



2019

21-23 JUNE

SAN FRANCISCO

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

Management of “terminal agitation”: Evidence versus pragmatism

MASCC/ISOO

Annual Meeting on Supportive Care in Cancer

www.mascc.org/meeting

Follow us on Twitter: @CancerCareMASCC

Professor Gregory Crawford MBBS, MPH, MD, FRACGP, FACHPM
Senior Consultant Palliative Medicine & Director of Research and Education

Northern Adelaide Palliative Service, Northern Adelaide Local Health Network

Professor of Palliative Medicine
Discipline of Medicine, University of Adelaide, South Australia



#MASCC19

Conflict of Interest Disclosure

Gregory Crawford, MBBS, MD, FACHPM

- Salary:
- SA Health
- Other:
- President, Australasian Chapter of Palliative Medicine, Royal Australasian College of Physicians
- Chairman, Palliative Care South Australia





Outline

- Definitions
- Delirium
- Causes
- Assessment
- Investigation
- Management



Definitions

- Terminal restlessness
- Terminal agitation
- Delirium



Setting

- Common in last days and weeks of life
- Can be distressing for patients and family
- Up to 88% develop delirium in the last hours or days of life (Lawlor, Bush 2015)



Desired outcome

- Patient who is:
 - Awake
 - Alert
 - Calm
 - Cognitively intact
 - Not psychotic
 - Communicating coherently



2019

21-23 JUNE

SAN FRANCISCO

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



What is delirium?

- Abrupt onset
- Fluctuating confusion
- Inattention
- Reduced awareness of environment
 - Memory, orientation, language, visuospatial ability, perception
- Hallucinations
- Disturbances of sleep-wake cycle



Classifications

- Hyperactive
 - Restlessness and agitated behaviour dominate
- Hypoactive (easily missed)
 - Drowsiness and inactivity dominate
- Mixed



Causes

- Physical factors + physiologically vulnerable “brain” → confusion, changes in perception, altered behaviours
- Frequently under-diagnosed (de la Cruz et al 2015)



Physical factors

- Metabolic
 - \uparrow Ca, \uparrow Na, \downarrow Na, \uparrow BGL, \downarrow BGL, dehydration
- Organ failure
- Drugs
 - BZD, steroids, anticholinergics, opioids etc and MORE
- Sepsis
- Brain pathology
 - Tumour, ischaemia, status epilepticus
- Hypoxia
- Drug withdrawal



Drugs

- Anxiolytics, hypnotics
- Opioids
- Corticosteroids, NSAIDs
- Anticonvulsants
- Anticholinergics
 - Scopolamine (hyoscine hydrobromide)
 - Atropine
 - Belladonna alkaloids
 - Drugs with established anticholinergic activity, e.g. tricyclic antidepressants, diphenhydramine, promethazine, hyoscine butylbromide
- Other psychoactive: antipsychotics, antidepressants, levodopa, lithium
- Anti-infectives: ciprofloxacin, acyclovir, ganciclovir
- Histamine H2 blockers
- Omeprazole
- Immunomodulators: interferon, interleukins, cyclosporin
- Medication polypharmacy



2019

21-23 JUNE

SAN FRANCISCO

**SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE**



Assessment tools

- Mini Mental State Examination
- Delirium screening tools
 - 4AT
 - Confusion Assessment Method
 - Nursing Delirium rating scale (Nu-DESC)
 - Single Question in Delirium
- Severity assessment tools
 - Memorial Delirium Assessment Scale
 - Delirium Rating Scale



4 AT /12

- | | | | |
|----|--|---|----------------------------|
| 1. | ALERTNESS | <ul style="list-style-type: none">• Normal• Mild sleepiness for <10 seconds• Clearly abnormal | <p>0</p> <p>0</p> <p>4</p> |
| 2. | AMT4 (<i>age, date of birth, place, year</i>) | <ul style="list-style-type: none">• No mistakes• 1 mistake• 2 or more mistakes/untestable | <p>0</p> <p>1</p> <p>2</p> |
| 3. | ATTENTION (<i>months of the year backwards</i>) | <ul style="list-style-type: none">• Achieves 7 months or more correctly• Starts but scores <7 months• Untestable | <p>0</p> <p>1</p> <p>2</p> |
| 4. | ACUTE CHANGE OR FLUCTUATING COURSE <i>previous 2 weeks & still in last 24hrs</i> | <ul style="list-style-type: none">• No• Yes | <p>0</p> <p>4</p> |



Memorial Delirium Assessment Scale (MDAS)

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



2019

21-23 JUNE

SAN FRANCISCO

SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE



Investigation

- Context relevant
- Often a progressive, irreversible process in last stages of life
- Reversible causes particularly drugs



Practical approach

- Consider stage of disease and GoC
- Drugs
 - Deprescribe, Reduce, Rotate/Switch
- Alcohol or other withdrawal
- Collateral history re rate of onset etc
- Investigate if consistent with GoC
 - Metabolic and haematological parameters
 - Blood cultures
 - MSSU
 - CXR
 - CT/MRI



Treatment – non pharmacological

- Promote normal sleep wake cycle
 - Lighting levels
 - Noise
- Safety
 - Risk assessment
 - 1:1 nursing
 - Pressure pad alarms
 - Remove hazardous objects
- Re-orientation
 - Clock
 - Glasses, hearing aids, interpreters
 - Clear communication
 - Continuity of staff
 - Family to assist with orientation



Medication

- What is the evidence
- Controversies
- When does agitation and delirium become a refractory symptom that might be considered for palliative sedation?



Cochrane Systematic Reviews

- Interventions for preventing delirium in hospitalised non-ICU patients
(Siddiqi, Harrison et al, 2016)
 - 39 trials, 16,082 participants, 22 interventions
 - 14 trials placebo-controlled, 10 compared 2 different interventions
 - 32 in surgery patients (orthopaedic)



- Strong evidence supporting multi-component interventions to prevent delirium
- No clear evidence that cholinesterase inhibitors, antipsychotic medications or melatonin reduce the incidence of delirium
- The role of drugs and other anaesthetic techniques to prevent delirium remains uncertain

Cochrane Systematic Reviews

- Drug therapy for delirium in terminally ill adult patients
(Candy, Jackson et al, 2012)
 - Prospective trials with or without randomisation or blinding
 - One trial met the inclusion
 - 30 hospitalised AIDS patients receiving one of three agents
 - chlorpromazine, haloperidol and lorazepam
 - Insufficient evidence to draw conclusions about the role of drug therapy in the treatment of delirium in terminally ill patients



Cochrane Database of Systematic Reviews

- Benzodiazepines for delirium
(Lonergan, Luxenberg, Sastre 2009)
- To determine the effectiveness and incidence of adverse effects of benzodiazepines in the treatment of non-alcohol withdrawal related delirium.
- Only one trial satisfying the selection criteria
- No adequately controlled trials could be found to support the use of benzodiazepines in the treatment of non-alcohol withdrawal related delirium among hospitalised patients, and at this time benzodiazepines cannot be recommended for the control of this condition.



Cochrane Systematic Reviews

- Palliative pharmacological sedation for terminally ill adults

(Beller, van Driel et al, 2015)

- To assess the evidence for benefit of palliative pharmacological sedation on quality of life, survival, and specific refractory symptoms in terminally ill adults during last few days of life
 - RCTs, quasi-RCTs, non-RCTs and observational studies
- 14 studies, 4167 adults, 95% cancer



- Insufficient evidence about the efficacy of palliative sedation in terms of person's quality of life or symptom control
- 5 studies showed that sedatives did not fully relieve delirium or breathlessness
- No difference in time from admission or referral to death
- Did not hasten death
 - From low quality studies



Guidelines

- ESMO 2018 (Bush, Lawlor et al, 2018)
 - Clinical assessment, diagnosis and screening
 - Management of potential reversible causes
 - Non-pharmacological interventions
 - Pharmacological interventions
- NICE, UK
- Therapeutic Guidelines, Australia



Table 7. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System^a)

Levels of evidence

- I Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
- II Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
- III Prospective cohort studies
- IV Retrospective cohort studies or case-control studies
- V Studies without control group, case reports, expert opinions

Grades of recommendation

- A Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
- B Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
- C Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, . . .), optional
- D Moderate evidence against efficacy or for adverse outcome, generally not recommended
- E Strong evidence against efficacy or for adverse outcome, never recommended

^aBy permission of the Infectious Diseases Society of America [179].

Non-pharmacological

- No research evidence (V, C)
- Hydration is not more effective than placebo in preventing delirium (II, C)



Pharmacological interventions

- No evidence based recommendations (V, C)
- Deprescribing (V, B)
- Opioid rotation (V, B)



Guideline medication

- Haloperidol or Risperidone has no demonstrable benefit mild to moderate (I, D)
- Olanzapine may offer benefit in the symptomatic management of delirium (III, C)
- Quetiapine may offer benefit in the symptomatic management of delirium (V, C)
- Methylphenidate may improve cognition in hypoactive delirium (V, C)
- Benzodiazepines are effective at providing sedation and potentially anxiolysis in the acute management of severe symptomatic distress associated with delirium (II, C)



Management

- Diagnose underlying cause
- Correction of reversible factors
- Balancing of drugs that provoke or maintain delirium
- Management of symptoms
- Goals of care



Support and education

- Relatives have access to written information pre-emptively + wider family
- Access to educational and psychological support for families
- Whole of healthcare team educational interventions



WELL, I HAVE
SOME BAD
NEWS



WE'RE AT THE END
OF THE LINE
WITH YOUR
TREATMENT



YOU MEAN
I'M CURED?



NO, I MEAN YOU
SHOULD CONSIDER
SETTLING YOUR AFFAIRS



AFFAIRS? MY
HUSBAND'S DEAD



NO. ER...
YOU'LL BE
SEEING ELVIS
SOON,



IN
MEMPHIS?



WELL, SEE
YA LATER



BYE NOW



NICE delirium guidelines pharmacological

- Atypical antipsychotics, typical antipsychotics or benzodiazepines are currently used in clinical practice to manage the symptoms of delirium but the evidence for this is limited.
- One moderate-quality study showed that typical and atypical antipsychotics were clinically and cost effective compared with placebo, but there is no evidence for benzodiazepines.
- Pharmacological agents that alter the course of delirium or control particular symptoms might be useful in treating delirium, but we need to determine whether the medication should be given routinely or for selected symptoms, and what adverse events may occur.



Therapeutic Guidelines Delirium

- <https://www.tg.org.au>



Nonpharmacological management

Delirious patients must be nursed in a setting where they can be observed at all times, as their behaviour may be unpredictable. Vital signs should be monitored closely and careful attention paid to ensuring adequate hydration, nutrition and pain relief. A calm and quiet atmosphere, frequent prompts concerning orientation, clear and precise communication, and a night-light are helpful. Delirious patients should be approached from the front, not the side, as peripheral stimuli are more likely to be misinterpreted as hostile. Staff should clearly state their identity, role (eg nurse, doctor) and the purpose of their approach each time they interact with the patient. The patient is likely to be more settled in the presence of a familiar person (eg relative or friend). Very disturbed patients may need individual care from a trained staff member.

The delirious patient must be observed at all times.

Explaining the nature of the diagnosis and the reasons for any unusual behaviours or ideas to the patient's close relatives is likely to reduce their bewilderment and distress.

If delusions or hallucinations are causing distress, or if behavioural disturbance threatens the patient's treatment or care, or is causing significant threat to others, an antipsychotic is indicated. Use:

1 haloperidol 0.5 mg orally, as a single dose



OR

1 olanzapine 2.5 mg orally, as a single dose



OR

1 risperidone 0.5 mg orally, as a single dose.



If oral administration is impossible and symptoms are severe, use:

1 haloperidol 0.5 mg IM, as a single dose



OR

1 olanzapine 2.5 mg IM, as a single dose.



Terminal agitation



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 0.5 mg 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 [[Note 7](#)] [[Note 8](#)]



OR

- 1 midazolam 2.5 mg 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.



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:

- 1 clonazepam 0.2 to 0.5 mg sublingually or subcutaneously, 12-hourly, and 0.2 to 0.5 mg 2-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 4 mg in 24 hours [\[Note 7\]](#) [\[Note 8\]](#)



OR

- 1 clonazepam 0.5 to 1 mg/24 hours by continuous subcutaneous infusion, and 0.2 to 0.5 mg sublingually or subcutaneously, 2-hourly as required. Monitor response and adjust dose as needed. Usual total maximum dose 4 mg in 24 hours [\[Note 7\]](#) [\[Note 8\]](#) [\[Note 9\]](#)



OR

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



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



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

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



OR

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



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

What it means in practice

- Evidence for the impact of environmental factors on cognitively vulnerable
- Consider clinical practices and features of environment which may increase the risk or severity of delirium, or worsen disorientation
- Minimise the medication burden wherever possible
- Educate and counsel caregivers
- Assess for delirium should first identify potentially reversible causes and attempt to treat them
- Pharmacological management of delirium is at present based on expert opinion and, on that basis, low dose haloperidol can be recommended as first line treatment.



Summary

- A significant problem
- Very little evidence to guide decision-making
- Excellent guidelines are generally consistent



On line resources

- <https://www.tg.org.au/>
- <https://www.nice.org.uk/>
- <https://www.caresearch.com.au/>



References

- Agar MR, Lawlor PG et al. Efficacy of oral risperidone, haloperidol, or placebo for symptoms of delirium among patients in palliative care. A randomised clinical trial. *JAMA Internal Medicine* 2017(1):33-42.
- Beller EM, van Driel ML et al. Palliative pharmacological sedation for terminally ill adults. *Cochrane Systematic Review*. 2015 <https://doi/10.1002/14651858.CD010206.pub2>
- Burry L, Mehta S et al. Antipsychotics for treatment of delirium in hospitalised non-ICU patients. *Cochrane Systematic Review*. 2018 <https://doi/10.1002/14651858.CD005594.pub2>
- Bush SH, Lawlor PG, Ryan K, Centeno C, Lucchesi M, Kanji S, Siddiqi N et al. Delirium in adult cancer patients: ESMO Clinical Practice Guidelines. *Annals of Oncology* 2018 29 (Supplement 4): iv143-iv165
- Bush SH, Tierney S, Lawlor PG. Clinical assessment and management of delirium in the palliative care setting. *Drugs* 2017 77(15):1623-1643.
- Candy B, Jackson K et al. Drug therapy for delirium in terminally ill adult patients. *Cochrane Systematic Review*. 2012 <https://doi.org/10.1002/14651858.CD004770.pub2>
- Cherny NI et al on behalf of the ESMO Guidelines Working Group. ESMO Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation. *Annals of Oncology* 2014, 25 (Suppl 3) iii143-iii152
- de la Cruz M, Fan J, Yennu S et al. The frequency of missed delirium in patients referred to palliative care in a comprehensive cancer center. *Support Care Cancer* 2015; 23: 2427-2433.
- Hosker C. Delirium and agitation at the end of life. *BMJ* 2016; 353: i3085 doi:10.1136/bmj. i3085
- Kehl KA. Treatment of terminal restlessness: a review of the evidence. *J Pain Palliat Care Pharmacother*. 2004;18(1):5-30.
- Lawlor PG, Bush SH. Delirium in patients with cancer: assessment, impact, mechanisms and management. *Nat Rev Clin Oncol* 2015; 12: 77-92.
- Loneragan E, Luxenberg J, Sastre AA. Benzodiazepines for delirium. *Cochrane Systematic Review* 2009 <https://doi.org/10.1002/14651858.CD006379.pub3>
- Neufeld KJ, Yue J et al. Antipsychotic medication for prevention and treatment of delirium in hospitalised adults: A systematic review and meta-analysis. *J Am Geriatr Soc* 2016; 64:705-14
- Schrijver EJ, de Graaf K et al. Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: A systematic review of current evidence. *Eur J Intern Med* 2016; 27:14-23.
- Siddiqi N, Harrison JK et al. Interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Systematic Review*. 2016 <https://doi/10.1002/14651858.CD005563.pub2>

