Optimising Sedation and Delirium management in the ICU: a complex systems level challenge

Tim Walsh
Professor of Critical Care, Edinburgh University
Staff education, regular sedation and analgesia quality feedback, and a sedation monitoring technology for improving sedation and analgesia quality for critically ill, mechanically ventilated patients: a cluster randomised trial


Summary
Background Optimal sedation of patients in intensive care units (ICUs) requires the avoidance of pain, agitation, and unnecessary deep sedation, but these outcomes are challenging to achieve. Excessive sedation can prolong ICU stay, whereas light sedation can increase pain and frightening memories, which are commonly recalled by ICU survivors. We aimed to assess the effectiveness of three interventions to improve sedation and analgesia quality: an online education programme; regular feedback of sedation–analgesia quality data; and use of a novel sedation-monitoring technology (the Responsiveness Index [RI]).

Methods We did a cluster randomised trial in eight ICUs, which were randomly allocated to receive education alone (two ICUs), education plus sedation–analgesia quality feedback (two ICUs), education plus RI monitoring

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*Full list of investigators provided in the appendix

Around **25-30% of ICU survivors** have frightening and/or traumatic memories early after ICU discharge.
Patient recall of intensive care

• Pain and frightening memories are frequently recalled by ICU survivors

• Frightening and delusional memories associated with post-trauma psychological morbidity after critical illness
  Parker AM et al. Critical Care Medicine 2015; 43(5):1121-9
Top Priorities for Intensive Care Research

This James Lind Alliance (JLA) Priority Setting Partnership aimed to identify and prioritise unanswered questions about adult intensive care that are important to people who have been critically ill, their families, and the health professionals who care for them.

After a process spanning 2 years, the top 3 priorities in intensive care research have been set and a further 9 identified.

Top 3 priorities for intensive care research

1. How can patients who may benefit from intensive care be identified early and admitted to the ICU at the right time?

2. How can patients and their families be best supported as they start living at home again (e.g., health and social care services, ICU support groups, long-term follow-up)?

3. What is the best way to identify patients with, or at risk of delirium or agitation—how should the immediate and long-term effects of delirium or agitation be monitored and managed?

Other high priorities for Intensive care research (unranked):

- What is the best way to prevent, diagnose and treat hospital-acquired infection (e.g., ventilator-associated pneumonia, bloodstream infections related to the use of invasive lines)?

- When should physical rehabilitation start and what rehabilitation methods during and after critical illness achieve the best outcomes for patients?

- How can we enhance patient comfort during intensive care (i.e., minimise pain).
“What is the best way to identify patients with, or at risk of delirium or agitation – how should the immediate and long-term effects of delirium or agitation be monitored and managed?“

"How can we enhance patient comfort during intensive care (ie, minimise pain, discomfort, agitation and anxiety) and does this improve patient outcome?"

Perspectives

• Critical Care Physician
• Critical Care Nurse
Daily Interruption of Sedative Infusions in Critically Ill Patients Undergoing Mechanical Ventilation
John P. Kress, M.D., et al
NEJM 2000 Volume 342:1471-1477

No difference in adverse events
Lower neurological investigation rates in “wake up” group
Similar outcomes with midazolam and propofol
Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial
Girard TD et al. Lancet 2008; 371: 126

<table>
<thead>
<tr>
<th>Table 3: Main outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention group (n=167)</strong></td>
</tr>
<tr>
<td>Ventilator-free days*</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Median</td>
</tr>
<tr>
<td>Time to discharge (days)</td>
</tr>
<tr>
<td>From intensive care</td>
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<tr>
<td>From hospital</td>
</tr>
<tr>
<td>28-day mortality</td>
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<tr>
<td>1-year mortality</td>
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<tr>
<td>Duration of brain dysfunction (days)</td>
</tr>
<tr>
<td>Coma</td>
</tr>
<tr>
<td>Delirium</td>
</tr>
<tr>
<td>RASS at first successful SBT</td>
</tr>
<tr>
<td>Complications</td>
</tr>
<tr>
<td>Any self-extubation</td>
</tr>
<tr>
<td>Self-extubation requiring reintubation‡</td>
</tr>
<tr>
<td>Reintubation‡</td>
</tr>
<tr>
<td>Tracheostomy</td>
</tr>
</tbody>
</table>

Data are mean (SD), n (%), or median (IQR). RASS=Richmond agitation-sedation scale. SAT=spontaneous awakening trial. SBT=spontaneous breathing trial. *Ventilator-free days from study day 1 to 28. †Greater than 25% of patients in the SBT group remained in the hospital at study day 28. ‡Reintubation within 48 hours of extubation.
Intervention group:
- Higher benzodiazepine and opioid use
- Greater perceived nursing workload
- No ‘beneficial’ effects
A protocol of no sedation for critically ill patients receiving mechanical ventilation: a randomised trial

Thomas Strøm, Torben Martinussen, Palle Toft

Lancet 2010; 375: 475–80

Trend to lower mortality
Lower ventilation days
Higher nursing resource use
Higher rates of agitation in non-sedated group
No patient-based psychological/experience measure
Does daily sedation interruption reduce the time critically ill adults spend on breathing machines compared to other sedation strategies?

**Background:** critically ill patients require life-support technologies such as mechanical ventilation (breathing machines) and can experience pain, anxiety, and sleep deprivation related to their illness. Good pain control and adequate sedation are important but too much sedative drug can increase the time on breathing machines and the chance of harmful effects such as pneumonia.

Medications that are available have many properties that make them difficult to use in critically ill patients. Without careful adjustments these properties can lead to a build up of drug in the body. These medications are given as continuous infusions, so that blood levels remain stable, and dose changes are left to clinician judgement. In order to avoid drug build up, several methods can be used to adjust doses. Some studies claim that an interruption, or stopping the drug for a period of time each day, will allow the body to clear the drugs and lead to patients being more awake and ready for earlier liberation from the breathing machine.

**Search date:** current to February 2014.

**Study characteristics:** we included nine studies involving 1282 critically ill patients receiving mechanical ventilation. Studies compared daily sedation interruption to strategies that did not include an interruption. Studies were conducted worldwide and involved both medical and surgical critically ill patients.

**Key results:** we did not find strong evidence that daily sedation interruption reduced the duration of mechanical ventilation, length of stay in the intensive care unit (ICU) or hospital, death, or the amount of drug used. The effect on adverse events such as accidental removal of the breathing tube or invasive devices, or the rate of delirium was uncertain. However, tracheostomy was performed less often in those who were managed with daily sedation interruption. Sedation practices are known to vary worldwide, and as such an analysis of studies conducted in North America showed a reduction in time on the breathing machine for those who were managed with daily sedation interruption compared to those who were not.

Inconclusive evidence

Context specific
Early deep sedation associated with higher mortality (in adjusted analyses)
Early deep sedation is associated with decreased in-hospital and two-year follow-up survival

Felix Balzer, Björn Weiß, Oliver Kumpf, Sascha Treskatsch, Claudia Spies, Klaus-Dieter Wernecke, Alexander Krannich and Marc Kastrup

During first 48 hours in ICU
RASS score -2 to 0
RASS score ≤ -3
What does this tell us?

- Protocolized approaches can improve sedation-related outcomes
- Heavy focus on avoiding deep sedation
- Effectiveness of protocolised approaches context specific

- Deep sedation associated with adverse outcomes
- Early deep sedation associated with adverse outcomes
Implications of minimising sedation

- Admission
- "Old"
- "New"
- Avoidance of unnecessary or unintended prolongation
- Dealing with prolonged periods of wakefulness

Discharge
Implications of minimising sedation

- Tolerance of intubation and invasive ventilation
  - Analgesia
  - Antinociception
  - Airway reflexes
- Minimising risk of delirium
- Managing agitation
- Managing Pain/discomfort
Perspectives

• Critical Care Physician
• Critical Care Nurse
"I just think that people waking up is one of the hardest things we have to witness here, because people are uncomfortable, they get a fright. You know it is quite nerve racking sometimes because you don’t know what is going to happen..."

- Conflict, power, fear, and guilt cycles
- “Damned if you do; damned if you don’t”
Clinical Practice Guidelines for the Prevention and Management of Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disruption in Adult Patients in the ICU

• 37 recommendations (only 3 strong; 34 conditional)
• Need for integrated approach
• Consider Pain, Agitation, and Delirium

• Uncertainty how to drive system level quality improvement
  ‘we may know what do to but we are unsure how to do it’

Interpreting and implementing the 2018 pain, agitation/sedation, delirium, immobility, and sleep disruption clinical practice guideline.
Balas MC et al. Critical Care Medicine. 46 (9) (pp 1464-1470), 2018.
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*Full list of investigators provided in the appendix
• Measures that capture:
  • Agitation
  • Unnecessary deep sedation
  • Pain
  • Relevant adverse events in mechanically ventilated patients
• Focus groups for face and construct validity
• Comparison with existing measures for criterion validity
• Methods for charting for “process control”
• Assessment in practice
Sedation Quality Assessment Tool (SQAT)

- Every 12 hour nursing shift
- Face validity (focus groups)
- Criterion validity (comparison with BPS and RASS score)
- Reliability (inter-rater clinical staff and comparison with single researcher)

**Section 1**
Date shift started: [ ] Time of completion (24hr): [ ] Pt Key No: [ ]

**Section 2**
Has this patient received mechanical ventilation via endotracheal or tracheostomy tube during the past 12 hours? (Please circle). Yes No

**Section 3**
Has this patient received continuous intravenous infusion/intermittent bolus of sedative during past 12 hours? (Please circle). Yes No

**Section 4**
Has this patient received continuous intravenous infusion/intermittent bolus of analgesic drug during past 12 hours? (Please circle). Yes No

**Section 5**
Is this patient currently receiving neuromuscular paralysis? (Please circle). Yes No

**Section 6**
What is the patient’s facial expression over the previous hour? (Tick)
- Relaxed most of the time
- Frowning most of the time
- Facial grimacing most of the time

In response to moving the patient, how are their limbs over the previous hour? (Tick)
- Easy to move most of the time
- Difficult to move most of the time
- Actively resisting movement most of the time
- Limb movement contraindicated clinically

How compliant is the patient with the ventilator over the previous hour? (Tick)
- Not currently on ventilator
- Tolerating ventilation well most of the time
- Tolerating ventilation but coughing/puking frequently
- Unable to control ventilation due to poor patient synchronisation despite different modes tested

**Section 7**
Please tick ONLY ONE of the following boxes that best represents your patient at this moment in time:
- On observation patient is currently alert and calm
- On observation patient is currently combative or violent or dangerous/aggressive towards staff or pulling/removing tubes, catheters or drains
- On observation patient is anxious or apprehensive; or displaying frequent non-purposeful movement
- My patient opens their eyes in response to me calling their name
- Movement is observed in response to me calling their name but they do not open their eyes
- My patient does not respond to their name being called but movement is observed in response to physical stimulation
- My patient shows no response to physical stimulation

**Section 8**
During the past 12 hours, from your knowledge of this patient, has the patient displayed any of the following behaviours (please tick):
- Combative or violent; dangerous or aggressive towards staff; pulling or removing tubes, catheters or drains?
- If YES to above, was this in association with a sedation hold

**Section 9**
Has the patient received any of the following therapeutic interventions in the last 12 hours? (Please tick):
- Advanced ventilator modes (prone ventilation, high frequency oscillatory ventilation; nitric oxide; APRV; PEEP ≥ 15 cm H2O) and/or Therapeutic hypothermia

Please place the form in the DESIST box once completed.

DESIST study, Sedation Quality Assessment Tool (SQAT) version 3.2 (09/02/2012)
Sedation Quality Assessment Tool (SQAT)

- Every 12 hour nursing shift
- Face validity (focus groups)
- Criterion validity (comparison with BPS and RASS score)
- Reliability (inter-rater clinical staff and comparison with single researcher)

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<thead>
<tr>
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<th>Date shift started:</th>
<th>Time of completion (24hr):</th>
<th>Pt Key No:</th>
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</table>

<table>
<thead>
<tr>
<th>Section 2</th>
<th>Has this patient received mechanical ventilation via endotracheal or tracheostomy tube during the past 12 hours? (Please circle)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Section 3</td>
<td>Has this patient received continuous intravenous infusion/intermittent bolus of sedative during past 12 hours? (Please circle)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Section 4</td>
<td>Has this patient received continuous intravenous infusion/intermittent bolus of analgesic drug during past 12 hours? (Please circle)</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Section 5</td>
<td>Is this patient currently receiving neuromuscular paralysis? (Please circle) If YES, proceed to section 9.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Please choose the option that best describes your patient. Tick ONLY ONE response for each question:

### What is the patient’s facial expression over the previous hour?

<table>
<thead>
<tr>
<th>Option</th>
<th>Tick</th>
</tr>
</thead>
<tbody>
<tr>
<td>relaxed most of the time</td>
<td></td>
</tr>
<tr>
<td>frowning most of the time</td>
<td></td>
</tr>
<tr>
<td>facial grimacing most of the time</td>
<td></td>
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</tbody>
</table>

### In response to moving the patient, how are their limbs over the previous hour?

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<th>Option</th>
<th>Tick</th>
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</tr>
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<td>difficult to move most of the time</td>
<td></td>
</tr>
<tr>
<td>actively resisting movement most of the time</td>
<td></td>
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### How compliant is the patient with the ventilator over the previous hour?

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Sedation Quality Assessment Tool (SQAT)

- Every 12 hour nursing shift
- Face validity (focus groups)
- Criterion validity (comparison with BPS and RASS score)
- Reliability (inter-rater clinical staff and comparison with single researcher)
Most valid and reliable pain/discomfort metrics

• Proportion of SQAT periods with poor relaxation
• Proportion of SQAT periods with poor ventilator synchronisation
• Proportion of SQAT periods with agitation
• Proportion of SQAT periods with unnecessary deep sedation
• Proportion of SQAT periods with overall optimum sedation

• Proportion of care periods and patients with sedation-related adverse event
Poor relaxation was present for 9.5% of nursing shifts

Poor ventilator synchronisation was present for 7% of nursing shifts

Optimum sedation was present for 69% of nursing shifts

Excessive sedation was present for 4% of nursing shifts
Proportion of care period with different quality measures during 12 months of data collection

<table>
<thead>
<tr>
<th>Quality process measure</th>
<th>ICU (number of SQAT periods used to assess optimum sedation rate)</th>
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<td>Agitation</td>
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<td>Poor relaxation</td>
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<td>Overall sedation optimum</td>
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<tr>
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<td>45</td>
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</tbody>
</table>
Primary outcome

Proportion of DESIST care periods with optimum sedation

*Care period without agitation, excessive sedation, poor limb relaxation, or poor ventilator synchronisation*

Adverse events

*Unplanned removal of nasogastric (NG) tube, central line, arterial line or drain; unplanned extubation; staff injury; or patient injury.*

1. Proportion of days during mechanical ventilation on which a sedation-related adverse event occurred.

2. Proportion of patients receiving mechanical ventilation in whom a sedation-related adverse event occurred.
Study Design: modified cluster randomised trial
Setting: 8 ICUs in Scotland
DESIST Sedation Quality Feedback (Four ICUs)

- Algorithms developed to generate process control charts to describe proportions of patients over time

- Reports and slide sets fed back every two months during post-intervention period
  - Sedation quality
  - Adverse event rates
<table>
<thead>
<tr>
<th>Proportion during this period</th>
<th>Proportion during baseline period</th>
<th>Effect on sedation quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excessive sedation was present for <strong>12%</strong> of nursing shifts</td>
<td><strong>15%</strong></td>
<td>3% <strong>LOWER</strong> rate of excessive sedation</td>
</tr>
<tr>
<td>Agitation was present for <strong>7%</strong> of nursing shifts</td>
<td><strong>14%</strong></td>
<td>7% <strong>LOWER</strong> rate of agitation</td>
</tr>
<tr>
<td>Poor relaxation (a measure of pain and discomfort) was present for <strong>9.5%</strong> of nursing shifts</td>
<td><strong>19.5%</strong></td>
<td>10% <strong>LOWER</strong> rate of poor relaxation</td>
</tr>
<tr>
<td>Poor ventilator synchronisation was present for <strong>7%</strong> of nursing shifts</td>
<td><strong>11.5%</strong></td>
<td>4.5% <strong>LOWER</strong> rate of poor ventilator synchronisation</td>
</tr>
<tr>
<td>0 sedation related adverse events occurred during this period</td>
<td><strong>20</strong> (October 2012 – November 2013)</td>
<td></td>
</tr>
<tr>
<td><strong>Overall, optimum sedation was present for 69%</strong> of nursing shifts</td>
<td><strong>58%</strong></td>
<td>11% <strong>HIGHER</strong> rate of optimum sedation</td>
</tr>
</tbody>
</table>
2-3 hours of learning

9 modules:
1. Why is it important to get sedation right?
2. Assessing sedative state
3. Commonly used agents in sedation
4. Avoiding excessive sedation
5. Assessing pain and discomfort in ICU
6. Managing agitation
7. Managing delirium
8. Drug withdrawal
9. Helping patients sleep in the ICU

Knowledge-based assessment test for most modules to achieve “pass”

LearnPro NHS: http://www.learnpro.co.uk

http://packagemanager.learnprouk.com
Open access username: desisttest
DESIST Responsiveness monitoring (4 ICUs)

- Novel technology developed through GE Healthcare/Edinburgh University collaboration
- Continuous alert to potential excessive sedation
- Utilises previous 60 minutes of facial EMG data (forehead electrodes) to generate index of “average arousal”
**Proof of concept trial**

- Single centre parallel group RCT
- Technology modified nurse decision-making
- Trends towards quicker achievement of higher responsiveness and earlier extubation
- Safe and acceptable to staff

Baseline rates of sedation quality
(based on 881 patients; >9000 12-hour care periods)

<table>
<thead>
<tr>
<th>Sedation-Analgesia Quality Measure</th>
<th>% of care periods with measure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Outcome</strong></td>
<td></td>
</tr>
<tr>
<td>Optimum Sedation</td>
<td>56.1</td>
</tr>
</tbody>
</table>
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Figure 3: Estimates of effects of each intervention on sedation-anaesthesia quality measures at the care period level, and sedation-related adverse events

Figure shows ORs with 95% CIs. For the sedation-anaesthesia quality measures, OR > 1 indicates an increase in the outcome with the intervention (improvement); for the sedation-related adverse event outcomes, an OR < 1 indicates a decrease in the outcome with the intervention (improvement). Data from all ICUs were combined in a single statistical model to explore the independent effects of each of the three interventions. Results are from multi-level generalised linear model to estimate the effects of each intervention. OR = odds ratio.

Multi-level generalised multilevel mixed modelling
Statistical approach to detect effects in complex datasets
Effects presented as Odds Ratios
Impact of interventions in DESIST

Education
- On line education was feasible and enabled training of all staff in a highly efficient trackable manner
- Staff knowledge improved significantly following education, and was sustained during follow-up
- Staff found the package useful and relevant
- Implementation was associated with fewer sedation-related adverse events

Sedation process data feedback
- Regular feedback of sedation ‘processes’ had no effect on outcomes
- Staff found it too distant and difficult to understand in isolation to change practice

Novel bedside technology driving change
- Decreased deep sedation and improved overall sedation quality
- Staff had mixed views; challenged decision-making
- Data showed limited use of monitor to alter decisions
Importance of delirium

Clinical
• Associated with major adverse clinical outcomes

Economic
• Associated with greater illness cost and loss of Quality Adjusted Life Years (QALYs)

Patient centred
• Frightening memories
• Sleep disturbance
• Possibly psychological outcomes (via frightening/delusional memories)

Research shows clear association but does not prove causal relationship
Clinical manifestations

Sub-syndromal classification
• Agitated  \(\approx 10\%\)
• Hypoactive  40-60\%
• Mixed  20-40\%

Spectrum of severity
Interaction with sedation

Hallucinations and delusions common
• not necessary for diagnosis
• Frightening memories associated with increased Post-traumatic stress
Some causes of agitation

Synchrony with ventilator
Analgesia
Delirium
is
Bowels
Anxiety
Drug withdrawal

Not all agitation is delirium
Agitation may be multifactorial
Minimising risk of delirium

Pre-emptive antipsychotic medication

• Important to distinguish \textit{elective surgical populations} from \textit{non-elective mixed ICU populations}

• Some evidence for low dose prophylaxis in elective surgery:
  • Risperidone (cardiac surgery; Prakanrattana U et al. Anaesth Intensive Care 2007; 35: 714-9)

• Dexmedetomodidine
Efficacy of perioperative dexmedetomidine on postoperative delirium: systematic review and meta-analysis with trial sequential analysis of randomised controlled trials

X. Duan¹,², M. Coburn²,*, R. Rossaint², R. D. Sanders³, J. V. Waesberghe² and A. Kowark²

- 18 studies (3309 patients)
- Explored cardiac/non-cardiac; timing; age
- Typical dose 0.2 microgram/kg/hour
- Variable duration and use of loading dose
- Explored range of secondary outcomes (mortality, length of stay)
Cardiac surgery

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DEX group</th>
<th>Control group</th>
<th>Odds ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1 cardiac surgery</strong></td>
<td><strong>Events</strong></td>
<td><strong>Total</strong></td>
<td><strong>Events</strong></td>
<td><strong>Total</strong></td>
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<tr>
<td>Balkanay OO 2015</td>
<td>0</td>
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<td>1</td>
<td>28</td>
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<td>Corbett SM 2005</td>
<td>1</td>
<td>43</td>
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<td>46</td>
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<td>Djaiani G 2016</td>
<td>16</td>
<td>91</td>
<td>29</td>
<td>92</td>
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<tr>
<td>Li X 2017</td>
<td>7</td>
<td>142</td>
<td>11</td>
<td>143</td>
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<td>Liu X 2016</td>
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<td>2</td>
<td>32</td>
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<td>Maldonado JR 2009</td>
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<tr>
<td>Park JB 2014</td>
<td>6</td>
<td>67</td>
<td>17</td>
<td>75</td>
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<td>Priye S 2015</td>
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<tr>
<td>Shehabi Y 2009</td>
<td>13</td>
<td>152</td>
<td>22</td>
<td>147</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>646</strong></td>
<td>655</td>
<td>42.3%</td>
<td>0.41 [0.26, 0.63]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>45</td>
<td>118</td>
<td>646</td>
<td>655</td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.05; Chi² = 9.01, df = 8 (P = 0.34); I² = 11%</td>
<td></td>
<td></td>
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<tr>
<td>Test for overall effect: Z = 4.07 (P &lt; 0.0001)</td>
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</table>

**2 non-cardiac surgery**

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>DEX group</th>
<th>Control group</th>
<th>Odds ratio</th>
<th>M-H, Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Chang J 2017</td>
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<td>29</td>
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<td>Deiner S 2017</td>
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<td>Guo Y 2015</td>
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<td>Huang F 2014</td>
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<tr>
<td>Liu Y 2016</td>
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<td>99</td>
<td>43</td>
<td>98</td>
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<tr>
<td>Ma P-P 2013</td>
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<td>30</td>
<td>11</td>
<td>90</td>
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<td>Su X 2016</td>
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<td>350</td>
<td>79</td>
<td>350</td>
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<td>Wan LJ 2011</td>
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<td>102</td>
<td>31</td>
<td>98</td>
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<tr>
<td>Yang X 2015</td>
<td>2</td>
<td>39</td>
<td>5</td>
<td>40</td>
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<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>970</strong></td>
<td>1038</td>
<td>57.7%</td>
<td>0.33 [0.18, 0.59]</td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>97</td>
<td>230</td>
<td>970</td>
<td>1038</td>
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<tr>
<td>Heterogeneity: Tau² = 0.44; Chi² = 24.96, df = 7 (P = 0.0008); I² = 72%</td>
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<tr>
<td>Test for overall effect: Z = 3.71 (P = 0.0002)</td>
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</tbody>
</table>

**Total (95% CI)**

<table>
<thead>
<tr>
<th>Odds ratio</th>
<th>M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.35 [0.24, 0.51]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 142 and 348, Heterogeneity: Tau² = 0.26; Chi² = 33.94, df = 16 (P = 0.006); I² = 53% Test for overall effect: Z = 5.47 (P < 0.00001) Test for subarachnoid differences: Chi² = 0.32, df = 1 (P = 0.57). I² = 0%
Peri/post operative dexmedetomidine

- Decreases post-operative delirium
- Consistent effects in all surgery types
- Effects seen in younger and older groups
- Suggestion of greater effect with longer infusions (around 10-12 hours or until end of MV)

- Inadequate information quality for mortality and length of stay outcomes
- Uncertainty about optimum dose/timing
Minimising risk of delirium

Pre-emptive antipsychotic medication in mechanically ventilated ICU patients

  • Reduced use of sedatives and opiates
  • Agitation reduced

• REDUCE RCT: prophylactic low dose haloperidol no effect on 28 days survival (N = 1789), or delirium outcomes (JAMA. 2018;319(7):680-690. doi:10.1001/jama.2018.0160)

• Evidence of harm (greater mortality) with rivastigmine (van Eijk MM, et al. Lancet 2010; 376; 1829-37)
Minimising risk of delirium

α2-agonists

- **MENDS** (Pandharapande et al JAMA; 2007; 298:2644)
  - Dex (continuous) vs lorazepam (intermittent)
  - Similar prevalence of delirium (high risk group)
  - Shorter duration; less coma days with dex
  - Post-hoc sub-group analysis suggested possible mortality benefit in sepsis patients

- **SEDCOM** (Riker et al JAMA; 2009; 301:489)
  - Dex (continuous) vs midazolam (continuous)
  - 22% ARR in delirium; reduced delirium days

- **PRODEX and MIDDLEX**
  - PRODEX less effect on ventilation days
  - Delirium not diagnosed using CAM-ICU

- Role of clonidine (much cheaper) uncertain
• 18 trials; only one with clonidine (low quality)
• 17 trials with dexmedetomidine
• Comparator mostly benzodiazepines (some propofol)
• Mixed populations

• No effect on mortality
• Effects on ICU stay (mean 1 days) and duration of MV (mean 2 days)
• No effect on delirium
FIGURE 11 Meta-analysis for ICU length of stay: all available data (including transformed and imputed data). IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; PROPOFOL, propofol compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.

FIGURE 15 Meta-analysis for incidence of delirium. IV, inverse variance; LORAZ, lorazepam compared with dexmedetomidine; MIDAZOLAM, midazolam compared with dexmedetomidine; SC, standard care compared with dexmedetomidine.
Effect of Dexmedetomidine on Mortality and Ventilator-Free Days in Patients Requiring Mechanical Ventilation With Sepsis: A Randomized Clinical Trial

Yu Kawazoe, MD, PhD; Kyohei Miyamoto, MD; Takeshi Morimoto, MD, PhD, MPH; Tonomori Yamamoto, MD; Akihiro Fuke, MD; Atsunori Hashimoto, MD, PhD; Hiroyuki Koami, MD; Satoru Beppu, MD, PhD; Yoichi Katayama, MD; Makoto Itoh, MD; Yoshimori Ohta, MD; Hitoshi Yamamura, MD, PhD; for the Dexmedetomidine for Sepsis in Intensive Care Unit Randomized Evaluation (DESIRE) Trial Investigators

- Sepsis patients in Japan; mean APACHE 23
- Hypothesis based on post hoc analysis of MENDS trial
  - Septic sub-group mortality benefit (compared to lorazepam): 16% versus 41% mortality
  - Sample size for 20% ARR (200 patients)
- Unblinded trial; comparator usual care
- Co-primary outcome of 28 days mortality and ventilator free days
- Delirium as secondary outcome
Mortality 23% versus 31%; 8% ARR in mortality (ns)
VFDs 20 days versus 18 days (ns)
Improved sedation quality (as defined in trial)
No difference in delirium/coma
Pre-emptive α2 agonists

• Evidence for dexmedetomidine uncertain
• Benefits on delirium may be greatest for lower risk-of-death groups
• Unproven possible effects on mortality in higher illness severity groups
  • Signal-to-noise ratio for other outcomes may be higher in sicker patients
• Expensive drug
• SPICE III trial results ‘imminent’

• Evidence for clonidine as superior to current usual care and/or non-inferior to dexmedetomidine lacking
ALPHA-2 AGONISTS FOR SEDATION TO PRODUCE BETTER OUTCOMES FROM CRITICAL ILLNESS

A randomised, parallel-group, allocation concealed, controlled, open, phase 3 pragmatic clinical and cost-effectiveness trial with internal pilot (HTA 16/93/01)

Three arm trial
Propofol versus Dexmedetomidine versus Clonidine
Treating **established** delirium in the ICU patient

- Evidence limited to small studies
- Frequently agitated/non-agitated delirium not distinguished
- Most compare haloperidol, atypical antipsychotics (olanzapine, risperidone, quetiapine), and/or placebo
- Relative side effects/safety uncertain

- **No evidence to support routine treatment of hypoactive delirium with pharmacological therapy**
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness
MIND-USA investigators

• Haloperidol versus ziprasidone versus placebo
• ICU patients with delirium (agitated and non-agitated) N = 566 (90% hypoactive delirium)
• No effect on delirium or coma, or days alive
Agitated delirium

• Important to exclude and treat other causes of agitation

• Haloperidol and atypical antipsychotics useful for management from patient safety perspective
  • Decrease need for sedative drugs
  • May support delirium resolution
  • Main issues are side effects (extrapyramidal; QT-prolongation; interaction with other drugs)

• Dexmedetomidine (and clonidine)
Effect of Dexmedetomidine Added to Standard Care on Ventilator-Free Time in Patients With Agitated Delirium
A Randomized Clinical Trial

Additional of dexmedetomidine to standard care associated with:
• Reduced time to extubation
• Quicker resolution of delirium
• Lower use of antipsychotics
How can we make and measure ICU wide improvements?

• Challenging and complex issue
• Important to clinicians, providers, and patients
• Requires acknowledgement of perspectives of different professional groups and patients
• Quality tracking tools offer potential to measure process that could drive improvement, but are insufficient in isolation
• System-level education is a cheap and valued intervention worth implementing across ICU networks
• Technology based approaches are potential methods to alter clinical decision-making, but require further evaluation
• Key trials may provide clear evidence regarding relative effectiveness of propofol versus alpha2-agonists