Delirium: Prevention with Melatonin

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Disclosures

• Centre for Collaborative Drug Research, University of Toronto
  – pilot grant to support melatonin feasibility study
Delirium - Possible therapies

- SCCM guidelines: no effective drug for prevention or treatment
  - promote use of non-pharmacological approaches (e.g., re-orientation, early mobilization) for both prevention and treatment

- Despite conflicting evidence, many pharmacological agents (e.g., antipsychotics, benzodiazepines, $\alpha_2$) are routinely used to manage ICU delirium AND are continued after discharge

- Antipsychotics commonly used to manage symptoms despite limited supporting evidence and studies of harm in non-critically ill patients
Pathophysiology

- No single cause
- Multi-factorial & likely synergism in multiple cerebral assaults

Current hypotheses include
- Neuroinflammation
- Impaired cerebral oxidative metabolism
- Disturbances of neuroendocrine and neurotransmitter linked to cognition, behavior & mood
  - e.g. serotonin, the precursor of melatonin
Melatonin

- A neuro-hormone produced by the pineal gland during hours of darkness

- Multiple biological effects
  - Primary role: regulation and synchronization of the sleep cycle
  - It accelerates sleep initiation and improves sleep maintenance and efficiency
Delirium and link to melatonin

• Sleep-wake cycle disturbances not diagnostic of delirium, but many delirium tools assess sleep patterns (e.g., ICDSC)

• Studies indicate up to 75% of ICU patients with delirium display changes in sleep architecture

• Observational studies demonstrate abnormal melatonin secretion
<table>
<thead>
<tr>
<th>Study</th>
<th>Purpose</th>
<th>Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miyazaki 2003 SICU N=41</td>
<td>Melatonin &amp; <strong>ICU psychosis</strong></td>
<td>[serum] melatonin 00:00 day before surgery, at 00:00, 06:00, 12:00, and 18:00 on POD1-4, POD2, and POD3,</td>
<td><strong>Correlation between ICU psychosis and irregular melatonin secretion</strong> (p=0.0001)</td>
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<tr>
<td>Yoshitaka 2013 SICU N=40</td>
<td>Perioperative melatonin &amp; delirium</td>
<td>[plasma] melatonin 08:00 before surgery, 1h post-op, and 08:00 POD 3 &amp; 4.</td>
<td><strong>Δ [melatonin] independently associated with delirium risk</strong> (OR 0.5, p=0.047)</td>
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<tr>
<td>Mekontson Dessap 2015 ICU N=70</td>
<td>Impact of delirium during weaning and associated circadian melatonin.</td>
<td>[urine] aMT6s q3h first 24h of weaning from MV</td>
<td><strong>D</strong>elirium associated with significant reduction in peak, mean, amplitude, and total values of aMT6s during first 24h of weaning (p= 0.019).</td>
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Data to support delirium prevention with melatonin
## Prevention studies: Non-ICU

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
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<th>Adverse events</th>
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</thead>
<tbody>
<tr>
<td>Al-Aama 2011</td>
<td>0.5 mg melatonin qHS or placebo for 14 days, or until discharge</td>
<td>↓ incident delirium in melatonin group (p &lt;0.02); no difference in delirium severity between groups</td>
<td>Melatonin: N=1 nightmares and N=1 “floating” feeling and talking to dead wife</td>
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<tr>
<td>GIM N=122</td>
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<tr>
<td>Sultan 2010</td>
<td>Placebo or melatonin 5 mg or midazolam 7.5 mg or clonidine 100 μg</td>
<td>↓ Incidence melatonin vs. all other groups (p=0.003)</td>
<td>None reported with melatonin</td>
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<tr>
<td>Hip Surgery N = 203</td>
<td>Drug given night before and 90 mins prior start Sx</td>
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<tr>
<td>De Jonghe 2014</td>
<td>3 mg melatonin qHS or placebo, started day of admission, x 5 days</td>
<td>Delirium: 29.6% melatonin vs. 25.5% placebo fewer in melatonin group had long-lasting delirium (&gt; 2 days) (P&lt;0.001)</td>
<td>None reported</td>
</tr>
<tr>
<td>DBRCT Sx N=378</td>
<td>[surgery took place on day 1 or 2 of admission]</td>
<td>NS difference in median duration and over all severity</td>
<td></td>
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<tr>
<td>Hatta 2014</td>
<td>8 mg ramelteon qHS or placebo, until delirium developed or x7 days</td>
<td>Delirium: 3% ramelteon vs. 32% placebo RR 0.09 CI 0.01-0.69, p = 0.03</td>
<td>None reported</td>
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<tr>
<td>RCT ICU and GIM N=67</td>
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<tr>
<td>Dianatkhah 2015 DBRCT</td>
<td>3 mg melatonin 10 mg oxazepam qHS from 3 days before Sx until discharge</td>
<td>Primary outcome: sleep disturbance Delirium: 6.1% melatonin vs. 12.7% placebo (NS)</td>
<td>None reported</td>
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<tr>
<td>N=137</td>
<td></td>
<td></td>
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<tr>
<td>Adult; CABG surgery</td>
<td></td>
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<tr>
<td>Ford 2014 DBRCT ONGOING</td>
<td>3 mg melatonin qHS or placebo, starting 2 days before surgery, for a total of 7 days</td>
<td>1° outcome: incidence of delirium 2° outcomes: severity and duration, hospital LOS, referrals to mental health services, depression and anxiety, cognition</td>
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<tr>
<td>Cardiac Sx N=210</td>
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<td>• ≥50 years; elective or semi-elective</td>
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<tr>
<td>Martinez 2017 Pro-MEDIC</td>
<td>4 mg melatonin qHS or placebo up to 14 days</td>
<td>1° outcome: incidence of delirium 2° outcomes: severity and duration, hospital LOS, referrals to mental health services, depression and anxiety, cognition</td>
<td></td>
</tr>
<tr>
<td>DBRCT Not yet recruiting</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>N = 850</td>
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<tr>
<td>Burry 2017 DBRCT Mixed ICU</td>
<td>0.5 mg melatonin or 2 mg melatonin or placebo qHS up to 14 days</td>
<td>1° outcome: feasibility 2° outcomes: pharmacokinetics, delirium, sleep</td>
<td></td>
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<tr>
<td>N = 69</td>
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<td></td>
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<tr>
<td>Not yet recruiting</td>
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Feasibility of melatonin for prevention of delirium in critically ill patients: a protocol for a multicentre, randomised, placebo-controlled study (MELLOW)
MELLOW: general study aims

1. Assess feasibility of conducting a future full scale RCT of similar design

2. Provide better understanding of melatonin pharmacokinetics in critically ill patients

3. Determine appropriate dosing, drug administration issues (specifically protocol adherence), adverse drug effects, and recruitment rates based on inclusion and exclusion criteria, delirium (incidence, time to onset, duration, delirium-free days), sleep quality (self-reported, rest-activity cycles measured with actigraphy)

<table>
<thead>
<tr>
<th>Site</th>
<th>Location</th>
<th>N=69 total</th>
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<tbody>
<tr>
<td>Mount Sinai Hospital</td>
<td>Toronto</td>
<td><strong>30</strong></td>
</tr>
<tr>
<td>Sunnybrook Health Sciences Centre</td>
<td>Toronto</td>
<td><strong>18</strong></td>
</tr>
<tr>
<td>Hopital du Sacre-Coeur</td>
<td>Montreal</td>
<td><strong>21</strong></td>
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Outcomes: feasibility

1. Protocol adherence – Primary outcome
   Overall proportion of study doses administered in the prescribed qHS administration window (i.e. between 21:00 and to 23:59 hours), divided by total number of eligible study days

2. Recruitment
   Proportion of ICU patients screened meeting inclusion criteria, number of and reasons for exclusion, and consent rate of eligible individuals

3. Time in motion
   Coordinators at each site will capture amount of time needed to screen, consent, and enroll patients, complete study procedures, and collect data
Outcomes: pharmacokinetics

Nested sample: 5 subjects from each group will have [plasma] melatonin measured using mass spectroscopy \((t_0, t_{0.5}, t_1, t_2, t_4, t_6, t_8, t_{12})\) Day 1

1. Peak concentration (Cmax)
2. Time of peak concentration (Tmax)
3. Morning concentration (C9AM)
4. Half-life (T\(^{1/2}\))
5. Mean apparent clearance (CL/F)
6. Mean apparent volume of distribution (V/F)
7. Area under the concentration-time curve (AUC)

Because light regulates melatonin secretion, we will measure light using a lux-meter at the time of each sample.
Outcomes: clinical and safety

1. Incidence of delirium
2. Duration of delirium
   • Number of days with (ICDSC score of ≥4)
3. Delirium- and coma-free days
4. Sleep (Richards Campbell Sleep Questionnaire)
   • Self-reported sleep quality by patient and/or assisted by nurse
   • Rest-activity cycles using actigraphy (Montreal site only)
5. Duration of mechanical ventilation
6. Length of stay
   • ICU and hospital
7. Hospital discharge disposition
8. Mortality
   • ICU and hospital
9. Adverse events
   • Melatonin literature reports few adverse events – headache, vivid dreams, drowsiness
MELLOWS: interventions

- Dosed qHS until ICU discharge, death, or 14 days
- Identical 5mL suspensions for PO/NG administration
- ICU team responsible for all other pharmacological and non-pharmacological approaches to patient management (pain, agitation, sedation, delirium, and sleep) according to local practice

<table>
<thead>
<tr>
<th>Arm</th>
<th>Dose</th>
<th>N</th>
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<tr>
<td>Low dose melatonin</td>
<td>0.5 mg</td>
<td>23</td>
</tr>
<tr>
<td>High dose melatonin</td>
<td>2.0 mg</td>
<td>23</td>
</tr>
<tr>
<td>Placebo</td>
<td>0 mg</td>
<td>23</td>
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</tbody>
</table>
MELLOW: criteria

Inclusion
1. Critically ill ≥18 years
2. Anticipated ICU LOS >48 hours

Exclusion
1. ICU admission >48 hours prior to screening
2. Unable to assess for delirium (e.g. history of severe cognitive or neurodegenerative illness)
3. Delirium positive prior to randomization (ICDSC ≥4)
4. Anticipated withdrawal of life-sustaining therapy
5. Unable to communicate reliably in English (or French)
6. Absolute contraindications for enteral medication
7. Active seizures
8. Known pregnancy
9. Legally blind
10. Known allergy to melatonin
Treatment studies...

MELT-It study –
Melatonin for treatment of Delirium in the Intensive Care Unit
Lisa Burry, Louise Rose
Melatonin for prevention of ICU delirium? – Not yet

• Intuitive given proposed pathophysiology
• Serum melatonin levels are found to be lower after surgery and in delirious post-op patients
• Promising drug:
  – No association with delirium
  – Clean adverse events and interaction profile
  – It does not changes in sleep architecture, have hangover effects or abuse potential
  o Inexpensive (so worldwide applicability)