Assessment and Management of Delirium in Palliative Care: Seeking a Balanced Strategy

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Disclosure of Commercial Support

• SUNDIPS has received financial support from:
  – Gillin Family and Bruyère Foundation
  – Bruyère Research Institute in kind support (BRI)

• The melatonin RCT study has received support:
  – DOM Research grant (PL/SB); BRI is Sponsor
  – Jamieson Pharmaceuticals supplied the medications

• Co-investigator/-applicant in recently awarded grants:
  – BAMO 2014 (Delirium CPGs); BAMO 2014 (Scoping Review)
  – Cancer Australia 2016 (Prevention study)
  – National Breast Cancer Fund Australia 2016 (Prevention study)

➤ Potential for conflict(s) of interest: Nil
Objectives

Following this presentation, attendees will be

(1) better able to clinically *assess* and *recognize* delirium in the context of PC;

(2) better able to appreciate the need for a *balanced* approach to management;

(3) more familiar with *recent studies* and their potential to advance our knowledge of delirium management;

(4) more aware of the many *gaps in our knowledge* of delirium.
# Case Vignette: “Frank”…..Background Hx

[Lawlor et al JPSM 2014; PubMed PMCID: PMC4128755]

<table>
<thead>
<tr>
<th>Context</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td><strong>Pre-cancer</strong></td>
<td>• Frank, 72 yo ♂, lived with his 70 yo wife in a 2-storey suburban home.</td>
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<tr>
<td></td>
<td>• Ambulatory and independent in ADLs</td>
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<tr>
<td><strong>Cancer diagnosis</strong></td>
<td>• 8/12 ago, Dx with non-small cell lung cancer</td>
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<tr>
<td><strong>Staging and management</strong></td>
<td>• Stage 111B; ECOG performance = 1 initially</td>
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<td></td>
<td>• Partial response to initial chemo-radiation;</td>
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<tr>
<td></td>
<td>• ChemoTx discontinued 3/12 ago; much weaker.</td>
</tr>
</tbody>
</table>

Milford
Apr 27th 2018
Case Vignette: “Frank” …..1st Delirium
[Lawlor et al JPSM 2014; PubMed PMCID: PMC4128755]

- **Presentation A+E:** Acute cognitive impairment; agitation; + 2 near falls
- **Hx from wife:** dozes off in conversation; daytime sleepiness; awake all night; appears to have visual hallucinations; abdo pain; resp distress
- **Assessment:** SOMCT 16/28; CAM +ve; mixed psychomotor features
- **Decisions:** aggressive vs conservative Rx; distressing for wife;
- **Investigations & Rx:** admitted; Rx pneumonia, Rx of ↑Ca++; haloperidol
- **Outcome:** delirium improved by Day 3 of adm and ? reversed by Day 5;
  - Re-staging revealed hepatic and adrenal metastases (Stage IV)
  - No brain metastases on MRI scan.
  - ECOG now decreased to 3.
  - Discharged home under GP + community palliative care team.
Case Vignette: “Frank” ……2nd Delirium

[Lawlor et al JPSM 2014; PubMed PMCID: PMC4128755]

- Despite some **episodic mild cognitive deficits**, he remained **at home for 4/52, but now develops another episode of delirium.**

- The possibility of a **recurrent hypercalcaemia** was discussed with Frank’s wife. However, given their wish at this point for **solely comfort care without any further blood work, investigation of this episode of delirium was not pursued.**

- Due to **family exhaustion** and their concern about **inadequate pain control**, Frank was admitted to an inpatient hospice, where subcut morphine controlled his pain and **low dose midazolam was used to control his delirium prior to his death 7 days later.**
Delirium: across the spectrum in healthcare

Ubiquitous neuropsychiatric syndrome
- Spans all medical and surgical specialties
- “Everyman’s psychosis”

Underpinnings of advances in the last decade
- ICU studies / Post-Op / Geriatrics / Liaison Psychiatry / Emergency Dept / Palliative Care
- Economic drivers / demographic changes

Delirium Studies in Palliative Settings
- SUNDIPS (Studies to UNderstand Delirium In Settings)
- SUNRISE (Studies to UNderstand & Improve Delirium in Palliative SEtings) Palliative
Studies to *UNderstand* and *Improve* Delirium Care in Palliative *Settings*

Universities of Hull & York (UK)
University of Ottawa & Carleton University (Canada)
University of Technology Sydney (Australia)

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Studies to *UNderstand* Delirium *In* Palliative *Settings*

Research Planning Meeting June 2012 (Bruyère)
SUNDIPS series published in JPSM 2014
Delirium in Palliative Care: Pivotal issues

**Epidemiology**
- Prevalence; screening; diagnosis
- Risk factors: identification; prevention

**The Delirium Experience**
- Phenomenological aspects
- Family / Caregiver experience

**Reversibility**
- Varies with setting and goals of care

**Symptomatic Management**
- Antipsychotic medications
- Guidelines & Use of Palliative Sedation

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Figure 2. Graphical representation of delirium prevalence and incidence rates in specialist palliative care inpatient units from results of included studies.

Hosie A et al. Palliative Med 2012
Table 1. Diagnostic Criteria for Delirium.

**Source of Criteria**

**DSM-5***

The presence of delirium requires all the criteria to be met:
- Disturbance in attention and awareness
- Disturbance develops acutely and tends to fluctuate in severity
- At least one additional disturbance in cognition
- Disturbances are not better explained by a preexisting dementia
- Disturbances do not occur in the context of a severely reduced level of arousal or coma
- Evidence of an underlying organic cause or causes

**Confusion Assessment Method (CAM)†**

The presence of delirium requires features 1 and 2 and either 3 or 4:
- Acute change in mental status with a fluctuating course (feature 1)
- Inattention (feature 2)
- Disorganized thinking (feature 3)
- Altered level of consciousness (feature 4)

* The criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5).
† The criteria are adapted from Inouye et al.
NuDESC Score

Sequential NuDESC Assessment #

NuDESC Items: monitor severity / screen

1. Disorientation [0-2]
2. Inappropriate behaviour [0-2]
3. Inappropriate communication [0-2]
4. Illusions / Hallucinations [0-2]
5. Psychomotor retardation [0-2]
Screening & Diagnosing Delirium in Palliative Care

**No Burden**
Observational Tools

- NuDESC
- DOS
- RADAR

**Low Burden**
Mixed Format Tools / Tests

- CAM
- 4AT
- SQID
- NEECHAM
- MOYB etc

**Higher Burden**
Cognitive Assessment Tools

- MMSE
- SOMCT
- CTD

***Confirmatory diagnostic test ***

- Routine clinical practice: ? CAM
- Research: ? DSM-5 Delirium Dx Criteria
The balance of protective, predisposing and precipitating factors of delirium illustrating an individual patient’s balance of predisposing and protective factors. This balance is disturbed by the occurrence of a precipitating factor and delirium develops.

Delirium pathogenesis in PC Settings

Baseline vulnerability

- Age / Mental Status
- Multisystem impairment
- Nutritional status
- Functional status

Superimposed ppts

- Medications
- Volume depletion
- Infection
- Metabolic factors
- Hypoxia
- Environmental
88% of deaths preceded by delirium for at least 6 hours

Median duration of reversed delirium: 3.5 days (1-22)

Median # of precipitants per episode of delirium: 3 (1-6)

Delirium episode reversed in 50% of episodes

**Delirium Reversal** vs **Delirium Non Reversal**
- **Psychoactive Medications** HR=6.69 (95% CI: 1.49-29.6)
- **Hypoxic encephalopathy** HR=0.32 (95% CI: 0.15-0.7)
- **Non-Respiratory Infection** HR=0.23 (95% CI: 0.08-0.64)
Partly reversible

Non reversible

Multifactorial etiology

Desired goals of care

Approaching the Rx of precipitants

Partly reversible

Reversible
Rationale:
• Lack of clarity exists re definition of delirium recovery and related outcomes; aim was to clarify the definitions of delirium recovery used in the literature

Results:
• 56 studies included; only 2 used clinical criteria alone; most studies used one validated scale. A *variety of 16 different terms* used to define the “recovery of delirium”
Results

- **Dementia patients**
  - 6.3% Full recovery
  - 11.3% Partial recovery
  - 74.6% No recovery
  - 7.7% Death

- **No Dementia patients**
  - 14.3% Full recovery
  - 17.0% Partial recovery
  - 50.9% No recovery
  - 17.9% Death
A MULTICOMPONENT INTERVENTION TO PREVENT DELIRIUM IN HOSPITALIZED OLDER PATIENTS

Sharon K. Inouye, M.D., M.P.H., Sidney T. Bogardus, Jr., M.D., Peter A. Charpentier, M.P.H., Linda Leo-Summers, M.P.H., Denise Acampora, M.P.H., Theodore R. Holford, Ph.D., and Leo M. Cooney, Jr., M.D.
Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature

Felipe Martinez1,2, Catalina Tobar3,4, Nathan Hill5

7 studies included (n=1691)
P: Hip Fracture/Orth Unit x3; Acute Med x2; CCU x1; ICU x1
I: Physio / Reorientate / Family / avoid sensory depr / educate
C: Usual care
O: Multicomponent interventions reduced incident delirium; RR=0.73, 95% CI 0.63-0.85, p<0.0001
Interventions for preventing delirium in hospitalised non-ICU patients

Najma Siddiqi¹, Jennifer K Harrison², Andrew Clegg³, Elizabeth A Teale³, John Young⁴, James Taylor⁵, Samantha A Simpkins⁴

- 39 trials; n=16,082; 22 different interventions/comparisons
- 22 in surgical settings; 7 in general medical/geriatric settings

- Multicomponent Interventions (MCIs)
  - MCIs vs usual care: reduced delirium incidence, 7 studies (n=1950) (mod quality) [RR=0.69, 95%CI: 0.59-0.81]
    - Medical, 4, n=1365, [RR=0.63, 95%CI: 0.43-0.92] vs
    - Surgical, 3, n=585, [RR=0.71, 95%CI: 0.59-0.85]
  - Dementia, 1 study, n=50, [RR=0.90, 95%CI: 0.59-1.36]
Delirium prevention in terminal cancer: assessment of a multicomponent intervention

Pierre Gagnon¹,²,³,⁴,⁵,⁶*, Pierre Allard⁷, Bruno Gagnon⁸, Chantal Mérette⁶ and François Tardif¹,⁵

Conclusion: A simple multicomponent preventive intervention was ineffective in reducing delirium incidence or severity among cancer patients receiving end-of-life care. Delirium prevention remains a difficult challenge in terminally ill cancer patients.

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Delirium prevention in terminal cancer: assessment of a multicomponent intervention

Pierre Gagnon\textsuperscript{1,2,3,4,5,6,*}, Pierre Allard\textsuperscript{7}, Bruno Gagnon\textsuperscript{8}, Chantal Mérette\textsuperscript{6} and François Tardif\textsuperscript{1,5}

Figure 2. Delirium-free survival of patients in the intervention group vs the usual-care (control) group. Kaplan–Meier survival analysis was used ($P = 0.822$)
Melatonin decreases delirium in elderly patients: A randomized, placebo-controlled trial†

Tareef Al-Aama¹,², Christopher Brymer¹, Iris Gutmanis³,⁴,⁵, Sarah M. Woolmore-Goodwin⁴, Jacquelin Esbaugh⁴ and Monidipa Dasgupta¹,⁵

**Aim:** To evaluate efficacy of melatonin in decreasing delirium

**Design:** Randomized, double-blind, placebo controlled study

**Setting:** An Int Med service in a tertiary care centre, London, ON.

**Study Pop:** N=145, ≥ 65yo, admitted via ER to medical unit

**Intervention:** Melatonin 0.5mg or Placebo qhs x14 days

**Assessments:** CAM (Confusion Assessment Method)

**Results:**
- Lower risk of delirium in Melatonin Group (12% vs 31%, p=0.014)
- Odds Ratio (Adj) = 0.19 (95% CI, 0.06-0.62)

**Conclusion:** Exogenous low dose melatonin may protect against delirium
Kaplan-Meier Plot (Melatonin vs Placebo Groups)

At risk
med_grp = 0 30
med_grp = 1 30

Time (days)
Placebo Melatonin

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Neuropathogenesis of Delirium: Review of Current Etiologic Theories and Common Pathways Jose R. Maldonado
Fig. 2 Recognition and propagation of peripheral immune stimuli in the CNS. The initial interaction of circulating inflammatory mediators (e.g. cytokines and lipopolysaccharide) with the neurovascular unit occurs through a vast number of receptors and is associated with an increased paracellular permeability of the blood-brain-barrier. In addition to systemic inflammation, other factors affect the integrity of BBB including hypoxia, ischaemia and pain. Recognition of peripheral inflammatory stimuli in the BBB is followed by a cascade of events leading to microglia activation and subsequent modulation of adjacent cells including astrocytes and neurons (represented with dashed reciprocal arrows).
Systemic infection and delirium: when cytokines and acetylcholine collide

Willem A van Gool, Diederik van de Beek, Piet Eikelenboom

A Normal situation

Systemic infection

Resting microglia

Cholinergic inhibition of microglia

Activated microglia

TNFα → TNFα

Delirium of limited duration and severity

B Old age, incipient neurodegenerative disease, or anticholinergic drug treatment

Systemic infection

Resting microglia → Primed microglia

Reduced cholinergic inhibition of microglia

Overactivated microglia

Neurodegeneration

TNFα → TNFα → TNFα

Severe, prolonged delirium → Dementia

Lancet 2010;375:773-75
“I don’t like to commit myself about heaven or hell – you see, I’ve friends in both places”

“God created war so that Americans would learn geography”

“If your only tool is a hammer then every problem looks like a nail.”
Drug therapy for delirium in terminally ill adult patients (Review)

Candy B, Jackson KC, Jones L, Leurent B, Tookman A, King M

- 2012 Review included **one trial**:  
  - Breitbart et al 1996  
  - Trial of Haloperidol vs Chlorpromazine vs Lorazepam  
  - Study population: hospitalized AIDS patients (n=30)
Δ Haloper n=11
○ Chlorpr n=13
• Lorazep n=6

1st 24 hrs of Rx, mean mg doses (range):
• Haloper, 2.8 (0.8-6.3)
• Chlorpr, 50.0 (10-70);
• Lorazep, 3.0 (0.5-10.0)

Mean DRS scores for all (N= 30)
• 20.1 at Day 1 (range=14-28),
• 13.3 on Day 2 (range=3-26),
• 12.8 at the end of treatment (range=3-26).

Breitbart et al AJPsych 1996
Population

- Adult patients receiving hospice or palliative care (PC)
- with advanced, progressive disease that was no longer curable
- who required inpatient care by a specialist PC team
- 11 Australian sites
Review of previous Randomized Clinical Trials (RCTs):


All studies Inadequately powered
Review of previous RCT studies (adequately powered):


Girard TD, Pandharipande PP, Carson SS, et al;

Findings:
- No difference in number of delirium-free days in those receiving antipsychotic medications.
Results

❖ Primary analysis (Intention to Treat):
  • Risperidone arm: delirium symptom scores: 0.48 Units (95% CI, 0.09-0.86; \( P = .02 \)) higher than placebo at study end.
  • Haloperidol arm: delirium symptom scores: 0.24 Units (95% CI, 0.06-0.42; \( P = .009 \)) higher than placebo at study end.

❖ Secondary analysis (Mixed model):
  • Risperidone arm: delirium symptom scores per day higher relative to placebo: 0.24 Units (95% CI, 0.11-0.38; \( P < .001 \)).
  • Haloperidol arm: delirium symptom scores per day relative to placebo: 0.21 Units (95% CI, 0.08-0.34; \( P = .002 \))
The dependent variable was delirium score at each day. The independent variables comprise the covariates in Table 2, group, time, and 2 interaction terms, time $\times$ risperidone and time $\times$ haloperidol. The relative difference in improvement between groups at 72 hours was determined using the `lincom` function in Stata. Placebo vs risperidone: $P < .001$; placebo vs haloperidol: $P = .002$. Error bars indicate 95% CIs.
**Figure 1.** MDAS Scores (Delirium Severity) Over the Study Period by Study Arm

- Placebo vs Risperidone $p = 0.01$
- Placebo vs Haloperidol $p = 0.015$

Error bars = 95% CI
Model adjusted for covariates in Table 2
Key Points:

• Behavioral, communication, and perceptual symptoms of delirium were greater in those treated with antipsychotic drugs vs. placebo
  • Finding mirrored in delirium severity, (higher MDAS scores in patients in both antipsychotic arms vs. placebo).
• Better symptom control in patients in placebo arm occurred without increased use of rescue midazolam
• Outcomes and direction of findings in the haloperidol and risperidone groups for key measures were similar, suggesting an antipsychotic class effect, limiting likelihood of type II error.

Limitations:

➢ Oral solution / Midazolam / Mild-mod severity delirium

Conclusions:

➢ “individualized management of delirium precipitants and supportive strategies result in lower scores and shorter duration of target distressing delirium symptoms than when risperidone or haloperidol are added.”

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Effect of Lorazepam With Haloperidol vs Haloperidol Alone on Agitated Delirium in Patients With Advanced Cancer Receiving Palliative Care
A Randomized Clinical Trial

David Hui, MD, MSc; Susan Frisbee-Hume, MS; Annie Wilson, MSN; Seyedeh S. Dibaj, PhD; Thuc Nguyen, RN; Maxine De La Cruz, MD; Paul Walker, MD; Donna S. Zhukovsky, MD; Marvin Delgado-Guay, MD; Mariebenta Vidal, MD; Daniel Epner, MD; Akhila Reddy, MD; Kimerson Tanco, MD; Janet Williams, MPH; Stacy Hall, MSN; Diane Liu, MSc; Kenneth Hess, PhD; Sapna Amin, PharmD; William Breitbart, MD; Eduardo Bruera, MD

Humanizing the Treatment of Hyperactive Delirium in the Last Days of Life
Pratik P. Pandharipande, MD, MSCI; E. Wesley Ely, MD, MPH
Figure 2. Change in Richmond Agitation-Sedation Scale (RASS) Over the First 8 Hours After Treatment

A. RASS scores from baseline to 8 h

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Lorazepam + haloperidol</th>
<th>Placebo + haloperidol</th>
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<tbody>
<tr>
<td></td>
<td>29</td>
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<td>26</td>
<td>26</td>
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<table>
<thead>
<tr>
<th>Time, h</th>
<th>Placebo + haloperidol</th>
<th>Lorazepam + haloperidol</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0.5</td>
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<td>1</td>
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<td>1.5</td>
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<td>8</td>
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</table>

B. Distribution of RASS scores at 30 min and 8 h

<table>
<thead>
<tr>
<th>RASS score</th>
<th>0 to -2</th>
<th>-3 to -5</th>
<th>1 to 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 min</td>
<td>10</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Placebo</td>
<td>2</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>2</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>8 h</td>
<td>2</td>
<td>16</td>
<td>8</td>
</tr>
</tbody>
</table>

A, Time 0 indicates immediately before treatment administration. Error bars indicate 95% CIs. Both treatments were associated with significant reduction in the mean RASS score within the first 30 minutes of treatment. RASS score remained relatively stable for both groups over the 8-hour observation period. Lorazepam + haloperidol was associated with a significantly greater reduction in RASS score than placebo + haloperidol at 8 hours (P < .001, 2-sided Wilcoxon rank sum test). B, A larger proportion of patients had hyperactivity (RASS score, 1 to 4) in the placebo + haloperidol group at both 30 minutes and 8 hours (P = .001 for both time points). In contrast, a larger proportion of patients had sedation in the lorazepam group (RASS score, -3 to -5). The 2-sided Fisher exact test was used to compare the 3 categories of RASS scores between groups.
Antipsychotic Medication for Prevention and Treatment of Delirium in Hospitalized Adults: A Systematic Review and Meta-Analysis

Karin J. Neufeld, MD, MPH,*a Jirong Yue, MD,§s Thomas N. Robinson, MD, MPH,‖ Sharon K. Inouye, MD, MPH,*a*††b and Dale M. Needham, MD, PhD††b

Medical and Surgical Settings

19 studies

Conclusion:

- Current evidence does not support the use of antipsychotics for prevention or treatment of delirium.
- Additional methodologically rigorous studies using standardized outcome measures are needed.
“I’ve never wished a man dead, but I have read some obituaries with great pleasure.”

“Suppose you were an idiot. And suppose you were a Member of Congress. But then I repeat myself.”
Ottawa’s Rideau Canal on a sunny winter day
Pragmatic, Best Practice Approach to Delirium Mx

- Pursue Core Research Agenda Priorities

<table>
<thead>
<tr>
<th>Action</th>
<th>Priority Areas</th>
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</thead>
<tbody>
<tr>
<td>Make a balanced therapeutic decision</td>
<td>Burden vs benefit / Pt wishes vs medical bias</td>
</tr>
<tr>
<td>Talk to the family</td>
<td>Clarify goals of care / Educate &amp; Support</td>
</tr>
<tr>
<td>Consider a timed trial of therapeutic intervention</td>
<td>eg antibiotics for 24-48 hours</td>
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<tr>
<td>Target potentially reversible precipitants, eg opioids</td>
<td>Especially medications / Opioid Δ / dose reduce</td>
</tr>
<tr>
<td>Provide symptomatic Rx</td>
<td>Antipsychotic vs Benzo / Pal Sedation / Monitor</td>
</tr>
<tr>
<td>Pursue research agenda: SUNDIPS / SUNRISE</td>
<td>Epidemiologic studies / Management strategies</td>
</tr>
</tbody>
</table>

- Burden vs benefit
- Pt wishes vs medical bias
- Clarify goals of care
- Educate & Support
- Especially medications
- Opioid Δ / dose reduce
- Antipsychotic vs Benzo
- Pal Sedation / Monitor
- Epidemiologic studies
- Management strategies