“Terminal Agitation”
- What Is The Role Of Antipsychotics?

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Overview

- What do we mean by Agitation & Terminal Agitation?
  - Terminology
- Assessment
- Differential diagnosis / causes
- Management
  - Reverse cause
  - Non-drug
    - Drug
      - **Antipsychotics**

Would you use Antipsychotics for Terminal Agitation?

Yes

No

Don’t know

Would you use Antipsychotics for Terminal Agitation?

n cause

mes occasionally never

Case

Phoned for advice

58 year old lady

Advanced breast cancer

Deteriorating

Developed distress and agitation

Terminal Agitation?

Want to administer antipsychotics

Next steps???

Terminal Agitation

- Who uses the term?
- What do we mean?

- Agitation
- Terminal

- Delirium – hyperactive (at EoL)

Agitation

A state of anxiety or nervous excitement

Anxious, restless and occasionally aggression

Terminal

At the end of life

- Cause or effect?
- Retrospective diagnosis?

Terminal Agitation

Agitation due to someone being at the end of life

- Not a distinct diagnosis

Cause: advanced disease, cytokines, drug/toxin metabolism, BBB???

Irreversible?

- Treatment of underlying cause not possible, practical, or consistent with the goals of care
- Do everything necessary to get comfortable?

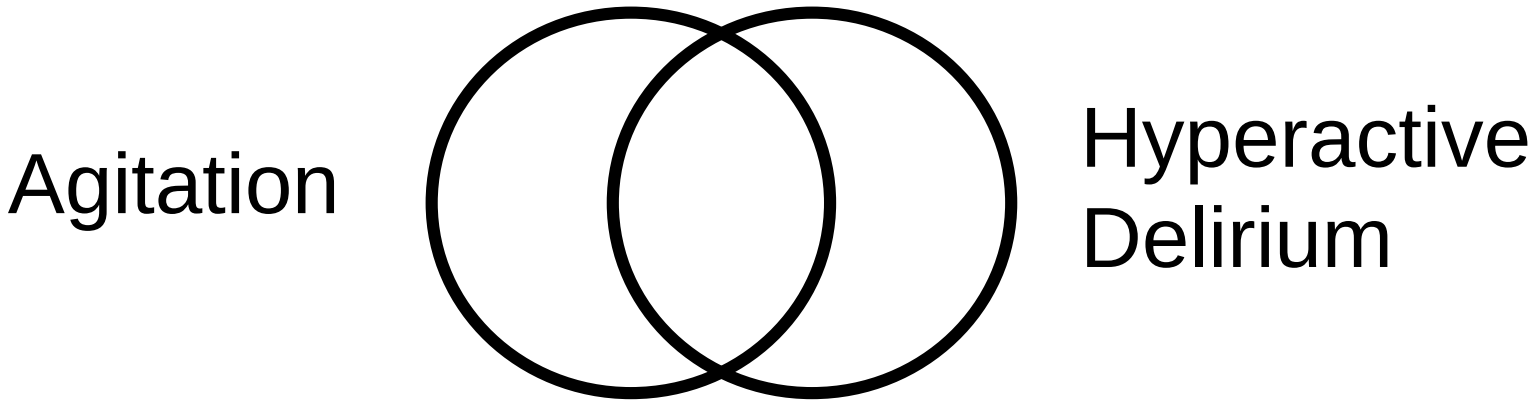
Approach

- Assessment (Hx, Ex, Ix)
  - Diagnose - presentation
  - Find the cause
  - Impact on patient/family/staff
- Explanation (patient/family/staff)
- Treat the cause
- Non-Pharmacological
- Drugs

Differential diagnosis

Agitation can be a symptom of delirium

Patients can become agitated without delirium



Cause of Terminal Agitation

- Urinary retention
- Constipation
- Discomfort (hot/cold, dehydration)
- Psychological, emotional or spiritual distress
- Pain, nausea, itch
- Alcohol intoxication or alcohol withdrawal
- Nicotine withdrawal
- Sepsis
- Organ failure (renal/liver/resp)
  - altered blood levels including urea and creatinine, calcium, sodium, glucose
  - oxygen deficiency (hypoxia)
- Brain tumour, metastases, cerebral oedema
- Medication: opioids, corticosteroids
- Medication withdrawal
- Delirium

- Some of these can be reversed (if appropriate)
- Sometimes the patient even improves

Non-Pharmacological Management

- Calm environment
  - Single room
- Not overcrowded
  - Limit people / visitors

- Presence of family members/loved ones for reassurance
- Explanation of the condition/causes and methods of management are given to family
- Positioning – discomfort may be adding to agitation
- Catheter **if** urine retention

Plan decided on an individual patient basis

Family support - Survey Results

Most respondents indicated that **formal support was not provided to family carers** (153/270, 57% inpatient; 97/161, 60% community)

- Verbal support most commonly provided in both inpatient (64/270; 24%) and community settings (35/161; 22%)
- **Low frequency of providing palliative care specific** information leaflets or **generic** information leaflets about delirium in either setting

(Boland et al 2018)

How to communicate with a person with delirium

A person with delirium may have a hard time understanding what people are saying and feel that they are not being understood.

- Face the person with delirium when speaking to them;
- Use a calming voice;
- Speak slowly and in short simple sentences;
- Present one idea at a time;
- If needed, repeat what you have said;
- Avoid contradicting the person. Instead, accept what they say and use distraction to shift their attention to something else;
- Do not make quick movements or gestures as these may be misinterpreted as aggressive;
- If the person with delirium is distressed by touch, then comfort and redirect them verbally instead.

How you can help care for a person with delirium

It can be reassuring for a person with delirium to see and hear familiar people.

- Help re-orient them by telling them *where* they are, *who* they are, and *who you are*.
- Place a clock, calendar and personal objects where they can see them.
- Help them put on their glasses and hearing aids. Check that their hearing aids are working and make sure they have their dentures.
- Keep noise and visitors to a minimum.
- Ideally, keep their room light during the day with curtains opened, and dark at night.
- Provide familiar items, such as family photos, comforters, blankets and sleepwear.

What Is The Role Of Antipsychotics?

In non-delirium agitation:

None

- Drugs
  - Benzodiazepine
    - ensure **not** delirium

What if it is hyperactive delirium?

Drugs for hyperactive delirium?

Medications are generally not recommended in most cases

If needed, use the lowest effective dose for the shortest possible time to relieve symptoms

Oral preferred; if not possible, subcutaneous

(Gaertner et al. 2019)

Drugs for hyperactive delirium - antipsychotics

Antipsychotics do not ‘treat’ delirium *per se*, but rather the symptoms

Underlying cause/s needs to be reversed to treat the delirium

Antipsychotics in delirium - evidence

Two recent randomised controlled trials of pharmacological management in adult palliative care inpatients

Antipsychotics in delirium - evidence

Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care

Regular oral risperidone and oral haloperidol associated with higher delirium symptom scores and more extrapyramidal side effects in mild-to-moderate severity delirium

Haloperidol associated with shorter overall survival in long-term follow-up (secondary outcome)

Not EoL

Agar *et al 2017*

Antipsychotics with Benzodiazepines - evidence

Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care

Single-centre randomised placebo-controlled trial in end-of-life severe delirium and agitation on intravenous haloperidol

Patients who were administered intravenous lorazepam added to haloperidol had less agitation than haloperidol and placebo at eight hours

Hui *et al 2017*

Benzodiazepines in delirium

Sedative and anxiolytic

Caution is needed - can exacerbate delirium

Exception is use in alcohol/benzodiazepine withdrawal (reverses the underlying cause).

In severe delirium where sedation is required, a patient on antipsychotics may respond to the addition of a benzodiazepine (in the lowest effective dose)

(Gaertner et al. 2019)

Antipsychotics in delirium - haloperidol

If danger, distressing hallucinations and non-pharmacological measures are ineffective, then:

- Lowest dose of haloperidol as required that works. Start with PRNs. Usual daily maximum: <5mg/24h.

“Terminal Agitation” - Role Of Antipsychotics?

- Priority is **assessment** – what’s going on?
- Identify and reverse cause (if appropriate)
- Family / staff
- If not delirium – none
  - Use non-pharmacological measures (if needed benzodiazepines)
- If hyperactive delirium –non-pharmacological measures +/- low doses antipsychotics PRN (+/- benzodiazepines)

Case

58 year old lady

Advanced breast cancer

Deteriorating

Developed distress and agitation

Terminal Agitation?

Want to administer antipsychotics

Case continued

- Was thought to be in last day(s) of life
- Not thought to be delirium
- No reversible causes of agitation found
- Support given to family and staff
  - Who supported the patient
  - Non-pharmacological measures
- Low doses of midazolam used
  - No antipsychotics used
- Patient was settled and died the next day

Thank you

- Questions?

What is Delirium

- Disorientation in time, place +/- person
- Impaired concentration + attention
- Impaired cognitive state/communication
  - Language, Speech, Memory, Perceptions, Constructional
- Wakefulness: insomnia + nocturnal agitation
- Reduced cooperation
- Overactive psychomotor activity
  - irritability + aggression

Delirium Presentation

Hyperactive – uncooperative, difficult to care for

Hypoactive - caring for these patients is not problematic to staff

- Patient appears to be napping on and off throughout the day
- Unable to sustain attention when awakened, quickly falling back asleep
- Misses meals, medications, appointments
- Does not ask for care or attention

Agar *et al*, RCT

JAMA Intern Med. 2017;177(1):34-42.

Efficacy of Oral Risperidone, Haloperidol, or Placebo for Symptoms of Delirium Among Patients in Palliative Care

Double-blind, parallel-arm, dose-titrated RCT

11 Australian inpatient hospice or hospital palliative care services

Adults receiving palliative care, with:

- life-limiting illness
- delirium (DSM-IV, MDAS score >6)
- delirium symptoms score (sum of NuDESC: behavioural, communication, and perceptual) of 1 or more

Dose

Dosing based on prior controlled trials

- <65 years: 1mg first dose, then 0.5mg bd
  - Doses titrated by 0.25mg on day 1 and by 0.5 mg thereafter to a maximum dose of 4mg/d
- >65 years: half loading, initial, maximum doses

  - Alongside management of delirium precipitants and non-pharmacological strategies

Han CS, Kim YK. A double-blind trial of risperidone and haloperidol for the treatment of delirium. Psychosomatics. 2004;45(4):297-301.

a priori outcomes

Primary:

- average of 2 delirium symptom scores on day 3

Secondary:

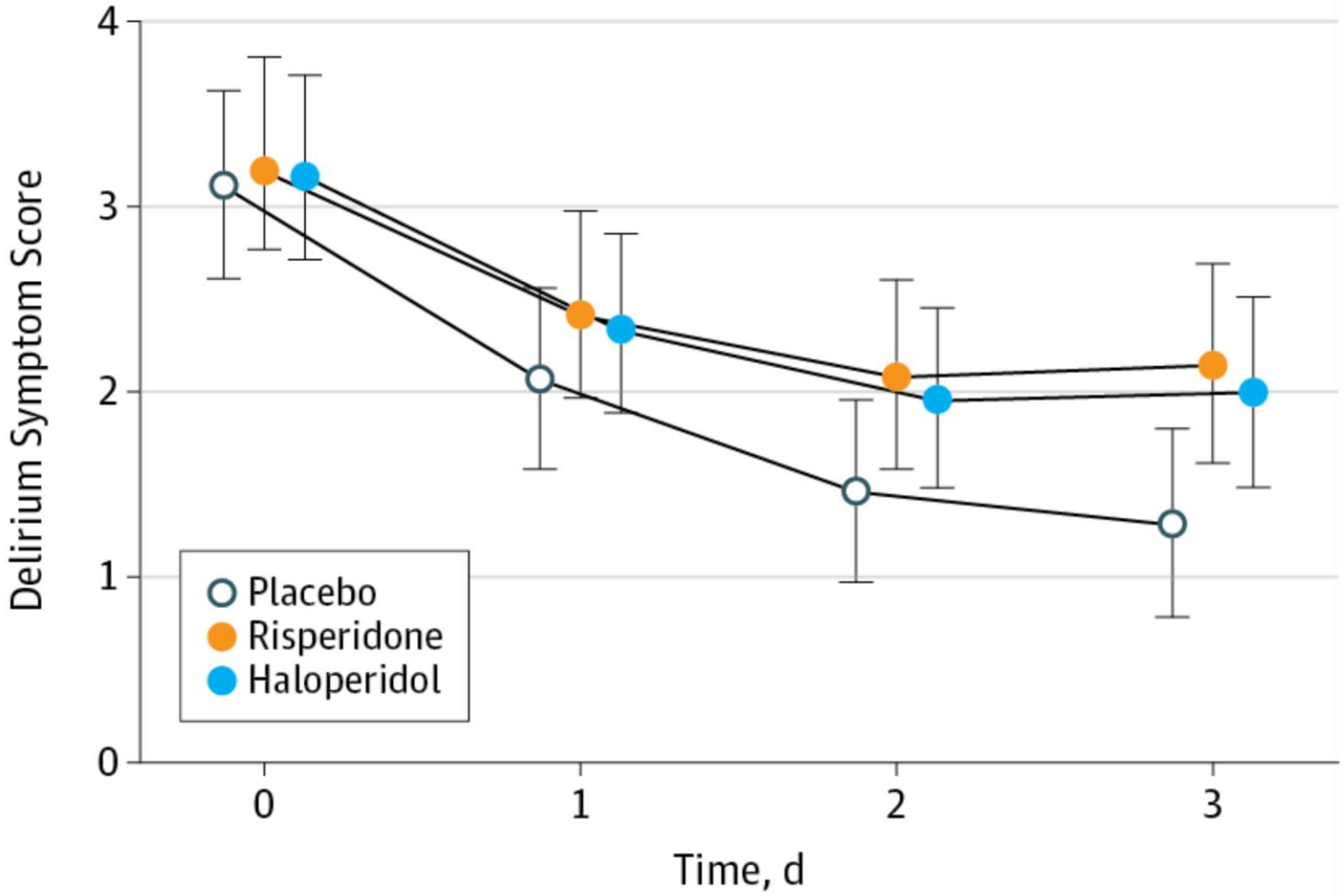
- daily MDAS score
- lowest delirium symptoms score
- midazolam use
- extrapyramidal symptoms, sedation

Agar et al. JAMA Intern Med. 2017;177(1):34-42

Results

- n=247: 82 risperidone; 81 haloperidol; 84 placebo
- No significant differences in baseline characteristics
- **Delirium symptom scores higher in patients taking haloperidol or risperidone vs. placebo**

Agar et al. JAMA Intern Med. 2017;177(1):34-42

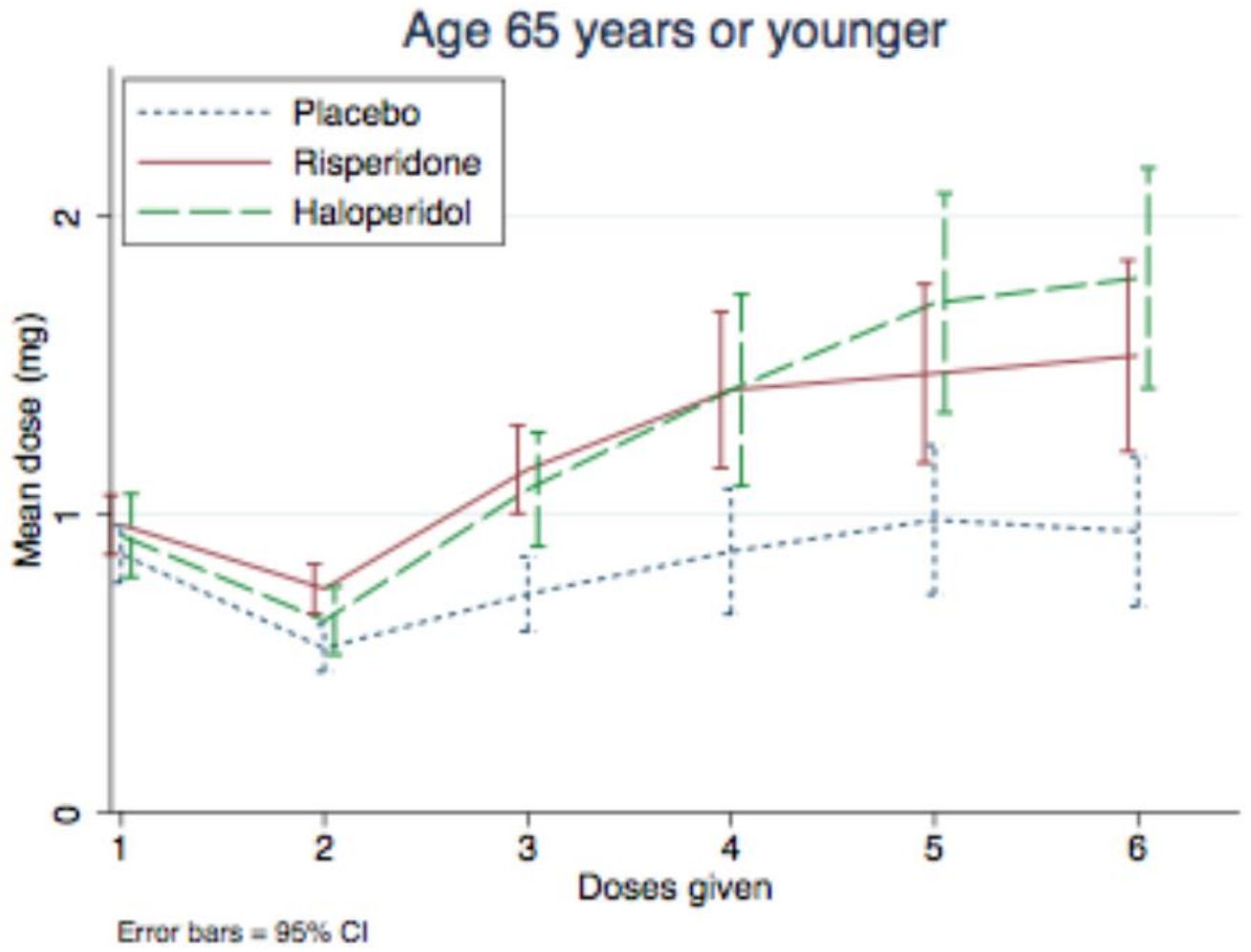


No. at risk					
Placebo	84	63	59	55	
Risperidone	82	58	49	39	$P < 0.001$
Haloperidol	81	64	55	51	$P = 0.002$

Agar et al. JAMA Intern Med. 2017;177(1):34-42

- More extrapyramidal effects with risperidone and haloperidol vs placebo
  - None serious
- More sedation, especially with haloperidol
- Median survival
  - 26 days placebo
  - 17 days risperidone
  - 16 days haloperidol
- Haloperidol 73% more likely to die vs placebo ($P = 0.003$)
- Low doses used…

Agar et al. JAMA Intern Med. 2017;177(1):34-42



Agar et al. JAMA Intern Med. 2017;177(1):34-42

- Less Midazolam used in placebo compared with risperidone and haloperidol ($P = 0.007 – 0.02$)

- For those who needed midazolam, no difference in the median dosage
  - median (IQR) dosage:
    - 2.5 mg (2.5-5.0 mg) for placebo and risperidone
    - 4 mg (2.5-5.0 mg) for haloperidol

Agar et al. JAMA Intern Med. 2017;177(1):34-42

Study Conclusion

Individualized management of delirium precipitants and non-pharmacological strategies results in **better** control of delirium symptoms than with the addition of risperidone or haloperidol

Agar et al. JAMA Intern Med. 2017;177(1):34-42

Delirium Assessment

- Clinical notes and patient review
  - Consciousness, somnolence, behavior, cooperativeness, concentration, mood lability, executive function, short term memory
  - Time course
- Collateral information
  - Staff, family/friends
    - baseline function, personality, psych history
- Medication review
  - PRNs, recent meds discontinued or started
  - Substance dependence (?withdrawal - inc. alcohol)
- Recent medical illness and interventions
- Examination, investigations

Trigger Questions – identify delirium

Acute change in

1. Behaviour
2. Function
3. Cognition
4. Sleep wake cycle

Fluctuates

Testing

- Serial 7’s
- spelling WORLD backwards
- months of the year backward
- counting down from 20

Mini mental status exam (MMSE)

- not sensitive in identifying delirium
- repeated can reveal fluctuant course
  - Orientation/concentration

Confusion Assessment Method

Requirement for delirium = 1, 2 **AND** either 3 **OR** 4

1. Abrupt change?
2. Inattention, can't focus?

3. Disorganized thinking? Incoherent, rambling, illogical?
4. Altered level of consciousness? (Hyper-alert to stupor?)

Sensitivity (94 to 100%), specificity (90 to 95%)

Memorial Delirium Assessment Scale

1. Reduced level of awareness
2. Disorientation
3. Short-term memory impairment
4. Impaired digit span
5. Reduced ability to maintain and shift attention
6. Disorganized thinking
7. Perceptual disturbance
8. Delusions
9. Decreased or increased psychomotor activity
10. Sleep-wake cycle disturbance