Randomised double blind placebo controlled phase II trial of melatonin for prevention of delirium in inpatients with advanced cancer

Agar M, Lawlor P, Caplan G, Ely EW, Lam L, de Souza P, Nikles J, McCaffrey N, Bush S, Draper B, Sanderson C, Luckett T, Rowett D, Philip J, Chye R, Le B, Martin P, Clark K, Bellemore F, Byfieldt N, Chambers J, Dowd A, McCarthy G, Petrie N, West P, Wilcock J, Currow D.

Background

- Delirium is highly prevalent during hospital admission for advanced cancer
  - Reported incidence of new episodes during admission 20 -45%
  - Prevalence on admission 28-48%
- Multiple risk factors are associated with delirium occurrence
- On average, a person with cancer and delirium will have at least 3 contributing factors for delirium at any one time

Hosie 2013, Lawlor 2000

Delirium impact

- Increased mortality
  - Risk extends to discharge even if delirium is treated
- Declining functioning and cognition
- Risk of needing institutional care
- Health system costs – longer length of stay and more complex care needs
- Patient distress during and on recollection of experience
- Distressing for family and health professionals witnessing delirium

Metitieri 2000, McCusker 2002, Marcantonio 2000, Breitbart 2002

CURRENT STRATEGIES FOR DELIRIUM PREVENTION

	Pharmacological	Non-pharmacological
Intervention	Anticholinesterases, atypical antipsychotics (risperidone), typical antipsychotics (haloperidol)	Proactive geriatric consultation, nursing interventions, and multicomponent interventions (e.g. Hospital Elder Life Programme [HELP]) targeting risk factors - cognition/orientation, mobility, hearing, vision, sleep-wake cycle, hydration
Setting/pop	Post-operative	Medical, surgical, geriatric
Efficacy	No agent shows definite promise Risperidone – modest incidence reduction (Prakanrattana, 2007) Haloperidol – reduced severity (Schrader, 2008)	Multicomponent intervention meta-analysis - 11 studies OR 0.47 (95%CI, 0.38-0.58); 4 RCTs OR 0.56 (95%CI, 0.42-0.76) (Hshieh, 2015)
Limitations	Underpowered, incomplete follow-up with potential for missed delirium episodes	Blinding difficult, small sample sizes

Issues with multicomponent interventions

- Require large-scale administrative and system changes

- Ongoing clinician engagement and education

- Upfront additional costs for intervention per patient (approx. $US600/patient)

- Cognitive and exercise components may not
  - be feasible for patients with advanced cancer with fatigue and functional decline
  - be sustainable as cancer progresses, which is the period which corresponds to increasing delirium risk

Rizzo 2001, Gagnon 2012

How might melatonin work?

- The underlying hypothesis is that circadian disturbance initiates an at-risk prodrome state that progresses to delirium when the patient is exposed to other medical insults

- Supplemental exogenous melatonin
  - promotes maintenance or resetting of the natural 24-hour circadian rhythm of the sleep-wake cycle, and/or
  - directly prevents delirium by decreasing the breakdown of both tryptophan and serotonin by inducing a negative feedback cascade

CURRENT EVIDENCE FOR MELATONIN IN DELIRIUM PREVENTION

Study	Population	Intervention	Comparator	Delirium incidence
Al Aama 2010	Medical inpatients >65 (n=145)	0.5mg for 14 days at night or until discharge	placebo	(12% vs 31%, p=0.014) (measured using CAM)
Sultan 2010	Inpatients >65 undergoing hip arthroplasty under spinal analgesia (n=300)	90 min pre-op and then at sleep time on day of operation - 3 interv arms: 1. 5mg melatonin 2. 7.5mg midazolam 3. 100mcg clonidine	no sedation	9.43% vs 32.65% (p=not cited)
De Rooij 2014	Hip fracture (n=452)	3mg for five days from 24 hours of admission	placebo	Reduced duration of delirium (>2 days 25% melatonin vs 54% in control, p=0.02)
Hatta 2014/ Stany 2015	65-89 year olds with serious medical illness in ICU or medical ward (n=67)	Ramelteon (melatonin receptor agonist) 8mg every night for 7 days	placebo	Lower risk of delirium (3% vs 32%, p=0.003; RR 0.09, 95% CI 0.01-0.69)

Safety

- Melatonin has a favourable adverse effect profile with few serious side effects reported

- The commonly reported adverse events are headaches, dizziness, nausea, and drowsiness, usually transient and mild

- In acutely ill medical/ICU patients minimal side effects seen:

  – Al Aama study, two participants out of 145 in melatonin arm had side effects (vivid dreams, floating sensation [resolved within 24 hrs]) which could be attributable to delirium event

  – Hatta 2014 had no adverse events attributable to Ramelteon (which is 3- 6 fold more potent agonist compared to melatonin)

Background – key messages

- Delirium is highly prevalent, with significant impacts (morbidity, mortality, cost)

- People with advanced cancer are subject to multiple insults with high propensity to cause delirium

- Prevention should be a priority because once delirium occurs even if treated/reversed poor outcomes still occur

Background – key messages

- Prevention has focused on non-pharmacological strategies
  - The most at-risk advanced cancer patient cannot participate in exercise and cognitive components due to fatigue or functional decline

- Clinical and laboratory data identify a role for circadian rhythm abnormalities in delirium pathophysiology

- Three RCTs have demonstrated support for melatonin as a safe preventative agent, and one study of a melatonin agonist

Prospective, randomised, parallel-group, multi-centre Phase II trial of oral melatonin prolonged release 2mg versus placebo taken daily during inpatient oncology or palliative care admission
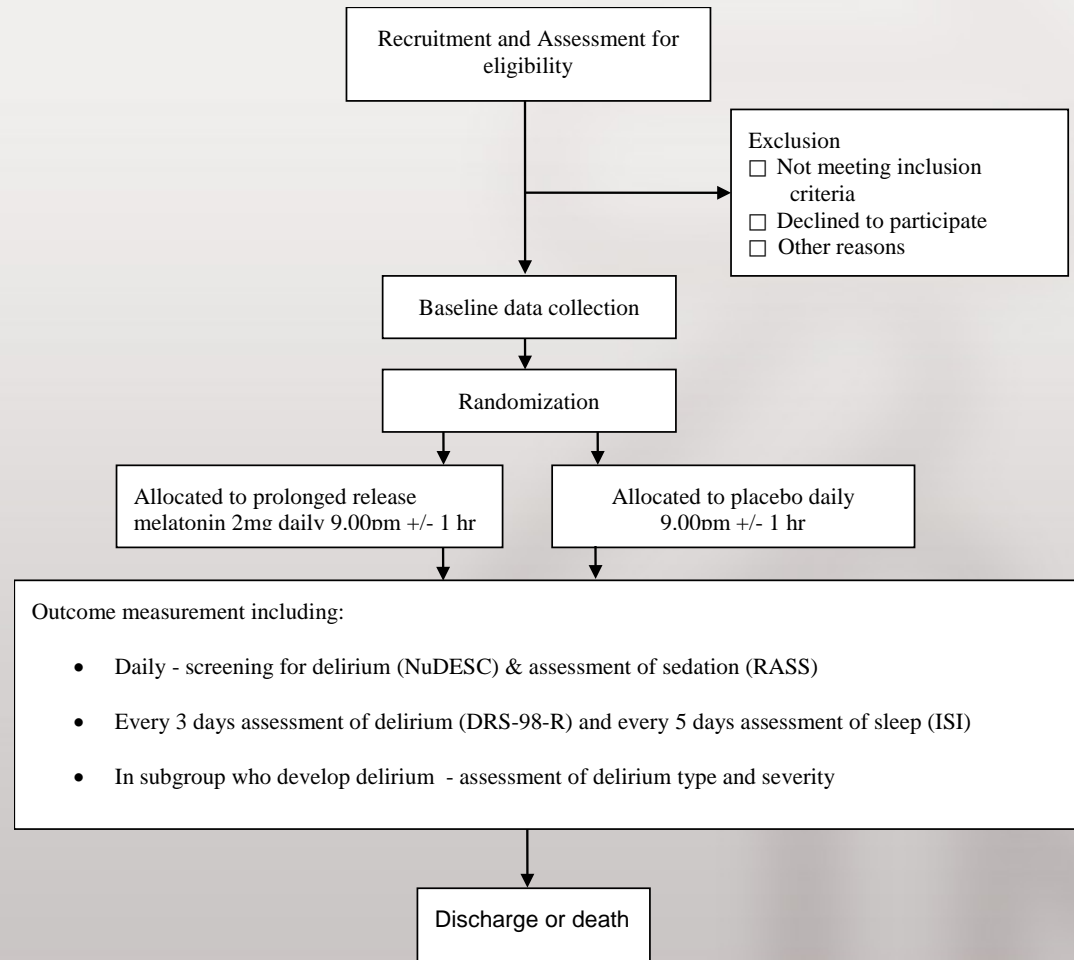
Aims

- Primary

  - To test the feasibility of conducting a phase III RCT to evaluate the effect of oral prolonged-release melatonin in preventing delirium in people with advanced cancer during hospital admission.

- Secondary aims

  - To obtain preliminary data on efficacy

  - To test tolerability of melatonin in advanced cancer population

Study flow diagram

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        ┌─────────────────────────────────┐
        │ Recruitment and Assessment for  │
        │           eligibility           │
        └─────────────────────────────────┘
                      │
                      │         ┌──────────────────────────────┐
                      ├────────→│ Exclusion                    │
                      │         │ ☐ Not meeting inclusion      │
                      │         │    criteria                  │
                      │         │ ☐ Declined to participate    │
                      │         │ ☐ Other reasons              │
                      │         └──────────────────────────────┘
                      ↓
        ┌─────────────────────────────────┐
        │     Baseline data collection    │
        └─────────────────────────────────┘
                      │
                      ↓
        ┌─────────────────────────────────┐
        │          Randomization          │
        └─────────────────────────────────┘
              │                   │
              ↓                   ↓
   ┌────────────────────┐  ┌────────────────────┐
   │ Allocated to       │  │ Allocated to       │
   │ prolonged release  │  │ placebo daily      │
   │ melatonin 2mg daily│  │ 9.00pm +/- 1 hr    │
   │ 9.00pm +/- 1 hr    │  │                    │
   └────────────────────┘  └────────────────────┘
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Outcome measurement including:

- Daily - screening for delirium (NuDESC) & assessment of sedation (RASS)

- Every 3 days assessment of delirium (DRS-98-R) and every 5 days assessment of sleep (ISI)

- In subgroup who develop delirium - assessment of delirium type and severity

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        ┌─────────────────────────────────┐
        │        Discharge or death       │
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Inclusion criteria – very broad

- Age $\geq$ 18 years

- English speaking

- Informed consent

- Capable of completing assessments and complying with the study procedures

- Admission to an acute or subacute inpatient palliative care or oncology facility

- Advanced cancer

Exclusion criteria – very minimal

- Current delirium

- Australian Karnofsky Performance Status (AKPS)$\leq$ 30

- Current melatonin or agomelatine use

- Moderate or severe dementia

- Contraindication to melatonin
  - Allergy
  - Seizure in last one month
  - Concomitant cimetidine use
  - On warfarin with markedly nontherapeutic INR
  - Active alcohol abuse
  - Severe hepatic impairment

Primary outcome (feasibility)

- Percentage of randomized patients who progress to complete study intervention (until delirium, discharge or death)

- ≥60% threshold for feasibility of Phase III

Secondary outcomes - efficacy

- Incidence of delirium
  - Delirium Rating Scale-Revised-98 (DRS-R-98) total score ≥17.75 and
  - Diagnostic and Statistical Manual of Mental Disorders Version IV Text Revised (DSM-IV-TR)
- Time to delirium onset
- Delirium symptom profile, subtype and severity
- Sleep quality (ISI)

Secondary outcomes - feasibility

- Percentage screened participants eligible

- Percentage eligible patients randomized

- Percentage completing delirium screening (primary outcome in Phase III)
  - Feasibility defined as 95% participants with complete data on DRS-R-98 and NuDESC

Secondary outcomes - toxicity

- National Cancer Institute Common terminology criteria for adverse events (CTCAE)

Randomisation and blinding

- Randomisation via online software by central registry using blocks of 6

- Patients, clinicians and trials nurses blinded

- Study drug re-packaged with study IDs by central pharmacy and dispensed in order at each site

Statistics

- Sample size of 30 considered sufficient to meet aims related to feasibility
- Analyses – descriptive only

Sample characteristics (N=30)

Patients' Characteristics	Melatonin (n=14)	Placebo (n=16)*	Results
Age			
Mean (s.d.)	73.0 (11.3)	72.7 (10.5)	Mann-Whitney U p=0.98
Median (IQR)	72.0 (15.0)	73.0 (11.0)	
Sex male	9 (64.3%)	10 (62.5%)	Fisher Exact p=1.00
Language English	14 (100%)	15 (93.7%)	Fisher Exact p=1.00
Has a carer	8 (57.1%)	8 (50%)	Fisher Exact p=0.73
Cancer type**			
Prostate	4 (28.5%)	3 (18.7%)	Fisher Exact p=0.67
Lung	4 (28.5%)	2 (12.5%)	Fisher Exact p=0.37
Hematological	3 (21.4%)	1 (6.2%)	Fisher Exact p=0.30
Other urological	1 (7.1%)	2 (12.5%)	Fisher Exact p=1.00
Head and neck, pancreas, colorectal	1 (7.1%)	1 (6.2%)	Fisher Exact p=1.00
Breast, gynaecological, other	0	2 (12.5%)	Fisher Exact p=0.49
Skin	0	1 (6.2%)	
CNS	1 (7.1%)	0	Fisher Exact p=1.00
AKPS			
Mean (s.d.)	60.7 (8.3)	62.5 (11.8)	Mann-Whitney U p=0.84
Median (IQR)	60.0 (20.0)	60.0 (20.0)	
ISI			
Mean (s.d.)	7.4 (6.0)	6.1 (6.6)	Mann-Whitney U p=0.40
Median (IQR)	5.5 (9.0)	5.0 (10.0)	
RASS			
Median (IQR)	0 (0)	0 (0)	NA
CMI			
Mean (s.d)	9.1 (2.3)	7.5 (3.6)	Mann-Whitney U p=0.60
Median (IQR)	9.5 (4.0)	8.5 (6.0)	
Delirium risk factors			
Age 80+ years	6 (42.9%)	4 (25.0%)	Fisher Exact p=0.44
SBT >4	6 (42.9%)	6 (37.5%)	Fisher Exact p=1.00
Infection	0	1 (6.2%)	Fisher Exact p=1.00
Neoplasm (intracranial)	1 (7.1%)	0	Fisher Exact p=0.47
Neoplasm (systemic)	12 (85.7%)	11 (68.7%)	Fisher Exact p=0.40
Restraint	0	0	NA
Cannot access aids to hearing/sight	0	1 (6.2%)	Fisher Exact p=1.00
Indwelling catheter	1 (7.1%)	1 (6.2%)	Fisher Exact p=1.00

* One patient withdrew after the baseline data collection before starting the day 1 assessment; ** some patients were diagnosed with more than one cancer type. AKPS=Australian Karnofsky Performance Status; CMI=Charlson Comorbidity Index; ISI Insomnia Severity Index; NA=not applicable; RASS Richmond Agitation Sedation Scale; SBT Short Blessed Test

Results – primary outcome

- 20/30 (67%) patients randomised remained on trial until discharge, death or delirium
  - >60% indicative of Phase III feasibility
- Median 6.5 days on trial (IQR 3.25-18.75)

Results – secondary outcomes (efficacy)

- Delirium incidence
  - Melatonin group 1/14 (7%)
  - Placebo group 4/16 (25%)
- Delirium events too few to compare time to onset, subtypes and severity
- Too few patients with follow-up data on sleep (ISI) and sedation (RASS) to enable meaningful analysis

Results – secondary outcomes (feasibility)

- Percentage screened eligible = 91/282 (33%)
  - percentage eligible varied between sites
  - Most common exclusions AKPS<30, delirium, NESB
- Percentage eligible randomised = 30/91 (33%)
- Percentage with complete delirium screening data
  - DRS-R-98 78% days 1-7 + then 68% thereafter
    - 50% weekends, 90% weekdays (p=0.015)
  - NuDESC 78% days 1-7 + then 73% thereafter
  - < 95% threshold for feasibility

Results – secondary outcomes (toxicity)

- 6 serious adverse events (SAEs) (NCICTC grade 3+)
- 4 SAEs in Melatonin group (two in same patient)
  - anaemia, dyspnoea, pain and death
- All were rated 'unrelated' or 'unlikely to be related' to intervention

Learnings - eligibility

- Phase III may benefit from site profiling
- Formulation could not be taken via PEG
- 14 patients excluded for unanticipated reasons
  - vomiting
  - preparing for surgery
  - awaiting transfer
  - admission expected to be short and/or not for palliative care
  - anxiety

Learnings - recruitment

- 61/90 (68%) eligible patients refused
- Preventative nature of intervention may pose new challenges for PaCCSC recruitment:
  - patients may not have considered risk of delirium or realise how serious and unpleasant it is
  - patients may feel they have enough to worry about with current conditions

Trial nurse perspective (Sacred Heart)

- Facilitators
  - Easy-to-follow protocol
  - Patients keen to contribute, appreciated daily interaction
  - Routine NuDESC Delirium Assessment at Sacred Heart an advantage
  - Ward staff engaged
- Barriers
  - Daily assessments – repetitive, sometimes burdensome
  - Further training of clinical staff in delirium assessments would be beneficial

Conclusions

- Feasibility of Phase III
  - Randomisation, retention and blinding demonstrated feasible
  - Recruitment and daily delirium screening will need substantial resourcing and resourcefulness
  - Nurse feedback has informed improvements to CRFs
- Efficacy in preventing delirium
  - Sufficient promise for further testing at Phase III
  - Pilot not powered to inform practice

Acknowledgements – site staff

- Barwon Health (VIC) – Dr Peter Martin, Anna Dowd

- Braeside (NSW) – Julie Wilcock, Nichole Petrie

- Newcastle Calvary Mater (NSW) – Prof Katy Clark, Naomi Byfieldt

- Royal Melbourne (VIC) – Dr Brian Le, Gillian McCarthy

- Sacred Heart St Vincent's (NSW) – A/Prof Richard Chye, Penny West, Joanne Chambers, Frances Bellemore

Acknowledgements - PaCCSC

- Linda Devilee, National Manager
- Belinda Fazekas, National Project Officer
- Louise Fazekas-Giles, Administration Officer

Additional slides

Role of melatonin in delirium pathophysiology

- Complex interactions between systems implicated in delirium (dopamine, GABA, cacetylcholine and hypothalamic-pituitary-adrenal axis); and circadian system

- Chemical and inflammatory processes in delirium may disrupt suprachiasmatic nucleus production of melatonin

- Delirium manifestations suggest disturbed circadian rhythm integrity
  - (sleep wake symptoms, activity levels altered for what is appropriate for time of day, vivid dreams)

- Low melatonin (often lacking circadian rhythm changes) and tryptophan levels have been seen in delirium

- Melatonin regulation is altered by psychoactive medications commonly used in palliative care/Cancer.
  - Opioids increase melatonin secretion, benzodiazepines may impair light induced phase shifts of circadian rhythms and corticosteroids have a suppressive effect

Flacker 1999, Fitzgerald 2013

Delirium manifestations which suggest circadian system integrity disturbance

- 75-100% of cancer patients with delirium have sleep – wake cycle disturbance
  - Delirious patients take longer to fall to sleep, sleep for shorter intervals and get less sleep at night as a whole
- Attention (a primary cognitive deficit in delirium) acts as an entrainment signal to the circadian timing system
- Loss of mediation of activity level appropriate for time of day

Circadian rhythm disturbance in delirium

- Inflammatory processes in delirium may disrupt suprachiasmatic nucleus signalling

- Changed hepatic enzyme activity and oral intake may stimulate enterochromaffin cells to produce melatonin and raise levels at wrong time.

- Tryptophan deficiency occurs postoperatively and in ICU settings leading to serotonin and melatonin deficiency

- Psychoactive medications alter melatonin regulation
  - Opioids increase melatonin secretion, benzodiazepines impair light phase shifts in circadian rhythm, corticosteroids have suppressive effect

Delirium Rating Scale – Revised – 98 (DRS-R-98) [1]

DELIRIUM RATING SCALE-R-98 (DRS-R-98)

This is a revision of the Delirium Rating Scale (Trzepacz et al. 1988). It is used for initial assessment and repeated measurements of delirium symptom severity. The sum of the 13 item scores provides a severity score. All available sources of information are used to rate the items (nurses, family, chart) in addition to examination of the patient. For serial repeated ratings of delirium severity, reasonable time frames should be chosen between ratings to document meaningful changes because delirium symptom severity can fluctuate without interventions.

DRS-R-98 SEVERITY SCALE

1. Sleep-wake cycle disturbance
Rate sleep-wake pattern using all sources of information, including from family, caregivers, nurses' reports, and patient. Try to distinguish sleep from resting with eyes closed.

0. Not present
1. Mild sleep continuity disturbance at night or occasional drowsiness during the day
2. Moderate disorganization of sleep-wake cycle (e.g., falling asleep during conversations, napping during the day or several brief awakenings during the night with confusion/behavioral changes or very little nighttime sleep)
3. Severe disruption of sleep-wake cycle (e.g., day-night reversal of sleep-wake cycle or severe circadian fragmentation with multiple periods of sleep and wakefulness or severe sleeplessness.)

2. Perceptual disturbances and hallucinations
Illusions and hallucinations can be of any sensory modality. Misperceptions are "simple" if they are uncomplicated, such as a sound, noise, color, spot, or flashes and "complex" if they are multidimensional, such as voices, music, people, animals, or scenes. Rate if reported by patient or caregiver, or inferred by observation.

0. Not present
1. Mild perceptual disturbances (e.g., feelings of derealization or depersonalization; or patient may not be able to discriminate dreams from reality)
2. Illusions present
3. Hallucinations present

3. Delusions
Delusions can be of any type, but are most often persecutory. Rate if reported by patient, family or caregiver. Rate as delusional if ideas are unlikely to be true yet are believed by the patient who cannot be dissuaded by logic. Delusional ideas cannot be explained otherwise by the patient's usual cultural or religious background.

0. Not present
1. Mildly suspicious, hypervigilant, or preoccupied
2. Unusual or overvalued ideation that does not reach delusional proportions or could be plausible
3. Delusional

4. Lability of affect
Rate the patient's affect as the outward presentation of emotions and not as a description of what the patient feels.

0. Not present
1. Affect somewhat altered or incongruent to situation; changes over the course of hours; emotions are mostly under self-control
2. Affect is often inappropriate to the situation and intermittently changes over the course of minutes; emotions are not consistently under self-control, though they respond to redirection by others
3. Severe and consistent disinhibition of emotions; affect changes rapidly, is inappropriate to context, and does not respond to redirection by others

5. Language
Rate abnormalities of spoken, written or sign language that cannot be otherwise attributed to dialect or stuttering. Assess fluency, grammar, comprehension, semantic content and naming. Test comprehension and naming nonverbally if necessary by having patient follow commands or point.

0. Normal language
1. Mild impairment including word-finding difficulty or problems with naming or fluency
2. Moderate impairment including comprehension difficulties or deficits in meaningful communication (semantic content)
3. Severe impairment including nonsensical semantic content, word salad, muteness, or severely reduced comprehension

6. Thought process abnormalities
Rate abnormalities of thinking processes based on verbal or written output. If a patient does not speak or write, do not rate this item.

0. Normal thought processes
1. Tangential or circumstantial
2. Associations loosely connected occasionally, but largely comprehensible
3. Associations loosely connected most of the time

7. Motor agitation
Rate by observation, including from other sources of observation such as by visitors, family and clinical staff. Do not include dyskinesia, tics, or chorea.

0. No restlessness or agitation
1. Mild restlessness of gross motor movements or mild fidgetiness
2. Moderate motor agitation including dramatic movements of the extremities, pacing, fidgeting, removing intravenous lines, etc.
3. Severe motor agitation, such as combativeness or a need for restraints or seclusion

8. Motor retardation
Rate movements by direct observation or from other sources of observation such as family, visitors, or clinical staff. Do not rate components of retardation that are caused by parkinsonian symptoms. Do not rate drowsiness or sleep.

0. No slowness of voluntary movements
1. Mildly reduced frequency, spontaneity or speed of motor movements, to the degree that may interfere somewhat with the assessment.
2. Moderately reduced frequency, spontaneity or speed of motor movements to the degree that it interferes with participation in activities or self-care
3. Severe motor retardation with few spontaneous movements.

9. Orientation
Patients who cannot speak can be given a visual or auditory presentation of multiple choice answers. Allow patient to be wrong by up to 7 days instead of 2 days for patients hospitalized more than 3 weeks. Disorientation to person means not recognizing familiar persons and may be intact even if the person has naming difficulty but recognizes the person. Disorientation to person is most severe when one doesn't know one's own identity and is rare. Disorientation to person usually occurs after disorientation to time and/or place.

0. Oriented to person, place and time
1. Disoriented to time (e.g., by more than 2 days or wrong month or wrong year) or to place (e.g., name of building, city, state), but not both
2. Disoriented to time and place
3. Disoriented to person

10. Attention
Patients with sensory deficits or who are intubated or whose hand movements are constrained should be tested using an alternate modality besides writing. Attention can be assessed during the interview (e.g., verbal perseverations, distractibility, and difficulty with set shifting) and/or through use of specific tests, e.g., digit span.

0. Alert and attentive
1. Mildly distractible or mild difficulty sustaining attention, but able to refocus with cueing. On formal testing makes only minor errors and is not significantly slow in responses
2. Moderate inattention with difficulty focusing and sustaining attention. On formal testing, makes numerous errors and either requires prodding to focus or finish the task
3. Severe difficulty focusing and/or sustaining attention, with many incorrect or incomplete responses or inability to follow instructions. Distractible by other noises or events in the environment

11. Short-term memory
Defined as recall of information (e.g., 3 items presented either verbally or visually) after a delay of about 2 to 3 minutes. When formally tested, information must be registered adequately before recall is tested. The number of trials to register as well as effect of cueing can be noted on scoresheet. Patient should not be allowed to rehearse during the delay period and should be distracted during that time. Patient may speak or nonverbally communicate to the examiner the identity of the correct items. Short-term deficits noticed during the course of the interview can be used also.

0. Short-term memory intact
1. Recalls 2/3 items; may be able to recall third item after category cueing
2. Recalls 1/3 items; may be able to recall other items after category cueing
3. Recalls 0/3 items

12. Long-term memory

Can be assessed formally or through interviewing for recall of past personal (e.g., past medical history or information or experiences that can be corroborated from another source) or general information that is culturally relevant. When formally tested, use a verbal and/or visual modality for 3 items that are adequately registered and recalled after at least 5 minutes. The patient should not be allowed to rehearse during the delay period during formal testing. Make allowances for patients with less than 8 years of education or who are mentally retarded regarding general information questions. Rating of the severity of deficits may involve a judgment about all the ways long-term memory is assessed, including recent and/or remote long-term memory ability informally tested during the interview as well as any formal testing of recent long-term memory using 3 items.

0. No significant long-term memory deficits
1. Recalls 2/3 items and/or has minor difficulty recalling details of other long-term information
2. Recalls 1/3 items and/or has moderate difficulty recalling other long-term information
3. Recalls 0/3 items and/or has severe difficulty recalling other long-term information

13. Visuospatial ability

Assess informally and formally. Consider patient's difficulty navigating one's way around living areas or environment (e.g., getting lost). Test formally by drawing or copying a design, by arranging puzzle pieces, or by drawing a map and identifying major cities, etc. Take into account any visual impairments that may affect performance.

0. No impairment
1. Mild impairment such that overall design and most details or pieces are correct; and/or little difficulty navigating in his/her surroundings
2. Moderate impairment with distorted appreciation of overall design and/or several errors of details or pieces; and/or needing repeated redirection to keep from getting lost in a newer environment despite, trouble locating familiar objects in immediate environment
3. Severe impairment on formal testing; and/or repeated wandering or getting lost in environment

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DRS-R-98 OPTIONAL DIAGNOSTIC ITEMS

These three items can be used to assist in the differentiation of delirium from other disorders for diagnostic and research purposes. They are added to the severity score for the total scale score, but are NOT included in the severity score.

14. Temporal onset of symptoms

Rate the acuteness of onset of the initial symptoms of the disorder or episode being currently assessed, not their total duration. Distinguish the onset of symptoms attributable to delirium when it occurs concurrently with a different preexisting psychiatric disorder. For example, if a patient with major depression is rated during a delirium episode due to an overdose, then rate the onset of the delirium symptoms.

0. No significant change from usual or longstanding baseline behavior
1. Gradual onset of symptoms, occurring over a period of several weeks to a month
2. Acute change in behavior or personality occurring over days to a week
3. Abrupt change in behavior occurring over a period of several hours to a day

15. Fluctuation of symptom severity

Rate the waxing and waning of an individual or cluster of symptom(s) over the time frame being rated. Usually applies to cognition, affect, intensity of hallucinations, thought disorder, language disturbance. Take into consideration that perceptual disturbances usually occur intermittently, but might cluster in period of greater intensity when other symptoms fluctuate in severity.

0. No symptom fluctuation
1. Symptom intensity fluctuates in severity over hours
2. Symptom intensity fluctuates in severity over minutes

16. Physical disorder

Rate the degree to which a physiological, medical or pharmacological problem can be specifically attributed to have caused the symptoms being assessed. Many patients have such problems but they may or may not have causal relationship to the symptoms being rated.

0. None present or active
1. Presence of any physical disorder that might affect mental state
2. Drug, infection, metabolic disorder, CNS lesion or other medical problem that specifically can be implicated in causing the altered behavior or mental state

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Sites

- Barwon Health (VIC)
- Braeside (NSW)
- Newcastle Calvary Mater (NSW)
- Royal Melbourne (VIC)
- Sacred Heart St Vincent's (NSW)