

THE STRANGE CASE OF DR JEKYLL AND MR HYDE: CAN WE EFFECTIVELY MANAGE SUDDEN BEHAVIOUR CHANGES IN THE DYING PATIENT?

Delirium is the most common reason for a sudden change of behaviour in a seriously ill patient.

DAVID CAMERON, MB ChB, MPraxMed, MPhil (Pall Med), FCFP (SA)

Associate Professor, Department of Family Medicine, University of Pretoria and Senior Consultant, Foundation for Professional Development

David Cameron has been honorary consultant to Sungardens Hospice since 1987. He has a special interest in medical education, clinical mentorship, promoting authentic learning and evidence-based practice in primary care.

Correspondence to: David Cameron (david.cameron@up.ac.za)

The phone rings, it's 2 am, on the line is Sr Rebecca, the nurse on night duty at the Hospice, 'Sorry to wake you, but Mr Robertson has become very restless; he is refusing to take his medication and he is trying to get out of bed. He says we are trying to kill him.' In the background I can hear the commotion. 'Let me out of here! Stop, Stop, Stop!' This is followed by other loud noises and then a glass smashes on the floor.

By now I was wide awake. What was happening? Earlier, I had seen Ted Robertson on the ward round. He is a 68-year-old retired engineer with advanced non-small cell cancer of the lung. Apart from some dyspnoea, he was comfortable and lucid. The pain from the metastatic lesions in his ribs was well controlled on 1 g paracetamol 6 hourly, a stable oral dose of 90 mg long-acting morphine and ibuprofen 600 mg every 12 hours. Apart from the usual laxatives to prevent constipation, he was only taking oxazepam 15 mg to help him sleep. I had added no new medication in the past 72 hours. I had even thought of suggesting that he could be discharged. What had brought about this unexpected change? It was no use speculating. So many things could be responsible for Ted's sudden confusion. I needed to go and help to sort the out the problem before he injures himself or one of the nursing staff.*

In 1886 Robert Louis Stevenson published a short novel, *The Strange Case of Dr Jekyll and Mr Hyde*, in which the respectable Dr Henry Jekyll is transformed into an aggressive evil monster, Mr Edward Hyde. The change was caused by Jekyll drinking a self-concocted potion.¹

As I drove to the hospice I thought of possible reasons causing Ted Robertson to undergo such a change. Was it his condition or was it something we were giving him?

Ted's changed behaviour is a common clinical problem facing those caring for patients with advanced medical conditions. Such patients may suddenly appear anxious, tearful or depressed. They may become agitated and demanding or respond in an irrational way. They may even become restless and aggressive. Initially it may be difficult to understand what is causing the problem. Such patients may even be labelled 'difficult or uncooperative'. In this situation it is important to consider delirium, as this is the most common reason for a sudden change of behaviour in a seriously ill patient.

Definition

Delirium is an altered state of mind characterised by confusion of recent onset and variable severity. It is a collective term for the various causes of acute confusion rather than a specific diagnosis.²

*Although Ted Robertson is a fictitious patient created out of many similar encounters, the above scenario will be familiar to any health professional caring for dying patients.

There are four key features that need to be present to make the diagnosis of delirium:³

- **A changed level of consciousness.** The patient has difficulty focusing, sustaining or shifting attention. The patient may be agitated and restless or may be abnormally drowsy. Disorientation may be present but is not an essential feature in making the diagnosis.
- **A disturbance of the process of thinking (cognition).** The patient has short-term memory loss, disorganised thinking, speaking and problem solving. (Pre-existing dementia needs to be excluded.) Hallucinations and delusions may be present but are not essential features in making the diagnosis of delirium.
- The above changes are of **recent onset** and may **fluctuate** over a period of hours.
- There is definite clinical evidence that the disturbance is caused by the abnormal physiology of an underlying **general medical condition**.

Delirium may present in different clinical forms.⁴ It is helpful to recognise delirium early before a patient becomes overtly aggressive. There are three clinical sub-types of delirium:

- **Hyperactive delirium.** The patient is restless, irritable, agitated and may become aggressive or inappropriate in their behaviour.
- **Hypoactive delirium.** The patient is inactive, disinterested and incoherent.
- **Mixed delirium.** The patient fluctuates between hypo- and hyperactive delirium. This is the most common sub-type (>50%).

Risk factors that predispose to delirium include advanced age, poor vision, deafness, existing cognitive impairment/dementia, liver, bone and brain metastases, head trauma, dehydration, infection, the use of benzodiazepines (daily dose equivalent (DDE) >2 mg lorazepam), opioids (DDE >90 mg morphine) and cortisone (DDE >15 mg dexamethasone).⁴⁻⁸

There are thus several possible causes of Ted's delirium. Was it the 'concoction' of drugs I was giving him? Did he have cerebral metastases? Was he dehydrated or was there some other metabolic abnormality such as hypercalcaemia? Had he developed a severe infection?

Delirium is common in a palliative care setting. About 30 - 40% of admissions are due to sudden confusion and more than 80% of advanced cancer patients will develop some degree of delirium during the terminal phase of their illness.^{4,5,7,8}

Recognising delirium

The Confusion Assessment Method (CAM) is a simple way of screening for delirium.⁶ A helpful screening tool for delirium based on the CAM has been developed by the Institute for Palliative Medicine at San Diego Hospice, California. It asks four questions in a standardised format:

- Is there sudden onset of confusion (hours - days)?
- Does the patient have difficulty focusing attention?
- Is the patient's thinking disorganised or incoherent?
- Overall how would you rate this patient's level of consciousness?

Table I. The Confusion Assessment Guide modified by the Institute for Palliative Medicine, San Diego Hospice, California (used with permission)

| DELIRIUM SCREENING GUIDELINE | |
|---|--|
| Confusion Assessment Method (CAM) | |
| A diagnosis of delirium is suggested if questions 1 & 2 are YES with either YES from 3 OR anything other than alert in 4. | |
| 1. ACUTE ONSET Is there sudden onset of confusion (hrs-days)? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain | 3. DISORGANISED THINKING Is the patient's thinking disorganised or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, unpredictable switching from subject to subject? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain |
| 2. INATTENTION Does the patient have difficulty focusing attention, for example, easily distracted, or has difficulty keeping track of what is being said? <input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain | 4. ALTERED LEVEL OF CONSCIOUSNESS Overall how would you rate this patient's level of consciousness? <input type="checkbox"/> Alert <input type="checkbox"/> Vigilant (hyper-alert, overly sensitive to stimuli) <input type="checkbox"/> Lethargic (drowsy, easily aroused) <input type="checkbox"/> Stupor (difficult to arouse) <input type="checkbox"/> Coma (unarousable) <input type="checkbox"/> Uncertain |

Table II. Conditions that need to be differentiated from delirium

| | Delirium | Depression | Dementia | Psychosis |
|-----------|-----------------------|---|--|----------------|
| Alertness | Abnormal | Normal | Normal | Normal |
| Onset | Sudden and recent | Gradual | Gradual | Gradual |
| Course | Fluctuates frequently | May vary slightly and be worse in morning | Progressive, may be slightly worse in evening ('sundowning') | No fluctuation |

These questions can be printed on a card and used as part of the routine assessment of all patients admitted to a ward or hospice (see Table I).

The CAM's sensitivity is 94 - 100% and its specificity is 90 - 95%.⁶

Differential diagnosis

Delirium should be differentiated from depression, dementia and major psychotic illness (see Table II).⁴ The key features of delirium are the change in alertness, recent onset and fluctuating course.

Elderly patients with dementia can develop delirium on top of their dementia. Where possible try to establish from the main caregiver what the person's baseline function was previously and how they appear in comparison during this examination.

After a careful examination of Ted, I could find no clinical evidence of severe infection or dehydration. His vital signs were normal. He denied any headache and had no obvious neurological signs of cerebral metastases. There was no history of previous alcohol abuse. I estimated his prognosis as weeks rather than months. I therefore decided against arranging a brain scan. As he already had bone metastases, neurosurgery

was contraindicated and radiotherapy would offer no benefit.⁹ I assumed that the most likely reversible cause would be his medication. I was now faced with a dilemma. How could I reduce his analgesia without aggravating his pain? Considering that a build-up of morphine metabolites (especially M-3-G) can cause neurotoxicity,⁴ I decided to change the morphine to a fentanyl transdermal patch (50 µ/hr).

Management of delirium

Correct reversible factors where possible

The underlying mechanism for delirium is thought to be an imbalance of neurotransmitters (a deficiency of acetylcholine and an excess of dopamine). The causes of this imbalance are multi-factorial and most delirious patients will have three or more contributing causes.^{4,5,7}

For those who like mnemonics: DIMTOP⁹

- Drugs, e.g. opioids, anticholinergics, benzodiazepines, regular drugs omitted (especially alcohol)
- Infection, e.g. UTI, chest, meningitis or wound
- Metabolic, e.g. hypo/hypernatraemia, hypercalcaemia
- Trauma, e.g. hypoperfusion, fat embolism (fractures)
- Oxygen lack/hypercarbia

- Pressure (intracranial), pain, poisons, psychiatric.

Reversibility

While some studies have shown that up to 50% of episodes of delirium may be reversible, reversibility is dependent on a number of interrelated factors.^{7,8} The prognosis is poorer in the presence of advanced age, severe cognitive impairment and poor vital organ function. There is no easy way of predicting reversibility.

It remains prudent to treat all cases of delirium as potentially reversible while remaining sensitive to the needs of patients that have actively entered the final 24 - 48 hours of life, where the balance between minimising risk factors for delirium versus achieving optimal levels of comfort requires careful consideration.⁸

Special investigations

Delirium can often be adequately assessed and managed without any special investigations. Most reversible causes are clinically apparent. The benefit of any intervention needs to be weighed up against the distress that it will cause to a dying patient. In selected cases where the prognosis is still good and resources are available, appropriate investigations may be helpful. It is, however, inappropriate to blindly screen for every possible abnormality 'just in case'. Empirical treatment for common causes is ethically appropriate, effective and humane.

Having already scrapped the idea of a brain scan, I also decided not to check for hypercalcaemia. I felt we needed to stabilise his condition first and come back to this later, if necessary.

Delirium

I helped Ted to drink a glass of juice and encouraged the staff to give small amounts of fluids every 2 hours.

Box 1. Indications for more active management of patients with suspected brain metastases¹⁰

- If the patient's general performance status is good and if the patient is keen on further treatment, a brain scan can be arranged.
- Solitary, accessible metastases may benefit from surgery. (NB: Less than a third of cerebral metastases are single.)
- Whole-brain irradiation could be considered for multiple metastases for the relief of severe headache. Whole-brain irradiation does not improve survival. It should not be considered if there are metastases in other organs and if the patient's performance status is poor.
- Chemotherapy could be considered for certain lymphomas, small-cell lung cancer and germ-cell tumours.

Consider disease-specific palliative therapy^{4,5,7,8,10}

- Where appropriate rehydrate patients.
- Review all medications, stop or reduce the dose of all non-essential drugs and recheck for previous excessive alcohol or illicit drug use.
- An empirical trial of steroids for suspected brain metastases.
- The decision to arrange a scan will depend on the patient's general condition (see Box 1).¹⁰
- Most infections should be appropriately treated unless the patient has signs of impending death (within 24 - 48 hours).
- Consider using rehydration and bisphosphonates for hypercalcaemia.

Explanation to patient and family^{11,12}

Ted's wife had arrived at the hospice at the same time as I had. I allowed her to remain with him so that she could help to calm him down and also so that I could explain my thinking as we went along. She agreed to stay with him for the night.

Institute non-pharmacological interventions⁴

- Calmly reassure the delirious patient that he/she is safe and will be helped to feel less distressed.
- Regularly orientate him/her for time and place.
- Arrange for a family member to be present for as much time as possible. Limit the number of visitors.
- Identify and maintain nursing staff consistency where possible.
- Place familiar personal objects or photos in the room.

Table III. Dosage of haloperidol for mild delirium without agitation

| Drug | Dose | Frequency | Comment |
|------------------------|---------------|---|---|
| Haloperidol (Serenace) | 0.5 - 2 mg PO | Every hour prn x 3 (Notify dr if 3 doses are not effective. This allows a review of the situation so that the dose can be adjusted if needed) | Usual effective dose is 0.5 - 2 mg/day Maintenance: previous day's total used given as a single daily dose and same prn dose for breakthrough symptoms NB: Medication is not always needed but as agitation may occur unexpectedly in a new environment consider its use for a short period |

Table IV. Dosage of haloperidol for delirium with mild agitation but no aggression

| Drug | Dose | Frequency | Comment |
|------------------------|-------------|---|---|
| Haloperidol (Serenace) | 1 - 2 mg SC | Every 30 min prn x 3 (Notify dr if 3 doses are not effective) | Usual effective dose is 6 - 12mg/day Maximum 100 mg/day Maintenance: previous day's total used given as a single or divided dose plus the same prn dose for breakthrough symptoms |

Table V. Dosage of haloperidol for delirium with agitation, restlessness and aggression

| Drug | Dose | Frequency | Comment |
|------------------------|-----------------------|---|--|
| Haloperidol (Serenace) | 3 - 5 mg SC, IM or IV | Every 30 min prn x 3 (Notify dr if 3 doses are not effective) | Up to 1 200 mg IV per day has been safely used. Occasionally prolongation of the Q-T interval may occur An aggressive delirious patient may be dangerous and calming the patient must be an urgent priority for all staff (see second-line drugs) |

Table VI. Dosage of chlorpromazine as an alternative first-line drug if haloperidol is not available

| Drug | Dose | Frequency | Comment |
|----------------------------|---------------------------|--|---|
| Chlorpromazine (Largactil) | 12.5 - 50 mg PO, IM or IV | Every 2 - 4 hours prn x 3 (Notify dr if 3 doses are not effective) | More sedating than haloperidol May cause hypotension |

Table VII. Additional second-line drugs when sedation is needed

| Drug | Dose | Frequency | Comment |
|--------------------------|--|---|--|
| Lorazepam (Ativan) | 1 - 2 mg PO, SL, IV | Every hour prn x 3 (Notify dr if 3 doses are not effective) | |
| Midazolam (Dormicum) | 3 - 5 mg SC or IV 1 mg continuous SC infusion | Per hour | For rapid sedation Titrate the dose according to effect. Max 10 mg/hour |
| Promethazine (Phenergan) | 50 mg PO, IM, IV | 8 hourly | Very sedating but helpful as an adjunct to other drugs |

- Encourage walking, or if bedridden, range of motion exercises.
- Maintain appropriate lighting at night.
- Play soothing music.
- Provide gentle back massage and a glass of warm milk rather than a sleeping tablet.
- Reduce noise as far as possible.
- Optimise vision and hearing (check that the hearing aid is working).

NB: Physical restraints are **not** necessary. They may aggravate the situation and cause injury. Effective calming and, if necessary, sedation is possible by means of appropriate medication at effective dosages.

Prescribe appropriate first-line treatment¹²

Haloperidol is the initial drug of choice. It calms the agitated patient without sedating

Box 2. The Clock Drawing Test

The CAM is useful for screening for delirium but it does not measure the severity of the delirium nor does it assess the degree of change in response to treatment or to the worsening of the patient's condition. In severely ill patients it may be unduly burdensome to carry out time-consuming assessments of mental state. However, in some patients it may be helpful to objectively measure improvement or deterioration.

A test that is relatively simple and quick to perform is the Clock Drawing Test (CDT).¹² First, the patient is asked to draw a clock with all the numbers on it. Then the patient is asked to put the hands on the clock to make it read 2:45. The instructions can be repeated but no further directions are given. The drawing is scored according to the correct sequence and spacing of the numbers and the correct placement of the hands. The CDT assesses comprehension, visuo-spatial abilities, concentration, numerical knowledge, visual memory and executive function. It also provides a visual record of changes in cognitive ability.

them (see Tables III - VI). The dose can be safely titrated until the desired effect is achieved.

Consider additional second-line treatment where sedation is needed

If a patient is restless and aggressive, and sedation is needed, benzodiazepines are useful (Table VII). However, they should not be used alone as first-line treatment as they may result in increasing confusion, disinhibition and falls. They are particularly useful in patients with delirium due to alcohol withdrawal.

I gave Ted 5 mg haloperidol and 5 mg midazolam intravenously and then Sr Rebecca set up a syringe driver with 10 mg haloperidol and 15 mg midazolam to run over 12 hours. (In settings where

syringe drivers are not available, one can give suitable medication by intermittent subcutaneous injection.)

Review assessment and management

Care and routine observations should be non-burdensome. While the CAM is useful for detecting delirium, it does not assess the response to treatment. The Clock Drawing Test can be helpful to assess progress or deterioration (see Box 2).¹³

The dose of the drugs being used to control the delirium can be reduced as soon as the patient is no longer agitated. Where there is refractory agitated delirium, proportionate sedation may need to be continued until the patient dies.⁴

Involve the whole interdisciplinary team

Managing a delirious patient requires a well-functioning team. Clear notes setting out the goals of care, progress and reasons for new decisions will help to keep everyone up to date and working towards the same end. The family needs to be supported and to be kept involved in the decision making as much as possible.

Referral to an appropriate service or a more experienced clinician

Delirium presents many complex clinical and ethical challenges. If the degree of uncertainty about the diagnosis and management is interfering with proper care, the advice of a more experienced palliative care clinician needs to be sought.

Both Ted and I slept well for the rest of the night. Ted was gradually weaned off sedation and remained pain free and lucid until he died peacefully 3 weeks later.

Conclusion

For many years it has been good clinical practice to treat pain by careful assessment and appropriately rapid increased doses of effective analgesia. Surely the time has come for us to take the same approach to delirium?

References available at www.cmej.org.za

IN A NUTSHELL

- Delirium is the most common reason for a sudden change of behaviour in a seriously ill patient.
- It is an altered state of mind characterised by confusion of recent onset and variable severity.
- Risk factors that predispose to delirium include advanced age and pre-existing dementia; the use of benzodiazepines, opioids and cortisone; liver, bone and brain metastases; dehydration; infection; head trauma, poor vision and deafness.
- The Confusion Assessment Method (CAM) is a simple way of screening for delirium.
- The key features of delirium that help to differentiate it from dementia, depression and psychosis are the change in alertness, recent onset and fluctuating course.
- The underlying mechanism for delirium is thought to be an imbalance of neurotransmitters (a deficiency of acetylcholine and an excess of dopamine).
- A reversible cause may be found in about 50% of cases of delirium.
- Empirical treatment for common causes is ethically appropriate, effective and humane.
- Physical restraints are inappropriate, dangerous and inhumane. Use appropriate medication in effective doses.
- Haloperidol is the drug of first choice and can safely be given in a wide variety of doses. A benzodiazepam can be added if sedation is needed.
- The Clock Drawing Test is a simple and rapid way of assessing progress or deterioration.