ROLE OF ANTIPSYCHOTICS IN DELIRIUM MANAGEMENT

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This chapter will attempt to answer following questions regarding the role of antipsychotics in delirium treatment:

1. What are DSM-5 criteria for delirium diagnosis & subtypes?
2. What dose of haloperidol is preferred for delirium management: in adults, elderly and as intravenous infusion?
3. How is olanzapine compared to haloperidol for delirium management
4. Olanzapine is preferred over haloperidol in which patient population?
5. How is quetiapine compared to haloperidol for delirium management?
6. What dose of quetiapine is found effective in delirium?
7. Does quetiapine have impact on reducing severity of non-cognitive aspects of delirium?
8. Does quetiapine have impact on time of delirium resolution and associated agitation
9. Prophylactic administration of which antipsychotic have shown to prevent postoperative delirium in elderly patients?
10. Can risperidone be used for management of delirium in elderly patients?
11. Which antipsychotic is known to have poorer delirium response in patients >= 70 years of age?
12. Should antipsychotics be added to manage specific symptoms of delirium that are known to be associated with distress in patients with mild to moderately severe delirium?
13. Do antipsychotics reduce the delirium severity, resolve symptoms, or alter mortality?
14. Which scales were utilized by studies for monitoring delirium severity and response?
(1) DSM-5 criteria for delirium diagnosis & Subtypes?

- Disturbance of **attention** (ie, reduced ability to direct, focus, sustain, and shift attention) and **awareness** (reduced orientation to the environment).

- The disturbance develops over a **short period of time** (usually hours to few days), represents a **change from baseline** attention and awareness, and tend to **fluctuate in severity** during the course of a day.

- Additional disturbance in **cognition** (eg, memory deficit, disorientation, language disturbance, visuospatial ability, or perceptual disturbance)

- These disturbances in attention, awareness & cognition- are **not better explained by another preexisting, established, or evolving neurocognitive disorder** and do not occur in the context of a severely reduced level of arousal (such as coma).

- Evidence from the history, physical examination, or laboratory findings that the disturbance is a **direct physiologic consequence of** another medical condition, substance intoxication or withdrawal, or exposure to toxin, or is due to multiple etiologies.
Delirium Subtypes includes:

(A) **Hyperactive**: increased psychomotor activity that may be accompanied by

- mood lability
- agitation, and/or
- refusal to cooperate with medical care.

(B) **Hypoactive**: reduced psychomotor activity that may be accompanied by

- sluggishness
- lethargy
- may approaches stupor.

(C) **Mixed Level of Activity**: normal level of psychomotor activity.
(2): What dose of haloperidol is preferred for delirium management: in adults, elderly and as intravenous infusion?

- According to APA practice guidelines: haloperidol is pharmacological treatment of choice for delirium.
- can be administered orally, intramuscularly, or intravenously.
- Initial dose (adult): 1-2 mg every 2-4 hours
- Initial dose (elderly patients): 0.25-0.50 mg every 4 hours.
- Continuous intravenous infusion of haloperidol: initiated with a bolus dose of up to 10 mg followed by infusion of up to 5-10 mg/hour (monitor ECG for QTc).

This chapter will focus on available literature (primarily randomized controlled trials) on other antipsychotics role in delirium management.
(3) How is olanzapine compared to haloperidol for delirium management?

Following trial will attempt to answer this question:

**Jain et al. 2017 (Olanzapine vs Haloperidol open label randomized trial)**

Reference: 11 (pdf)

Scale: Memorial Delirium Assessment Scale (MDAS).

Medication Dosages:

- **Haloperidol**: 1–4 mg/day either orally or by nasogastric tube.
- **Olanzapine**: 2.5–10 mg/day either orally or by nasogastric tube.

Results:

- **Mean daily dose of haloperidol**: 2.10 mg (range = 1–5 mg).
- **Mean daily dose of olanzapine**: 5.49 mg (range = 2.5 mg).
- **At the end of study period**: MDAS scores in olanzapine and haloperidol groups were 8.43 and 8.00, respectively (this difference was not significant statistically with P = 0.765).
- **Improvement in all domains of delirium seen in both groups**: consciousness, attention and concentration, memory, thinking, psychotic symptoms, psychomotor activity, and sleep.

Conclusion:

Patients with delirium responded well to low doses of both haloperidol and olanzapine.
(4) Olanzapine is preferred over haloperidol in which patient population?

Following trial will attempt to answer this question:

Skrobik et al. 2004 (Olanzapine vs Haloperidol prospective randomized trial)

Reference: 10 (pdf) (pubmed)

Primary Outcome Measure (Scale): Delirium Rating Scale Revised 98 (DRS-R-98).

Medication Dosages:

- Haloperidol: initiated at 2.5–5 mg every 8 hours.
- Olanzapine: initiated at 5 mg daily.
- Patients > 60 years: lower initial dosage (haloperidol 0.5–1 mg, or olanzapine 2.5 mg).
- Subsequent titration was based on clinical judgment.

Results:

- Delirium Index decreased over time in both groups.
- administered dose of benzodiazepines also decreased over time in both groups.
- Clinical improvement was similar in both treatment arms.
- Olanzapine patients had no adverse effects attributable to the drug, whereas 6 patients receiving haloperidol developed extrapyramidal signs.
Conclusions:

- In ICU delirium, olanzapine is a treatment alternative to haloperidol.
- Its use could benefit patients with underlying Parkinson’s disease, prolonged QT interval, or oropharyngeal dysfunction, which preclude the safe administration of haloperidol.
(5) How is quetiapine compared to haloperidol for delirium management?

(6) What dose of quetiapine is found effective in delirium?

Following two trials will attempt to answer these question:

(Study#1): Maneeton et al. 2013 (Quetiapine vs Haloperidol randomized controlled trial: first head-to-head trial)

Reference: 8 (pdf)

Total participants: 52

Primary Outcome Measure (Scale): Delirium Rating Scale Revised 98 (DRS-R-98).

Dose of medications:

- quetiapine 25–100 mg/day.
- haloperidol 0.5–2.0 mg/day.

Results:

- Mean (SD) doses of quetiapine: 67.6 (9.7) mg/day.
- Mean (SD) doses of haloperidol: 0.8 (0.3) mg/day.
- Mean (SD) times to response for quetiapine: 1.7 (0.1) days.
- Mean (SD) times to response for haloperidol: 1.9 (1.6) days.
• Mean (SD) times to remission for quetiapine: 2.6 (1.9) days.

• Mean (SD) times to remission for haloperidol: 1.8 (1.5) days.

• Hypersomnia was common in the quetiapine-treated patients (33.3%), but not significantly higher than that in the haloperidol-treated group (21.4%).

Conclusion:

Low-dose quetiapine and haloperidol may be equally effective and safe for controlling delirium symptoms.

(Study#2): Grover et al. 2016 (Quetiapine vs Haloperidol single blind randomized controlled trial)

Reference: 9 (pdf)

Total participants: 63

Primary Outcome Measure (Scale): Delirium Rating Scale Revised 98 (DRS-R-98).

Dose of medications: Flexible dosing regimen used:

Haloperidol: 0.25-10 mg/day flexible dose used:

• haloperidol is usually administered in the dose of 0.25 mg two to three times a day and titrated as per the requirement and majority of the patients are managed with 0.75 to 2.5 mg of haloperidol per day.

• In case of agitation, a dose of 1.25 to 2.5 mg is given intravenously and same is repeated as per need.

Quetiapine: 12.5-75 m/day flexible dose used:
12.5 mg/daily dose was started and depending on the need the dose was increased to 75 mg/day.

**Results:**

- **Mean dose of haloperidol:** $0.67 \pm 0.35$ mg/day (range 0.25-1.25)
- **Mean dose of quetiapine:** $26.63 \pm 15.61$ mg/day (range 12.5-75)
- The effectiveness of both the medications was similar in adult and elderly ($\geq 60$ years) patients.
- At the end of the trial, 68.75% and 67.74% of subjects in the haloperidol and quetiapine group respectively had mean DRS-R-98 scores below 10.
- By 6th day, 12 (37.5%) patients in haloperidol group and 9 (29.03%) patients in the quetiapine group had DRS-R98 score of “0” with no significant difference between the two groups ($P = 0.47$).

**Conclusion:**

Quetiapine in low dose is as beneficial as haloperidol in management of delirium.
(7) Does quetiapine have impact on time of delirium resolution and associated agitation?

Following trial will attempt to answer this questions:

**Devlin et al. 2010 (Quetiapine vs Placebo randomized controlled trial)**

Reference: 7 (pubmed)

Total participants: 36

Dose of quetiapine:

- 50 mg every 12 hrs.
- dose was increased every 24 hrs (50 to 100 to 150 to 200 mg every 12 hrs) if more than one dose of haloperidol was given in the previous 24 hrs.
- medication was continued until the intensive care unit team discontinued it because of delirium resolution, therapy > or = 10 days, or intensive care unit discharge.

**Results:** Quetiapine was associated with:

- **shorter time to first resolution of delirium** [1.0 (interquartile range [IQR], 0.5-3.0) vs. 4.5 days (IQR, 2.0-7.0; p =.001)]

- **reduced duration of delirium** [36 (IQR, 12-87) vs. 120 hrs (IQR, 60-195; p =.006)], and

- **less agitation** (Sedation-Agitation Scale score > or = 5) [6 (IQR, 0-38) vs. 36 hrs (IQR, 11-66; p =.02)].
• mortality (11% quetiapine vs. 17%) and intensive care unit length of stay (16 quetiapine vs. 16 days) were similar.

• subjects treated with quetiapine were more likely to be discharged home or to rehabilitation (89% quetiapine vs. 56%; p = .06).

• Subjects treated with quetiapine required fewer days of as-needed haloperidol [3 [(IQR, 2-4)] vs. 4 days (IQR, 3-8; p = .05)].

• incidence of QTc prolongation and extrapyramidal symptoms was similar between groups.

• more somnolence was observed with quetiapine (22% vs. 11%; p = .66).

Conclusions:

• Quetiapine added to as-needed haloperidol results in faster delirium resolution, less agitation, and a greater rate of transfer to home or rehabilitation.
(8) Does quetiapine have impact on reducing severity of non-cognitive aspects of delirium?

Following trial will attempt to answer this question:

Tahir et al. 2010 (Quetiapine vs Placebo randomized controlled trial)

Reference: 6 (pubmed)

Primary Outcome Measure (Scale): Delirium Rating Scale Revised 98 (DRS-R-98).

Total participants: 42.

Dose of quetiapine: not known (?)

Results:

• quetiapine group improved more rapidly than the placebo group: recovered 82.7% faster.

• In terms of the DRS-R-98 non-cognitive subscale: quetiapine group improved 57.7% faster.

Conclusions:

• Quetiapine has the potential to more quickly reduce the severity of noncognitive aspects of delirium.

• This study was underpowered for treatment comparisons at specific points in time but nonetheless detected significant differences when analyzing the whole study period.
(9) Prophylactic administration of which antipsychotic have shown to prevent postoperative delirium in elderly patients?

Following three studies (one positive study for olanzapine & haloperidol and one negative for haloperidol) in elderly patients will attempt to answer this question:

(Study #1): Larsen et al. 2010 (randomized controlled trial)

Reference: 12 (pubmed)

Total participants: 495 elderly patients age ≥65 years.

Medication Dosages: 5 mg preoperative and 5mg postoperative prior to discharge to inpatient nursing floor.

Results:

- The incidence of delirium was significantly lower in the olanzapine group than in the placebo group.
- this held true for both knee- and hip-replacement surgery.
- However, delirium lasted longer and was more severe in the olanzapine group.
- Advanced age, high level of medical comorbidity, an abnormal albumin level, and having knee-replacement surgery were independent risk factors for postoperative delirium.

Conclusion:

Administration of 10 mg of oral olanzapine perioperatively was associated with a significantly lower incidence of delirium.
Total participants: 457 patients 65 yrs or older who were admitted to the intensive care unit after noncardiac surgery.

Medication Dosages: Haloperidol (0.5 mg intravenous bolus injection followed by continuous infusion at a rate of 0.1 mg/h for 12 hrs; n = 229) or placebo (n = 228) was randomly administered from intensive care unit admission.

Results:

- **Incidence of delirium during the first 7 days after surgery:** haloperidol (15.3%) and placebo (23.2%).

- **Mean time to onset of delirium:** haloperidol (6.2 days [5.9-6.4]) and placebo (5.7 days [5.4-6.0]).

- **Mean number of delirium-free days** were significantly longer: haloperidol (6.8 ± 0.5 days) and placebo (6.7 ± 0.8 days).

- **Median length of intensive care unit stay** was significantly shorter: haloperidol (21.3 hrs [20.3-22.2]) and placebo (23 hrs [20.9-25.1]).

- No significant difference with regard to all-cause 28-day mortality between the two groups.

- **No drug-related side effects** were documented.

Conclusion:

For elderly patients admitted to intensive care unit after noncardiac surgery, short-term prophylactic administration of low-dose intravenous haloperidol significantly decreased the incidence of postoperative delirium.
(Study#3): Kalisvaart et al. 2010 (randomized controlled trial)

Reference: 14 (pubmed)

Total participants: 430 hip-surgery patients aged 70 and older.

Medication Dosages: Haloperidol 1.5 mg/day oral or placebo was started preoperatively and continued for up to 3 days postoperatively.

Results:

- Patients with postoperative delirium: haloperidol (15.1%) and placebo (16.5%)
- Delirium duration: haloperidol (5.4 days) versus placebo (11.8 days)
- Mean number of days in the hospital: haloperidol (17.1 +/- 11.1) and placebo (22.6 +/- 16.7)
- No haloperidol-related side effects were noted.

Conclusion:

- Low-dose haloperidol prophylactic treatment demonstrated no efficacy in reducing the incidence of postoperative delirium.
- Low-dose haloperidol prophylactic treatment did have a positive effect on the severity and duration of delirium.
- Haloperidol reduced the number of days patients stayed in the hospital, and the therapy was well tolerated.
(10) Can risperidone be used for management of delirium in elderly patients?

Hakim et al. 2012 (randomized parallel arm trial)

Reference: 13 (pubmed)

Total participants: 101 elderly patients age ≥65 years, who experienced subsyndromal delirium after on-pump cardiac surgery.

Medication Dosages: 0.5 mg risperidone every 12 hour orally versus placebo.

• Initially, risperidone was administered and if symptoms were not controlled, haloperidol was administered.

Results:

• Delirium experienced by patients: risperidone (13.7%) and placebo (34%)

• Two (3.9%) patients in the risperidone group experienced extrapyramidal manifestations versus one (2%) in the placebo group (P = 1.0).

Conclusion:

Administration of risperidone to elderly patients who experienced subsyndromal delirium after on-pump cardiac surgery was associated with significantly lower incidence of delirium.
(11) Which antipsychotic is known to have poorer delirium response in patients >or=70 years of age?

Following trial will attempt to answer this question:

Kim SW et al. 2010 (randomized comparative trial)

Reference: 16 (pubmed)

Total participants: 32 patients with median age of 70 yr.

Scale: Delirium Rating Scale Revised 98 (DRS-R-98).

Medication Dosages:

- Risperidone: oral 0.25- 2 mg/day X 7 days.
- Olanzapine: oral 1.25- 7.5 mg/day X 7 days.

Results:

- On the first day after drug treatment, there was a trend toward greater improvement in the DRS-R-98 score in the olanzapine group compared with the risperidone group, but it did not reach statistical significance (p = 0.076).
- Response rates did not differ significantly between the two groups: risperidone (64.7%) and olanzapine (73.3%).
• Response to risperidone was significantly poorer in patients \( \geq 70 \) years of age compared with those aged <70 years.

• There was no significant difference in the safety profiles, including extrapyramidal symptoms.

Conclusion:

Risperidone and olanzapine were equally effective in reducing delirium symptoms. The response to risperidone was poorer in the older age group.
Should antipsychotics be added to manage specific symptoms of delirium that are known to be associated with distress in patients with mild to moderately severe delirium?

Following trial is the largest randomized controlled study on this topic and will attempt to answer this question:

**Agar et al. 2017** (largest randomized controlled trial, n= 247)

Reference: 2 ([pdf](#))

**Setting:** palliative care

**Inclusion Criteria:**

Participants needed to meet the following 3 criteria:

1. Delirium diagnosed DSM IV criteria.
2. Memorial Delirium Assessment Scale (MADS) score of 7 or more.
3. Presence of the target symptoms of delirium associated with distress: based on the Nursing Delirium Screening Scale (NuDESC).

**Medications:**

- Age-adjusted titrated doses of oral **risperidone**, **haloperidol**, or placebo solution were administered every 12 hours for 72 hours, based on symptoms of delirium.
• **Participants ≤ 65 years**: 0.5 mg loading dose administered with the first dose of 0.5 mg, then 0.5 mg maintenance doses every 12 hours. Doses could be titrated by 0.25 mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4 mg/day.

• **Participants > 65 years**: loading, initial, and maximum doses were halved.

• Doses were increased if the sum of NuDESC scores for items 2, 3, and 4 (delirium symptoms score) was 1 or more at the most recent assessment, conducted every 8 hours.

• Dose reduction to the prior dose could occur for adverse effects, resolution of delirium (MDAS score of <7 for 48 hours), or resolution of symptoms (all NuDESC item scores <1 for 48 hours).

• Study treatment duration was 72 hours, with the last assessment performed 12 hours after the sixth dose.

**Results:**

• **Delirium Symptoms**: both risperidone and haloperidol had significantly greater delirium symptom scores than placebo group.

• **Delirium severity**: higher MDAS score per day for both antipsychotics vs placebo.

• **Behavioral, communication, and perceptual symptoms of delirium associated with distress**: greater in those treated with antipsychotic drugs.

• **Extrapyramidal effects**: risperidone and haloperidol have statistically significantly greater mean extrapyramidal effects compared to placebo.

• **Poorer overall survival in the haloperidol group** compared with those in the placebo group.

**Conclusions:**

• **Antipsychotic drugs should not be added to manage specific symptoms of delirium that are known to be associated with distress in patients receiving palliative care who have mild to moderately severe delirium.**
(13) Do antipsychotics reduce the delirium severity, resolve symptoms, or alter mortality?

Cochrane Database of Systematic Reviews 2018

Reference: 5 (pubmed)

This included: randomised and quasi-randomised trials comparing:

1. antipsychotics to nonantipsychotics or placebo
2. typical to atypical antipsychotics for the treatment of delirium in adult hospitalised (but not critically ill) patients.

Results:

(a) Delirium Severity:

- Antipsychotic treatment did not reduce delirium severity compared to non-antipsychotic drugs (very low-quality evidence).
- There was no difference between typical and atypical antipsychotics (low-quality evidence).

(b) Delirium Symptoms:

- There was no evidence antipsychotics resolved delirium symptoms compared to non-antipsychotic drug regimens (very low-quality evidence).
- There was no difference between typical and atypical antipsychotics (low-quality evidence).

(c) Mortality:
• Antipsychotics did not alter mortality compared to nonantipsychotic regimens (low-quality evidence).

• There was no difference between typical and atypical antipsychotics (low-quality evidence).

(d) Extrapyramidal symptoms (EPS)

• Antipsychotics did not have a higher risk of EPS compared to non-antipsychotic drugs (very-low quality evidence).

• No increased risk of EPS with typical antipsychotics compared to atypical antipsychotics (very low-quality evidence).

(e) Others:

• No trial reported on hospital length of stay, hospital discharge disposition, or health-related quality of life.

Conclusions:

Antipsychotics did not reduce delirium severity, resolve symptoms, or alter mortality.
(14) Which scales were utilized by studies for monitoring delirium severity and response?

(1) Delirium Rating Scale Revised 98 (DRS-R-98)

(2) Memorial Delirium Assessment Scale (MADS)
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