R = 0.44, 95%CI 0.31 to 0.62, p < 0.0001, Q =	

3.57, p = 0.18, I^2 = 38% Agitated behaviour: 2 RCTs, N = 395, RR = 1.62, 95%CI 1.28 to 2.07, p = 0.000077, Q= 0.06, p = 0.81, I^2 = 0% Global state – CGI-S endpoint score: 2 RCTs, N = 390, MD = -0.73, 95%CI -0.96 to -0.51, p < 0.0001, Q= 0.00, p = 0.97, I^2 = 0% Mental state – BPRS-total at 2 hours: 3 RCTs, N = 371 MD = -5.69, 95%CI -7.38 to -4.00, p < 0.0001, Q= 0.09, p = 0.95, I^2 = 0% Leaving the study early (lack of efficacy): 3 RCTs, N = 435, RR = 0.12, 95%CI 0.03 to 0.49, p = 0.0032, Q= 2.30, p = 0.32, I^2 = 13%	
Risks	*Significant increased risks with haloperidol of;* Extrapyramidal symptoms within 24 hours: 3 RCTs, N = 398, RR = 6.79, 95%CI 2.19-21.07, p = 0.0009, I^2 = 0% Need for anti-parkinson drugs: 1 RCT, N = 180, RR = 5.57, 95%CI 1.37-22.65, p = 0.016. One or more adverse events in 24 hours: 2 RCTs, N = 395, RR = 1.64, 95%CI 1.22-2.20, p = 0.001, I^2 = 0% Over-sedation: 2 RCTs, N = 313, RR = 3.36, 95%CI 1.42-7.99, p = 0.006, I^2 = 0% There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable apart from sedation and leaving the study early for any reason.
Precision in results	Precise apart from agitated behaviour, leaving the study early, and adverse effects. Unable to assess MDs.
Directness of results	Direct
Haloperidol vs. aripiprazole	
Significant, small benefit of less need for additional injection with haloperidol; 2 RCTs, N = 473, R = 0.78, 95%CI 0.62 to 0.99, p = 0.045, Q = 0.70, p = 0.40, I^2 = 0% *No significant difference between groups for;* Agitated behaviour: 2 RCTs, N = 477, RR = 1.07, 95%CI 0.92 to 1.26, p = 0.37, Q= 0.17, p = 0.68, I^2 = 0% Need for benzodiazepines: 2 RCTs, N = 477, RR = 1.26, 95%CI 0.74 to 2.16, p = 0.39, Q= 0.95, p = 0.33, I^2 = 0% Global state – CGI-I endpoint score: 2 RCTs, N = 470, MD = -0.02, 95%CI -0.23 to 0.19, p = 0.84, Q= 0.26, p = 0.61, I^2 = 0%	

Mental state – BPRS-total at 2 hours: 1 RCT, N = 102 MD = -2.03, 95%CI -5.76 to 1.70, *p* = 0.29	
Risks	*Significant increased risks with haloperidol of;* Insomnia (IM): 1 RCT, N = 360, RR = 2.08, 95%CI 1.01-4.27, *p* = 0.046 Dyspepsia: 1 RCT, N = 360, RR = 10.41, 95%CI 1.36-79.76, *p* = 0.024 Dystonia (IM): 2 RCTs, N = 477, RR = 6.63, 95%CI 1.52-28.86, *p* = 0.012, I^2 = 0% Extrapyramidal (IM): 1 RCT, N = 360, RR = 9.46, 95%CI 1.22-73.13, *p* = 0.031 Extrapyramidal (oral): 1 RCT, N = 360, RR = 7.09, 95%CI 1.65-30.58, *p* = 0.0086 Use of anti-parkinson drugs: 1 RCT, N = 360, RR = 4.94, 95%CI 2.50-9.78, *p* < 0.0001 Increased severity of adverse effect after 2nd injection: 1 RCT, N = 360, RR = 1.34, 95%CI 1.03-1.74, *p* < 0.05 Overall adverse effects by 72 hours: 1 RCT, N = 360, RR = 1.33, 95%CI 1.04-1.70, *p* < 0.05 *Significant increased risks with aripiprazole of;* Nausea (IM): 2 RCTs, N = 477, RR = 0.18, 95%CI 0.05-0.60, *p* = 0.005, I^2 = 0%. There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable.
Precision in results	Precise apart from need for additional benzodiazepine and adverse effects. Unable to assess MDs.
Directness of results	Direct
Haloperidol vs. chlorpromazine	
Significant small to medium-sized benefit of chlorpromazine over haloperidol for; Sedation: 1 RCT, N = 39, RR = 1.93, 95%CI 1.04 to 3.60, *p* = 0.039 *Significant large size benefit of haloperidol over chlorpromazine for;* Any global improvement: 2 RCTs, N = 89, RR = 0.15, 95%CI 0.05 to 0.49, *p* = 0.0017, Q= 0.09, *p* = 0.76, I^2 = 0% Leaving the study early (any reason): 4 RCTs, N = 153, RR = 0.21, 95%CI 0.07 to 0.71, *p* = 0.011,	

Q= 0.87, *p* = 0.35, I^2 = 0% *No significant difference between groups for;* Need for urgent additional injection: 1 RCT, N = 30, RR = 1.07, 95%CI 0.89 to 4.26, *p* = 0.45	
Risks	*Significant increased risks with chlorpromazine of;* Drowsiness: 1 RCT, N = 39, RR = 0.06, 95%CI 0.01-0.42, *p* = 0.0049. There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable.
Precision in results	Precise apart from sedation, need for urgent injection and adverse effects.
Directness of results	Direct
Haloperidol vs. droperidol	
Significant medium-sized effect of more need of additional injection with haloperidol; 2 RCTs, N = 255, RR = 2.38, 95%CI 1.27 to 4.47, *p* = 0.0068, Q = 0.03, *p* = 0.85, I^2 = 0% *No significant difference between groups for;* Sedation: 1 RCT, N = 228, RR = 1.07, 95%CI 0.44 to 2.60, *p* > 0.05 Need for benzodiazepines: 1 RCT, N = 228, RR = 0.31, 95%CI 0.07 to 1.44, *p* > 0.05	
Risks	There were no significant differences in adverse events.
Consistency in results	Consistent where applicable
Precision in results	Imprecise
Directness of results	Direct
Haloperidol vs. loxapine	
Significant benefit of loxapine over haloperidol for; Mental state - BPRS score: 1 RCT, N = 52, MD = 6.10, 95%CI 4.48 to 7.72, *p* < 0.00001 *No significant difference between groups for;* Tranquilisation: 1 RCT, N = 54, RR = 4.31, 95%CI 0.54 to 34.48, *p* = 0.17 Aggression: 1 RCT, N = 30, RR = 1.10, 95%CI 0.69 to 1.76, *p* = 0.1769 Global state – CGI-I improvement at endpoint: 1 RCT, N = 35, RR = 0.40, 95%CI 0.12 to 1.32, *p* = 0.13	

Global state – not sedated by 120 minutes: 1 RCT, N = 30, RR = 7.00, 95%CI 0.98 to 50.16, *p* = 0.053 Leaving the study early (any reason): 1 RCT, N = 35, RR = 0.94, 95%CI 0.42 to 2.13, *p* = 0.89 Leaving the study early (adverse effects): 1 RCT, N = 35, RR = 2.84, 95%CI 0.12 to 65.34, *p* = 0.51	
Risks	*Haloperidol had increased risk of;* Drowsiness (oral admin): 1 RCT, N = 35, RR = 33.16, 95%CI 2.15-511.57, *p* = 0.012. There were no significant differences in other adverse events.
Consistency in results	Not applicable; 1 RCT
Precision in results	Imprecise
Directness of results	Direct
Haloperidol vs. olanzapine	
Significant benefit of haloperidol over olanzapine for; Time to discontinuation of medication: 1 RCT, N = 100, MD = -3.48, 95%CI -6.28 to -0.68, *p* = 0.015 *Significant small benefit of olanzapine over haloperidol for;* Sedation (asleep by 2 hours): 1 RCT, N = 257, RR = 1.16, 95%CI 1.02 to 1.32, *p* = 0.025 Agitation (ABS change score): 1 RCT, N = 85, MD = 2.70, 95%CI 0.38 to 5.02, *p* = 0.022 Leaving the study early (any reason): 2 RCTs, N = 147, RR = 1.66, 95%CI 1.04 to 2.65, *p* = 0.35, Q = 0.00, *p* = 1.0, I^2 = 0% Leaving the study early (adverse event): 1 RCT, N = 100, RR = 8.67, 95%CI 1.13 to 66.75, *p* = 0.038 *No significant difference between groups for;* Need for additional tranquilisation: 3 RCTs, N = 392, RR = 1.06, 95%CI 0.75 to 1.51, *p* = 0.73, Q = 2.51, *p* = 0.29, I^2 = 20% Reduction in agitation by 2 hours (PANSS-EC): 1 RCT, N = 45, RR = 0.96, 95%CI 0.58 to 1.58, *p* = 0.86 Agitation (ACES change score): 1 RCT, N = 46, MD = -0.30, 95%CI -1.34 to 0.74, *p* = 0.57 Agitation (PANSS-EC endpoint score): 1 RCT, N = 246, MD = -1.08, 95%CI -2.44 to 0.28, *p* = 0.12, Q = 0.60, *p* = 0.44, I^2 = 0% Hostility: 1 RCT, N = 49, RR = 0.35, 95%CI 0.01 to 8.12, *p* = 0.51 Need for benzodiazepines (in 24 hours): 2 RCTs, N = 343, RR = 1.05, 95%CI 0.63 to 1.74, *p* = 0.85, Q = 2.42, *p* = 0.12, I^2 = 59%	

Need for additional restraint or seclusion: 1 RCT, N = 100, RR = 0.96, 95%CI 0.40 to 2.29, *p* = 0.93 Days to discharge: 1 RCT, N = 100, MD = -0.60, 95%CI -1.85 to 0.65, *p* = 0.35 Global state – CGI-I change score: 1 RCT, N = 243, MD = 0.00, 95%CI -0.20 to 0.20, *p* = 1.00 Global state – CGI-I endpoint score: 1 RCT, N = 42, MD = -0.10, 95%CI -0.65 to 0.45, *p* = 0.72 Global state – CGI-S change score: 1 RCT, N = 86, MD = 0.00, 95%CI -0.24 to 0.24, *p* = 1.00 Anxiety: 1 RCT, N = 49, RR = 0.35, 95%CI 0.01 to 8.12, *p* = 0.51 Delusions: 1 RCT, N = 49, RR = 0.35, 95%CI 0.01 to 8.12, *p* = 0.51 Nervousness: 1 RCT, N = 100, RR = 2,17, 95%CI 0.70 to 6.74, *p* = 0.18 PANSS Total: 1 RCT, N = 100, MD = 4.70, 95%CI -0.18 to 9.58, *p* = 0.059 BPRS-positive: 1 RCT, N = 46, MD = -0.30, 95%CI -2.11 to 1.51, *p* = 0.75 BPRS-total: 1 RCT, N = 46, MD = -0.70, 95%CI -5.42 to 4.02, *p* = 0.77 Leaving the study early (lack of efficacy): 1 RCT, N = 100, RR = 0.43, 95%CI 0.09 to 2.13, *p* = 0.30	
Risks	*Olanzapine had decreased risk of:* One or more drug related effects: 1 RCT, N = 149, RR = 1.26, 95%CI 1.01-1.59, *p* = 0.045 Dystonia: 2 RCTs, N = 343, RR = 12.92, 95%CI 1.67-99.78, *p* = 0.014, I^2 = 0% Extrapyramidal effects: 2 RCTs, N = 343, RR = 7.65, 95%CI 1.78 - 32.98, *p* = 0.0063, I^2 = 0% Movement disorder (SAS): 1 RCT, N = 242, RR = 1.31, 95%CI 0.56-2.06, *p* = 0.00061. There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable.
Precision in results	Imprecise
Directness of results	Direct
Haloperidol vs. perphenazine	
No significant difference between groups for; Global improvement: 1 RCT, N = 44, RR = 0.46, 95%CI 0.04 to 4.68, *p* = 0.51	
Risks	There were no significant differences in adverse events.
Consistency in results	Not applicable – 1 RCT.

Precision in results	Imprecise
Directness of results	Direct
Haloperidol vs. quetiapine	
No significant difference between groups for; Agitation: 1 RCT, N = 80, RR = 0.10, 95%CI -0.56 to 0.76, $p > 0.05$	
Risks	There were no significant differences in adverse events.
Consistency in results	Not applicable – 1 RCT.
Precision in results	Imprecise
Directness of results	Direct
Haloperidol vs. risperidone	
Significant small benefit of haloperidol for; Sedation by 30 minutes: 1 RCT, N = 162, RR = 0.84, 95%CI 0.74 to 0.95, $p = 0.0057$ Aggression at 30 minutes: 1 RCT, N = 147, MD = -0.50, 95%CI -0.58 to -0.42, $p < 0.00001$ *No significant difference between groups for;* Agitation - PANSS-EC score: 1 RCT, N = 124, RR = 0.96, 95%CI 0.79 to 1.16, $p = 0.67$ Discontinued due to severe agitation: 1 RCT, N = 124, RR = 0.33, 95%CI 0.01 to 8.03, $p = 0.50$ Needing additional benzodiazepine: 2 RCTs, N = 286, RR = 0.98, 95%CI 0.65 to 1.47, $p = 0.92$, Q = 0.14, $p = 0.71$, $I^2 = 0\%$ Additional dose of lorazepam: 1 RCT, N = 147, MD = -0.10, 95%CI -0.49 to 0.29, $p = 0.61$ Time to additional dose: 1 RCT, N = 147, MD = 0.20, 95%CI -2.17 to 2.57, $p = 0.87$ Global state CGI-S at 24 hours: 1 RCT, N = 162, RR = 0.89, 95%CI 0.51 to 1.58, $p = 0.70$ Leaving the study early (any reason): 1 RCT, N = 124, RR = 0.33, 95%CI 0.01 to 8.03, $p = 0.50$	
Risks	*Haloperidol had decreased risk of:* Heartbeat change: 1 RCT, N = 162, MD = -9.40, 95%CI -9.99 to -8.81, $p < 0.0001$. *Risperidone had decreased risk of:* Akathisia: 1 RCT, N = 162, RR = 0.30, 95%CI 0.24-0.36, $p < 0.0001$. There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable.

Precision in results	Precise for sedation, agitation, akathisia. Unable to assess MDs.
Directness of results	Direct
Haloperidol vs. thiothixene	
No significant difference between groups for; Need for rapid tranquilisation: 1 RCT, N = 30, RR = 1.07, 95%CI 0.89 to 1.28, *p* = 0.47 Agitation: 1 RCT, N = 44, RR = 0.28, 95%CI 0.01 to 6.52, *p* = 0.43 No response to injection: 1 RCT, N = 44, RR = 2.50, 95%CI 0.57 to 11.05, *p* = 0.23	
Risks	*Thiothixene had decreased risk of:* Drowsiness: 2 RCTs, N = 74, RR = 1.72, 95%CI 1.02-2.90, *p* = 0.041, I^2 = 0%. There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable
Precision in results	Mostly imprecise
Directness of results	Direct
Haloperidol vs. ziprasidone	
Significant medium-sized benefit of ziprasidone for; Global state CGI-S at 72 hours: 1 RCT, N = 132, RR = 0.34, 95%CI 0.13 to 0.55, *p* = 0.0018 *Significant benefit of haloperidol for;* Mental state – PANSS negative: 1 RCT, N = 231, MD = -4.19, 95%CI -5.71 to -2.67, *p* < 0.0001 *No significant difference between groups for;* Agitation at 2 hours: 1 RCT, N = 231, MD = 0.06, 95%CI -1.13 to 1.25, *p* = 0.92 Needing anxiolytic by 7 days: 1 RCT, N = 132, RR = 1.11, 95%CI 0.84 to 1.48, *p* = 0.47 Need hypnotics for night-sedation: 1 RCT, N = 132, RR = 0.71, 95%CI 0.20 to 2.50, *p* = 0.60 Mental state – PANSS total: 1 RCT, N = 231, MD = 2.45, 95%CI -2.19 to 7.09, *p* = 0.30 Mental state – PANSS positive: 1 RCT, N = 231, MD = 1.11, 95%CI -0.45 to 2.67, *p* = 0.16 Mental state – PANSS general: 1 RCT, N = 231, MD = 0.0, 95%CI -2.27 to 2.27, *p* = 1.0 Mental state – BPRS-change at 72 hours: 3 RCTs, N = 511, MD = -0.43, 95%CI -1.93 to 1.07, *p* = 0.58, Q = 8.96, *p* = 0.01, I^2 = 78% Leaving the study early (adverse events): 2 RCTs, N = 508, RR = 2.40, 95%CI 0.45 to 12.75, *p* =	

0.30, Q = 0.79, p = 0.37, I^2 = 0%	
Risks	*Ziprasidone had decreased risk of:* Any adverse event: 4 RCTs, N = 799, RR = 1.74, 95%CI 1.47-2.06, p < 0.0001, I^2 = 54% Akathisia: 3 RCTs, N = 739, RR = 2.32, 95%CI 1.34-4.01, p = 0.0025, I^2 = 24% Dystonia: 2 RCTs, N = 508, RR = 10.26, 95%CI 1.67-63.17, p = 0.012, I^2 = 0% Extrapyramidal: 2 RCTs, N = 508, RR = 19.13, 95%CI 7.59 -48.21, p < 0.0001, I^2 = 0% Use of antiparkinson drug: 1 RCT, N = 132, RR = 3.30, 95%CI 1.82-5.97, p = 0.000084 Myotonia: 1 RCT, N = 231, RR = 3.84, 95%CI 1.85-8.00, p = 0.00032 Blurred vision: 1 RCT, N = 231, RR = 3.97, 95%CI 1.15-13.68, p = 0.029 Dry mouth: 1 RCT, N = 231, RR = 2.97, 95%CI 1.22-7.22, p = 0.016 Hypersalivation: 1 RCT, N = 231, RR = 2.55, 95%CI 1.11-5.87, p = 0.028 Abnormal ECG: 2 RCTs, N = 607, RR = 0.38, 95%CI 0.17-0.84, p = 0.018, I^2 = 0% There were no significant differences in other adverse events.
Consistency in results	Consistent where applicable, apart from BPRS change scores.
Precision in results	Imprecise apart from global state.
Directness of results	Direct
Haloperidol vs. other agents	
Significant, medium-sized benefit of zuclopenthixol over haloperidol for; Need for rapid tranquilisation: 1 RCT, N = 70, RR = 2.54, 95%CI 1.19 to 5,46, p = 0.017 *No difference between haloperidol and flunitrazepam for;* Aggression: 1 RCT, N = 28, RR = 1.15, 95%CI 0.86 to 1.55, p = 0.35 *No difference between haloperidol and lorazepam for;* Sedation: 1 RCT, N = 60, RR = 1.05, 95%CI 0.76 to 1.44, p = 0.77 Need for rapid tranquilisation: 1 RCT, N = 66, RR = 1.14, 95%CI 0.91 to 1.43, p = 0.24	

Global improvement: 1 RCT, N = 44, RR = 1.10, 95%CI 0.70 to 1.71, *p* = 0.69 BPRS endpoint score: 1 RCT, N = 37, RR = 3.26, 95%CI -4.13 to 10.65, *p* = 0.39 *No difference between haloperidol and midazolam for;* Need for rescue drug: 1 RCT, N = 84, RR = 1.14, 95%CI 0.46 to 2.87, *p* = 0.78	
Risks	*There were no significant differences in adverse events apart from fewer extrapyramidal symptoms with lorazepam;* 1 RCT, N = 66, RR = 15.00, 95%CI 2.11 -106.49, *p* = 0.0068
Consistency in results	Not applicable
Precision in results	Imprecise
Directness of results	Direct
Haloperidol vs. combinations	
Haloperidol vs. haloperidol plus lorazepam - favours combination for; Asleep by 3 hours: 1 RCT, N = 67, RR = 1.83, 95%CI 1.11 to 3.02, *p* = 0.018 Global improvement: 1 RCT, N = 45, RR = 2.67, 95%CI 1.25 to 5.68, *p* = 0.011 *Haloperidol vs. haloperidol plus lorazepam - no significant difference between groups for;* Needing additional injection: 1 RCT, N = 67, RR = 1.05, 95%CI 0.87 to 1.27, *p* = 0.62 *Haloperidol vs. haloperidol plus promethazine - favours combination for;* Asleep by 20 minutes: 1 RCT, N = 316, RR = 1.60, 95%CI 1.18 to 2.16, *p* = 0.0025 *Haloperidol vs. haloperidol plus promethazine - no significant differences between groups for;* Needing additional tranquilisation: 1 RCT, N = 316, RR = 1.67, 95%CI 0.71 to 3.91, *p* = 0.24 Further aggression by 24 hours: 1 RCT, N = 316, RR = 1.06, 95%CI 0.68 to 1.65, *p* = 0.80 Need restraints: 1 RCT, N = 316, RR = 1.21, 95%CI 0.84 to 1.76, *p* = 0.30 Leaving the study (any reason): 1 RCT, N = 316, RR = 1.03, 95%CI 0.54 to 1.94, *p* = 0.94 *Haloperidol vs. haloperidol plus midazolam - favours haloperidol for;* Agitation: 1 RCT, N = 60, MD = -11.20, 95%CI -12.24 to -10.16, *p* < 0.00001 Aggression: 1 RCT, N = 60, MD = -1.90, 95%CI -2.58 to -1.22, *p* < 0.00001 Needing additional tranquilisation: 1 RCT, N = 60, RR = 0.27, 95%CI 0.10 to 0.71, *p* = 0.008 Need restraints: 1 RCT, N = 60, RR = 0.29, 95%CI 0.13 to 0.61, *p* = 0.0011 *Haloperidol vs. haloperidol plus levomepramine - no significant difference between groups for;* Global improvement: 1 RCT, N = 19, RR = 8.18, 95%CI 0.50 to 133.66, *p* = 0.14	

Haloperidol vs. haloperidol plus risperidone - no significant difference between groups for; Agitation over 24 hours: 1 RCT, N = 100, MD = 0.34, 95%CI -2.34 to 3.02, $p > 0.05$ *Haloperidol vs. risperidone plus clonazepam - no significant differences between groups for;* Sedation by 4 hours: 1 RCT, N = 205, RR = 0.82, 95%CI 0.66 to 1.03, $p = 0.084$ Agitation by 2 weeks: 1 RCT, N = 100, MD = -0.88, 95%CI -2.34 to 0.58, $p = 0.24$ *Haloperidol vs. ziprasidone plus clonazepam - no significant difference between groups for;* Agitation by 1 week: 1 RCT, N = 71, MD = -0.19, 95%CI -1.57 to 1.19, $p > 0.05$ *Haloperidol vs. quetiapine plus valproate - no significant difference between groups for;* Agitation: 1 RCT, N = 60, RR = 1.17, 95%CI 0.44 to 3.06, $p = 0.75$ PANSS-EC: 1 RCT, N = 60, MD = 0.02, 95%CI -2.31 to 2.35, $p = 0.99$ *Haloperidol vs. olanzapine plus valproate - favours combination;* Agitation after 7-14 days: 1 RCT, N = 64, MD = 1.82, 95%CI 0.61 to 3.03, $p < 0.05$	
Risks	*Haloperidol plus promethazine resulted in fewer;* Overall adverse effects: 2 RCTs, N = 316, RR = 2.01, 95%CI 1.07-3.80, $p = 0.031$, $I^2 = 82\%$ Dystonia: 1 RCT, N = 316, RR = 19.48, 95%CI 1.14 -331.92, $p = 0.04$. *Risperidone plus clonazepam resulted in more;* Overall adverse effects: 1 RCT, N = 205, RR = 1.72, 95%CI 1.29-2.29, $p = 0.00023$ Extrapyramidal symptoms: 1 RCT, N = 205, RR = 2.22, 95%CI 1.52-3.23, $p = 0.000033$
Consistency in results	N/A for outcomes with 1 RCT, inconsistent otherwise.
Precision in results	Unable to assess MDs, mostly imprecise otherwise.
Directness of results	Direct

Ostinelli EG, Hussein M, Ahmed U, Rehman FU, Miramontes K, Adams CE

Risperidone for psychosis-induced aggression or agitation (rapid tranquillisation)

Cochrane Database of Systematic Reviews 2018; 4: CD009412

View review abstract online	
Comparison	**Efficacy of risperidone for reducing agitation or aggression compared to other agents.**
Summary of evidence	**Low quality evidence (small samples, some imprecision, some indirectness) is unable to determine differences between risperidone and haloperidol, olanzapine, quetiapine, risperidone plus oxcarbazepine or risperidone plus valproic acid of agitation or aggression.**
Risperidone vs. haloperidol	
No significant differences between groups for; Agitation: 1 RCT, N = 124, RR = 1.04, 95%CI 0.86 to 1.26, $p > 0.05$ Need for restraints: 1 RCT, N = 28, RR = 2.00, 95%CI 0.43 to 9.21, $p > 0.05$	
Risks	There were no significant differences between groups.
Consistency in results	N/A – 1 RCT
Precision in results	Precise for agitation only.
Directness of results	Authors state some outcome measures are indirect.
Risperidone vs. olanzapine	
No significant differences between groups for; Agitation: 1 RCT, N = 29, MD = 2.50, 95%CI -2.46 to 7.46, $p > 0.05$ Need for restraints: 1 RCT, N = 29, RR = 1.43, 95%CI 0.39 to 5.28, $p > 0.05$	
Risks	There were no significant differences in movement disorders.
Consistency in results	N/A – 1 RCT
Precision in results	Imprecise
Directness of results	Authors state some outcome measures are indirect.
Risperidone vs. quetiapine	
Significant benefit of quetiapine for; Aggression: 1 RCT, N = 40, MD = 1.80, 95%CI 0.20 to 3.40, $p < 0.05$	

Risks	There were no significant differences between groups in akathisia.
Consistency in results	N/A – 1 RCT
Precision in results	Imprecise
Directness of results	Authors state some outcome measures are indirect.
Risperidone vs. combinations	
Risperidone vs. risperidone plus oxcarbazepine - favours combination; 1 RCT, N = 68, MD = 2.70, 95%CI 0.42 to 4.98, $p < 0.05$ *No significant differences between groups for;* Global state: 1 RCT, N = 68, MD = -0.20, 95%CI -0.61 to 0.21, $p > 0.05$ *Risperidone vs. risperidone plus valproic acid - no significant differences between groups for;* Aggression: 1 RCT, N = 54, MD = 1.07, 95%CI -0.20 to 2.34, $p > 0.05$	
Risks	There were no significant differences between groups in extrapyramidal symptoms or akathisia.
Consistency in results	N/A – 1 RCT
Precision in results	Imprecise
Directness of results	Authors state some outcome measures are indirect.

Ostinelli EG, Jajawi S, Spyridi S, Sayal K, Jayaram MB

Aripiprazole (intramuscular) for psychosis-induced aggression or agitation (rapid tranquillisation)

Cochrane Database of Systematic Reviews 2018; 1: CD008074

View review abstract online

Comparison	**Efficacy of aripiprazole for reducing agitation or aggression compared to placebo or other agents.**
Summary of evidence	**Moderate to high quality evidence (large samples, consistent, some imprecision, direct) finds small benefits of aripiprazole over placebo for agitation and needing fewer additional injections. Compared to haloperidol those on aripiprazole**

	needed more additional injections, but there were no differences in agitation. **Moderate quality evidence (small sample, precise, direct) finds small benefits for agitation and global state with olanzapine over aripiprazole, although there was more somnolence with olanzapine.**
Aripiprazole vs. placebo	
Significant, small benefits with aripiprazole for; Less agitation: 2 RCTs, N = 382, RR = 1.50, 95%CI 1.17 to 1.92, $p = 0.0013$, $I^2 = 0\%$ Fewer additional injections: 2 RCTs, N = 382, RR = 0.69, 95%CI 0.56 to 0.85, $p = 0.00054$, $I^2 = 0\%$	
Risks	There were no significant differences between groups.
Consistency in results	Consistent
Precision in results	Precise for fewer additional injections only.
Directness of results	Direct
Aripiprazole vs. haloperidol	
Significant, small benefits with haloperidol for; Fewer additional injections: 2 RCTs, N = 477, RR = 1.28, 95%CI 1.00 to 1.63, $p = 0.049$, $I^2 = 0\%$ *There were no significant differences between groups for;* Agitation: 2 RCTs, N = 477, RR = 0.94, 95%CI 0.80 to 1.11, $p = 0.48$, $I^2 = 0\%$	
Risks	There were no significant differences between groups.
Consistency in results	Consistent
Precision in results	Imprecise for additional injections, precise for agitation.
Directness of results	Direct
Aripiprazole vs. olanzapine	
Significant, small benefits with olanzapine for; Less agitation: 1 RCT, N = 80, RR = 0.77, 95%CI 0.60 to 0.99, $p < 0.05$ Better global state: 1 RCT, N = 80, MD = 0.58, 95%CI 0.01 to 1.15, $p < 0.05$	

Risks	There were no significant differences between groups in overall adverse effects, however aripiprazole resulted in less somnolence.
Consistency in results	N/A – 1 RCT
Precision in results	Precise for agitation, unable to assess MDs.
Directness of results	Direct

Dold M, Li C, Tardy M, Khorsand V,Gillies D, Leucht S

Benzodiazepines for schizophrenia

CochraneDatabase of Systematic Reviews 2012; Issue 11. Art. No.: CD006391. DOI: 10.1002/14651858.CD006391.pub2

View review abstract online

Comparison	**Benzodiazepines plus antipsychotics (varying) vs. antipsychotics (varying) plus placebo, treatment duration 24 hours to 10 weeks. Route of drug administration unspecified.**
Summary of evidence	**Moderate to low quality evidence (small sample imprecise, direct) suggests people receiving adjunct benzodiazepines were more likely to be sedated for up to one hour but were not less aggressive after one hour than those on antipsychotics alone. Use of antiparkinson medication was significantly lower and somnolence was significantly higher with benzodiazepines.**

Sedation and aggressive behaviour

Medium effect sizes suggested significantly increased sedation in the benzodiazepine group at 30 minutes, reducing to a small effect by 60 minutes, with no difference in rate of sleeping at 12 hours;

Tranquilised at 30 minutes: 1 RCT, N = 45, RR = 2.25, 95%CI 1.18 to 4.30, *p* = 0.014

Tranquilised at 60 minutes: 1 RCT, N = 45, RR = 1.39, 95%CI 1.06 to 1.83, *p* = 0.019

Asleep at 12 hours: 1 RCT, N = 67, RR = 0.85, 95%CI 0.51 to 1.41, *p* = 0.53

No significant difference was reported in aggressive behaviour following treatment;

Mean aggression score at 1 hour: 1 RCT, N = 67, WMD = -3.00, 95%CI -8.27 to 2.27, *p* = 0.26

Mean aggression score at 12 hours: 1 RCT, N = 67, WMD = 0.00, 95%CI -5.27 to 5.27, *p* = 1.0

Risks	Use of antiparkinson medication was significantly lower and

	somnolence was significantly higher in the benzodiazepine group. There were no significant differences in risk of cardiovascular reaction, ataxia, dystonia, anorexia, allergic reaction, blurred vision, confusion, depression, diarrhoea, dizziness, drowsiness, excitation, gastrointestinal reaction, headache, dry mouth, salivation, insomnia, lactation, restlessness, sensory disturbance, sleep disorder or vomiting.
Consistency in results	N/A – 1 RCT
Precision in results	Imprecise or unable to assess WMD.
Directness of results	Direct

Explanation of acronyms

BPRS = Brief Psychiatric Rating Scale, CGI = Clinical Global Impressions Improvement scale, 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), MD = mean difference, N = number of participants, *p* = statistical probability of obtaining that result ($p < 0.05$ generally regarded as significant), N/A = not applicable, PANSS = Positive and Negative Syndrome Scale, Q = Q statistic for the test of heterogeneity, RR = risk ratio, vs. = versus, WMD = weighted mean difference

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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[10].

† 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).

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. Less than 0.4 represents a small effect, around 0.5 a medium effect, and over 0.8 represents a large effect[10].

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[11]. 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[10];

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

§ 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[12].

‖ 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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