MANAGEMENT OF DELIRIUM AND AGITATION IN THE PALLIATIVE CARE SETTING

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Delirium - definition

- Acute syndrome involving a global cerebral dysfunction of the brain with a complex neuropathogenesis and multiple causes[1]
- ‘Acute brain failure’ when stressors exceed the brain’s homeostatic reserve

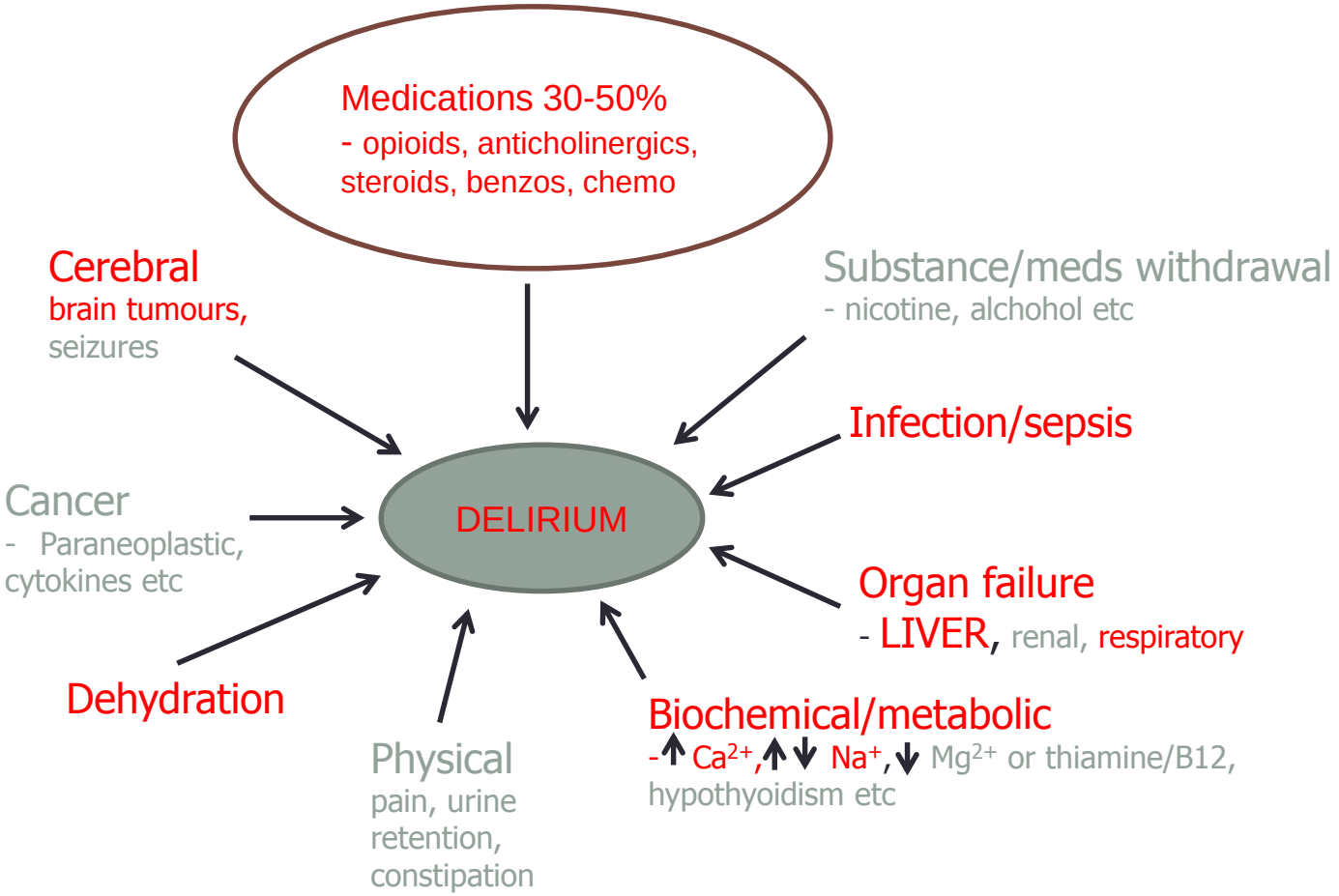
Delirium - symptoms

- Attention – reduced ability to focus, sustain and shift attention
- Awareness – reduced orientation to environment
- Rapid development and fluctuation symptoms
- Abnormal cognition – poor memory recall, calculations, writing and language
- Disorders of perception and thoughts – hallucinations/paranoia
- Disorders of sleep-wakefulness cycle
- Motor abnormalities
  - Hyperactive - Restlessness, thrashing, plucking
  - Hypoactive – withdrawn, uncommunicative
  - Mixed

Pathogenesis

- Not well understood

- Neuroinflammatory hypothesis – pro-inflammatory cytokines in CNS – neuronal dysfunction
- Blood brain barrier integrity compromise
- Oxidative stress
- Neurotransmitter hypothesis – dopamine/cholinergic imbalance
- Glucocorticoid excess – increased susceptibility brain injury
- Melatonin dysregulation – sleep/wake cycle



Main causes – study of 213 cancer pts[2]
Hyperactive = liver failure, opioid toxicity, steroids
Hypoactive = dehydration-related conditions

Who gets delirium at EOL?

- 13-42% hospice admissions

- 1 study found that 88% of cancer pts had delirium in hours/days before death[3]

Risk Factors

- Older age – homeostenosis (reduced reserve)
- Sleep deprivation
- Pre-existing cognitive impairment
- Severe illness state
- Infection
- Poor performance status
- Lung Ca

Investigations

- Often a progressive irreversible process at EOL
- Decision to investigate will depend upon:
  - Likely nature of underlying cause
  - The stage of illness
  - Goals of pre-established care with the patient
  - Prognostic factors
- Nearly always worth reviewing meds as account for 30-50% cases[3]

Poor prognostic factors[3]

- Severe delirium
- Irreversible precipitating factors
- Greater degree of cognitive impairment
- Hypoactive
- Previous episodes of delirium

Investigations

- Review drugs
- Check for urine retention/constipation
- Consider withdrawal states
- Collateral hx for baseline cognition and speed of onset
- Options if appropriate:
  - Bloods (incl B12/Folate, TFTs)
  - Cultures, MSU
  - CXR, LP, EEG, CT head

Management

- Optimise the environment
- Treat reversible causes
- Control symptoms
  - Non-drugs
  - Drugs
- Communication to patient and family

Optimise the environment

- Promote normal sleep/wake cycle
  - Lighting
  - Noise
- Safety
  - Risk assess. Consider 1:1 nursing
  - Pressure alarm pads, remove hazardous stuff
- Re-orientation
  - Clock etc, glasses, hearing aid, pictures etc

Re-orientation

- providing appropriate lighting and clear signage; a clock and a calendar should also be easily visible to the person at risk
- talking to the person to re-orientate them by explaining where they are, who they are, and what your role is
- introducing cognitively stimulating activities (for example, reminiscence)
- facilitating regular visits from family and friends

Treat reversible causes

- Only about 50% delirium reversible[5]
- Often multiple factors need addressing
- If opioids suspected – reduce dose or switch +/- IV fluids
- Treat infection

Evidence Base

- Very limited high quality evidence in palliative care setting
- There are a number of prospective RCT *comparator* trials mainly in *non-palliative* setting which appear to support the use of anti-psychotics in tx of delirium
- There are a small number of placebo controlled trials in non-palliative setting
- There is 1 placebo controlled trial in palliative care

Randomized *placebo*-controlled trials (not palliative):

- Small study in ITU – more rapid resolution of sx with quetiapine[6]
  - prospective, multicentre, randomized double blind placebo-controlled trial of quetiapine. Underpowered study – 36pts. Allowed rescue haloperidol
- Small study COE - more rapid resolution of sx with quetiapine[7]
  - RCT of quetiapine in care of elderly pop. Underpowered study 42 pts, mean delirium scores tended to reduce more rapidly in quetiapine group but did not reach statistical significance at each time point.
- ITU study – no effect of haloperidol[8]
  - RCT of haloperidol vs ziprasidone vs placebo. Reasonably powered study but still small no.s 103pts total. Allowed rescue haloperidol. Neither drug significantly increased no. of days pts were alive without delirium
- ITU study – no effect of haloperidol[9]
  - Double blind placebo-controlled RCT. 71 pts given haloperidol, 70 placebo. Haloperidol 2.5mg IV 8hrly given in fixed regimen irrespective of coma or delirium status! Allowed rescue haloperidol. Haloperidol did not significantly increased no. of days pts were alive without delirium. Sedation higher in Halo group

Randomized *placebo*-controlled trials (not palliative):

- ITU study – Haloperidol and Ziprasidone did not significantly alter the duration of delirium[11]
  - Randomized double blind placebo-controlled trial. Well-powered study 566 pts. Neither drug significantly affected the number of days a patient was alive without delirium or coma. 118 patients also received a non-trial antipsychotic (they didn't provide details) although use similar across all 3 groups.
- Number of studies in variety of settings using anti-psychotics to try to prevent delirium – none successfully

Randomized *placebo*-controlled trial - Palliative Care

- 1 study. Double-blind placebo-controlled trial of haloperidol and risperidone[10]
- Well powered study 247 pts
- Doses were titrated
  - O.5mg loading then 0.5mg bd. Titrated by 0.5mg/day up to max 4mg/d
  - Doses halved for >65. midazolam allowed as rescue
- Risperidone and Haloperidol groups had significantly higher delirium scores than placebo group (p=0.02/0.009), and more extrapyramidal S/Es (p=0.03/0.01)
- Participants in the placebo group had better overall survival than haloperidol (p=0.003) and risperidone (p=.14)
- A potential issue with this trial is that it was restricted to **mild-moderate delirium severity**

Randomized *placebo*-controlled trial - Palliative Care

- They used a composite subscore of the nursing Delirium Screening Scale as primary outcome measure – criticism of this as the subscore not studied for this use before. The absolute differences in scores were not large despite being significant.
- Used relatively low doses of anti-psychotics (mean <2mg/d)
- Nearly half the risperidone group dropped out
- Is it harder to demonstrate efficacy in mild forms of illness (akin to difficulty with antidepressant trials). May need very large no.s pts to demonstrate benefit.
- The need for titration was higher in the drug arms, midazolam use lower in placebo grp, agitation and sedation scores lower in haloperidol group. This could indicate the delirium was not the ‘same’ between the groups.
- Effects on mortality need to be carefully considered given the patient population

Evidence base

- Definitive evidence for management of delirium in palliative care setting remains lacking
- Uncertainty over whether anti-psychotics help resolve delirium or control symptoms

Approach in light of uncertainty?

- Individualised approach
- Targeted use of antipsychotics for delirium where level of behavioural disturbance, psychotic features and distress warrant intervention e.g
  - Patients who are very distressed
  - Not amenable to verbal and non-verbal de-escalation techniques
  - Patients who pose an immediate danger to themselves or to others
- Challenge of deciding when delirium is refractory and to shift focus of treatment

- Do patients with more predominant psychotic features respond better to anti-psychotics??

Drugs - antipsychotics

- Evidence base does not clearly favour one drug over another
- Therapeutic doses and optimal dose titration schedule remain to be clearly defined
- Best practice guidelines in palliative care setting recommend starting with Haloperidol

Drug treatment

- Haloperidol (dopamine antagonist)
  - Mild-mod distress/not danger
    - **0.5-1.5mg stat PO or SC and titrate 2 hrly as necessary (if necessary 0.5 to 1 to 1.5mg)**
  - Distress severe/danger to others
    - **1.5-3mg stat +/- benzodiazepine and titrate 2 hrly**
    - **Increase if necessary to 5mg**
  - Maintenance dose based on initial cumulative dose that settled patient – max 10mg/24hr (usually <5mg)
  - Lower starting doses in elderly
  - Review need daily and consider stopping or reducing (if cause treated)

Drug treatment

- Haloperidol
  - Side effects
    - Extrapyramidal (>70yrs)
    - Drowsiness (although less than atypicals)
    - Urinary retention, post hypotension, NMS
  - Avoid in Parkinsons or Lewy Body Dementia
    - Benzodiazepine or possibly Quetiapine (d/w old age psych)
  - Try to avoid co-prescribing with metoclopramide

Drug treatment

- Behavioural disturbance in Dementia
  - Need to distinguish delirium/psychosis from long-term behavioural disturbance in dementia
  - Antipsychotics generally not indicated in latter and cause considerable long-term S/Es
  - Non-drug techniques most useful
  - If medication needed d/w old age psych team

Drug treatment

- Severe distress/agitation/psychosis
  - Usually with antipsychotic
  - Lorazepam 1-2mg stat 2-4 hrly
  - Midazolam 2.5-5mg SC stat (short-term effect only)
  - Or Midazolam 5-10mg/24hrs via syringe driver
  - Be very cautious prescribing benzodiazepine alone without antipsychotic in this context – can cause paradoxical agitation

Outcome

- Only ~50% delirium reversible in hospice setting
- Some people that have experienced delirium develop long term cognitive impairment
- Delirium can worsen/accelerate dementia
- Most patients with refractory delirium die within days or few weeks

Communication

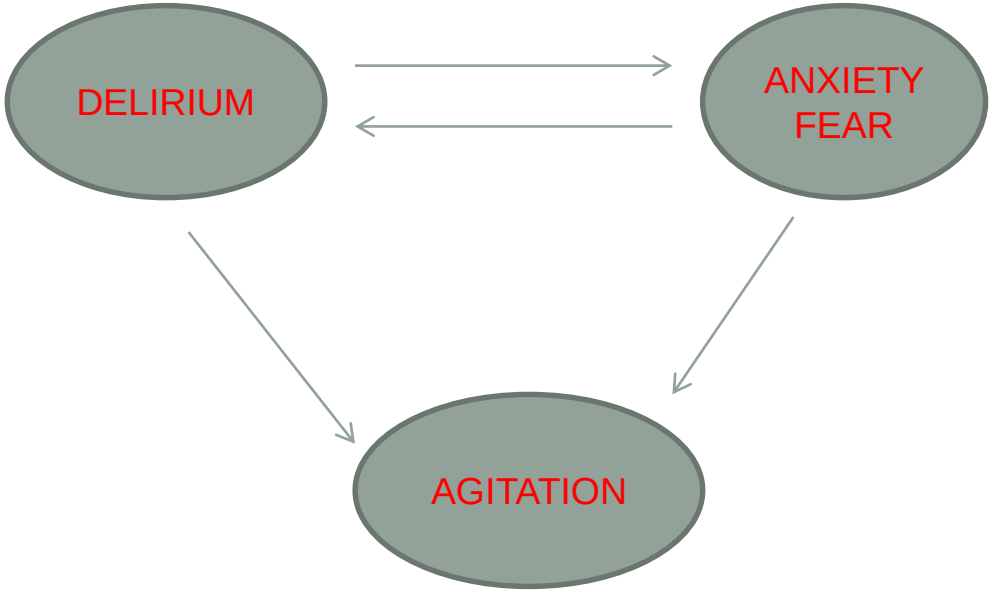
- Very distressing for families (education ↓)
- Explain that concentration and memory impaired
- Discuss any intended investigations and management
- Stress importance of calm environment etc
- Explain may be start of more rapid irreversible decline
- If poor prognostic factors warn may be near EOL and that sedation may be needed for distress
- Reassure that control of patient's distress priority
- Patient information leaflet
  - www.rcpsych.ac.uk/healthadvice/problemsdisorders/delirium.aspx
  - See attached also

Refractory hyperactive delirium/EOL

- = ‘Terminal agitation’

- Aim is to control distress during the dying process using minimum amount of medication necessary.

- Sedation is a consequence of treatment rather than the aim. i.e. aim is control of agitation rather than sedation per se.


DELIRIUM
ANXIETY
FEAR
AGITATION

Terminal agitation management

- Sykes & Thorns 2003 “sedative use in the last week of life and the implications for end-of-life decision making”
- No impact on survival overall
- Body of observational data from other countries that supports this view

Cochrane review 2015

- 14 studies reviewed (4167 patients)
- 95% cancer patients
- No randomised studies
- All case series (3 prospective)
- No studies measured QOL or well-being
- 5 measured symptom control but used differing methods so pooling not possible
- Only 1 study measured major adverse events and found none!
- 13/14 studies measured survival time from admission or referral to death and all demonstrated no significant difference between sedated and non-sedated patients

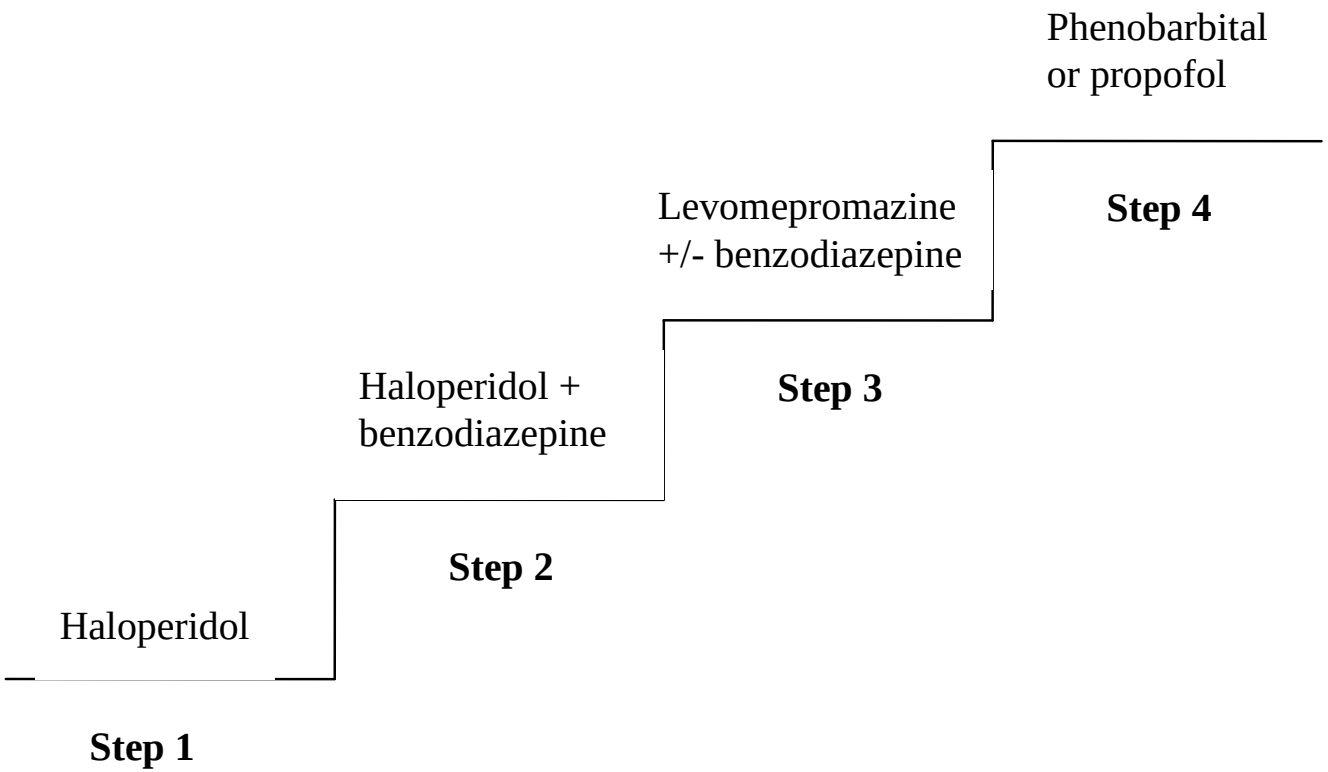
Terminal agitation

- As for delirium but lower threshold for sedating antipsychotic/starting syringe driver:
  - Specialist palliative care review
  - Haloperidol 2.5-5mg/24hrs increasing to 10mg/24hrs if required
  - Midazolam 10-20mg/24hrs and titrated as needed up to usual maximum of 60mg/24hrs (most patients only require 10-20mg/24hrs)
  - Some patients need other approaches

Terminal agitation

- Levomepromazine
  - Sedating antipsychotic
  - Dopamine antagonist, antimuscarinic
  - S/Es – as for haloperidol but more sedating
  - 12.5-25mg SC stat and prn 1 hrly
  - Maintenance by syringe driver – seek advice from SPC team (50-300mg/24hrs)

Drug treatment



References

1. Grassi et al, ‘Management of delirium in palliative care: a review’. Curr Psychiatry Rep 2015 Mar 17(3): 550
2. Morita et al, ‘Underlying pathologies and their associations with clinical features in terminal delirium of cancer patients’. J pain and symptom management. 2014; 48:215-30
3. Hosker et al, ‘Delirium and agitation at the end of life’. BMJ. 2016; 353 (9/6/16)
4. NICE. Clinical guideline CG103. 2010. Delirium: prevention, diagnosis and management.
5. Lawlor et al, ‘Occurrence, causes, and outcome of delirium in patients with advanced cancer: a prospective study’. Arch Intern Med. 200; 160(6):786-94
6. Devlin et al, ‘Efficacy and safety of quetiapine in critically ill patients with delirium: a prospective, multicenter, randomized, double-blind, placebo-controlled pilot study’. Critical care medicine. 38:419-427
7. Tahir et al, ‘A randomised controlled trial of quetiapine versus placebo in the treatment of delirium. J Psychosom res. 69:485-490
8. Girard et al, ‘Feasibility, efficacy and safety of antipsychotics for intensive care unit delirium: the MIND randomized placebo-controlled trial. Crit Care Med 38: 428-437
9. Page et al, ‘Efficacy of intravenous Haloperidol on the duration of delirium and coma in critically ill patients (HOPE-ICU): a randomised placebo-controlled trial’. Lancet Respir Med 2013;1(7)515-23
10. Agar et al, ‘Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliaitve care: a randomised clinical trial’. JAMA Intern Med. 2017;177:34-42
11. Girard et al, ‘Haloperidol and Ziprasidone for treatment of Delirium in Critical Illness’. NEJM. 2018. Oct 22