Drugs and weaning: a brief overview of pain, sedation, and agitation management

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Disclaimer

- No financial disclosures
- This is my interpretation of the literature
- Personal mission: to stop polypharmacy
Weaning

- **Definition:** liberation from mechanical ventilatory support

- **Process should start with intubation**
  - Readiness for weaning should be monitored daily, with consideration of both clinical trends and stability

References:

Boles JM Eur Respir J 2007 29:1033-1056
Estaban A NEJM 1995;332:345-350
Weaning criteria

- Resolution of underlying cause of acute respiratory failure
- Haemodynamic stability, defined as no need for vasoactive/inotropic drugs
- Absence of fever (preferable)
- Adequate gas exchange
  - \(P_aO_2:F_iO_2 > 200\) with a PEEP=5
- Adequate neurological status or cooperative sedation
  - Drive, Endurance, Energy consumption, Psychological wellbeing
ICU PAD Guidelines

Summary Recommendations

1. Assess all ICU patients for pain, sedation depth, and delirium.

2. Integrate pain, agitation/sedation, and delirium management:
   a. Treat pain first, then sedate!
   b. Avoid deep sedation!
   c. Preferentially use non-pharmacologic delirium management strategies.

3. Link PAD management → ventilator weaning, early mobility
ICU PAD Guidelines
ABCDEF Bundle Checklist*

✓ A – Assess, Prevent and Manage Pain
✓ B – Both SATs and SBTs
✓ C – Choice of Sedation
✓ D – Delirium: Assess, Prevent and Manage
✓ E – Early Mobility and Exercise
✓ F – Family Engagement and Empowerment

G – Get some sleep
H – Home meds & withdrawal
Synergistic Benefits of Integrated PAD Management

 SAT + SBT = ABC

 MV ↓ 3d
 LOS ↓ 4d
 Mort ↓ 32% (Girard 2008)

 ABC + EM = ABC+E

 ICU LOS ↓ 1.4d
 Hosp LOS ↓ 3.3d (Morris 2008)

 EM + SAT = A+E

 ↓ delirium 2d
 ↓ MV 2.4d
 ↑ Indep. FS (OR 2.3) (Schweickert 2009)
PAD Protocol + SATs + SBTs

Results:

- ↑ # of RASS, CAM-ICU assessments performed per day \((P = 0.01)\).
- ↓ mean hourly benzodiazepine dose by 34.8% \((P = 0.01)\).
- ↑ mean RASS scores (i.e., patients were less sedated) \((P = 0.01)\)
- **Multivariate Analyses: (i.e., SAP score, age, gender, weight)**

- ICU delirium risk ↓ by 33% \((OR, 0.67; 95\% CI, 0.49–0.91; P = 0.01)\)
- MV duration ↓ by 17.6% \((95\% CI, 0.6–31.7\%; P = 0.04)\).
- ICU LOS ↓ 12.4% \((95\% CI, 0.5–22.8\%; P = 0.04)\)
- Hospital LOS ↓ 14% \((95\% CI, 2.0–24.5\%; P = 0.02)\)
- No significant changes in VAP rate, mortality, or discharge status
How can we minimize sedation?

- Sedation protocols
- Daily sedation interruption
- No sedation
- Choice of drug or the method of administration (infusion vs. bolus)

Combination(s) of the above
Strategies endorsed by SCCM PAD

Protocol-directed sedation versus non-protocol-directed sedation to reduce duration of mechanical ventilation in mechanically ventilated intensive care patients (Review)

Aitken LM, Bucknall T, Kent B, Mitchell M, Burmeister E, Keogh SJ

Daily sedation interruption versus no daily sedation interruption for critically ill adult patients requiring invasive mechanical ventilation (Review)

Burry L, Rose L, McCullagh IJ, Fergusson DA, Ferguson ND, Mehta S
A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Summary

Background Standard treatment of critically ill patients undergoing mechanical ventilation is continuous sedation. Daily interruption of sedation has a beneficial effect, and in the general intensive care unit of Odense University Hospital, Denmark, standard practice is a protocol of no sedation. We aimed to establish whether duration of mechanical ventilation

No sedation group

- 4.2 fewer MV days
- shorter ICU and hospital LOS
- more agitated delirium – 20% vs 7%
- more haldol
- Sedative infusions in 18%, mainly ARDS
Benzodiazepines and ICU Delirium: A Systematic Review and Meta-Analysis of Randomized Trials

Irene J. Zaal, John W. Devlin, Marijn Hazelbag, Peter M. C. Klein Klouwenberg, Arendina W. van der Kooi, David S. Y. Ong, Olaf L. Cremer, Rolf H. Groenwold, and Arjen J. C. Slooter

Benzodiazepine-associated delirium in critically ill adults

Any route: OR 1.04 (per 5 mg midazolam, 1.02-1.05)
Infusions: OR 1.04 (1.03-1.06) vs. bolus 0.97 (0.88-1.05)

Benzodiazepine Versus Nonbenzodiazepine-Based Sedation for Mechanically Ventilated, Critically Ill Adults: A Systematic Review and Meta-Analysis of Randomized Trials

Gilles L. Fraser, PharmD, FCCM; John W. Devlin, PharmD, FCCM; Craig P. Worby, PharmD; Waleed Alhazzani, MD; Juliana Barr, MD, FCCM; Joseph F. Dasta, MSc, FCCM, FCCP; John P. Kress, MD; Judy E. Davidson, DNP, RN; Frederick A. Spencer, MD

Conclusions: Current controlled data suggest that use of a dexmedetomidine- or propofol-based sedation regimen rather than a benzodiazepine-based sedation regimen in critically ill adults may reduce ICU length of stay and duration of mechanical ventilation.
In all 4 trials patients who received dexmedetomidine were significantly more arousable, more co-operative and better able to communicate their pain than those who received propofol or midazolam (p ≤ 0.001 in all cases)

- Ventilator Free Days – mean diff 3.28 days
- Time to extubation - Mean diff 1.85 days favouring dexmedetomidine
Eligibility

- Adults who continue to require MV only because their degree of agitation is so severe sedation could not be lessened
- Required to meet all 3 criteria during the 4 h prior to randomization:
  1. need for mechanical restraint, antipsychotic or sedative medication, or both
  2. CAM-ICU + for delirium
  3. MAAS score ≥ 5, confirming psychomotor agitation

Primary Outcome
Median difference 19.5 hours
(95% CI 5.3 to 31.1 h, P<0.001)

Limitations
N = 72
Stopped early
Baseline imbalances
No weaning/extubation protocol
What about Sleep? Now patients are awake...

Diurnal sedative changes during intensive care: impact on liberation from mechanical ventilation and delirium

Higher night time doses independently associated with failure to...
1. Meet SBT screen
2. Pass SBT
3. Be extubated
What about sleep? Now patients are awake...

**BMJ Open** Pharmacological interventions to improve sleep in hospitalised adults: a systematic review

Salmaan Kanji,1,2 Alexandru Mera,3 Brian Hutton,2,4 Lisa Burry,5 Erin Rosenberg,6 Erika MacDonald,2,7 Vanessa Luks8

**Results:** After screening 1920 citations, 15 studies involving 861 patients were included. Medications studied included benzodiazepines, nonbenzodiazepine sedatives, melatonin, propofol and dexmedetomidine. Five studies were deemed to be of high quality.

**Conclusions:** There is insufficient evidence to suggest that pharmacotherapy improves the quality or quantity of sleep in hospitalised patients suffering from poor sleep. No drug class or specific drug was identified as superior even when compared to placebo or no treatment. Although 15 studies were included, the quality of evidence was limited by their quality and size. Larger, better-designed trials in hospitalised adults are needed.

Promote sleep: control light, noise, cluster patient-care activities, reduce nocturnal stimuli.
<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention and patients (N)</th>
<th>Age and sex</th>
<th>Study duration/treatment observation period</th>
<th>Setting</th>
<th>Patient characteristics</th>
<th>Concomitant sedatives, analgesics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Engelmann et al., 2014</td>
<td>Propofol infusion (n=34)</td>
<td>60.2±13 years* 88% male</td>
<td>24 hours/7 hours (BIS only evaluated for first 5 hours)</td>
<td>Surgical step down unit</td>
<td>Postoperative patients without sedation or mechanical ventilation</td>
<td>None reported</td>
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<td></td>
<td>Flunitrazepam (n=32)</td>
<td>59.9±11.0 years* 87.5% male</td>
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<td>Kondili et al., 2012 (crossover)</td>
<td>Propofol infusion (n=7)</td>
<td>73 (63–75) years† 50% male</td>
<td>48 hours/9 hours</td>
<td>Critical care unit</td>
<td>ICU patients with mechanical ventilation for two nights</td>
<td>None reported</td>
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<tr>
<td>Oto et al., 2011</td>
<td>No treatment (n=6)</td>
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<td></td>
<td>Midazolam infusion with daytime interruption (n=11)</td>
<td>68±11 years* 64% male</td>
<td>Not reported/9 hours for interrupted sedation group, 24 hours for continuous sedation group</td>
<td>Critical care unit</td>
<td>Mechanically ventilated adult ICU patients, receiving sedatives &gt;48 hours</td>
<td>Fentanyl, morphine for pain, additional midazolam for ‘as needed’ sedation</td>
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<tr>
<td></td>
<td>Midazolam continuous infusion (n=11)</td>
<td>72±9 years* 82% male</td>
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<tr>
<td>Bourne et al., 2008</td>
<td>Melatonin (n=12)</td>
<td>69.9±12 years* 33% male</td>
<td>4 nights/9 hours</td>
<td>Critical care unit</td>
<td>ICU patients requiring mechanical ventilation and tracheostomy to assist weaning</td>
<td>None reported</td>
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<tr>
<td></td>
<td>Placebo (n=12)</td>
<td>58.7±12.5 years* 58.3% male</td>
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<tr>
<td>Ibrahim et al., 2006</td>
<td>Melatonin (n=14)</td>
<td>63 (54–72) years† 57% male</td>
<td>At least 48 hours/8 hours</td>
<td>Critical care unit</td>
<td>ICU patients with tracheostomy, weaning from mechanical ventilation, GCS &gt;9, no sedatives for 12 hours</td>
<td>None reported</td>
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<tr>
<td></td>
<td>Placebo (n=18)</td>
<td>57 (46 to 68) years§ 61% male</td>
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<tr>
<td>Li et al., 2004</td>
<td>Lorazepam orally (n=10)</td>
<td>56.6 (20–78) years§ 44% male</td>
<td>14 nights/not reported</td>
<td>Rehabilitation unit in acute care hospital</td>
<td>Adults with diagnosis of either stroke/acquired brain injury, secondary insomnia</td>
<td>4 patients receiving antidepressants</td>
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<tr>
<td></td>
<td>Zopiclone orally (n=10)</td>
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<td>Morgan et al., 1997</td>
<td>Triazolam (n=119)</td>
<td>Range 19–71 years</td>
<td>24 hours/8 hours</td>
<td>Acute care unit</td>
<td>Hospitalised patients undergoing elective surgery</td>
<td>None reported</td>
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<tr>
<td></td>
<td>Zolpidem (n=120)</td>
<td>32% male</td>
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<tr>
<td>Feldmeier and Kapp, 1983</td>
<td>Midazolam orally (n=19)</td>
<td>33±13 years* 37% male</td>
<td>7 nights not reported</td>
<td>Hospital ward</td>
<td>Hospitalised patients with insomnia</td>
<td>None reported</td>
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<td></td>
<td>Oxazepam (n=15)</td>
<td>34±13 years* 27% male</td>
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<td></td>
<td>Placebo (n=16)</td>
<td>27±5 years* 50% male</td>
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<tr>
<td>Goetzke et al., 1983 (crossover)</td>
<td>Brotizolam orally (n=79)</td>
<td>48.9±12.7 years* 39% male</td>
<td>14 nights/not reported</td>
<td>Acute care unit</td>
<td>Hospitalised adult patients requiring a hypnotic due to sleep difficulties</td>
<td>None reported</td>
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<tr>
<td></td>
<td>Triazolam orally (n=79)</td>
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H: Home medication and withdrawal

- Consider withdrawal from home medications (e.g. SSRI), nicotine & alcohol.
- Consider withdrawal of sedatives & opioids used during the ICU stay.
Summary

• It is very important to consider pain, sedation, & agitation in the weaning process.

• Use ABCDEFGH to support the weaning process

• Consider the pharmacokinetics-dynamics of the drugs you select
  – Consider this at minimum daily as requirements will vary