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: 18 August 2022
Medicine (INN): Olanzapine (IM, orodispersible)
Medicine (ATC): N05AH03
Indication (ICD10 code): Delirium F05.0/.1/.8/.9
Patient population: Adults with delirium who are agitated or considered a risk to themselves or others, and non-pharmacological measures are ineffective.
Prevalence of condition:
South African studies
- 12.3% of acute medical inpatients (Du Plooy, 2020)[1]
- 17.6% of acutely admitted people with HIV (Day, 2021)[2]

International studies
- Approximately 20% of general adult inpatients and 80% of mechanically ventilated patients in ICU (Nikooie, 2019)[3]

Level of Care: Primary Healthcare
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

- We conducted a review of Clinical practice guidelines, health technology assessments, systematic reviews of randomised controlled trials (RCTs), RCTs and where necessary systematic reviews of non-randomised/ observational studies or observational studies. Ongoing trials were also sought.
- Two systematic reviews, three RCTS and three clinical guidelines were identified, including comparisons of interest.
- All three clinical guidelines were of relatively high quality assessed against AGREE II. Only one makes a weak recommendation for olanzapine for the treatment of delirium
- Comparison of olanzapine to placebo, was reported in one clinical trial, which rated poor in terms of quality, as part of a systematic review. The impact of olanzapine on duration of delirium (days) was uncertain (MD=-2.4, 95% CI 3.51,-1.29, n = 103, 1 trial. Change in delirium severity, appeared to favour olanzapine (reduction in the delirium rating scale (DRS) MD = -11.1, 95% CI 15.51 to -7.69, n=103, 1 trial.
- For comparison of olanzapine versus haloperidol, change in delirium severity results were reported in most studies however these were at different time points and using different measures. Overall, there was no difference in delirium severity between olanzapine and haloperidol (generally very low to low certainty of evidence). Duration of delirium (days) did not differ significantly between haloperidol and olanzapine, in 1 trial, included in a systematic review (mean Difference (MD) 0.62 days, 95% CI 0.06 to 1.18).
- No reviews nor trials were identified comparing olanzapine to benzodiazepines in the treatment of delirium.

PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE 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)**
Type of recommendation				X	

Recommendation: The PHC/ Adult Hospital Level Committee suggests using olanzapine (orodispersible and parenteral formulations) as an option to manage delirium where non-pharmacological management is not sufficient and if haloperidol, intramuscular formulation is unavailable
Rationale: Available low-quality evidence shows that olanzapine is comparable to haloperidol.
Level of Evidence: Low to very low certainty evidence

Review indicator: Evidence of harm, efficacy
NEMLC RECOMMENDATION (20 OCTOBER 2022 MEETING): NEMLC recommended the use of olanzapine oro-dispersible tablet or IM injection for delirium with agitated and acutely disturbed behaviour. Once the patient is able to swallow, to continue with oral haloperidol or olanzapine, until behaviour is contained.
Monitoring and evaluation considerations
Research priorities

2. **Name of author(s)/motivator(s)**
   Lesley Robertson, Tamara Kredo, Mashudu Mthethwa, Natasha Gloeck, Shelley McGee, Trudy Leong

3. **Author affiliation and conflict of interest details**
   - Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: 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
   - Shelley McGee, Ophthalmological Society of South Africa: 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

4. **Introduction/ Background**
   The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5)[4] describes delirium as an acute disturbance in attention, awareness (reduced orientation to the environment), and cognition (e.g., memory deficit, disorientation, language, visuospatial ability, or perception). It develops within hours to days and tends to fluctuate during the day, worsening in the evenings. Delirium may be 'hyperactive', with increased mood lability, agitation, and/or uncooperative behaviour, or 'hypoactive', with poor responsiveness and stupor.

   Delirium is a physiological consequence of another medical condition, substance intoxication or withdrawal, exposure to a toxin, or multiple aetiologies. Treatment of delirium necessitates treatment of the underlying cause. Non-pharmacological measures to reduce confusion include a calm, predictable care environment, effective communication, verbal reorientation, and maintenance of the circadian rhythm. Medicine management of agitation, distress, or uncooperative behaviour may be necessary to facilitate nursing and treatment of the underlying condition. Currently, haloperidol, IM is recommended if non-pharmacological measures are insufficient. Haloperidol IM 5mg/ml and 20mg/2ml were discontinued in South Africa by Pfizer and supply has been erratic.

5. **Purpose/Objective i.e., PICO question**:
   - **Population**
     People ≥18 years treated for delirium (formally diagnosed using a validated tool) or sub-syndromal delirium (presence of some delirium symptoms) in an acute care (e.g., primary health clinic/ community health clinic/ hospital emergency room, medical or surgical ward), intensive care, or palliative care setting. Exclude studies solely focusing on people with substance intoxication or withdrawal or people in psychiatric care settings.
   - **Intervention**
     Olanzapine IM and orodispersible tablets, any dose
   - **Comparators**
     Haloperidol IM +/- promethazine IM, any dose

Benzodiazepines: any dose, given orally or IM
Placebo

- **Outcomes**

  Efficacy
  - Duration of delirium (days)
  - Change in delirium severity, assessed by validated instruments.
  - Change in agitation score
  - Delirium resolution (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms)
  - Use of physical restraint
  - Other – hospital/ intensive care unit (ICU) length of stay (days), hospital discharge disposition (e.g., rehabilitation, chronic care facility, home), health-related quality of life (as reported by study authors)

  Safety
  - Extrapyramidal side effects (EPS); use of anticholinergic medication
  - Adverse events as defined by the study authors (e.g., prolongation of the QTc interval, sudden cardiac death, cerebral vascular events, seizures, extrapyramidal effects, long-term cognitive impairment (e.g., change in Mini Mental Status Exam or as reported by study authors))
  - Mortality

- **Study types**

  Clinical practice guidelines, health technology assessments, 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. **Data sources**:
   Clinical Practice Guidelines sources searched were the Guidelines International Network (GIN) Library, the National Institute for Health and Care Excellence (NICE) and the British Association of Clinical Pharmacology, as well as relevant clinical practice guidelines from Australia, New Zealand and Canada on their government websites, searched via Google. Systematic reviews and randomised controlled trials were sought in PubMed, the Cochrane Library, and Epistemonikos.

b. **Search strategy –** A search strategy was developed for PubMed and adapted to other databases (Appendix 1). A search for systematic reviews and RCTs was conducted on PubMed, the Cochrane Library, and Epistemonikos on 4 March 2022 (Appendix 1). The search was inclusive of all populations (with acute agitation or delirium) as the two review topics were happening in parallel and this was most efficient approach for searching and screening.

Screening, data extraction and analysis, evidence synthesis: Records were uploaded into the reference management software, COVIDENCE. Titles and abstracts were screened independently and in duplicate (NG, MM, TK, LR). Thereafter, full text screening was done by two reviewers, including tagging the study design (RCT or SR) and the population (delirium or acute agitation) and checked by a third reviewer. Discrepancies were discussed with LR and TK to finalise selection. We took a step-wise approach, screening for systematic reviews first and then for RCTs. Data extraction for included reviews was done by one reviewer and checked by a second reviewer. Eligible clinical guidelines were appraised with the AGREE II tool by two reviewers (MM and NG). Eligible systematic reviews were appraised using the AMSTAR II Checklist, and eligible RCTs were assessed for Risk of Bias using the Cochrane's RoB 2.0 Tool. Data was extracted into Characteristics of Included studies tables (tables 2 and 3). For dichotomous outcomes, we reported risk ratios (RR) with 95% confidence intervals (CI). We reported results from the review or trial where possible. Despite the intervention in these studies being haloperidol, and olanzapine being the comparator, outcomes of results were not reanalysed in RevMan to align with the review

question as denominators for the systematic reviews were not available and we wanted to keep the results standardised. Where available, we reported on the GRADE (level of certainty) of the evidence.

c. Excluded studies: Reasons for excluding full-texts were agreed in duplicate with a third reviewer finalizing any disputes.

Results:

1. Search results

We searched PubMed, Epistemonikos and the Cochrane Library on 4 March 2022. We identified 778 records which were imported for screening, with 147 duplicates removed. Furthermore, three records were identified from experts in the field and three were identified through reference searching. We screened 636 abstracts, of which 541 were irrelevant. 95 full-text studies were assessed for eligibility; 86 studies were excluded. There were nine included studies: two systematic reviews, three RCTs and four ongoing studies.

The Prisma Flow Chart is available in Appendix 2.

2. Description of included clinical guidelines, systematic reviews and RCTs

Table 1 reports a summary of the guidelines, Table 2 reports the main characteristics and outcomes of the included systematic reviews, and Table 3 reports the main characteristics and outcomes of included randomised controlled trials. Appendix 2 describes the excluded studies and Appendix 3 provides a summary of ongoing trials.

2.1. Clinical guidelines:

We identified three guidelines

1. National Institute for Health and Care Excellence (NICE). Delirium: diagnosis, prevention and management[6]
2. Scottish Intercollegiate Guidelines Network (SIGN). Risk reduction and management of delirium[7]
3. Victorian Government Department of Human Services. Clinical practice guidelines for the management of delirium in older people[8]

Following appraisal with AGREE II, all three were assessed as moderate to good quality (see Table 1). The NICE guideline was first issued in July 2010, and updated in March 2019. This guideline offers guidance around modifiable risk factors to identify people at risk of developing acute delirium, diagnosis of delirium in long-term, critical and acute care settings, and pharmacological as well as non-pharmacological interventions for reducing delirium incidence and consequences, and reducing the severity, duration and consequences of delirium in adults (18 years and older) in a hospital or long-term residential care. This guideline had an overall AGREE II score of 83%. Of note is that olanzapine was removed from the updated NICE guideline (2019), as haloperidol now has UK marketing authorisation for delirium treatment (though, discontinued from the South African market).

The SIGN delirium guideline was first published in March 2019. This guideline provides guidance for reducing the risk of delirium, as well as the detection, assessment, treatment and follow up of adults with delirium in all settings (patient homes, long term care, hospitals, and hospices). This guideline had an overall AGREE II score of 67%.

The Victorian Government Department of Human Services' guideline for the management of delirium in older people was published in 2006 and provides recommendations in the assessment and management of older people (65 years and older, or 45 years and older in in Aboriginal and Torres Strait Islander people) in Australia in hospitals, and across healthcare settings, as well as the prevention of delirium in at-risk older people, identifying and defining appropriate health service provision and management options to ensure the best possible health outcomes. This guideline had an overall AGREE II score of 83%.

Recommendations related to this review (olanzapine vs haloperidol) are summarized in Table 1. Domain scores for the AGREE II Appraisals can be found in Appendix 3.

Table 1: Summary of Guidelines and AGREE II scores

Name	Recommendation	AGREE II
National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management**	The NICE group recommends that if a person with delirium is distressed or considered a risk to themselves or others and verbal and non-verbal de-escalation techniques are ineffective or inappropriate, consider giving short-term (usually for 1 week or less) *haloperidol or olanzapine*, starting at the lowest clinically appropriate dose and titrating cautiously according to symptoms (conditional, very low certainty evidence) In the most recent review of this guidance (2019) olanzapine was removed as a treatment option in favour of haloperidol, which had achieved authorisation for the indication of delirium in the United Kingdom.	83%
Scottish Intercollegiate Guidelines Network (SIGN). **Risk reduction and management of delirium**.	The SIGN group states "Because the studies identified are underpowered, larger trials are needed before recommendations can be made on the use of antipsychotics for the treatment of patients in ICU with delirium." (1++ - High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias)	67%
Victorian Government Department of Human Services. **Clinical practice guidelines for the management of delirium in older people.**	The Victorian Government Department of Human services recommends that antipsychotic medication should only be used for the treatment of severe behavioural disturbances and or severe emotional disturbances when there is clear intent for its use (e.g. severe agitation interfering with sleep-wake cycle). When used, "Titrated antipsychotics need to be closely monitored by nursing and medical staff. The dosage and frequency should be titrated carefully against the level of agitation at each review. Titration must commence from a low dose typically commencing with the equivalence of 0.25-0.50mg of haloperidol; olanzapine 2.5 mg orally; or risperidone 0.25 mg orally." (III-2 – a comparative study with concurrent controls (non-randomised experimental trial, cohort study, case-control study, interrupted time-series with a control group))	83%

2.2 Systematic reviews

We identified two systematic reviews for inclusion

1. Finucane 2020. Drug therapy for delirium in terminally ill adults[9]
2. NICE Review within the NICE guideline[6]

Finucane 2020[9], a Cochrane Systematic Review, reviewed evidence of pharmacological therapy for delirium management in terminally ill adults (including terminal agitation, distress or restlessness). The setting was not specified. The NICE review[6] reviewed delirium management in hospitalized participants (age 18 years or older) regardless of whether in a surgical, medical, ICU and emergency ward, mental health settings, and long-term care settings. In both reviews, delirium was defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-5 or earlier criteria).

Primary outcomes assessed in Finucane 2020 were 1) delirium symptoms within 24 to 48 hours, 2) agitation score within 24 to 48 hours and 3) the number of adverse events (including extrapyramidal side effects). Secondary outcomes included 1) the use of any rescue medication (such as midazolam), 2) cognitive status and 3) survival.

Primary outcome measures in the NICE review were 1) duration of delirium and 2) number recovered from delirium. The secondary outcomes included 1) severity of delirium, 2) length of stay, 3) incidence of cognitive impairment or dementia, 4) number of patients in hospital discharged to new long-term care placement, 5) mortality, 6) number of patients with persisting delirium, 7) quality of life (patient), 8) quality of life (carer), and

9) adverse effects associated with the intervention (including extrapyramidal side effects). Outcome results are summarised in Table 2.

There was only one included RCT (Lin 2008) in Finucane 2020 that compared haloperidol to olanzapine. The full text for the included RCT was not found despite extensive searching (searching online databases, contacting trial and review authors). Two outcomes of interest were reported in this RCT and are further detailed in Table 2.
Within the NICE review, olanzapine was considered in two comparisons: olanzapine versus no treatment (one RCT, Hu 2006 – 103 participants, full text not available for review) and haloperidol versus olanzapine (Hu 2006 and Skrobik 2004, Skrobik 2004 is summarized below under the RCTs, Table 3). Finucane 2020 had a moderate AMSTAR II rating. The quality was marked down as authors did not explain their selections of study designs included in the review. The NICE review had a high AMSTAR II rating of 4. GRADE evidence ratings are summarized in Table 2.

2.3 RCTs

We identified three randomised controlled trial for inclusion

1. Skrobik 2004. Olanzapine vs haloperidol: treating delirium in a critical care setting[10]
2. Jain 2017. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium[11]
3. Van der Vorst 2020. Olanzapine versus haloperidol for treatment of delirium in patients with advanced cancer: a phase III randomized clinical trial[12]

The trials were conducted in three countries (Canada (one site), India (one site) and The Netherlands (five sites)). Sample sizes varied from 73 to 100 participants and took place in a medical-surgical ICU (Skrobik 2004[10]), medical emergency wards (Jain 2017[11]) and a medical oncology ward or high-care hospice facility (van der Vorst 2020[12]). All three trials compared haloperidol to olanzapine. In Skrobik 2004, participants were randomised to haloperidol, initiated at 2.5 to 5mg 8 hourly (either orally or via an enteral tube) or olanzapine at 5mg daily. Older patients (60 years and above) received a lower starting dose (haloperidol 0.5 to 1mg, olanzapine 2.5mg). Titration thereafter was based on clinician judgment. In Jain 2017, the mean daily doses of olanzapine and haloperidol were 5.49mg (range 2.5mg) and 2.10mg (range 1 to 5mg) respectively. Doses were determined by the participants' Memorial Delirium Assessment Scale (MDAS) score. In van der Vorst 2020, dosing was age-adjusted and based on clinical practice guidelines. Patients under 75 years old were started on haloperidol 1mg or olanzapine 5mg. This was titrated every 40min for haloperidol and two hours for olanzapine, according to the delirium observation scale (DOS) to a maximum on day 1 of 20mg po or 10mg subcutaneously (sc) for haloperidol, and 20mg po or IM for olanzapine. The doses were halved for patients 75 years and older.

Jain 2017 reported on duration of delirium (days). Skrobik 2004, Jain 2017 and van der Vorst 2020 reported on change in delirium sensitivity – however, the three trials used different instruments of measuring this outcome and so we could not compare in meta-analysis (Skrobik 2004 used change in delirium index scores, Jain 2017 used mean MDAS scores at baseline and at the end of the study period, and van der Vorst used delirium response rate (DRR) as defined by Delirium Rating Scale-R-98 (DRS-R-98) assessment). Van der Vorst 2020 reported on delirium resolution (days). In terms of safety outcomes, Skrobik 2004 and van der Vorst 2020 reported on extrapyramidal side effects. Jain 2017 and van der Vorst 2020 reported on adverse events.

Two of the trials (Skrobik 2004 and Jain 2017) were rated as having a high risk of bias. Skrobik 2004 was rated high due to quasi-randomization of allocation sequence and baseline differences between allocation groups, no information around participant blinding and effects of assignment, no information around a prespecified plan or protocol. Jain 2017 was rated high due to this being a single-blind study, limited information on statistical methods, no information around data available for all participants and missingness, potential bias from researchers not being blinded, and no information around a pre-specified analysis plan. Van der Vorst 2020 was rated as having some concerns of bias due to no information around pre-specified plan or protocol.

3. Description of excluded studies

We excluded 86 full texts – 41 for wrong indication, 16 were awaiting classification, 10 for wrong study design, 7 for wrong intervention, 5 for wrong patient population, 3 for wrong outcomes, 3 for wrong language and 1 registered trial was stopped with recruitment issues. The excluded studies with reasons are listed in Appendix 2.

EFFECTIVENESS OF THE INTERVENTION

Comparison	Number of studies
1. Olanzapine vs Haloperidol	2 systematic reviews, 3 RCTs (one is quasi-randomised)
2. Olanzapine vs Benzodiazepines	0 studies identified
3. Olanzapine vs Placebo	1 systematic review

Comparison 1: Olanzapine vs Haloperidol

Efficacy

Critical outcomes: None of the 5 included studies reported on the following outcomes:

- change in agitation score,
- use of physical restraint,
- hospital/ICU length of stay,
- hospital discharge disposition and
- health related quality of life

Important outcomes

1. **Duration of delirium (days):**
   - *NICE review 2010 (updated in 2019):* The effect of haloperidol compared to olanzapine on duration of delirium is uncertain. Mean Difference (MD) 0.62 days, 95% CI 0.06 to 1.18, one RCT, n = 146, 1 trial, very low certainty evidence due to study quality, and imprecision
   - *Jain 2017:* The mean duration of treatment (days) was similar, 3.57 days (+- 0.92 days) in the olanzapine arm and 3.37 days (+- 0.71 days) in the haloperidol arm.

2. **Change in delirium severity:**

   Results were reported from three studies at different time points and using different measures. Overall, they found there was no difference in delirium severity between olanzapine and haloperidol.

   - *Finucane 2020:* Change in delirium severity: there may be little or no difference in change in delirium severity with olanzapine compared to haloperidol (Very low certainty evidence due to critical imprecision)
     1) within 24 hours: the mean difference (MD) between treatment arms was 2.36 (95% CI -0.75 to 5.47).
     2) between 24 and 48hrs: MD 1.90 (95% CI -1.50 to 5.30)
   - *NICE review:* There may be no difference in change in delirium severity score (delirium Rating Scale – DRS) comparing haloperidol and olanzapine. MD 0.7, 95% CI 0.45 to 1.85, n =146, 1 trial, moderate certainty evidence rated down due to poor study quality)
   - *Skrobik 2004:* There was a comparable reduction in the DI score in both groups over time (ANOVA time effect p 0.02, group effect p 0.83, interaction effect p 0.64)
   - *Jain 2017:* the mean MDAS score at baseline was 18.49 in the olanzapine group and 17.79 in the haloperidol group (the groups were comparable at baseline, p 0.791). The mean MDAS score at the end of the study period was 8.43 in the olanzapine group and 8.00 in the haloperidol group.
   - *Van der Vorst 2020:* The delirium response rate (DRR) was in the Olanzapine arm was 45% (95% CI 31 to 59) and 57% (95% CI 43 to 71) in the haloperidol arm (ΔDRR −12%; odds ratio [OR], 0.61; 95% CI, 0.2–1.4)

3. **Delirium resolution** (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms): Results were reported from three studies. Overall, they found there was little or no difference in delirium resolution between olanzapine and haloperidol.
   - *NICE review:* There may be little to no difference comparing haloperidol and olanzapine. Risk Ratio (RR) 0.99, 95% CI 0.8 to 1.21, p=0.24, I^2=27%, n = 218, 2 trials (low certainty evidence due to poor study quality and indirectness from delirium assessment).
   - *Van der Vorst 2020:* The TRR (time from randomisation to resolution) was 4.5 days (95% CI 3.2 to 5.9) in the Olanzapine and 2.8 days (95% CI 1.9 to 3.7) in the haloperidol arm.

Safety

1. **Mortality**
   - Not reported.
2. **Extrapyramidal side effects (EPS):**
   - *NICE review:* We are uncertain about the difference in occurrence of EPS between haloperidol and olanzapine groups, RR 8.2, 95% CI 0.48 to 140.09, n = 73 , 1 quasi-RCT (very low certainty evidence due to study design limitations, and imprecision). Six participants rated low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1–4 for the Simpson-Angus scale) in the haloperidol arm. There were no extrapyramidal manifestations in the olanzapine arm.
   - *Van der Vorst 2020:* six participants (12.2%) experienced EPS in the haloperidol group (three with tremors, two with muscle stiffness and one with QTc prolongation), compared to four (8.2%) in the olanzapine group (two with tremors, one with dizziness and one with muscle stiffness).

3. **Requiring anticholinergic medication:**
   - *Skrobik 2004:* no participants in either the haloperidol or olanzapine groups received prophylactic or therapeutic antiparkinsonian therapy.

4. **Adverse events:**
   - *Jain 2017:* There were two participants in the olanzapine group with adverse effects (one with excessive sedation, one with akathisia), and three in haloperidol group (drug-induced parkinsonism). All side effects were mild in severity. EPS were not defined separately but included under adverse events and as such have been reported here.
   - *Van der Vorst 2020:* 13 out of 46 patients (26.5%) in the olanzapine arm and 16 out of 49 patients (32.7%) in the haloperidol arm reported treatment-related adverse effects of any grade. Five patient (10.2%) in the olanzapine group and 10 patients (20.4%) in the haloperidol group reports Grade 3 or above TRAEs (OR 0.4, 95% CI 0.1 to 1.4, p=0.16). There were no treatment-related deaths.

Comparison 2: Olanzapine vs Benzodiazepines

None of the included studies compared olanzapine to benzodiazepines

Comparison 3: Olanzapine vs Placebo (NICE review)

Efficacy

Critical outcomes: The NICE review did not report on the following outcomes:

- change in agitation score
- use of physical restraint, hospital/ICU length of stay
- hospital discharge disposition and
- health related quality of life.

Less critical outcomes:

1. **Duration of delirium (days):** We are uncertain of the effect of olanzapine compared to placebo on duration of delirium MD=-2.4, 95% CI -3.51,-1.29, n = 103, 1 trial. (Low certainty evidence due to very poor study quality and imprecision)

2. Change in delirium severity: There is probably a reduction in the delirium rating scale (DRS) in favour of olanzapine compared to placebo MD = -11.1, 95% CI -15.51 to -7.69, n=103, 1 trial. (Moderate certainty evidence due to poor study quality and imprecision)

3. **Delirium resolution** (defined as reduction of delirium rating scale below a target set by the authors or complete resolution of symptoms): Outcome "Complete Response" reported that there is probably a more rapid resolution of delirium symptoms in favour of the olanzapine compared to placebo, RR=3.68, 95% CI 1.63 to 8.33, n=103, 1 trial. (Moderate certainty evidence due to poor study quality, indirectness and imprecision)

Safety

For this comparison, the NICE review did not report on extrapyramidal side-effects, if anticholinergic medication was required, drug-related adverse events or mortality.

Conclusion

We identified two reviews and three trials addressing the outcomes of interest, comparing olanzapine to haloperidol. In patients with delirium, there is probably little or no difference in olanzapine compared to haloperidol in the outcomes of interest. We are uncertain about the difference in occurrence of extrapyramidal side-effects and other adverse events in olanzapine compared to haloperidol.

We identified one review addressing the outcomes of interest, comparing olanzapine to placebo. In patients with delirium, we are uncertain of the effect of olanzapine compared to placebo in duration of delirium. There is probably a reduction in the delirium rating scale and a more rapid resolution of delirium symptoms in favour of olanzapine compared to placebo. There were no data on any safety outcomes.

Due to small study sizes and methodological limitations in the studies, the evidence was generally of low to very low certainty. This indicates a research gap. Larger rigorous RCTs are needed.

Table 2: Characteristics of Included Systematic Reviews: Delirium

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION *vs* COMPARATOR	OUTCOMES & MAIN FINDINGS	COMMENTS
Comparison 1: Haloperidol compared to Olanzapine					
Finucane AM, Jones L, Leurent B, Samson EL, Stone P, Tookman A, et al. Drug therapy for delirium **in terminally ill adults**. Cochrane Database Sys. Rev. 2020;1. Doi: 10.1002/14651858.CD004770.pub3	Systematic review	Terminally ill adults (18 years or older) with delirium symptoms Included studies: RCTs	Haloperidol compared to Olanzapine	Delirium symptoms within 24 hours n= 28, one trial mean difference (MD) 2.36 (95% CI -0.75 to 5.47, p=0.14) Delirium symptoms between 24 and 48 hours n=24, one trial MD 1.9 (95% CI -1.5 to 5.3, p=0.27) **Very low certainty** (both outcomes), downgraded by 3 levels due to so few data that the results were highly susceptible to chance	AMSTAR – Moderate quality • Study design not explained • No meta-analysis
NICE Review (within CPG) National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management** [Internet]. [London]: NICE; 2010 [updated July 2020]. (Clinical guideline 103 [CG103]). Available from: https://www.nice.org.uk/Guidance/CG103	Systematic review	Adult patients (18 years or older) in a hospital setting (surgical, medical, ICU, or emergency departments) or in long-term residential care with delirium. Included studies: RCTs and quasi randomized trials. Non-randomised studies (NRS) were included only if no other evidence, with preference to large cohort studies and comparative non-randomised designs. Exclusion criteria: Younger than 18 years Receiving end-of-life care Intoxication and or acute withdrawal from drugs or alcohol, with associated delirium	Haloperidol compared to olanzapine	Complete response (resolution) n=219, 2 trials RR=0.99 (95% CI 0.8 to 1.21, p=0.24, I^2=27%) **Low certainty** downgraded due to poor study quality (not blinded, inadequate sequence generation and allocation concealment, funding and outcome possibly inadequate) and imprecision. Duration of delirium n=146, 1 trial MD=0.62 (95% CI 0.06 to 1.18) **Very low certainty**, downgraded for very poor study quality, imprecision and reported as “time to take effect” in responders only, likely to be biased Severity of Delirium n=146, 1 trial MD=0.7 (95% CI 0.45 to 1.85) **Moderate certainty,** downgraded due to poor study quality (not blinded) and imprecision (number of patients < 400)	AMSTAR – High quality • Data extraction not in duplicate

				Adverse events n=73, 1 included trial RR=8.2 (95% CI 0.48 to 140.09) **Very low certainty**, downgraded due to very poor study quality (quasi-randomised, not blinded) and imprecision(wide confidence interval)	
Comparison 2: Olanzapine vs placebo					
NICE Review (within CPG) National Institute for Health and Care Excellence (NICE). **Delirium: diagnosis, prevention and management** [Internet]. [London]: NICE; 2010 [updated July 2020]. (Clinical guideline 103 [CG103]). Available from: https://www.nice.org.uk/Guidance/CG103	Systematic review	Adult patients (18 years or older) in a hospital setting (surgical, medical, ICU, or emergency departments) or in long-term residential care with delirium. Included studies: RCTs and quasi randomized trials. Non-randomised studies (NRS) were included only if no other evidence, with preference to large cohort studies and comparative non-randomised designs. Exclusion criteria: Younger than 18 years Receiving end-of-life care Intoxication and or acute withdrawal from drugs or alcohol, with associated delirium	Olanzapine compared to placebo	Complete response n=103, 1 included trial RR=3.68 (95% CI 1.63 to 8.33) **Moderate certainty** due to poor study quality (not blinded) indirectness (indirect outcome through delirium assessment method) and imprecision (number of events < 300). Duration of delirium n=103, 1 included trial MD=-2.4 (95% CI 3.51 to -1.29) **Very low certainty** due to poor study quality (evidence of confounding and not blinded) and imprecision (wide confidence interval). Severity of Delirium n=103, 1 included trial MD=-11.1 (95% CI 14.51 to -7.69) **Moderate certainty** due to poor study quality (not blinded) and imprecision (number of patients < 400).	AMSTAR – High quality • Data extraction not in duplicate

Table 3: Characteristics of Included Randomised Controlled Trials: Delirium

CITATION	STUDY DESIGN	POPULATION (N)	INTERVENTION *vs* COMPARATOR	OUTCOMES & MAIN FINDINGS	RISK OF BIAS
Comparison 1: Haloperidol versus Olanzapine					
Skrobik YK, Bergeron N, Dumont M, Gottfried SB. Olanzapine vs haloperidol: treating delirium in a **critical care setting**. Intensive Care Med. 2004;30:444-9. Doi: 10.1007/s00134-003-2117-0	Design Prospective quasi-randomized trial. Single blinding (treating nurses and physician not blinded to assigned drug) Duration July 2000 to September 2001. Funding Peer-reviewed grant from the Zyprexa fund, Eli-Lilly, North America Ethics Protocol approved by the institutional scientific and ethics committee	Adults aged 18 to 75 years admitted to medical-surgical ICT in Montreal. All patients with delirium (as defined below) were considered eligible for the study. Sample size 73 included in final analysis (Haloperidol n=45, Olanzapine n=28) 103 considered eligible, 80 informed consent obtained, 3 withdrawn, 2 status changed to "no active treatment", 1 suspected drug interaction, 1 data lost Inclusion criteria Admitted for more than 24 hours, participants screened 3 times daily for delirium with the ICU Delirium Screening Checklist (ICU-DSC). In participants with a score >= 4 or with clinical manifestations of delirium, diagnosis confirmed by physician using DSM-IV criteria. Exclusion criteria Pregnant patients who received antipsychotic medication within 10 days prior to admission; Pregnant patients with contraindications to haloperidol or olanzapine; Gastrointestinal dysfunction that did not allow oral or enteral drug administration; Neurological status did not allow neuropsychiatric examination e.g. coma Other caveats Patients who developed agitation were allowed intravenous haloperidol ("rescue haloperidol")	Intervention Enteral olanzapine 5mg daily (>60yrs: 2.5mg daily) Comparator Enteral haloperidol 2.5 to 5mg every 8 hours (>60yrs: 0.5 to 1 mg 8 hourly) Subsequent titration based on clinical judgement. Benzodiazepine use noted as adjuvant therapy.	Outcomes 1. Change in mean daily delirium scores (delirium index (DI) scores) 2. Adjunct benzodiazepine use requirements over time 3. Use of rescue haloperidol, opiates, sedatives, Ramsay scores, vital signs and liver function tests in both groups. 4. Presence of extrapyramidal side effects (EPS) Results 1. Comparable reduction in DI score over time was noted in both groups, with no difference (ANOVA time effect p=0.02, group effect p=0.83 interaction effect p=0.64) 2. Benzodiazepines: Analysis of variance did not identify any difference between the two groups, at any of the 5 measurement times (interaction effect p=0.94 group effect p=0.9). 3. " The dose of rescue haloperidol, opiates, sedatives other than benzodiazepines, Ramsay scores, vital signs, and liver function tests were no different between groups." 4. Haloperidol: 6 rated low scores on extrapyramidal symptom testing (1 for the Ross Chouinard, 1–4 for the Simpson-Angus scale). Olanzapine: no extrapyramidal manifestations or adverse effects	**HIGH RISK OF BIAS** All outcomes: **High risk of bias** in domain 1 due to quasi-randomisation of allocation sequence and baseline differences between allocation groups, **some concerns** in domain 2 due to no information around participant blinding and effects of assignment, and **some concerns** in domain 5 due to no information around a prespecified plan or protocol. **Low risk of bias** in domains 3 and 4.

Jain R, Arun P, Sidana A, Sachdev A. Comparison of efficacy of haloperidol and olanzapine in the treatment of delirium. Indian J Psychiatry. 2017;59(4):451-6. Doi: 10.4103/psychiatry.IndianJ Psychiatry_59_17	Design Open label, randomized controlled study. Randomisation through computer-generated random number table Duration December 2011 to December 2012. Patients assessed every 24 hours until delirium resolution. Trial registry Registered with the Clinical Trial Registry-India CTRI/2016/10/007331 Ethics Approved by local institutional ethics committee Funding None Other Assessment of delirium through Confusion Assessment Method (CAM), and diagnosis using DSM-IV criteria. Delirium severity assessed with Memorial Delirium Assessment Scale (MDAS). Simpson-Angus Scale (SAS) used to assess EPS	Delirious patients admitted to medicine emergency ward and referred to the Department of Psychiatry for consultation at the Government Medical College and Hospital, Chandigarh, India. Sample Size 100 132 enrolled; 32 dropped out after randomization and were not included in the final analysis; Olanzapine n=47 Haloperidol n=53 Inclusion criteria Delirious patient plus >18 years old; Verbally responsive; No dementia Exclusion criteria Mechanically ventilated; Mute; Currently on antipsychotics for any reason; Experiencing alcohol or benzodiazepine withdrawal delirium; Hypersensitivity to either olanzapine or haloperidol in the past.	Intervention Olanzapine, enteral only, 2.5 to 10mg daily orally or via nasogastric tube (NGT) Comparator Haloperidol, enteral only, 1 to 4mg orally or via NGT tube Doses based on MDAS scores of mild, moderate or severe delirium.	Outcomes 1. Efficacy of olanzapine and haloperidol in delirium 2. Tolerability of olanzapine and haloperidol in delirium 3. Phrenology of delirium and pattern of symptom improvement with treatment Results • Delirium severity – mean MDAS score (baseline) 18.49 olanzapine group, 17.79 haloperidol group (groups comparable at baseline, p=0.791). mean MDAS score (end study period) 8.43 olanzapine group, 8.00 haloperidol group; 54.7% reduction in mean MDAS scores (54.4% in olanzapine group and 55% in haloperidol group • Pattern of symptom improvement ○ Severity of attention on day 2 and severity of disorganized thinking on days 2 and 3 were less in the olanzapine group (p<0.05). ○ Severity of perceptual disturbances on day 4, and severity of psychomotor disturbances on days 3 and 4 were less in the haloperidol group (p<0.05). • Duration of treatment– mean duration of treatment (days) 3.57 olanzapine (+- 0.92 days), 3.37 haloperidol (+- 0.71 days), (p=0.233) • Drug-related adverse effects – 2 in olanzapine group (1 with excessive sedation, 1 with akathisia), 3 in haloperidol group (drug-induced parkinsonism). All side effects were mild in severity.	**HIGH RISK OF BIAS** All outcomes: **Some concerns** in domain 1 due to this being a single-blind study, **some concerns** in domain 2 due to single-blind study and limited information on statistical methods, **high risk of bias** in domain 3 due to no information around data available for all participants and missingness, **high risk of bias** in domain 4 due to potential bias from researchers not being blinded, and **some concerns** domain 5 due to no information around a pre-specified analysis plan.
Van der Vorst MJDL, Neefjes ECW, Boddaert MSA, Verdegaal BATT, Beeker A, Teunissen SCC, et al. Olanzapine versus haloperidol for treatment of delirium in patients with advanced cancer: a phase III randomized clinical trial. Oncologist.	Design Multicentre, randomized controlled, phase III trial. Conducted at five sites in the Netherlands. Study terminated early as unlikely to reach the predefined efficacy criteria. Trial registry	Patients ≥ 18 years old with advanced cancer, admitted to a medical oncology ward or high-care hospice facility Sample size 100 50 allocated to each group	Intervention Olanzapine, po or IMI Comparator Haloperidol, po or sc	Outcomes: *Primary endpoint:* Delirium Response Rate (DRR) on days 1 to 7 after randomization as defined by DRS-R-98 assessment *Secondary endpoints:* TRR (time from randomization to resolution of delirium in days) TRAEs (treatment related adverse events), according to the CTCAE version 4.03	**SOME CONCERNS** All outcomes: **Some concerns** in domain 5 due to no information around pre-specified plan or protocol. **Low risk of bias** in domains 1 to 4.

2020; 25:e570-7. Doi: https://doi.org/10.1634/theoncologist.2019-0470	NCT01539733 Duration January 2011 to July 2016 Funding Netherlands Organization for Health Research and Development (ZonMw) Palliative Care Program (No. 11510011). Ethics Written informed consent	Olanzapine – 9 discontinued treatment. Analysis – Intention-to-treat (ITT) n=49, per protocol n = 40 Haloperidol – 8 discontinued treatment. Analysis – ITT n = 49, per protocol n = 41 Inclusion criteria 18 years or older; Advanced cancer; Admitted to medical oncology ward or high-care hospice facility; Fluent in the Dutch language; Diagnosed with delirium. Exclusion criteria Diagnoses of glaucoma, Parkinson's disease, dementia or psychiatric disorders interfering with delirium assessment; history of neuroleptic malignant syndrome or convulsions; delirium due to substance withdrawal cardiac conduction abnormalities; Currently using other neuroleptic medication or lithium.		Delirium-related distress for patients and their caregivers assessed by DEQ Results DRR: Olanzapine 45% (95% CI 31 to 59) Haloperidol 57% (95% CI 43 to 71) (ΔDRR −12%, odds ratio [OR] 0.61, 95% CI 0.2–1.4 p = 0.23) (ITT) TRR: Olanzapine 4.5 days (95% CI 3.2 to 5.9) Haloperidol 2.8 days (95% CI 1.9 to 3.7) (p = 0.18) DRR for motor subtypes (ITT) Hyperactive OR 0.5, 95% CI 0.1 to 2.1, p=0.50 Hypoactive OR 0.2, 95% CI 0.04 to 1.5, p=0.12 Mixed OR 1.8, 95% CI 0.4 to 7.9, p=0.49 Safety TRAEs of any grade Olanzapine arm: 13 patients (26.5%) Haloperidol arm: 16 patients (32.7%) Grade ≥3 TRAEs Olanzapine arm: 5 patients (10.2%) Haloperidol arm: 10 patients (20.4%) (OR 0.4, 95% CI 0.1 to 1.4, p=0.16) No treatment related deaths Delirium-Related Distress Sixteen patients completed this DEQ in each treatment arm. Mean delirium-related distress level (0 – 4 numerical rating scale) Olanzapine 2.1 (SD 1.4) Haloperidol 2.3 (SD 1.4) Mean delirium-related distress level (spouse/caregiver) Olanzapine 3.0 (SD 1.2) Haloperidol 2.7 (SD 1.1) Mean delirium-related distress level (nurses) Olanzapine 1.1 (SD 1.1) Haloperidol 0.9 (SD 0.9)	

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 ☒ *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	For important outcomes there were limitations in the data: small study sizes, methodological limitations in the studies, the evidence was generally of low to very low certainty. No data on critical outcomes.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** Large ☐ Moderate ☐ Small ☒ None ☐	Olanzapine vs haloperidol: no difference (none) Olanzapine vs placebo: probably better efficacy (small and low levels of certainty) Olanzapine vs benzodiazepines: no data
QUALITY OF EVIDENCE OF HARM	**What is the certainty/quality of evidence?** High ☐ Moderate ☐ Low ☐ Very low ☒ *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	For important outcomes there were limitations in the data: small study sizes, methodological limitations in the studies, the evidence was generally of low to very low certainty. No data on critical outcomes
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge ☐ Moderate ☐ Small ☒ None ☐	Olanzapine vs haloperidol: no difference (none) Olanzapine vs placebo: probably better efficacy (small) Olanzapine vs benzodiazepines: no data
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention ☐ Favours control ☐ Intervention = Control ~~*or* Uncertain~~ ☒	Olanzapine vs haloperidol: no difference (intervention = control) Olanzapine vs placebo: probably better efficacy (favours intervention) – but very low level of certainty of evidence Olanzapine vs benzodiazepines: no data
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: N/A	
FEASABILITY	**Is implementation of this recommendation feasible?** Yes ☒ No ☐ Uncertain ☐	Olanzapine is not specifically registered for delirium; however, olanzapine oral is available in the public sector for other indications (bipolar disorder, schizophrenia). All formulations are available on the South African market. The loss of IM haloperidol is disruptive in the change of clinical practice.
RESOURCE USE	**How large are the resource requirements?** More intensive ☐ Less intensive ☐ Uncertain ☐	**Price of medicines:** **Medicine** | **Tender price (ZAR)*** | **100% OF SEP (ZAR)**** | **60% OF SEP (ZAR)** Haloperidol 5mg tablets, 500 | 23.23 | n/a | n/a

Haloperidol 5mg/5ml injection, single (discontinued)	n/a	45.68***	n/a
Olanzapine 10 mg injection	n/a	72.84	43.71
Olanzapine 5mg orodipersible (ODT, 30	n/a	267.41	160.45
Olanzapine 2.5mg tablet (SOT), 28	13.80	n/a	n/a

* Contract circular HP09-2021SD, August 2022
**SEP database, July 2022
***SEP database, February 2021 (Haloperidol injection discontinued)

Background:

- *Adult Hospital Level STG and EML, 2019 edition*

Recommends haloperidol IM injection, but this has been discontinued from the South African market.

- *NICE Guideline 2010 (updated in March 2019)*

Recommendations for olanzapine include:

- IM injection: 2.5–10 mg per day, depending on response; the effect was observed for one week; delirium had 3 occurred from 30 min to 17 days (Hu 2006)
- Orally or by enteral tube: given within 2 h of the diagnosis of delirium, initially 5 mg per day (patients over 60 years 2.5 mg) then titrated based on clinical judgement for up to 5 days (Skrobik 2004)
- Orally/ sublingually: initial dose 1.25–2.5 mg then adjusted, depending on response, to 1.25–20 mg per day; the effect was observed for one week; delirium had occurred from 30 min to 17 days (Hu 2006)

- *NEMLC report (Adult Hospital 2019 review of palliative care chapter)*

Haloperidol, oral: added
Haloperidol, SC/IV: added
Lorazepam, oral: added
Midazolam, SC/IV: added
Antipsychotic (haloperidol), oral/IV/SC: Low doses are generally recommended as 1strst line in guidelines, due to associated side-effects. However, a RCT (Agar,2017) showed that oral haloperidol and risperidone was less effective in reducing delirium symptoms than placebo and shortened overall survival. Limitations included the oral route of administration (possibly contributing to increased extrapyramidal side effects); increased administration of midazolam to the antipsychotic groups (possibly increasing paradoxical agitation and variable baseline demographics and precipitants of delirium were not reported in all groups. Cochrane review concluded that there is insufficient evidence to determine the role of medicine treatment for delirium in terminally ill patients; thus recommendations aligned with expert consensus.
***Recommendation:** Low dose haloperidol as 1st line treatment for delirium in palliative care at secondary level of care.*
Rationale: Aligned with guidelines.
Level of Evidence: III Guidelines

- *Pharmacokinetic study by Markowitz et al, 2006*

Both routes of ODT administration (above the tongue and sublingually) resulted in more measurable early concentrations relative to SOT. However, there were no statistically significant differences observed between any of the olanzapine exposures for observed pharmacokinetic parameters (C(max), T(max), AUC(0-8h)).

- *Medicines.org.uk: Olanzapine 5mg ODT tablets - Summary of Product Characteristics (SmPC)*

Olanzapine ODT should be placed in the mouth, where it will rapidly disperse in saliva, so it can be easily swallowed. Removal of the intact ODT from the mouth is difficult. Since the ODT is fragile, it should be taken immediately on opening the blister. Alternatively, it may be dispersed in a full glass of water or other suitable beverage (orange juice, apple juice or milk) immediately before administration. Olanzapine ODT is bioequivalent to olanzapine film-coated tablets, with a similar rate and extent of absorption. It has the same dosage and frequency of administration as olanzapine film-coated tablets. Olanzapine ODT may be used as an alternative to olanzapine film-coated tablets.

- *Pharmacokinetic parameters:*

On review of the pharmacokinetic properties of olanzapine ODT and SOT formulations, bioequivalence can be assumed.

	Tmax	T1/2	
Haloperidol, IM	10 minutes	13 to 35 hrs	*SAMF, 2022*
Olanzapine ODT	4 to 6 hrs	33 hrs	*Markowitz, 2006*
Olanzapine SOT	5 to 8 hrs	33 hrs	*Callaghan JT, 1999*
Olanzapine, IM	14 to 45 minutes	33 hrs	*FDA PI (drugs.com)*

Comparative cost analysis per treatment course *(comparing direct medicine prices):*

- **Haloperidol 0.5-1mg inj,** immediately 30 minutes later and 4-hourly to a max of 10mg per 24 hours *(Using the max dose of 2 x 5 mg inj per day for 3 days = 6 x 10 mg inj):* **R274.08** (Historic SEP price accessed through State S21)

- **Olanzapine 2.5-5mg inj**, immediately 30-60 minutes later and 4-hourly to a max of 20mg per 24 hours *(Using the max dose of 2 x 10 mg inj per day for 3 days = 6 x 10 mg inj):* **R437.06** (100% SEP) and **R262.24** (60% SEP).

- **Olanzapine 2.5-5mg SOT via NGT,** immediately 30-60 minutes later and 4-houlry to a max of 20mg per 24 hours *(Using the max dose of 8 x 2,5 mg tablets per day for 3 days = 24 x 2.5 mg tablets):* **R11.83** (Contract price)

- **Olanzapine 2.5-5mg ODT**, immediately 30-60 minutes later and 4-hourly to a max of 20mg per 24 hours *(Using the max dose of 4 x 5mg ODTs per day for 3 days = 12 x 5 mg ODT):* **R106.96** (100% SEP) and **R64.18** (60% of SEP)

NB: It is concerning to note that haloperidol injection had only been added to the NICE guidelines in 2019, as haloperidol was registered with the MHRA for delirium. Global vs local availability of medicines warrants investigation.

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 [ ] No [ ] Uncertain [X]	There is no information available about the acceptability of olanzapine to stakeholders. However, given the absence of other options in the management of delirium, it could be a viable and acceptable alternative.
EQUITY	**Would there be an impact on health inequity?** Yes [ ] No [X] Uncertain [X]	There is no available local survey data – based on expert opinion.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	18 August 2022	LR, SM, TK, NG, MM, TL	Olanzapine (all formulations) suggested as an option to haloperidol to manage delirium where non-pharmacological management is not sufficient (conditional recommendation, low to very low certainty evidence).
V1.0	28 Mar 2024	LR	Updated to reflect erratic supplies of haloperidol IM

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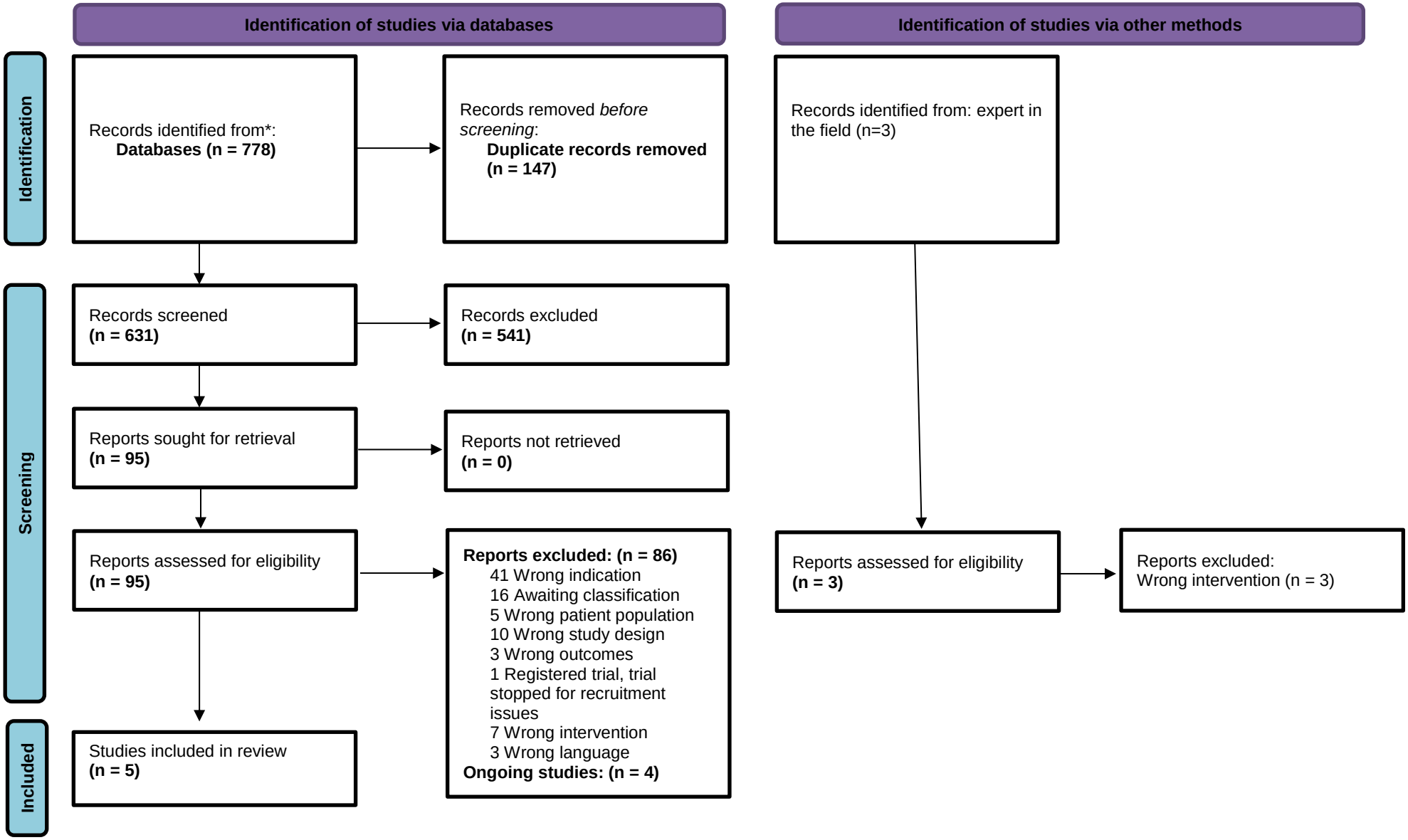
Appendix 1: Search Strategy

#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 Chart



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. For more information, visit: http://www.prisma-statement.org/

Appendix 3: AGREE II Appraisal Summary

Guideline	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	OA
NICE: DELIRIUM: diagnosis, prevention and management	94%	81%	88%	100%	67%	63%	83%
SIGN 157: Risk reduction and management of delirium	94%	97%	65%	81%	73%	58%	67%
Management of delirium in older people	100%	89%	72%	89%	50%	79%	83%

Domain 1: Scope and purpose
Domain 2: Stakeholder involvement
Domain 3: Rigour of development
Domain 4: Clarity of presentation
Domain 5: Applicability
Domain 6: Editorial independence
OA: overall assessment

Appendix 4: Table of excluded studies, with reasons

Author, date	Type of study	Reason for exclusion
1. Bak, 2019	SR*	Wrong indication
2. Belgamwar, 2005	SR	Wrong indication
3. Burry, 2018	SR	Wrong intervention
4. Burry, 2019	SR	Wrong intervention
5. Dundar, 2016	SR	Wrong indication
6. Fernández Sánchez, 2009	SR	Wrong indication
7. Huf, 2009	SR	Wrong language
8. Huf, 2016	SR	Wrong indication
9. Lacasse, 2016	SR	Wrong intervention
10. Maglione, 2011	SR	Wrong indication
11. Mühlbauer, 2021	SR	Wrong patient population
12. Nikooie, 2019	SR	Wrong intervention
13. Paris, 2021	SR	Wrong indication
14. Pelland, 2009	SR	Wrong language
15. Seida, 2012	SR	Wrong patient population
16. Shoptaw, 2009	SR	Wrong indication
17. Tulloch, 2004	SR	Wrong indication
18. Williamson, 2019	SR	Wrong indication
19. Yildiz, 2003	SR	Wrong language
20. Yildiz, Sachs 2003	SR	Wrong study design
21. Yunusa, 2019	SR	Wrong indication
22. Zaman, 2017	SR	Wrong indication
23. Baldaçara, 2011	RCT#	Wrong indication
24. Battaglia, 2003	RCT	Wrong indication
25. Battaglia, 2005	RCT	Wrong outcomes
26. Beasley, 1996	RCT	Wrong indication
27. Belgamwar, 2005	RCT	Wrong indication
28. Bozzatello, 2017	RCT	Wrong patient population
29. Breier, 2000	RCT	Awaiting classification
30. Breier, 2001	RCT	Awaiting classification
31. Breier, 2002	RCT	Wrong indication
32. Chan, 2014	RCT	Wrong indication
33. Clark, 2001	RCT	Wrong indication
34. David, 2001	RCT	Awaiting classification
35. Eli, 2005	RCT	Awaiting classification
36. Faay, 2020	RCT	Wrong indication
37. Fontaine, 2003	RCT	Wrong patient population
38. Gareri, 2004	RCT	Wrong indication
39. Hsu, 2010	RCT	Wrong indication
40. Huf, 2009	RCT	Wrong intervention
41. Huang, 2015	RCT	Wrong indication
42. Hwang, 2012	RCT	Awaiting classification
43. Jin, 2009	RCT	Awaiting classification
44. Katagiri, 2013	RCT	Wrong indication
45. Kinon, 2000	RCT	Wrong indication
46. Kinon, 2001	RCT	Wrong outcomes
47. Kinon, 2004	RCT	Wrong indication
48. Kittipeerachon, 2016	RCT	Wrong intervention
49. Kong, 2009	RCT	Awaiting classification
50. Krakowski, 2014	RCT	Wrong indication
51. Lindbord, 2003	RCT	Wrong outcomes
52. Meehan, 2001	RCT	Awaiting classification
53. Meehan, 2001 (1)	RCT	Awaiting classification
54. Meehan, 2001 (2)	RCT	Awaiting classification

55. Meehan, 2001 (3)	RCT	Wrong indication
56. Meehan, 2002	RCT	Wrong indication
57. Mintzer, 2002	RCT	Awaiting classification
58. Ono, 2008	RCT	Awaiting classification
59. Raveendran, 2007	RCT	Wrong indication
60. Schneider, 2006	RCT	Wrong indication
61. Smith, 2003	RCT	Awaiting classification
62. Street, 2000	RCT	Wrong patient population
63. Svestka, 2002	RCT	Awaiting classification
64. Verhey, 2006	RCT	Wrong indication
65. Villari, 2009	RCT	Wrong intervention
66. Wright, 2001	RCT	Awaiting classification
67. Wright, 2003	RCT	Wrong indication
68. Hirsch, 2019	Narrative review	Wrong study design
69. Houston, 2019	Narrative review	Wrong study design
70. Wagstaff, 2005	Narrative review	Wrong study design
71. Pascual, 2007	Observational study	Wrong study design
72. Walther, 2014	Observational study	Wrong study design
73. ACTRN12610000033044	Ongoing trial	Wrong indication
74. NCT00316238	Ongoing trial	Wrong indication
75. NCT00485810	Ongoing trial	Wrong indication
76. NCT00485901	Ongoing trial	Wrong indication
77. NCT011234082	Ongoing trial	Wrong indication
78. NCT00649510	Ongoing trial	Wrong indication
79. NCT00797277	Ongoing trial	Wrong indication
80. NCT00833300, 2009	Registered trial	Registered trial, trial stopped for recruitment issues
81. NCT00970281	Ongoing trial	Wrong indication
82. Elsayem, 2010	Pilot study	Wrong study design
83. Citrome, 2007	Quantitative review	Wrong study design
84. Srivastava, 2010	Summary of review	Wrong study design
85. deAlmeida, 2017	Review of reviews	Wrong study design
86. Jones, 2001	Summary of RCTs	Wrong study design

*SR = systematic review, #RCT = randomized controlled trial

Appendix 5: Table of Ongoing Trials

Citation	Study Design	Population (n)	Treatment
Arak University of Medical Sciences. IRCT20141209020258N114, first registered 3 July 2019, recruiting.	RCT with parallel assignment	50	Patients randomised to haloperidol 2.5mg (max 40mg) intramuscular injection (IMI) every 6 hours or olanzapine 2.5 to 10mg (max 20mg) orally
Arak University of Medical Sciences. IRCT20200927048852N1, first registered 13 October, recruiting.	Phase III RCT with parallel assignment	90	Patients randomised to haloperidol 2.5mg per day for up to 10 days or olanzapine 2.5mg to 10mg per day for up to 10 days or quetiapine 12.5 to 75mg per day
HCA Hospice Care. NCT04750395, first registered 11 February 2021, ongoing	RCT with parallel assignment	80	Patients randomised to transmucosal haloperidol, two doses of 2.5mg every 24 hours with up to two breakthrough doses or transmucosal olanzapine, two doses of 5mg with up to two breakthrough doses
Tan Tock Seng Hospital. NCT04833023, first registered 6 April 2021.	RCT with parallel assignment	72	Patients randomised to haloperidol oral solution 1mg (max 6mg in 24 hours), 2 hourly until max reached with midazolam 2mg as rescue dose (2mg q2h prn) or olanzapine orodispersible tablet 2.5mg (max 15mg in 24 hours), 2 hourly until max reached with midazolam 2mg as rescue dose (2mg q2h prn)