Agitation in last days of life

Dr Susan Haynes

Agitation at End of Life (Ref Caresearch)

Terminal restlessness is a cluster of symptoms and perhaps is a poorly understood and overly used term in the palliative care community. Most often described are a combination of agitation and altered mental state, occurring close to the end of life and may be referred to as agitated delirium. [8] There is no agreed definition of this condition. Its relationship with delirium, and its management and potential for reversibility are poorly understood.

Assessment must include a consideration of alternative diagnoses.

Last days of life: agitation (Ref PC TG)

Agitation, or terminal restlessness, is common as death approaches. Patients may be restless and unable to find a comfortable position in bed, try to get out of bed, or pluck at the sheets or the air.

Agitation in the last days of life can have many causes, including

- physical discomfort :
  poorly controlled pain,nausea, itch , urinary retention, faecal impaction,
- Myoclonus, partial complex seizures, paraneoplastic limbic encephalitis
- Delirium
- emotional distress, PTSD, psychotic disorder
- medication toxicity or metabolic changes.
- Withdrawal effects from medications, alcohol, nicotine or illicit substances.
- *In many is likely to be multifactorial, and it can be difficult to identify the cause(s).*

- Management of agitation includes identifying and addressing potential underlying causes if possible,

AND using general measures such as a calm environment and the presence of people well-known to the patient (as for delirium in palliative care, management).

Causes that can be addressed include :

- urinary retention, faecal loading of the rectum (treat with a rectally administrated laxative/ IDC),
- uncontrolled pain or other symptoms.
- Symptoms of withdrawal from long term medication (see below) or illicit substances

A nicotine patch may be useful for a smoker.

Last days of life: agitation

AND: DON'T FORGET THE IMPACT OF PHYSIOLOGICAL / PATHOPHYSIOLOGICAL CHANGES AT EOL :

IE:

- ***PREVIOUSLY WELL TOLERATED MEDICATIONS MAY HAVE ACTIVE METABOLITES WHICH ACCUMULATE AND CAUSE SYMPTOMS OR CHANGES IN PHARMACOKINETICS MAY INCREASE OR DECREASE THE CLINICAL EFFECTIVENESS***

- ***MAY BE WORTH TRYING OPIOID ROTATION OR REDUCING DOSES OF MEDICATIONS SUCH AS MORPHINE IF RENAL CLEARANCE OF DRUGS AND METABOLITES LIKELY IMPACTED***

Last days of life: Agitation & BZD

- Renal impairment may increase the CNS effects of BZD due to decreased clearance of active metabolites

- Hepatically cleared BZD have potential for drug-drug interactions through CYP450 and glucuronidation reactions, and must be used cautiously in hepatic impairment. Oxazepam (if swallowing) is preferred.

Managing Withdrawal symptoms from long-term medications when weaning has not occurred

Antipsychotics	Dyskinesia, nausea, vomiting, agitation	Regular parenteral antipsychotic. Seek specialist advice.
Benzodiazepines	Delirium, agitation, insomnia, seizures	Continuous parenteral benzodiazepine. Seek relevant specialist advice.
Beta-blockers	Rebound tachycardia, palpitations, re-emergence of angina	Parenteral opioid or benzodiazepine. Consider nitrate patch for angina.
Digoxin & other antiarrhythmics	Re-emergence of rapid atrial fibrillation or other arrhythmias, resulting in breathlessness.	Parenteral opioid or benzodiazepine.
Diuretics	Fluid retention associated with breathlessness or peripheral oedema.	Parenteral opioid or benzodiazepine.
Nitrates	Re-emergence of angina	Convert to nitrate patch. Treat symptoms with parenteral opioid.
Steroids	Hypothalamic-pituitary axis suppression in long-term use	May develop acute adrenal crisis and if concerned, seek relevant specialist advice.
	Re-emergence of painful inflammatory condition	Parenteral steroid.

Alpha-blockers	Rebound hypertension, agitation with sudden cessation	Parenteral opioid or benzodiazepine.
Anticholinergics	Anxiety, headache, dizziness	Parenteral opioid for headache or benzodiazepine for anxiety and dizziness.
	Nausea, vomiting	Parenteral antiemetic.
Anticonvulsants	Emergence or re-emergence of seizures	Continuous parenteral benzodiazepine. Seek relevant specialist advice.
Antidepressants	Dysphoric mood, agitation, headache	Parenteral opioid or benzodiazepine.
Anti-reflux medications	Heartburn, nausea.	Consider parenteral anti-reflux medication, parenteral anti-emetic and opioid.
Antiparkinsonians	Rigidity, resulting in pain	Parenteral opioid.

Last days of life: agitation (Ref PC TG)

If agitation persists despite general measures and addressing potential causes, consider prescribing a benzodiazepine or haloperidol – either may be tried first. If a patient remains agitated despite an adequate dose of the first drug tried, the second drug can be added.

For a patient with agitation who has not been taking benzodiazepines, a suitable as-required starting dose for anticipatory prescribing or intermittent symptoms is:

1. Clonazepam 0.2 to 0.5mg sublingually or subcutaneously, 2-hourly as required. Monitor response and adjust dose and frequency as needed. Review therapy after 3 doses, or sooner if the patient is not responding to treatment.

OR

1. Midazolam 2.5mg subcutaneously, 1-hourly as required. Monitor response and adjust dose and frequency as needed. Review therapy after 3 doses, or sooner if the patient is not responding to treatment. (Ref TG)

Last days of life: agitation (Ref PC TG)

Consider prescribing regular benzodiazepines if agitation is ongoing or if more than three as-required doses are needed in a 24-hour period. A suitable starting dose for regular therapy is:

- Clonazepam 0.2 to 0.5mg sublingually or subcutaneously, 12-hourly, and 0.2 to 0.5mg 2-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 4mg in 24 hours.

OR

- Clonazepam 0.5mg to 1mg/24 hours by continuous subcutaneous infusion, and 0.2 to 0.5mg sublingually or subcutaneously, 2-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 4mg in 24 hours.

OR

- Midazolam 10 to 20mg/24 hours by continuous subcutaneous infusion, and 2.5mg subcutaneously, 1-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 60mg in 24 hours.

Review benzodiazepine therapy if more than three as-required doses are needed in a 24-hour period in addition to regular therapy, or sooner if the patient is not responding to treatment.

Last days of life: agitation(Ref PC TG)

"Alternatively, or in addition to a benzodiazepine, haloperidol may be tried.

For a patient with agitation who has not been taking haloperidol or another antipsychotic drug, a suitable as-required starting dose for anticipatory prescribing or intermittent symptoms is:

- *Haloperidol 0.5 to 1mg subcutaneously, 4- hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 5mg in 24 hours.*

Consider prescribing regular haloperidol if agitation is ongoing or if more than three PRN doses are needed in 24 hours. A suitable starting dose for regular therapy is:

- *Haloperidol 0.5 to 1mg subcutaneously, 12-hourly, and 0.5 to 1mg 4-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 5mg in 24 hours.*

OR

- *Haloperidol 1 to 2.5 mg/24 hours by continuous subcutaneous infusion, and 0.5 to 1mg subcutaneously, 4-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 5mg in 24 hours. "*

- *NOTE : Use of anti-psychotics for treating delirium is contentious, evidence is poor, and evidence of harm- more of a concern when not dealing with last days of life, but remember potential for haloperidol to exacerbate symptoms, which may not be well recognised and misinterpreted as deterioration. Watch for signs of ADR eg cog-wheel rigidity. DO NOT USE HALOPERIDOL IN PT WITH PARKINSONIAN SX*

Last days of life: agitation (Ref TG)

For **a patient with agitation who is already taking an oral benzodiazepine**, but who is unable to swallow, consider changing to clonazepam administered subcutaneously or sublingually, or midazolam administered subcutaneously. Prescribe as-required doses for symptoms that are not controlled with regular doses. If unsure how to change the medication and or the route of administration, seek specialist advice.

For **a patient with agitation already taking oral haloperidol or another oral antipsychotic drug** and who is unable to swallow, consider changing to haloperidol by subcutaneous injection or continuous subcutaneous infusion. Prescribe as-required doses for symptoms that are not controlled with regular doses. If unsure how to change the medication and or the route of administration, seek specialist advice.

Note: Sublingual clonazepam 0.2 to 0.5mg is equivalent to 2 to 5 drops of clonazepam 2.5mg/ml oral liquid. Do not count drops directly into the mouth, count drops into a spoon first.
Note: Clonazepam has a long half-life (30 to 40 hours) and ongoing use of frequent doses can result in accumulation and excessive sedation. Once symptoms are controlled, reduce the frequency of as-required doses. Alternatively, midazolam has a shorter half-life and can be used for PRN doses.
Note: Clonazepam may be absorbed into PVC infusion tubing: non-PVC tubing is recommended, or adjust the dose to effect.

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	Approximate equiv doses	Sedation	Anxiolysis	Muscle relaxant	Anti-seizure	Duration of action	Onset of Action	Metabolism
Clonazepam	**0.25**-0.5mg PO*/subcut	✓	✓	✓	✓	**Long**	**PO** intermediate **subcut** rapid	CYP 3A4
Diazepam	**5**mg PO	✓	✓	✓	✓	**Long**	**PO** rapid **PR** rapid	CYP 2C19 3A4 ^
Lorazepam#	0.5-**1**mg PO	✓	✓	✓	✓	**Intermediate**	**PO** rapid **SL** rapid	Glucuronidation
Midazolam	**2.5**mg subcut 5mg intranasal	✓	✓	✓	✓	**Very Short**	**Subcut Intranasal** rapid	CYP 3A4, 3A5 ^
Oxazepam#	**30**mg PO	✓	✓	✓	✓	**Short**	**PO** rapid	Glucuronidation
Temazepam	**10**-20mg	✓	✓	✓	✓	**Short**	**PO** intermediate	Glucuronidation

Rapid = <30min Intermediate= 30-60min

*clonazepam drops 0.1mg= 1 drop ^ active metabolites # preferred in hepatic disease

Table 1: Comparison of benzodiazepine drugs

Last days of life: agitation

Additional or alternative sedatives used as 3rd + 4th line measures in PCU include:

1. **Levomepromazine** – starting at 12.5-25mg 4-hourly, up to 200mg in a 24 hour period via CSCI
2. **Phenobarbitone**
   - 100mg stat IM – subsequent dosing 200-600mg via CSCI (Uk guidelines 400-1200mg)
   - If uncontrolled seizures/status epilepticus at end of life – 200mg IM then 800-2400mg via CSCI over 24 hours.
   - (Doses over 1600mg in 24 hours CSCI – dilute to 17mls with water
   - Doses up to 1600mg dilute NaCL 0.9% via infusion pump)

Delirium in the Palliative Care Setting

One of the Potential Causes for Agitation/Restlessness at End of Life

Delirium

Evidence summary

Definition and prevalence

Delirium is defined as a condition of disturbed consciousness, with reduced ability to focus, sustain or shift attention. The DSM 5 [13]- revised diagnostic criteria for delirium require:

- disturbance of consciousness with a reduced ability to focus, sustain, or shift attention
- altered cognition or a perceptual disturbance (which is not better accounted for by dementia),
- symptoms develop over hours to days and tend to fluctuate during the course of the day, and
- evidence of an aetiological cause for the delirium.

Delirium may be

- hyperactive (presenting with agitation, hyperarousal, and restlessness), or
- hypoactive (presenting with drowsiness, lethargy and reduced levels of arousal), or
- a mixed pattern in which the symptoms fluctuate between hyperactive and hypoactive. [14]

Delirium (Ref Caresearch)

Assessment

Delirium is underdiagnosed, due in part, to the difficulty in assessing it. [3,15] It remains challenging to diagnose, particularly in children [19] and older people. [20] Hypoactive delirium in particular is under-diagnosed and is the most frequent subtype of delirium in palliative care settings.

Delirium

- Is extremely common in palliative care patients – affecting 40 % in course of illness, increasing to 80 % at EOL

- Delirium is an independent predictor of mortality

Delirium in the PC Setting:

Is **Underdiagnosed-** especially hypoactive delirium

Is more common in people with previous cognitive impairment

Is important to diagnose for management , prognostication and in order to counsel families

Can be potentially reversible

Causes significant distress to patients, their families and staff

Makes it difficult to assess and treat other problems such as pain or depression

Diagnosing Delirium in PC settings

Symptom fluctuation means assessment should be part of routine care and is most accurately assessed if it is monitored regularly rather than intermittently

There are many validated tools – CAM, 4 AT

In PC setting there is often more than one likely predisposing or precipitating factor.

Educating and counselling caregivers is an important aspect of managing patients at risk for delirium or when delirium is diagnosed

Delirium Management (Ref Caresearch)

Approach to management

- Educate and reassure both patient and family about the nature of the problem.
- Manage precipitants as appropriate to the context. This usually includes reviewing medications, identifying infection, improving hydration, and attention to the environment of the patient (familiar, calm, non-threatening, safe).
- Pharmacological management with an antipsychotic should be considered if the patient is distressed or agitated.
- Monitor the safety of the patient and caregivers. Delirium may be a very difficult problem in the home environment, its progression is unpredictable, and admission is frequently required.

Fact Sheet: Antipsychotics - July 2019

SA Palliative Care Community Pharmacy Update

A joint initiative of South Australian Palliative Care Services

Psychoactive medicines are commonly used throughout the disease journey including the last days of life. This update reviews antipsychotic use in palliative care (Benzodiazepines discussed in the last update (253kb pdf)).

Delirium is common in palliative care and can be highly distressing to patients and their carers. Evidence supporting the use of antipsychotics in delirium is mixed with risk of greater harm than good in some patients. Hypoactive delirium is unresponsive to dopamine antagonists.

Delirium at End of Life

Delirium is common in palliative care and can be highly distressing to patients and their carers. Evidence supporting the use of antipsychotics in delirium is mixed with risk of greater harm than good in some patients. Hypoactive delirium is unresponsive to dopamine antagonists.

Palliative Sedation Therapy

Dr Sue Haynes

Definition

Palliative Sedation Therapy (PST) is the monitored use of medications to lower a patient's awareness in order to provide relief of symptoms that are refractory to usual measures, are distressing and result in considerable suffering if unrelieved (Cherny et al 2009, Morita et al 2005).

Key Guidance (ANZSPM guidelines on use PST 2017)

ANZSPM considers PST to be an important and necessary approach in selected patients with life limiting illness with refractory symptoms.

ANZSPM considers PST to be an essential high level skill, which is ethically acceptable when used for selected patients with refractory symptoms in accordance with international guidelines (Cherny et al 2009).
PST should be considered to be an extraordinary measure, utilised by skilled and experienced Palliative Care Clinicians in a Multi-Disciplinary setting. PST should only be utilised after a comprehensive assessment of the patient's symptoms, psychosocial needs, and spiritual needs (Braun et al 2003).

Key Guidance cont.

PST needs to be distinguished from other types of sedation used in palliative care.
Ordinary sedation is defined as sedation used to relieve anxiety, restlessness and insomnia (Quill 2009).
Proportionate palliative sedation is defined as the use of medication actively titrated to relieve symptoms but not produce unconsciousness (Quill 2009).

PST is distinct from euthanasia by virtue of the intent and the action.(ie to reduce consciousness not to end life)

Sedation for refractory distress in palliative care

Sedation for refractory distress, or palliative sedation, is the use of sedation for a patient with life-limiting illness to relieve severe symptoms that are resistant to all other treatments, usually until death occurs. The intention of palliative sedation is to relieve intolerable symptoms, not to hasten death. It is considered a measure of last resort and is suitable for only a small group of patients. (Note that many patients who are dying need some degree of mild or intermittent sedation to relieve agitation or other symptoms as death approaches; this is not considered to be palliative sedation.)

A decision to prescribe palliative sedation should not be taken lightly, and should be discussed in depth with all of the healthcare providers involved in direct care of the patient. There are many factors to consider when making this decision, including the patient's wishes, their prognosis, and the goals of care. If a patient's symptoms are difficult to control and palliative sedation is being considered, seek specialist palliative care support.

Sedation for refractory distress in palliative care cont.

Situations where palliative sedation is used generally cause some distress or disquiet for both family members and healthcare providers. Careful explanation and reassurance is important for the family, and members of the healthcare team may need extra support.

Healthcare providers have no reason to fear legal sanction when they provide adequate relief of pain and other distressing symptoms if the prevailing standards of palliative care are adhered to, and the decision is documented; they should be comfortable giving medication doses that are sufficient to achieve effective relief of the patient's symptoms.

Case 1 – MR R

-80 year old married man, second marriage. Wife 7 years older but in good health. Considered himself her provider/protector

-Both changed their ACDs when VAD was legalised – VAD was added to his wish list

-History of metastatic prostate cancer with extensive bony, lung and liver metastases.

-Had a fall prior to his admission to PCU – all over the body pain, poor mobility and unable to look after himself.

-He started the VAD discussion in the community

Case 1 – Mr R

-Belief system: considered himself a spiritual person, but did not belong to a religious group – liked Buddhist philosophy

-On presentation, not interested in symptom management, very much focused his energy on completing the VAD process. In a lot of pain from his known bony metastases. Very frail. Had his hands in the Anjali Mudra position most of the time when he was visited by doctors. Cried a lot of the time during reviews. “I need to die.”

-His wife – totally supported his decision to die - “ it is time for him to die. I would want the same thing if I were him.”

-His condition deteriorated very rapidly while he was waiting to complete his VAD process – more confused, unable to hold a proper conversation but very clear still that he wanted to die. During this time, he had multiple medication changes aimed at pain management and anxiety management

Case 1 – Mr R

-OxyContin titrated to 20mg bd

-Dexamethasone trialled for bone pain and general well-being – 4mg daily

-Paracetamol 1 g tds

-Required multiple doses of Oxycodone for breakthrough pain

Case 1 – Mr R

-All agreed he was too confused to undergo the VAD process.

-CSCI was started due to increasing difficulty swallowing

-His wife asked for him to be sedated as she felt he would be too distressed if he continued to wake up each morning alive.

-CSCI was titrated over 48 hours and he was sedated for 5 days prior to his death. CSCI contained 60mg morphine, 30mg midazolam and 5mg haloperidol.

Case 2 – Mr I

-78 year old widowed man, known to a country palliative care service

-Lived alone but had supportive children

-Background of 5 years of progressive metastatic non small cell lung cancer – treated with multiple lines of chemotherapy

-History of progressive decline in function with worsening shortness of breath and difficulty swallowing with marked weight loss

-His CT 6 weeks prior to his death showed widespread multilobular infiltration in the right hemithorax extending into the mediastinum with worsening mass effect on the trachea, oesophagus, left atrium and SVC and worsening mass effect on the right liver lobe

Case 2 – Mr I

-He presented to hospital 3 days prior to his death with an acute respiratory distress, described trying to cough up sputum but unable to do so. He was found to be hypoxic by SAAS with SaO2 of 70% on room air. He was brought to ED and his symptoms settled with a combination of nebulized Ventolin, oxygen supplementation, and morphine. He was thought to have a degree of mucus plugging.

-He insisted on going home wishing for end of life care at home. He was sent home with end of life medications including morphine, midazolam, hyoscine and haloperidol. The local palliative care service reviewed him on the day of discharge.

-Mr I continued to have episodes of respiratory distress at home. His son moved in to help.

Case 2 – Mr I

-His son struggled to keep him comfortable – administered 2 doses of morphine and midazolam – settled for a short time only to wake up with severe distress

-He was transferred to the palliative care unit only after 1 night being at home.

-On arrival, he was calm and able to engage with the nursing staff.

-Whilst he was waiting for a medical assessment on the ward, he became very distressed when he started coughing trying to clear his secretions. He became cyanosed and agitated with marked respiratory effort.

Case 2 – Mr I

-His SaO2 was unrecordable due to severe peripheral cyanosis.

-He looked scared.

-He asked to be sedated because he was scared of coughing and having another respiratory distress.

-He was awake enough to say his goodbye to his 3 children before he was sedated.

-He had 10mg midazolam and 5mg morphine during the acute episode and was commenced on CSCI 15mg morphine/20mg midazolam.

-He died within 24 hours of admission.