South African National Essential Medicine List
Primary Healthcare/ Adult Hospital Level of Care Medication Review Process
Component: Emergencies and injuries

MEDICINE REVIEW

1. Executive Summary

Date: 29 September 2022
Medicine (INN): Olanzapine
Medicine (ATC): NO5AH03
Indication (ICD10 code): Aggressive / disruptive behaviour (R45.1/R45.4-6)
Patient population: Individuals that are ≥ 18 years old with suspected severe mental illness presenting with aggressive/ disruptive behaviour to any healthcare settings.
Prevalence of condition:
South African studies

- 54-100% of healthcare workers report workplace violence (number with patients as perpetrators unclear) (Njaka, 2020)

International studies

- 8–76% of psychiatric inpatients (Weltens, 2021)
- 9-100% of healthcare workers in Africa experience workplace violence (where reported, patients were perpetrators in 46- 54% of incidents) (Njaka, 2020)

Level of Care: Primary Healthcare and Adult Hospital Level of care
Prescriber Level: Doctor prescribed
Motivator/reviewer name(s): Lesley Robertson, Shelley McGee, Tamara Kredo, Natasha Gloeck, Mashudu Mthethwa, Trudy Leong
PTC affiliation: Lesley Robertson affiliated to Sedibeng District PTC, Gauteng

Key findings

- Haloperidol IM 5mg/ml and 20mg/2ml injections were not available and currently supply is erratic in the South African market. Currently, haloperidol IM with promethazine IM is current standard of care in the management of aggressive, disruptive behaviour among people with mental illness at primary and secondary adult hospital levels of care.
- We conducted a review of available evidence to determine the efficacy and safety of olanzapine in treating acute aggression or agitation in people with mental illnesses. Three international clinical practice guidelines were identified, all poor quality with AGREE II scores less than 50%. These guidelines included olanzapine IM as an option in the pharmacological management of aggressive behaviour.
- A literature search conducted on 4 March 2022 identified six systematic reviews (four of which were not included in the evidence synthesis because of low AMSTAR II ratings) and 13 RCTs.
- **Risk of no improvement** at 24 hours was less with olanzapine (19/99) than lorazepam (18/51), Risk Ratio (RR) 0.54 (95%CI 0.31 to 0.94; NNT 7 (95% CI 4 to 116), very low certainty evidence, although there was no difference in the first hour (RR 0.80 (95%CI 0.60 to 1.05).
- **Agitated behaviour** was less with olanzapine than lorazepam at 24 hours (Mean Difference (MD) -2.91 (95% CI -5.02 to -0.80), very low certainty evidence. Compared to an equivalent dose of haloperidol + promethazine, olanzapine resulted in a greater reduction in aggression (MD= -1.20 (95% CI -2.01 to -0.39)) and agitation (MD = -13.60 (95% CI -14.56 to -12.64)) at 2 hours, very low certainty evidence.
- **Need for additional medicines** was less with olanzapine than lorazepam at 24 hours (RR 0.50 (95% CI 0.33 to 0.75)), very low certainty evidence.
- **Risk of not being tranquil or asleep** at 30 minutes was no different between olanzapine and a higher equivalent dose of haloperidol (double) + promethazine ; RR = 1.67, 95 % CI (0.62 to 4.47), high certainty evidence).

- **No serious adverse events** were evident in the olanzapine, lorazepam, or haloperidol +promethazine groups.
- **Occurrence of any adverse event** was not different between olanzapine and lorazepam (similar rates of extrapyramidal side effects, dizziness, nausea, vomiting) or between olanzapine and haloperidol + promethazine (similar rates of hypotension and excessive sedation).
- Six of the 13 RCTs compared olanzapine to haloperidol or haloperidol + lorazepam. While a full synthesis of this evidence was not conducted, no difference in response between olanzapine (10mg) and haloperidol (range 5mg – 10mg) was noted.
- In summary, very low certainty evidence suggests olanzapine IM may be superior to lorazepam IM in improvement of global state, reduction of agitated behaviour, and need for additional medicines. Uncertain evidence suggests the effect of olanzapine IM may be similar to haloperidol IM + promethazine IM.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITTEE RECOMMENDATION:

Type of recommendation	We recommend against the option and for the alternative **(strong)**	We suggest not to use the option **(conditional)**	We suggest using either the option or the alternative **(conditional)**	We suggest using the option **(conditional)**	We recommend the option **(strong)**
				X	

Recommendation: Considering that haloperidol IM supply has been erratic in South Africa, we suggest using olanzapine oro-dispersible tablets or IM.

Rationale: The very low certainty evidence suggests olanzapine may be superior to lorazepam and to the combination of haloperidol and promethazine in reducing agitated or aggressive behaviour. There appears to be no difference in achieving sedation.

Level of Evidence: Very low certainty evidence

Review indicator: New evidence of benefit or harm

NEMLC RECOMMENDATION 8 DECEMBER 2022:

NEMLC accepted the proposal as recommended by the PHC/Adult Hospital Level Expert Review Committee (see above)

NEMLC RECOMMENDATION 14 MARCH 2024:

NEMLC retained the proposal as recommended by the PHC/Adult Hospital Level Expert Review Committee (see above)

Monitoring and evaluation considerations

Research priorities

Name of author(s)/motivator(s)

Lesley Robertson, Tamara Kredo, Mashudu Mthethwa, Natasha Gloeck, Shelley McGee, Trudy Leong

Author affiliation and conflict of interest details

Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no conflicts of interest related to olanzapine

Shelley McGee, Ophthalmological Society of South Africa: no conflicts of interest related to olanzapine

Tamara Kredo, Cochrane South Africa, South African Medical Research Council; Division of Clinical Pharmacology, Department of Medicine, and Division of Epidemiology and Biostatistics, department of Global Health, Stellenbosch University: no conflicts of interest related to olanzapine

Mashudu Mthethwa, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine

Natasha Gloeck, Cochrane South Africa, South African Medical Research Council: no conflicts of interest related to olanzapine

Trudy Leong, Right-To-Care as Secretariat-support to PHC/ Adult Hospital Level Committee of the National Essential Medicines List, NDoH: no conflicts of interest related to olanzapine

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BACKGROUND

Aggressive behaviour, often common among people with mental illness, includes verbally abusive language, specific verbal threats, intimidating physical behaviour and/or actual physical violence to self, others, or property [1]. Acute aggression / agitation is therefore a safety risk to patients and staff, which requires safe, effective, and rapid treatment [2]. Over the years, management of aggressive behaviour has advanced to prioritization of rapid symptom treatment instead of patient restraint and isolation [2]. Current management and standard of care for aggressive behaviour includes de-escalation and non-pharmacological measures, use of oral benzodiazepines, benzodiazepines IM, or haloperidol IM with promethazine IM if there is poor response to non-pharmacological measures and oral benzodiazepines. In South Africa, haloperidol IM 5mg/ml and 20mg/2ml injections is erratic.

There is a need to explore other available options such as Olanzapine IM. The purpose of this review was to study the effectiveness and safety of olanzapine in treating acute aggression / agitation in people with mental illnesses.

Research question

What is the efficacy and safety of olanzapine compared to 1) benzodiazepines, 2) haloperidol or 3) placebo for management of aggressive disruptive behaviour?

ELIBILITY CRITERIA FOR REVIEW

Population	Individuals that are ≥ 18 years old with suspected severe mental illness presenting with aggressive/ disruptive behaviour to any healthcare settings.
Intervention	Olanzapine intramuscular (IM) and orodispersible tablets, any dose
Comparators	• Haloperidol IM +/- promethazine IM, any dose • Benzodiazepines any dose, given orally or IM • Placebo
Outcomes	**Efficacy** • Response: ≥ 40% reduction in symptom scale or as defined by the study within 30 minutes, 2hours, and 24 hours • Mean difference in behaviour score within 2 hours and 24 hours; • requiring further injections/number of doses in 24 hours; • requiring additional benzodiazepines in 24 hours • Sedation • Others (secondary outcomes): leaving the study early; duration of hospital stay; patient/ caregiver satisfaction with care **Safety (time frame – within 24 hours)** • Requiring anticholinergic medication • Any adverse events • Serious adverse events • Mortality

Study designs	Clinical practice guidelines, systematic reviews of randomised controlled trials (RCTs), RCTs and, if the latter is unavailable, systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.

METHODS

A search strategy was developed for PubMed and adapted to other databases (Appendix 1). A search for systematic reviews and RCTs was conducted in PubMed, the Cochrane Library, and Epistemonikos on 4 March 2022. Clinical practice guidelines (CPGs) were sourced from the Guidelines International Network (GIN), the National Institute for Health and Care Excellence (NICE) and the British Association of Clinical Pharmacology, as well as relevant CPGs from Australia, New Zealand, and Canada on their government websites.

The search results of RCTs and systematic reviews were uploaded on to the Covidence systematic review management software (Melbourne, Victoria). As we were conducting reviews on olanzapine for aggression and delirium in parallel, the search included outputs relevant for both conditions, with screening for relevant studies done in duplicate. Duplicates were removed and screening of abstracts was conducted independently by the four reviewers (NG, MM, TK, LR). Conflicts were resolved by consensus and full text review was conducted by two reviewers (NG and MM). Conflicts were resolved by TK and LR during the full text review.

Eligible guidelines were appraised in duplicate using the AGREE II tool by two reviewers (MM and NG). Eligible systematic reviews were appraised using the AMSTAR II Checklist, and eligible randomised controlled trials were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data extraction for included systematic reviews and RCTs was conducted by one reviewer and verified by a second reviewer. The main characteristics of included studies are summarized in Tables 3 and 4. Risk ratios (RR) with 95% confidence intervals (CI) for dichotomous data and mean differences with standard deviation for continuous outcomes were reported. We found that the included systematic reviews defined olanzapine as the comparator and not the main intervention (the inverse of our PICO), hence, data were therefore re-analysed in RevMan5 (The Cochrane collaboration, United Kingdom) using olanzapine as the main intervention, for our outcomes of interest. Characteristics of additional relevant RCTs that were not reported in the included systematic reviews are summarized, including appraisal, in Table 4.

Exclusion of ineligible studies was reached by consensus between two reviewers and any disputes were settled by a third reviewer.

RESULTS

a. Results of search

A systematic search was conducted in PubMed, Cochrane library and Epistemonikos. The search yielded 778 records which were subsequently imported to Covidence for screening where 147 duplicates were removed (Appendix 2). Titles and abstracts of 637 studies were screened, and 541 studies were excluded. Full texts of 95 studies were assessed for eligibility and 73 studies were excluded (see Appendix 3 for list of excluded studies). We included 13 studies of which six were systematic reviews and seven RCTs. However, only two systematic reviews were considered of sufficient quality to be eligible for inclusion because of moderate - high AMSTAR II ratings. The four systematic reviews with low AMSTAR II rating are summarized in Appendix 4.

b. Guidelines

All guidelines that were identified and appraised were of poor quality, with AGREE II scores less than 50 % (Table 1).

Table 1: Guidelines and recommendations for management of acute aggression

Citation	Recommendation	AGREE II score
Patel MX, Faisil NS, Barned TR, Dix R, Dratcu L, Fox B, et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management	Pre- (rapid tranquilisation) RT: Oral, oral-inhaled and bucca olanzapine and risperidone are effective (Ib; A). Oral	42 %

of acute disturbance: De-escalation and rapid tranquillisation. J Psychopharmacol. 2018; 32(6):601-40. Doi: doi.org/10.1177/0269881118776738. [3]	haloperidol is effective and a baseline ECG is advised before use due to the risk of QTc prolongation (III; C). "RT: IM monotherapy – IM olanzapine is effective, but it should only be administered by itself and not concurrently with IM benzodiazepines due to risk of hypotension; thus, there should be an interval of at least 1 hour between the two (Ia; A).	
Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aus N Z J Psychiatry. 2016; 50(5):410-72. Doi: 10.1177/0004867416641195 [4].	Oral agents (including wafers) are preferable to medications given by injection. If parenteral antipsychotic agents are required, second-generation antipsychotic agents are preferred. Flowchart for pharmacological mx of acute behavioral disturbance in psychosis. Arousal level 2 to 3: lorazepam or olanzapine orally. Arousal level 3 to 4: Lorazepam AND olanzapine orally. Arousal level 4 to 5: olanzapine (1st line) IMI	33%
Queensland Health. Management of patients with Acute Severe Behavioural Disturbance in Emergency Departments. [Internet] Queensland: Queensland Health; 2016 [updated October 2021]. Available from: https://www.health.qld.gov.au/__data/assets/pdf_file/0031/629491/qh-gdl-438.pdf	Use sedation assessment tool Flow chart: sedation for acute behavioural disturbance in emergency department. +1: diazepam or olanzapine wafer or diazepam plus olanzapine Flow chart: sedation for acute behavioural disturbance in medically frail patients in emergency department. +1: diazepam or olanzapine wafer Flow chart: Sedation for acute behavioural disturbance in child/adolescent in ED Not know ASD or intellectual disability: +1: Diazepam or olanzepine wafer or risperidone +2 or +3: droperidol or consider olanzapine or ketamine if droperidol C/I	17 %

Included systematic reviews

Two systematic reviews were included in evidence synthesis. Zaman *et al* (2017) [5] compared benzodiazepines with antipsychotics, and placebo for the treatment of psychosis-induced aggression. The aim of the review was to compare the tranquilising or sedative effects of benzodiazepines versus antipsychotics / placebo in psychosis-induced aggression. The review was rated as high quality according to the Amstar II rating. Of the twenty trials included in the systematic review only one used olanzapine as the comparator. The quality of evidence was very low due to serious risk of bias, imprecision, and small size. The trial took place in hospitals in Romania and the US and included 201 adults with bipolar disorder who had psychosis induced agitation deemed clinically severe enough to require injections. A summary of the trial and effect sizes according to reported outcomes is presented in Table 2.

Huf *et al* (2016)[6] reviewed the effectiveness of haloperidol + promethazine on psychosis-induced aggression. This review was of moderate quality according to the AMSTAR II rating. Three studies compared haloperidol plus promethazine with olanzapine, with sample sizes ranging from 56 to 300. Study settings were psychiatric emergency rooms. Participants were adults with psychosis-induced aggressive behaviour. Other diagnoses such as drug or alcohol intoxication, dementia, non-psychotic mental illnesses, or learning disabilities were included if they did not exceed the proportion of participants with psychosis. Quality of evidence for included studies ranged from low to high. A summary of haloperidol plus promethazine versus olanzapine reported outcomes are presented in Table 2. Of note, dosing was only equivalent (haloperidol 5mg vs olanzapine 10mg) in one study (n=60); the largest study (n=300) used a higher equivalent dose of haloperidol vs olanzapine (10mg vs 10mg), and the smallest study (n=56) used a lower equivalent dose of haloperidol versus olanzapine (2.5mg vs 10mg, respectively).

Our outcomes of interest, summarized and re-analysed to match our PICO format from the two reviews, are presented below:

Effectiveness of the intervention

Comparison 1: Olanzapine vs benzodiazepines

The results below are from the included review (Zaman et al 2017) reporting of the trial, Battaglia *et al* 2003, n = 151 [7].

1. **Response: reported as 'Global state: No improvement (> 40% reduction Positive and Negative Syndrome Scale-Excited Component (PANSS-EC)'.**
   At 1 hour: Risk Ratio (RR) 0.80 (95%CI 0.60 to 1.05), very low certainty evidence
   At 24 hours: RR 0.54 (95%CI 0.31 to 0.94), very low certainty evidence.
   There may be a slight difference favouring olanzapine compared to lorazepam at 24 hours. However, with very low certainty evidence the overall result is uncertain.

2. **Behaviour: reported as 'Behavior: mean change/endpoint score (Agitated Behavior Scale, high = worse)'**
   At 24 hours: Mean difference -2.91 (95% CI -5.02 to -0.80). GRADE certainty of evidence was not reported.
   There may be a reduction in Agitated Behaviour Scale with olanzapine compared to lorazepam at 24 hours, but the evidence is uncertain.

3. **Requiring further injections/number of doses in 24 hours:** not reported.

4. **Requiring additional medicine in 24 hours**
   RR 0.50 (95% CI 0.33 to 0.75), very low certainty evidence.
   Olanzapine compared to lorazepam at 24 hours may result in less additional medication, however, the certainty of the evidence is very low and we are therefore uncertain of the true effect.

5. **Sedation: Tranquillization or asleep**
   At 24 hours: RR 1.34 (95%CI 0.51 to 3.55), very low certainty evidence. There may be no difference in tranquilization between olanzapine and benzodiazepines, however, the true effect is uncertain.

6. **Leaving the study early**
   RR = 0.17 (95%CI 0.02 to 1.61), very low certainty evidence.
   In the olanzapine group, 1/99 versus 3/51 participants in the benzodiazepine group left the study early for any reason.

7. **Duration of hospital stays:** not reported

8. **Patient/ caregiver satisfaction with care:** not reported

9. **Safety (time frame – within 24 hours):** not reported

10. **Requiring anticholinergic medication:** not reported

11. **Any adverse events**
    Extrapyramidal symptoms (EPS)
    - At 24 hours: RR 4.12 (95%CI 0.53 to 32.1). GRADE certainty of evidence was not reported, 8/99 in the olanzapine group vs 1/51 in the benzodiazepine group experienced extrapyramidal symptoms.
    - Use of medication for EPS: At 24 hours: RR 4.12 (95%CI 0.53 to 32.1). GRADE certainty of evidence was not reported. 8/99 in the olanzapine group vs 1/51 in the benzodiazepine group experienced extrapyramidal symptoms.

- Specific adverse effects:

Dizziness: RR 0.66 (95%CI 0.26 to 1.61). GRADE certainty of evidence was not reported. 9/99 participants in olanzapine group experienced dizziness, compared to 7/51 people in the benzodiazepine group.

Nausea: RR 0.13 (95%CI 0.01 to 1.12). GRADE certainty of evidence was not reported. 1/99 participants in olanzapine group experienced nausea, compared to 4/51 people in the benzodiazepine group.

Vomiting: RR 0.07 (95%CI 0.0 to 1.41). GRADE certainty of evidence was not reported. 0/99 participants in olanzapine group experienced vomiting, compared to 3/51 people in the benzodiazepine group.

12. **Serious adverse:** not reported

Comparison 2: Olanzapine vs haloperidol + promethazine

The results below are from the included review, Huf *et al* 2016 [6].

1. **Response: reported as 'Global state: No overall improvement'**
   Single trial, n = 300 (TREC-Vellore-II, dosing of haloperidol > dosing of olanzapine)
   By 30 minutes: RR = 1.74 (95% CI 1.10 to 2.76)
   by 2 hours: RR = 2.73 (95% CI 1.43 to 4.98)
   By 24 hours: not reported
   GRADE certainty of evidence was not reported.
   The risk of no improvement appears to be greater with olanzapine compared to haloperidol + promethazine.

2. **Behaviour: Mean difference in behaviour score within 2 hours and 24 hours**

   2a. Average aggression score (OAS, high score = bad)
   Single trial, n = 60 (equivalent dosing of haloperidol and olanzapine)
   by 2 hours: MD= -1.20 (95% CI -2.01 to -0.39)
   by 24 hours*:* not reported
   GRADE certainty of evidence was not reported. There is evidence that olanzapine may result in a greater reduction in the average aggression score compared to haloperidol + promethazine after 2 hours.

   2b. Average agitation score (OASS, high score=bad)
   Single trial, n = 60 (equivalent dosing of haloperidol and olanzapine)
   by 2 hours: MD = -13.60 (95% CI -14.56 to -12.64)
   by 24 hours**:** not reported
   GRADE certainty of evidence was not reported. There is evidence that olanzapine may result in a reduction in average agitation score compared to haloperidol + promethazine after 2 hours.

2c. Severe agitation

By 24 hours: RR 0.14 (95% CI 0.01 to 2.64), n = 56, 1 trial (dosing of haloperidol < dosing of olanzapine). GRADE certainty of evidence was not reported. 0/28 participants in the olanzapine group experienced severe agitation, compared to 3/28 people in the haloperidol + promethazine group.

3. **Requiring further injections/number of doses in 24 hours:** not reported
4. **Requiring additional benzodiazepines in 24 hours:** not reported

5. **Sedation:**

Single trial, n=300 (TREC-Vellore-II, dosing of haloperidol > dosing of olanzapine)

Not tranquil or asleep by 30 minutes: RR = 1.67, 95 % CI (0.62 – 4.47), high quality evidence. 10/150 and 6/150 in the olanzapine and the haloperidol + promethazine groups, respectively, were not tranquil or asleep by 30 minutes.

6. Leaving the study early:
by 30 minutes: RR= 0.33 (95%CI 0.01 to 8.12); n = 300, 1 trial.
by 2 hours: RR = 0.14 (95%CI 0.01 to 2.74); n = 300, 1 trial.
by 4 hours: RR = 0.09 (95% CI 0.01 to 1.63); n = 300; 1 trial.
by 24 hours: RR 0.33 (95% CI 0.04 to 3.01); n = 116, 2 trials.

There were no differences in leaving the study between olanzapine and haloperidol + promethazine groups.

7. Duration of hospital stay: not reported

8. Patient/ caregiver satisfaction with care: not reported

9. Safety (time frame – within 24 hours): not reported

10. Requiring anticholinergic medication: not reported

11. Any adverse events

a. Hypotension

RR 0.33 (95% CI 0.05 to 2.03), 2 trials, n = 116. GRADE certainty of evidence was not reported. 1/58 participants in olanzapine group experienced hypotension, compared to 4/58 people in the haloperidol + promethazine group.

b. Central nervous system - sedation – excessive

RR 1.50 (95% CI 0.26 to 8.64), 2 trials, n = 116, low quality of evidence.
3/58 participants in olanzapine group experienced severe agitation, compared to 2/58 people in the haloperidol + promethazine group.

Included RCTs

We summarized seven RCTs that were not reported in the included systematic reviews. Characteristics of the RCTs including outcomes, findings, and risk of bias assessment are summarized in Table 3.

Of the seven RCTs, three were conducted in Taiwan, one in Japan, one in the United States (US), and two were multi-country studies including Australia, Austria, Belgium, Czech Republic, Canada, France, Greece, Hungary, Israel, United Kingdom (UK), Spain and South Africa (SA). Participants were aged from 18 to 65 years and were mostly diagnosed with schizophrenia and /or schizophreniform or schizoaffective disorders. Studies were conducted in hospital or emergency room settings and participants were considered clinically agitated (minimum score ≥ 14 on the PANSS-EC scale). Sample sizes ranged from 42 to 311. Studies compared IM olanzapine (5 to 10 mg) with IM haloperidol (5 to 7.5 mg -/+ 2 mg lorazepam) or placebo. Measured outcomes were efficacy and safety across all studies. Efficacy outcomes included PANSS-EC scores, agitation-calmness evaluation scales (ACES), brief psychiatry rating scale total score (BRS), clinical global impression-severity index scale (CGI), Barnes akathisia rating scale (BARS) and Simpson-Angus scale (SAS). Risk of bias was unclear for all studies due to some concerns in one or more domains.

Future research directions:

- This review highlighted an important gap in the literature, larger and high methodological quality trials are required to sufficiently address this research question. Furthermore, most studies were conducted in high income countries, there is limited evidence from low-income settings and SA context.
- Updated high quality systematic reviews are also required.

Table 2. Characteristics of included systematic reviews

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION VS COMPARATOR	OUTCOMES AND EFFECT SIZE	APPRAISAL
Zaman H, Sampson SJ, Beck ALS, Sharma T, Clay FJ, Spyridi S, Zhao S, Gillies D. Benzodiazepines for psychosis-induced aggression or agitation. Cochrane Database of Systematic Reviews 2017, Issue 12. Art. No.: CD003079. DOI: 10.1002/14651858.CD003079.pub4. [5]	Systematic review of 20 RCTs examining effectiveness of benzodiazepines among people with psychosis-induced aggression or agitation. One RCT used olanzapine as a comparator	N=201 Adults with bipolar disorder (manic or mixed), deemed by a physician to have agitation severe enough to receive injections, minimum total PANSS-EC score of 14, and ≥ 1 individual item score of ≥ 4.	Lorazepam (2 to 5mg IM, n=51) versus olanzapine (10 to 25 mg IM, n=99), and versus placebo (n=51)	**1. Global state: Risk of no improvement in reduction of symptom scale (≥ 40% reduction Positive and Negative Syndrome Scale-Excited Component (PANSS-EC))** *Short term (<1 hour):* RR1.26, 95%CI 0.95 to 1.66, n=150 *Medium term (24 hours):* RR 1.84, 95%CI 1.06 to 3.18, n=150, 1 RCT **2. Behaviour: mean change/endpoint score (Agitated Behaviour Scale, high =worse)** *Medium term (24 hours):* MD 2.91, 95%CI 0.80 to 5.02, n = 149 **3. Requiring additional medicine** *Medium term (24 hours):* RR 2.02, 95% CI 1.33,3.07, n=150 **4. Tranquillization or asleep: sedation.** *Medium term (24 hours):* RR 0.75, 95% CI 0.28 to 1.98, n=150, 1 RCT **5. Adverse effects/events: Extrapyramidal symptoms (EPS).** *Medium term (24 hours):*RR 0.24, 95%CI 0.03 to 1.89, n=150, 1 RCT 6. **Adverse effects/events: use of medication for EPS** *Medium term (24 hours):* RR= 0.24, 95%CI 0.03 to 1.89 **7. Adverse effects/events: 3. Specific** Dizziness: RR= 1.51, 95%CI 0.60 to 3.82 Nausea: RR= 7.76, 95%CI 0.89 to 67.67 Vomiting: 13.46, 95%CI 0.71 to 255.70 **8. Leaving study early** RR=5.82, 95%CI 0.62 to 54.58, N = 150, 1 RCT	AMSTAR II rating HIGH ROB of the RCT: Low risk for attrition bias and selective reporting. High risk for other bias (industry funded) Unclear risk for selection bias and performance bias.

Huf G, Alexander J, Gandhi P, Allen MH. Haloperidol plus promethazine for psychosis-induced aggression. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD005146. DOI: 10.1002/14651858.CD005146.pub3.[6]	Systematic Review of six studies, examining the effectiveness of haloperidol and promethazine. Data relevant to six comparisons are presented. Three RCTs (Baldacara, 2011; Mantovani,2013; TREC-Vellore-II) used olanzapine as a comparator.	N=416 Adults with psychosis-induced aggression behaviour presenting to emergency rooms.	Haloperidol (2.5 – 10mg) + promethazine (25 – 50mg) versus olanzapine (5 – 10mg) Baldacara, 2011 (n=60) 5mg haloperidol vs 10 mg olanzapine (i.e., equivalent dosing) TREC-Vellore-II (n=300)– haloperidol 10mg vs olanzapine 10 mg (n=296) and 5mg vs 5mg (n=4) (note, dosing not equivalent) Mantovani, 2013 (n=56), haloperidol 2.5mg vs olanzapine 10mg (note, dosing not equivalent)	**Primary Outcomes** **1. Not tranquil or asleep at 30 mins** Single trial, n=300 RR = 0.60 (0.22 to 1.61), high quality evidence **2. Global state: Needing restraints or seclusion by 12 hours** Single trial, n=60 RR 5.00 (0.62 to 40.28), low quality evidence **3. Adverse effects: Specific and serious adverse effects by 24 hours** Two trials, n=116 RR 0.67 (0.12 to 3.84), low quality evidence **Secondary Outcomes,** **4. Tranquil or asleep: Average sedation score (Ramsay sedation scale)** Single trial, n=60 ***by 1 hour:*** MD= 0.20, 95% CI -0.26 to 0.66 ***by 2 hours:*** MD= 0.10, 95% CI -0.26 to 0.46 ***by 4 hours:*** MD=0.10, 95% CI -0.34 to 0.54 ***by 6 hours:*** MD= 0.10, 95% CI -0.15 to 0.35 ***by 12 hours:*** MD= 0.00, 95% CI -0.23 to 0.23 **5. Global state: No overall improvement** Single trial, N = 300 ***by 30 minutes:*** RR = 0.57, 95% CI 0.36 to 0.91 ***by 1 hour:*** RR = 0.40, 95% CI 0.21 to 0.75 ***by 2 hours:*** RR = 0.44, 95% CI 0.24 to 0.79 ***by 4 hours:*** RR = 0.47, 95%CI 0.22 to 1.01 **6. Global state: Needing restraints or seclusion** Single trial, N =300 ***by 30 minutes:*** RR = 1.02, 95% CI 0.71 to 1.47 ***by 1 hour:*** RR = 0.97, 95%CI 0.66 to 1.44 ***by 2 hours:*** RR = 0.79, 95% CI 0.51 to 1.25 ***by 4 hours:*** RR 0.63, 95% CI 0.34 to 1.14 ***by 12 hours:*** RR 5.00, 95% CI 0.62 to 40.28, N = 60, single trial 7. **Requiring additional drugs during initial phase - by 4 hours** Two trials, N = 356 RR = 0.52, 95% CI 0.37 to 0.74.	AMSTAR II rating Moderate quality ROB of the three relevant RCTs largely unclear. All three had low risk of attrition bias. Mantovani and TREC-Vellore-II had low risk of selection bias, but Mantovani had high risk of reporting bias.

				Moderate heterogeneity (Chi^2 =2.25; df=1.0; P=0.13; I^2=55%. **8. General - serious adverse effect** Single trial, N = 300 ***by 4 hours:*** RR = 0.33, 95% CI 0.04 to 3.17 ***at 2 weeks:*** RR = 0.33, 95%CI 0.01 to 8.12 **9. Specific adverse effects** **a. Cardiovascular - hypotension** Two trials, N = 116 RR 3.00, 95% CI 0.49 to 18.31 **b. Central nervous system - sedation – excessive** Two trials, N = 116 RR 0.67, 95% CI 0.12 to 3.84 **c. Extrapyramidal problems - 0 to 4 hours** Three trials, N = 416 RR 1.76, 95% CI 1.12 to 2.77. This subgroup had important levels of heterogeneity (Chi^2 =2.45; df=1.0; P=0.12; I^2=59%). **10. Specific behaviours: 1. Severe agitation** RR 7.00, 95% CI 0.38 to 129.55, N = 56, single study **11. Specific behaviours: 2. Average aggression score (OAS, high score=bad)** **Single trial, N = 60** ***by 1 hour:*** MD = 5.40, 95% CI 3.72 to 7.08 ***by 2 hours*:** MD= 1.20, 95% CI 0.39 to 2.01 ***by 4 hours*:** MD = -0.50,95% CI -0.68 to -0.32 **by 6 hours**: MD = -1.20, 95% CI -1.90 to -0.50 ***by 12 hours***: MD= -2.00, 95% CI -2.21 to -1.79 **12. Specific behaviors: 3. Average agitation score (OASS, high score=bad)** **Single trial, N = 60** ***by 1 hour*:** MD = 26.50, 95% CI 23.76 to 29.24 ***by 2 hours***: MD = 13.60, 95% CI 12.64 to 14.56 ***by 4 hours:*** MD = 4.00, 95% CI 3.47 to 4.53 **by 6 hours**: MD = 2.80, 95% CI 2.31 to 3.29 ***by 12 hours*:** MD = 1.7, 95% CI 1.44 to 1.96 **13. Hospital outcomes** Single trial, N = 300 ***admitted - by 4 hours*** RR = 0.81, 95% CI 0.56 to 1.16	

				not discharged - by 4 hours RR = 0.94, 95%CI 0.77 to1.16 **14. Leaving the study early** ***by 30 minutes*:** RR= 0.33, 95%CI 0.01 to 8.12; N = 300, 1 trial. ***by 2 hours:*** RR = 0.14, 95%CI 0.01 to2.74; N = 300, 1 trial. ***by 4 hours:*** RR = 0.09, 95% CI 0.01 to 1.63; N = 300; 1 trial. **by 24 hours:** RR 0.33, 95% CI 0.04 to 3.01; N = 116, 2 trials. ***by 2 weeks***: RR 0.71, 95% CI 0.33 to 1.56; N = 300, 1 trial. Service outcomes: Not discharged - by 4 hours	

Table 3: Characteristics of included RCTs

CITATION	STUDY DESIGN	POPULATION	INTERVENTION	OUTCOMES AND MAIN FINDINGS	RISK OF BIAS
a. OLANZAPINE VS HALOPERIDOL					
Chan HY; Ree SC; Su LW; Chen JJ; Chou SY; Chen CK; Chen YS A double-blind, randomized comparison study of efficacy and safety of intramuscular olanzapine and intramuscular haloperidol in patients with schizophrenia and acute agitated behavior. J Clin Psychopharmacol Jun 2014;34(3):355-8 [8].	Multicenter, randomized, double blind, controlled parallel group study Trial conducted at four trial centers between June 2004 and January 2005 in Taiwan. The study protocol was approved by the independent ethics committee at each center.	Patients aged 18 to 65 years with primary diagnosis of schizophrenia: Clinically agitated hospitalized due to an acute relapse, A minimum total score of ≥ 14 on the 5 items of PANSS-EC and at least 1 individual item score of ≥ 4 using the 1 to 7 scoring system before the first IM injection of the study drug. **N = 49** - 2 patients – olanzapine group and 1 patient – haloperidol group not included in the efficacy analysis (did not receive the study drug administration). 1 patient – olanzapine group was withdrawn because of the investigator's decision and not subjected to postbaseline assessment**. Overall, 45 patients** (92%) completed the 2-hour study period. Exclusion criteria: serious or unstable medical conditions, Treatment with BZDs within 4 hours before the first IM study drug administration, and Treatment with an injection depot neuroleptic within 1 injection interval before the study drug administration. Illness caused by substance abuse	Olanzapine IM 10 mg/d, N = 25 Haloperidol IM 7.5 mg/d, N = 24 over 24 hours.	Efficacy Olanzapine group and haloperidol group showed significant improvement at 2 hours in the primary efficacy analysis vs baseline (olanzapine, -9.0 ± 5.7, P < 0.001; haloperidol, - 7.9 ± 4.0, P < 0.001). Both treatments showed rapid onset of efficacy from 15 minutes. No difference in improvement between 2 groups except at the 1-hour visit where the olanzapine group showed significantly greater improvement (olanzapine, -8.5 ± 5.0; haloperidol, -6.3 ± 4.3, P = 0.013). Compared with baseline, both groups presented significant change at 2 hours in all secondary efficacy parameters including ACES (olanzapine, 2.6 ± 1.8, P < 0.001; haloperidol, 2.3 ± 1.8, P G 0.001), PANSS-derived BPRS total score (olanzapine, -17.9 ± 17.0, P< 0.001; haloperidol, -19.1 ± 15.9, p < 0.001), and PANSS-derived BPRS positive score (olanzapine, -4.7 ± 5.5, P < 0.001; haloperidol, -5.7 ± 5.3, P < 0.001). On the other hand, there were no significant differences between these 2 groups. Safety: 9 patients (36%) from the olanzapine group and 7 patients (29%) from the haloperidol group experienced at least 1 adverse event. The most frequently reported adverse event was insomnia in both groups with the incidence of 24% in olanzapine group and 25% in haloperidol group. The other adverse events were less than 5%, except for the haloperidol group that had 8% vomiting.	Some concerns D5 – selection of reported results.
Huang CL; Hwang TJ; Chen YH; Huang GH; Hsieh MH; Chen HH; Hwu HG	Prospective, randomized, parallel trial in three acute	**N = 67** Inclusion criteria: Recently hospitalized patients	10 mg IM olanzapine (n = 37)	Efficacy: PANSS-EC scores decreased significantly at 2 hours following the first injection in both	Low

Intramuscular olanzapine versus intramuscular haloperidol plus lorazepam for the treatment of acute schizophrenia with agitation: An open-label, randomized controlled trial. J Formos Med Assoc May 2015;114(5):438-45 [9].	psychiatric inpatient units [National Taiwan University Hospital (NTUH) and its Yun-Lin branch hospital, Yu-Li Psychiatric Hospital] in a 24-hour treatment period. Conducted between September 2006 to February 2009	18–65 years old with: Schizophrenia or schizoaffective disorder. Total score of ≥ 14 (of a maximum of 35) on the PANSS-EC scale and having a score of ≥ 4 (of a maximum of 7) on at least one of these five items of PANSS-EC being acutely agitated to the extent that parenteral antipsychotic therapy was indicated. <u>Exclusion criteria:</u> pregnant or lactating severe medical illnesses having received injectable depot antipsychotics within 1 month use of psychostimulants or reserpine within 1 week having received newly added oral or IM benzodiazepines within 4 hours having received newly added oral or rapid-acting IM antipsychotics within 2 hours; and history of allergic reaction or intolerance to the study medication(s).	5 mg IM haloperidol plus 2 mg IM lorazepam (n = 30). 24 hours	groups (olanzapine: –10.2 ± 6.5, t = 9.750, p < 0.001; haloperidol + lorazepam: –9.9 ± 5.6, t = 9.900, p < 0.001). The difference between haloperidol plus lorazepam and olanzapine was 0.3 units favoring olanzapine (with one-sided lower 97.5% confidence limit = −3); therefore noninferiority (−3 vs. −10.2 × 0.4 = −4.1) could be concluded. ACES scores increased significantly at 2 hours in both groups (olanzapine: 2.1 ± 1.7, t = 7.225, p < 0.001; haloperidol + lorazepam: 2.2 ± 1.7, p < 0.001). The percentage of responder (defined as at least 40% reduction from baseline on the PANSS-EC at 2 hours) was not significantly different between the two groups [19 (51%) in the olanzapine group vs. 11 (37%) in the haloperidol + lorazepam group; Fisher's exact test, p = 0.323]. <u>Safety:</u> The changes in SAS and Barnes Akathisia Rating Scale scores from baseline to 24 hours after the first injection showed no significant differences between the two groups. The incidences of adverse reactions were also not significantly different between the two groups. However, acute dystonia only occurred in the haloperidol plus lorazepam group.	
Hsu WY, Huang SS, Lee BS, Chiu NY. Comparison of intramuscular olanzapine, orally disintegrating olanzapine tablets, oral risperidone solution, and intramuscular haloperidol in the management of acute agitation in an acute care psychiatric ward in Taiwan. J Clin Psychopharmacol. 2010 Jun;30(3):230-4 [10].	Prospective, randomized, rater-blinded study comparing olanzapine IM, olanzapine ODT, risperidone OS, and intramuscular haloperidol (haloperidol IM) in an acute care psychiatric unit for the first 24 hours after admission.	**N=42** Patients in acute care psychiatric ward 18 to 65 years old; DSM-IV diagnosis: schizophrenia, bipolar I disorder, schizoaffective disorder, delusional disorder, or other psychotic disorders; and Excited component score of 14 or higher PANSS-EC, with a score of 4 or higher on at least 1 item (1- to 7-point scale). <u>Exclusion criteria</u>	Patients were randomly assigned to receive 1 of 4 interventions over a 24-hour period: 10-mg olanzapine IM (n = 11), 10-mg olanzapine ODT (n = 10), 3-mg risperidone oral solution (n = 10), or 7.5-mg haloperidol IM (n = 11).	<u>Efficacy</u> PANSS-EC score: Baseline PANSS-EC score, Olanzapine IM 25.55 ± 3.8, haloperidol 28.18 ± 2.82 Olanzapine IM vs Haloperidol IM 30 minutes: -5.00 ± 1.62, p = 0.0042 2 hours: -3.60 ± 1.47, p = 0.089 24 hours: -2.97 ± 1.31, p = 0.157 <u>Safety</u> The most reported and observed adverse effects related to medications were found	Some concerns D2-deviation from intended use and D5 selection of reported result.

		Pregnant or lactating women; patients with serious medical illnesses; closed-angle glaucoma; allergic reaction to olanzapine, risperidone, or haloperidol; received a long-acting antipsychotic agent injection.		in all the 4 groups. Drowsiness was most common. Olanzapine IM and olanzapine ODT produced more drowsiness than oral risperidone and haloperidol IM, but the difference was not significant.	
Kinon BJ; Ahl J; Rotelli MD; McMullen E. Efficacy of accelerated dose titration of olanzapine with adjunctive lorazepam to treat acute agitation in schizophrenia**.** Am J Emerg Med May 2004;22(3):181-6 [11].	Prospective, randomized, double-blind, multicenter, parallel 3-week study of acutely agitated inpatients diagnosed with schizophrenia, schizophreniform, or schizoaffective disorder.	**N = 100** Inclusion criteria: 18 to 50 years old PANSS Agitation subscale scores > 20 (0-60 scale) and Clinical Global Impressions-Severity (CGI) scale scores > 4 (1-7 scale). <u>Exclusion criteria:</u> Pregnant or lactating women or patients with serious unstable illnesses, including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, neurologic, immunologic, or hematologic disease, in which pharmacotherapy posed a substantial clinical risk or confounded diagnosis.	Oral olanzapine (10 mg per day), N = 52 or oral haloperidol (10 mg per day), N = 48 Plus lorazepam as needed (up to 12 mg per day)	Of the 57 patients who completed the study, significantly more were from the olanzapine treatment group than from the haloperidol treatment group (67.3% vs. 45.8%, P = .043, Fisher's exact test). The mean time to discontinuation was significantly greater for the olanzapine-treated patients than the haloperidol-treated patients (17.69 ± 6.51 days vs. 14.21 ± 7.65 days, respectively, P = .016, t test, 98 df). <u>Efficacy:</u> Significant within-group improvement was demonstrated in PANSS Agitation scores for both groups as early as 1 hour after initiating therapy (-5.79 ± 6.30 for olanzapine and -4.89 ± 6.05 for haloperidol, P <.001). Within-group mean changes from baseline continued to be significant at each assessment during the first 24 hours for both treatment groups. Olanzapine group experienced significantly greater improvement than the haloperidol group (P = .044, F test, 1.76 df) in mean PANSS Agitation scores (LOCF) (-14.00 ± 10.71 and -11.21 ± 11.67, respectively). <u>Safety:</u> Olanzapine vs haloperidol Dystonia, hypertonia, and increased salivation (0 % vs 8.3 %, p =0.05). Headache (11.5 vs. 25.0 %, p = .117) Nervousness (7.7 vs. 16.7 %, p= .223) Anxiety (11.5 vs. 4.2%, p= .272) Insomnia (5.7 vs. 13%, p= .305) Somnolence (17.3 vs. 25.0 %, p =.462)	Some concerns, D1- randomization sequence not described, D4 – measurement of outcome – not information on whether outcome assessors were aware of the intervention.

				Pain (9.6 vs. 10 %, p = 1.00) Agitation (9.6 vs. 10 %, p = 1.00)	
Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, Saunders JC, Krueger J, Bradley P, San L, Bernardo M, Reinstein M, Breier A. Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. Am J Psychiatry. 2001 Jul;158(7):1149-51. doi: 10.1176/appi.ajp.158.7.1149. PMID: 11431240 [12].	Double-blind, randomized, controlled trial conducted in hospitals in Australia, Austria, Belgium, Canada, the Czech Republic, France, Greece, Hungary, Israel, the Republic of South Africa, Spain, the United Kingdom, and the United States	**N = 311** Inpatients diagnosed with schizophrenia (according to the DSM-IV) who scored ≥ 14 on the PANSS-EC (≥4 on at least 1 item) clinically agitated. <u>Exclusion criteria:</u> Pregnant or lactating, Patients with serious medical conditions for whom treatment with medication posed a substantial clinical risk or confounded diagnosis.	Olanzapine 10 mg, N = 131 Haloperidol 7.5 mg, N = 126 or Placebo (saline), N = 54 over 24 hours	<u>Efficacy:</u> 91.6 % participants completed the study. Mean changes in excited component scores on the PANSS from baseline to 2 hours (adjusted for country differences): olanzapine: –7.7 ± 6.1, haloperidol: –7.6 ± 5.0 and placebo: –3.6 ± 5.2). The difference between olanzapine and haloperidol was 0.1 units favoring olanzapine (one-sided lower 97.5% confidence limit=–1.2); noninferiority (–1.2 versus –7.6 × 0.4=–3.0) was concluded. Mean changes in scores from baseline to 2 hours after the first injection on the Agitated Behavior Scale and Agitation Calmness Evaluation Scale (adjusted for country differences): Olanzapine: –8.3 ± 0.6 and 1.6 ± 0.1, respectively, Haloperidol: –8.2 ± 0.6 and 1.5 ± 0.1 respectively, Placebo: –4.8 ± 0.9 and 0.6 ± 0.2 Mean change from baseline in the PANSS-EC scale at 24 hours: olanzapine, haloperidol, and placebo (O: –6.5 ± 5.3, H: –6.7± 4.6, and P: –3.1 ± 5.1, respectively) (F=10.7, df=2, 298, p<0.001), Agitated Behavior Scale score (O: –6.4 ± 5.9, H: –6.6 ± 5.3, and P: –3.7 ± 6.7, (F=5.5, df=2, 298, p=0.004), Agitation Calmness Evaluation Scale score O: 0.8 ± 1.0, H: 1.1 ± 1.0, and P: 0.6 ± 1.2 (F=5.5, df=2, 298, p= 0.004). Pairwise comparisons (adjusted for country differences) of haloperidol and olanzapine, olanzapine, and placebo, respectively: **PANSS**: (t=–0.3, df=298, p=0.76; t=–4.2, df=	Some concerns D2- deviations from intended interventions – no information analysis used to estimate effect of intervention

Wright P; Meehan K; Birkett M; Lindborg SR; Taylor CC; Morris P; Breier A A comparison of the efficacy and safety of olanzapine versus haloperidol during transition from intramuscular to oral therapy. Clin Ther. 2003;25(5):1420-8 [13].				298, p<0.001; t=–4.4, df=298, p<0.001), the **Agitated Behavior Scale** (t=–0.1, df=298, p=0.91; t=–3.0, df=298, p=0.003; t=–3.1, df=298, p=0.002), and the **Agitation Calmness Evaluation Scale** (t=2.3, df=298, p=0.02; t=1.3, df=298, p=0.20; t=3.1, df=298, p=0.002 <u>Safety:</u> Acute dystonia: Olanzapine = 0 Haloperidol = 9 (7.1%), Fisher's exact p=0.001. Extrapyramidal syndrome: Olanzapine = 1 (0.8%), Haloperidol =seven (5.6%), p=0.03, Fisher's exact test. Received anticholinergics: Haloperidol-treated =26 (20.6%), Olanzapine-treated patients 6 (4.6%) (p<0.001, Fisher's exact test, or placebo patients 2 (3.7%) (p=0.003, Fisher's exact test). <u>2003 study</u> 85.5% (112/131) of olanzapine-treated patients and 84.1% (106/126) of haloperidol-treated patients completed the PO period. <u>Efficacy:</u> For the IM-treated patients continuing to the PO period, mean (SD) PANSS-EC scores were significantly reduced from the IM period baseline to the 24-hour IM end point with both olanzapine (-7.1 14.81; tZZZ = -14.59; P < 0.001) and haloperidol (-6.7 14.31; tZZZ = -13.06; P < 0.001, with no significant between-group differences. <u>Safety:</u> Haloperidol-treated patients spontaneously reported more acute dystonia and akathisia than olanzapine-treated patients during PO treatment (dystonia, 4.3%	Some concerns D2- deviations from intended interventions – no information analysis used to estimate effect of intervention.

				5 /116] vs 0% [0/122], respectively [P = 0.0261; akathisia, 5.2% [6/116] vs 0% [O/122], respectively [P = 0.0131). At PO period baseline, significant between group differences were found in scores on the BAS (Ft 221 = 9.26; P = 0.003) and the SAS (Fr 222 = 10.10; P = 0.002) due to a general worsening of mean EPS scores in the haloperidol group, however, no significant between-group differences were found in the changes in these scores from baseline to end point during the PO period.	
b. OLANZAPINE VERSUS PLACEBO					
Katagiri H; Fujikoshi S; Suzuki T; Fujita K; Sugiyama N; Takahashi M; Gomez JC. A randomized, double-blind, placebo-controlled study of rapid-acting intramuscular olanzapine in Japanese patients for schizophrenia with acute agitation. BMC Psychiatry Jan 2013; 13:20 [14].	Placebo-controlled, randomized, double-blind, parallel-group study in Japanese patients diagnosed with schizophrenia according to the diagnostic criteria specified in the DSM-IV-TR.	Outpatients with an exacerbation of schizophrenia with acute psychotic agitation who required hospitalization at a regular doctor visit or in an emergency room. In patients with acute psychotic agitation were eligible for this study. Patients with acute psychotic agitation were defined as those who met any of following 3 criteria: patients whose agitation occurred or worsened within the prior 2 weeks, patients who were considered to require rapid tranquilization, or patients who needed careful consideration for examination or treatment (for example, more than 1 medical staff, special room). Age 20 years – 65 years **N = 91** - 1 patient in the randomized group was excluded from full analysis due to discontinuation by physician's decision before the first IM injection. 1 patient was excluded from the efficacy analysis because	Olanzapine IM 10 mg, N = 45 Placebo, N = 45 over 24 hours	<u>Efficacy</u> Mean change of PANSS-EC total score: 2 hours: −9.2 ± 4.5 in IM olanzapine group, -2.8 ± 5.6 in IM placebo group, p < 0.001 The change from baseline to each evaluation timepoint (15, 30, 60 and 90 minutes, and 2 and 24 hours after the first IM injection) in PANSS-EC total scores was a secondary efficacy endpoint. At every timepoint, statistically significant differences were observed between IM olanzapine and IM placebo groups (p<.001 The maximum change in PANSS-EC total score in the IM olanzapine group was observed at the 2-hour time point. At the 24-hour timepoint the mean change in PANSS-EC total score in the IM olanzapine group decreased to −5.6 (from −9.2 at 2 hours), while IM placebo group remained at -2.8 (from −2.8 at 2 hours) (p=.008). At 2 hours after the first IM injection, the proportion of responders (≥40% decrease in the PANSS-EC total score) was 40% (18/45 patients) in the IM olanzapine group and	Some concerns D1 – randomization sequence not described. D2 – no further information on blinding and type of analysis used to estimate effect of intervention.

		of a problem in the maintenance of the blind. <u>Exclusion criteria:</u> Patients whose agitation continued more than 2 weeks before providing informed consent, Patients whose agitation was caused by substance abuse, neurologic conditions or the comorbidity of mental retardation or personality disorders, and Patients who had inadequately controlled diabetes, or patients whose treatments for diabetes had been changed within 4 weeks before the first IM injection of the investigational product.		13.6% (6/44 patients) in the IM placebo group At 2 hours after the first IM injection the mean agitation-calmness evaluation scale (ACES) score for IM olanzapine group was 3.5 ± 1.7 (n=45) and in the IM placebo group the mean was 2.2 ± 1.3 (n=44) <u>Safety:</u> Treatment-emergent adverse events were reported in 19 of the 90 patients during the study: 28.9% were in the IM olanzapine group, and 13.3% were in the IM placebo group. *somnolence* (IM olanzapine, n=7 [15.6%]; IM placebo, n=2 [4.4%]; p=.157) *blood urine present* (IM olanzapine, n=0; IM placebo, n=2 [4.4%]; p=.494). *Parkinsonism:* IM olanzapine group (2/43 patients, 4.7%), and in the IM placebo group (3/44 patients, 6.8%) (p=1.000)	

Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	<u>Olanzapine vs Benzos</u> Single trial with small sample size. <u>Olanzapine vs haloperidol + promethazine</u> Evidence uncertain – best quality RCT (n=300) used a higher equivalent dose of haloperidol. Other RCTs small and of very low certainty evidence.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large [ ] Moderate [ ] Small [X] None [ ]	<u>Vs lorazepam</u> Greater improvement (NNT 7, 95% CI 4 to 116) and slightly reduced agitation and need for additional medicines. <u>Vs haloperidol + promethazine</u> Possibly less improvement in global state but reduced aggression and agitation and no difference in sedation.
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	<u>Olanzapine vs Benzos</u> Single trial with small sample size. <u>Olanzapine vs haloperidol + promethazine</u> Evidence uncertain – best quality RCT (n=300) used a higher equivalent dose of haloperidol. Other RCTs small and of very low certainty evidence
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [ ] None [X]	There were no significant differences in safety outcomes
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [ ] Favours control [ ] Intervention = Control *or* Uncertain [X]	No evidence that undesirable effects with olanzapine are worse than those of lorazepam or haloperidol + promethazine.
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X]	N/a
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [X] No [ ] Uncertain [ ]	Generic formulations of olanzapine IM and olanzapine ODT are available in SA.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [ ]	**Price of medicines** **Medicine** | **Tender price (ZAR)** | **SEP (ZAR)** | **60% SEP ZAR** Haloperidol 5 mg tablet | 0.24* | - | - Haloperidol 5mg/ml injection | - | 45.68** | -

JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS

Lorazepam 4mg/ml injection	-	89.17***	53.50
Clonazepam 2mg/ml injection	-	55.49***	66.59
Midazolam 15mg/3ml injection	7.50****	-	-
Promethazine 50mg/2ml injection	8.22****	-	-
Olanzapine 10mg ODT	-	11.43***	6.86
Olanzapine 10 mg injection	-	72.84***	43.71

* Contract circular HP09-2021SD (weighted average price)
** SEP database, (S21 State access price)
***SEP database, July 2022 (cheapest generic price, if available)
**** Contract circular HP06-2021SVP

Comparative costing analysis

Notes:
1) Comparing maximum recommended adult doses of the various interventions.
2) Lorazepam 4mg/ml ampoule costed, noting wastage as the maximum single dose is 2mg.
3) If the medicine not available on tender, the price of the cheapest available generic was considered at 60% of SEP.
4) Olanzapine co-administered with parenteral benzodiazepines not recommended due to the possible safety concerns of respiratory depression (expert opinion).
5) Only direct medicine prices considered (excluding administration costs)

Recommended treatment protocols and price per treatment course

a. Current standard of care (PHC STG, 2020/ Adult Hospital Level STG, 2019)
If initial oral benzodiazepine dose not sufficient:
- Lorazepam, IM, 0.5–2 mg, immediately

OR
- Midazolam, IM, 7.5–15 mg immediately

OR
- Clonazepam, IM, 0.5–2 mg, immediately

(may repeat dose if required)

Inadequate response to benzodiazepines (after 30-60 minutes):
- Haloperidol, IM, 2.5–5 mg, immediately.

AND
- Promethazine, deep IM, 25–50 mg.

(may repeat dose if required)

COST FOR TREATMENT COURSE A (maximum dosing):

Treatment protocol	60%SEP + contract price (ZAR)
• Lorazepam protocol	214.81
• Midazolam protocol	122.80
• Clonazepam protocol	240.98

b. Proposed olanzapine recommendation
If initial oral benzodiazepine dose not sufficient:
- Olanzapine 5-10 mg, ODT, immediately

OR
- Olanzapine 5-10 mg, IM, immediately

(may repeat dose 30-60 minutes later, if required)

COST FOR TREATMENT COURSE B (maximum dosing):

Treatment protocol	60%SEP (ZAR)
• Olanzapine ODT	13.72
• Olanzapine, IM	87.41

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
		Other resources: n/a
VALUES, PREFERENCES, ACCEPTABILITY	**Is there important uncertainty or variability about how much people value the options?** Minor [ ] Major [ ] Uncertain [X] **Is the option acceptable to key stakeholders?** Yes [X] No [ ] Uncertain [ ]	There is no local survey data available, and judgements were based on Committee expert opinion through consensus.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [ ]	

Version	Date	Reviewer(s)	Recommendation and rationale
Initial	29 September 2022	LR, TK, MM, NG, SM, TL	Haloperidol IM is no longer available in South Africa, and olanzapine oro-dispersible tablets or IM may be considered as an alternative. Olanzapine may be superior to lorazepam and to the combination of haloperidol and promethazine in reducing agitated or aggressive behaviour (very low certainty evidence).
Version 2	14 March 2024	LR, TK, MM, NG, SM, TL	NEMLC, deliberated the erratic supply of Haloperidol IM, but retained the proposal as recommended by the PHC/Adult Hospital Level Expert Review Committee. Wording revisions regarding erratic Haloperidol IM supply was added to the review.

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3. Patel MX, Sethi FN, Barnes TR, Dix R, Dratcu L, Fox B, et al. Joint BAP NAPICU evidence-based consensus guidelines for the clinical management of acute disturbance: De-escalation and rapid tranquillisation. Journal of psychopharmacology (Oxford, England). 2018;32(6):601-40.10.1177/0269881118776738
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12. Wright P, Birkett MA, Meehan K, David SR, Brook S, Breier. A double-blind dose response study comparing intramuscular olanzapine, haloperidol and placebo in acutely agitated schizophrenic patients. Schizophrenia research (abstracts of the VIII international congress on schizophrenia research; 2001 april 28-may 2; british columbia, canada). 2001;49(1‐2 Suppl):250‐1,
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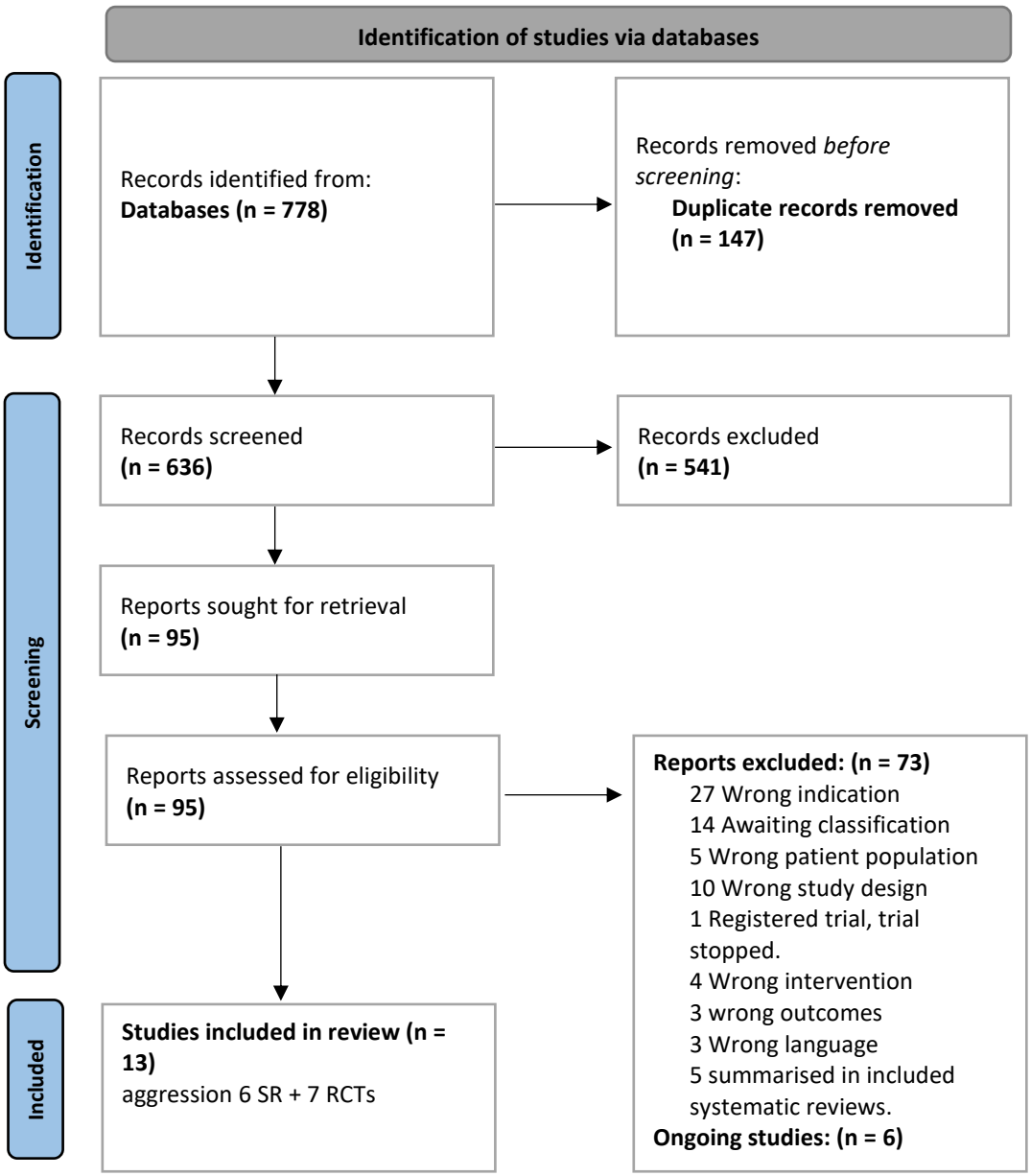
Appendix 1: Search strategy

#9	#1 AND #2 AND #8
#8	#3 OR #4 OR #5 OR #6 OR #7
#7	schizophrenia[mh] OR schizophreni*[tiab]
#6	dementia[mh] OR dementia*[tiab]
#5	confusion[mh] OR confus*[tiab] OR disorientat*[tiab] OR bewilderment[tiab] OR delirium*[tiab]
#4	paranoid disorders[mh] OR paranoi*[tiab]
#3	psychotic disorders[mh] OR psychosis[tiab] OR psychotic[tiab] OR psychoses[tiab] OR psychiatric disorder*[tiab] OR mental disorders[mh] OR mental illness*[tiab] OR mental disorder*[tiab] OR mood disorders [mh] OR mood disorder*[tiab] OR affective disorder*[tiab] OR bipolar disorder[mh] OR bipolar[tiab] OR mania*[tiab] OR manic[tiab]
#2	Search: aggression[mh] OR aggress*[tiab] OR disruptive behavior*[tiab] OR disruptive behaviour*[tiab] OR agitat*[tiab] OR violent behavior*[tiab] OR violent behaviour*[tiab]
#1	Search: olanzapine[mh] OR olanzapine*[tiab] OR zyprexa*[tiab] OR zolafren*[tiab] OR LY 170053[tiab] OR LY170053[tiab] OR LY 170052[tiab]

Appendix 2: PRISMA flow chat identified studies



Modified From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. http://www.prisma-statement.org/

Appendix 3: Excluded studies

Author, date	Type of study	Reason for exclusion
1. Finucane 2020	SR	Wrong indication
2. Fernández Sánchez, 2009	SR	Wrong indication
3. Belgamwar 2005	SR	Wrong indication
4. Burry, 2018	SR	Wrong indication
5. Burry, 2019	SR	Wrong indication
6. Nikooie, 2019	SR	Wrong indication
7. NICE review	SR	Wrong indication
8. Huf, 2009	SR	Wrong language
9. Lacasse, 2016	SR	Wrong intervention
10. Maglione, 2011	SR	Wrong indication
11. Mühlbauer, 2021	SR	Wrong patient population
12. Pelland, 2009	SR	Wrong language
13. Seida, 2012	SR	Wrong patient population
14. Shoptaw, 2009	SR	Wrong indication
15. Williamson, 2019	SR	Wrong indication
16. Yildiz, 2003	SR	Wrong language
17. Yildiz, Sachs 2003	SR	Wrong study design
18. Yunusa, 2019	SR	Wrong indication
19. Skrobik 2004	RCT	Wrong indication
20. Van der Vorst	RCT	Wrong indication
21. Jain 2017	RCT	Wrong indication
22. Beasley, 1996	RCT	Wrong indication
23. Bozzatello, 2017	RCT	Wrong patient population
24. Breier, 2000	RCT	Awaiting classification
25. Breier, 2001	RCT	Awaiting classification
26. Battaglia 2005	RCT	Wrong outcome
27. Clark, 2001	RCT	Wrong indication
28. David, 2001	RCT	Awaiting classification
29. Eli, 2005	RCT	Awaiting classification
30. Faay, 2020	RCT	Wrong indication
31. Fontaine, 2003	RCT	Wrong patient population
32. Gareri, 2004	RCT	Wrong indication
33. Huf, 2009	RCT	Wrong intervention
34. Hwang, 2012	RCT	Awaiting classification
35. Jin, 2009	RCT	Awaiting classification
36. Kinon, 2000	RCT	Wrong indication
37. Kinon, 2001	RCT	Wrong outcomes
38. Kittipeerachon, 2016	RCT	Wrong intervention
39. Kong, 2009	RCT	Awaiting classification
40. Krakowski, 2014	RCT	Wrong indication
41. Lindbord, 2003	RCT	Wrong outcomes
42. Meehan, 2001	RCT	Awaiting classification
43. Meehan, 2001 (1)	RCT	Awaiting classification
44. Meehan, 2001 (2)	RCT	Awaiting classification
45. Mintzer, 2002	RCT	Awaiting classification
46. Ono, 2008	RCT	Awaiting classification
47. Schneider, 2006	RCT	Wrong indication
48. Smith, 2003	RCT	Awaiting classification
49. Street, 2000	RCT	Wrong patient population
50. Svestka, 2002	RCT	Awaiting classification
51. Verhey, 2006	RCT	Wrong indication
52. Villari, 2009	RCT	Wrong intervention

53. Hirsch, 2019	Narrative review	Wrong study design
54. Houston, 2019	Narrative review	Wrong study design
55. Wagstaff, 2005	Narrative review	Wrong study design
56. Pascual, 2007	Observational study	Wrong study design
57. Walther, 2014	Observational study	Wrong study design
58. NCT00833300, 2009	Registered trial	Registered trial, trial stopped for recruitment issues
59. Elsayem, 2010	Pilot study	Wrong study design
60. Citrome, 2007	Quantitative review	Wrong study design
61. Srivastava, 2010	Summary of review	Wrong study design
62. deAlmeida, 2017	Review of reviews	Wrong study design
63. IRCT20200927048852N1 2020	Ongoing trial	Wrong indication
64. NCT00485901	Ongoing trial	Wrong indication
65. NCT04750395 2021	Ongoing trial	Wrong indication
66. IRCT20141209020258N114 2019	Ongoing trial	Wrong indication
67. NCT04833023 2021	Ongoing trial	Wrong indication
68. Jones, 2001	Summary of RCTs	Wrong study design
69. Battaglia 2003	RCT	Summarized in included systematic review
70. Baldacara 2011	RCT	Summarized in included systematic review
71. Raveendran 2007	RCT	Summarized in included systematic review
72. Mehaan 2002	RCT	Summarized in included systematic review
73. Breier 2002	RCT	Summarized in included systematic review

Appendix 4: Systematic reviews excluded from evidence synthesis

Citation	INTERVENTION	Appraisal
Paris G, Bighelli I, Deste G, Siafis S, Schneider-Thoma J, Zhu Y, Davis JM, Vita A, Leucht S. Short-acting intramuscular second-generation antipsychotic drugs for acutely agitated patients with schizophrenia spectrum disorders. A systematic review and network meta-analysis. Schizophr Res. 2021 Mar;229:3-11. doi: 10.1016/j.schres.2021.01.021. Epub 2021 Feb 17. PMID: 33607608.	Network meta-analysis of antipsychotics: Ziprasidone, olanzapine, aripiprazole, haloperidol and placebo	Low
Bak M, Weltens I, Bervoets C, De Fruyt J, Samochowiec J, Fiorillo A, Sampogna G, Bienkowski P, Preuss WU, Misiak B, Frydecka D, Samochowiec A, Bak E, Drukker M, Dom G. The pharmacological management of agitated and aggressive behaviour: A systematic review and meta-analysis. Eur Psychiatry. 2019 Apr;57:78-100. doi: 10.1016/j.eurpsy.2019.01.014. Epub 2019 Feb 2. PMID: 30721802.	Comparison of various antipsychotics including haloperidol plus promethazine, risperidone, olanzapine, droperidol and aripiprazole.	Low
Tulloch KJ, Zed PJ. Intramuscular olanzapine in the management of acute agitation. Ann Pharmacother. 2004 Dec;38(12):2128-35. doi: 10.1345/aph.1E258. Epub 2004 Nov 2. PMID: 15522977.	Olanzapine versus haloperidol / lorazepam monotherapy	Low
Dundar Y, Greenhalgh J, Richardson M, Dwan K. Pharmacological treatment of acute agitation associated with psychotic and bipolar disorder: a systematic review and meta-analysis. Hum Psychopharmacol. 2016 Jul;31(4):268-85. doi: 10.1002/hup.2535. Epub 2016 May 5. PMID: 27151529.	Comparison of antipsychotics of various including olanzapine, aripiprazole, risperidone, lorazepam or placebo	Low