The Exit Strategy:  
Use of Dexmedetomidine for Facilitating Extubation

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LEARNING OBJECTIVES

1. Identify complications associated with mechanical ventilation
2. Describe strategies and agents utilized for weaning of mechanical ventilation
3. Explain the mechanism of dexmedetomidine related to use in facilitating extubation
4. Evaluate clinical evidence regarding the role of dexmedetomidine for facilitating extubation
INTRODUCTION

I. Morbidity, Mortality & Economics Related to Prolonged Mechanical Ventilation
   a. Prolonged mechanical ventilation (MV) required in 3-6% admitted to adult intensive care units (ICUs)\(^1\)
   b. Morbidity & mortality
      1. In-hospital mortality: up to 52%\(^2\)
      2. Survival to acute care facility discharge: 49 - 91%\(^3\)
      3. Discharge from long-term acute care (LTAC) facilities: 50%\(^1\)
   c. Economics
      1. Resource utilization
         i. MV > 7 days: 37% total ICU resources consumed\(^2\)
      2. Expenditures
         i. MV costs: $2,000 per day\(^3\)
         ii. Cost associated with prolonged MV
            a. Inpatient charges: $120-135,000 per patient\(^2\)
            b. ICU charges: $24 billion per year\(^3\)

BACKGROUND: MECHANICAL VENTILATION

II. Mechanical Ventilation (MV)
   a. Therapeutic method to assist or replace spontaneous breathing delivered under positive pressure\(^4,5\)
   b. Indications\(^6\)

![Figure 1: Indications for MV](image)

* COPD: Chronic Obstructive Pulmonary Disease
~ ARF: Acute Respiratory Failure
c. Modes of mechanical ventilation (MV)\(^7,8\) (Appendix A)
   1. Assist-control ventilation (ACV)
   2. Pressure-support ventilation (PSV)
   3. Synchronized intermittent mandatory ventilation (SIMV)
   4. Continuous positive airway pressure (CPAP)

d. Complications of prolonged MV
   1. Patient discomfort\(^9\)
   2. Additional sedative and/or neuromuscular blockade requirements\(^9\)
   3. Pulmonary
      i. Airway trauma or barotrauma\(^5,9\)
      ii. Ventilator-induced lung injury\(^5,9\)
      iii. Ventilator-acquired pneumonia\(^3,5,9\)
      iv. Tracheal stenosis\(^5\)
      v. Inadvertent extubations\(^9\)
      vi. Endotracheal tube obstructions\(^9\)
   4. Cardiac\(^5\)
      i. Reduced cardiac output
      ii. Hypotension
      iii. Right ventricular ischemia
   5. Gastrointestinal\(^5\)
      i. Ileus
      ii. Hemorrhage
   6. Cerebrovascular\(^5\)
      i. Increased intracranial pressure

Figure 2: Causes of ARF
* ARDS: Acute Respiratory Distress Syndrome
III. Weaning from the Ventilator\textsuperscript{3,10}
   a. Transition from ventilatory support to spontaneous breathing by reducing support given by ventilator\textsuperscript{3,9,10}
   b. Two aspects
      1. Liberation from mechanical support\textsuperscript{3,10}
      2. Removal of artificial airway\textsuperscript{3,10}
   c. Epidemiology\textsuperscript{3}
      1. 31\% experience difficulty weaning
         i. Requiring up to 3 spontaneous breathing trials (SBT)(described later) or $\geq 7$ days from the first SBT to achieve successful weaning
      2. ICU mortality of difficult weaning patients: $\sim$25\%
   d. Pathophysiology of weaning failure
      1. Weaning failure: SBT failure, re-intubation &/or resumption of ventilator support $< 48$ h post-extubation\textsuperscript{3,10}
      2. Contributors to weaning failure
         i. Respiratory
            a. Ventilator - induced contributors
               1. Increased airway resistance\textsuperscript{3,11}
               2. Increased work of breathing\textsuperscript{3}
            b. Disease - induced contributors
               1. Increased airway resistance\textsuperscript{3,11}
               2. Decreased respiratory compliance\textsuperscript{3,11}
               3. Disturbances in gas exchange\textsuperscript{11}
         ii. Cardiac
            a. Increased cardiac workload\textsuperscript{3,11}
            b. Cardiac dysfunction prior to critical illness\textsuperscript{3,11}
         iii. Neuromuscular
            a. Depressed or inadequate central drive\textsuperscript{3,11}
            b. Peripheral neuromuscular dysfunction\textsuperscript{3,11}
            c. Critical illness neuromuscular abnormalities (CINMA)\textsuperscript{3}
         iv. Neuropsychological\textsuperscript{3,11}
            a. Delirium
            b. Anxiety
            c. Depression
         v. Metabolic\textsuperscript{3,11}
            a. Endocrine disturbances
            b. Acid-base disturbances
         vi. Nutrition and electrolytes
            a. Overweight\textsuperscript{3}
            b. Malnutrition\textsuperscript{3,11}
            c. Electrolyte abnormalities\textsuperscript{3,11}
e. Risk factors for weaning failure
   1. Neurological impairment
   2. Delirium
   3. Age > 70 years
   4. Prolonged duration of ventilation prior to extubation
   5. Anemia (hemoglobin < 10 g/dL or hematocrit < 30%)
   6. Severity of illness at time of extubation
   7. Use of continuous intravenous sedation

V. The Weaning Process
a. Stages of weaning

![Diagram of stages of weaning from MV]

**Figure 3: Stages of weaning from MV**

1. Stage 1: Treatment of ARF
   i. Treatment and resolution of disorder that caused ARF and prompted MV

2. Stage 2: Assessment of readiness to wean
   i. Begins when daily testing of physiological measures of weaning readiness are initiated
   ii. Ends when results of daily tests justify SBT (Appendix B)

3. Stage 3: SBT
   i. Assessment of patient’s ability to breath spontaneously
   ii. Repeated daily to determine earliest time for successful extubation

4. Stage 4: Extubation
   i. Removal of the endotracheal tube
   ii. Decision to remove artificial airway made on basis of
      a. Mental status
      b. Airway protective mechanisms
      c. Ability to cough
      d. Character of secretions

5. Stage 5: Re-intubation
   i. Replacement of the endotracheal tube for inability to sustain spontaneous ventilation
VI. **Non-Pharmacologic Strategies**
   a. Inspiratory muscle training\(^{11}\)
   b. Weaning protocols\(^3\)
   c. Rehabilitation\(^3\)

VII. **Pharmacologic Strategies**
   a. Antioxidant supplementation\(^{11}\)
   b. Analgesia\(^{13,14}\)
      1. Reduce use of opioids
         i. Guidelines for management of pain in MV recommend fentanyl\(^{14}\)
   c. Antipsychotics
      1. Guidelines for management of delirium in MV recommend haloperidol
      2. Haloperidol\(^{14-18}\)
         i. Mechanism of action: dopamine (D\(_1\) & D\(_2\)) receptor blockade
         ii. Dosing
            a. Initial IV bolus: 2-10 mg q15-30min
            b. Maintenance IV bolus: 5 mg or 25% last bolus dose q6h
         iii. Onset: 30-60 min
         iv. Half-life: 14-18 h
         v. Metabolism: hepatic glucuronidation & CYP 3A4
         vi. Adverse effects: hypotension, akathisia, somnolence, dystonia, blurred vision, extra-pyramidal symptoms (EPS), QT prolongation
   d. Sedation\(^{13,14}\)
      1. Reduce use of sedatives with respiratory depressive effects (i.e. benzodiazepines (BDZ), propofol)
      2. BDZ are most commonly administered sedatives in ICU\(^{17}\)
      3. Guidelines for management of sedation in MV recommend lorazepam and propofol\(^{13}\)

<table>
<thead>
<tr>
<th>MOA</th>
<th>Midazolam</th>
<th>Lorazepam</th>
<th>Propofol</th>
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<tbody>
<tr>
<td>GABA(_a)/BDZ receptor agonist</td>
<td>GABA(_a)/BDZ receptor agonist</td>
<td>GABA(_a) receptor agonist, N-methyl-D-aspartate (NMDA) &amp; Ca(^2+) channel antagonist</td>
<td></td>
</tr>
<tr>
<td>Pharmacodynamic effects</td>
<td>anxiolysis, sedation, hypnosis, amnesia</td>
<td>anxiolysis, sedation, hypnosis, amnesia</td>
<td>anesthesia, sedation, hypnosis, amnesia</td>
</tr>
<tr>
<td>Dose</td>
<td>IV loading dose: 0.01-0.05 mg/kg Maintenance infusion: 0.02-0.1 mg/kg/h</td>
<td>Intermittent IV boluses: 0.02-0.06 mg/kg Q2-6H Continuous infusion: 0.01-0.1 mg/kg/h</td>
<td>Continuous infusion: 5-80 mcg/kg/min</td>
</tr>
<tr>
<td>Onset</td>
<td>2-5 min</td>
<td>5-20 min</td>
<td>&lt; 2 min</td>
</tr>
<tr>
<td>Half-life</td>
<td>3-12 h</td>
<td>10-20 h</td>
<td>1-12 h</td>
</tr>
<tr>
<td>Metabolism</td>
<td>CYP 3A4/5; active metabolites</td>
<td>hepatic glucuronidation; inactive metabolites</td>
<td>hepatic hydroxylation &amp; glucuronidation; inactive metabolites</td>
</tr>
<tr>
<td>Adverse effects</td>
<td>decreased RR &amp; tidal volume, hypotension</td>
<td>respiratory depression, hypotension</td>
<td>hypotension, apnea, hypertriglyceridemia</td>
</tr>
</tbody>
</table>
DEXMEDETOMIDINE (PRECEDEX®)

VIII. Dexmedetomidine

a. Mechanism of Action\textsuperscript{13,20}
   1. Potent centrally acting $\alpha_2$ agonist
      i. Highly selective for $\alpha_2$ receptors
      ii. $\alpha_1 : \alpha_2$ binding affinity ratio of 1620:1
   3. Sedative, anxiolytic, sympatholytic, and analgesic properties

b. Background
   1. FDA approval: 1999 for use as continuous infusion in ICU for up to 24 h during MV\textsuperscript{13,20,21}
   2. Dosing for ICU sedation:
      i. 1 mcg/kg IV over 10 min, followed by maintenance infusion 0.2-0.7 mcg/kg/h up to 1.5 mcg/kg/h\textsuperscript{13,20,21}
      ii. Conversion from alternative sedation may not require loading dose\textsuperscript{21}
   3. Pharmacokinetics\textsuperscript{13,20,21}
      i. Onset of action: 15 min
      ii. Biphasic half-life ($t_{1/2}$)
         a. Distribution $t_{1/2}$: 6 min
         b. Terminal elimination $t_{1/2}$: 2 h
      iii. Metabolism: hepatic to inactive metabolites via cytochrome P-450 oxidation (primarily 2A6) and glucuronidation
      iv. Excretion: 95% urine; 5% feces
   4. Side effect profile
      i. Hypotension (30%)\textsuperscript{13,20,21}
      ii. Hypertension (12-16%)\textsuperscript{13,20,21}
      iii. Bradycardia (5-9%)\textsuperscript{13,20,21}
      iv. Cardiac arrhythmias, primarily atrial fibrillation (1-4%)\textsuperscript{13,20}

c. Sedative and anxiolytic effects
   1. Facilitated through locus coeruleus in central nervous system (CNS)\textsuperscript{13,20}
      i. Locus coeruleus: houses large number of adrenergic receptors, predominantly $\alpha_2$\textsuperscript{20}
         a. $\alpha_2$ receptors: antinociceptive, sedative, sympatholytic, hypothermic, and behavioral actions
   2. Induces state of arousable sedation\textsuperscript{13,20}
   3. Studies have demonstrated similar or superior efficacy in providing adequate sedation, assessed using validated agitation and sedation scales, when compared with placebo or commonly used ICU sedatives (i.e. midazolam or lorazepam) during MV\textsuperscript{13,20,22,23}

d. Analgesic effects
   1. Theorized to occur via activation of $\alpha_2$ receptor\textsuperscript{13}
      i. Synergistic analgesic effect with $\mu$ opioid agonists\textsuperscript{20}
   2. Opioid analgesic-sparing effect demonstrated in several studies\textsuperscript{13,20,24}
   3. Does not meet total analgesic requirements for ICU patients\textsuperscript{13,20}
**Effects on delirium**

1. Actions possibly related to $\alpha_{2a}$ receptor selectivity and activation, concomitant sedative and opioid dosage reduction\textsuperscript{13,20,24}

   i. $\alpha_{2a}$ receptor selectivity and activation\textsuperscript{24}
      
      a. $\alpha_{2a}$ selectivity permits minimal disruption of neurotransmitter pathways thereby decreasing likelihood of delirium
      
      b. $\alpha_{2a}$ agonism resulting in blockade of norepinephrine may lead to changes in the noradrenergic system decreasing development of delirium
   
   ii. Sedative and opioid dosage reduction\textsuperscript{13,20,24}
      
      a. Studies have demonstrated a relationship between opiate or GABAergic agent (i.e. BDZ and propofol) use and development of delirium
      
      b. GABA agonists interfere with physiologic sleep patterns vs. dexmedetomidine which promotes physiologic sleep-wake cycles

2. Trials have revealed significantly lower incidence, prevalence, and duration of delirium or coma in comparison with other sedatives\textsuperscript{13,20,22-24}

**Effects on respiratory function**

1. Does not exhibit respiratory depressive effects\textsuperscript{13,20}

2. Ability to provide sedation with opioid analgesic-sparing allows for less opioid-induced respiratory depression\textsuperscript{20}

3. Significantly greater PaO$_2$:FiO$_2$ ratio, measure of efficiency of oxygen exchange across lungs (Appendix B), pre- and post-extubation compared with placebo\textsuperscript{25}

4. Attenuates hyperdynamic cardiopulmonary response (hypertension, tachycardia, cough, etc.) during extubation compared with placebo\textsuperscript{26-28}

**History of dexmedetomidine in MV**

1. Pandharipande et al. – 2007\textsuperscript{22}

   i. Prospective, double-blind, randomized, controlled trial comparing dexmedetomidine (dex) vs. lorazepam on duration of delirium and coma in 106 MV medical/surgical ICU patients

   ii. Intervention: dex 0.15 - 1.5 mcg/kg/h or lorazepam 1 - 10 mg/h

   iii. Results:
      
      a. Greater number of delirium-free and coma-free days in dex-treated patients ($P = 0.01$)
      
      b. Achievement of nurse and physician target Richmond agitation-sedation scale (RASS) (Appendix C) score greater in dex-treated patients ($P = 0.04; P = 0.008$)
      
      c. No difference in ventilator-free days ($P = 0.22$)
      
      d. Median fentanyl dose greater in dex group ($P = 0.006$)
      
      e. Sinus bradycardia greater in dex group ($P = 0.03$)

   iv. Conclusion: Dex appears to decrease prevalence and duration of acute brain dysfunction (i.e. delirium and coma) and may be more effective in achieving target sedation compared with lorazepam.
2. Maldonado et al. - 2009
   i. Open-label, prospective, randomized clinical trial examining incidence of delirium with dex vs. propofol and midazolam in 118 patients undergoing cardiac-valve operations with cardiopulmonary bypass (CPB)
   ii. Intervention: dex 0.2 mcg/kg/h + 0.4 mcg/kg loading dose or propofol 25-50 mcg/kg/min or midazolam 0.5-2 mg/h
   iii. Results:
      a. Lower incidence and duration of delirium in dex treatment group vs. propofol and midazolam treatment groups (P < 0.001 for incidence and duration comparing dex vs. both groups)
      b. PRN fentanyl and morphine-equivalents greater in midazolam group vs. dex (P < 0.001 for both)
      c. No difference in intubation time between groups (dex vs. propofol, P = 0.91; dex vs midazolam, P = 0.34)
   iv. Conclusion: Use of dex for postoperative sedation appears to reduce incidence and duration of delirium when compared with midazolam or propofol.

3. Riker et al. - 2009
   i. Prospective, double-blind, randomized, multicenter, international comparator trial evaluating efficacy and safety of prolonged sedation with dex vs. midazolam in 375 MV medical/surgical ICU patients
   ii. Intervention: dex 0.8 mcg/kg/h ± 1 mcg/kg loading dose or midazolam 0.06 mg/kg/h ± 0.05 mg/kg loading dose
   iii. Results:
      a. Duration of study drug treatment shorter with dex (P = 0.01), likely resulting from shorter time to extubation (P = 0.01)
      b. Prevalence of delirium was lower in dex-treated patients (P < 0.001)
      c. Greater incidence of bradycardia in dex-treated patients (P < 0.001); greater incidence of tachycardia (P < 0.001) and hypertension requiring intervention (P = 0.02) in midazolam-treated patients
   iv. Conclusion: Used in conjunction with best sedation practices, dex appears to decrease time to extubation and reduce prevalence of delirium when compared with midazolam.

**Objective**
Utility of dex in facilitating extubation in mechanically ventilated (MV) patients difficult to wean and extubate secondary to agitation and continued need for sedation

**Design**
Single center observational analysis performed in Massachusetts

**Population**
- **Inclusion**
  - Located in an ICU, MV, requiring IV sedation, suitable for weaning and extubation ≤ 24 h of dex initiation, previous attempts at weaning sedation &/or analgesia resulted in agitation contributing to: patient ventilator dyssynchrony, prolonged need for intubation or inability to conduct successful SBT & traditional agents unsuccessful at controlling agitation
- **Exclusion**
  - HR < 50 BPM, acute heart failure, unstable angina, acute MI within last 30 days

**Methods**
- **Assessment**
  - Agitation assessed using RASS or Sedation-Agitation Scale (SAS) [Appendices C & D]
  - Considered agitated if: RASS score = +2 or SAS score = ‘agitated’
- **Intervention**
  - Recommended dosing of dex per product labeling (1 mcg/kg bolus + infusion at 0.2-0.7 mcg/kg/h)
  - Dosing and titration left to discretion of ICU team and nurse caring for patient

**Outcomes**
- Rate of extubation at 24 h and 48 h post-dex
- Mean time to extubation after dex
- Mean rate of propofol, midazolam, and morphine equivalent infusions before and after dex
- HR, MAP, and oxygen saturation before dex and at 1, 2, 4, 6, 12, and 24 h after dex

**Statistics**
- Data presented as mean ± SD
- Changes in hemodynamic variables at 0 h and at 6, 12, and 24 h after dex tested with repeated measures one-way ANOVA utilizing Tukey post-hoc analysis when appropriate
- Paired t-tests performed on all variables before and after dex
- Two-tailed P value < 0.05 considered statistically significant

**Results**
- 25 patients evaluated for dex therapy with 20 meeting criteria for treatment
  - Of the 5 patients not eligible, 3 did not require IV sedation and 3 had absence of agitation while weaning sedation &/or analgesia
- Baseline characteristics
  - 75% male
  - Mean age 50 ± 15 yrs
  - Mean weight 83 ± 21 kg
  - Common intermittent IV adjuncts prior to dex were haloperidol (45%) and lorazepam (40%)

**Dex infusion details**

<table>
<thead>
<tr>
<th>Duration of dex infusion (h); n = 20</th>
<th>29 ± 27</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dex infusion rate (mcg/kg/h); n = 20</td>
<td>0.53 ± 0.2</td>
</tr>
<tr>
<td>Dex infusion rate at extubation (mcg/kg/h); n = 14</td>
<td>0.43 ± 0.23</td>
</tr>
</tbody>
</table>

*One patient received a bolus*
### Results, cont.

<table>
<thead>
<tr>
<th></th>
<th>Extubation after dex initiation</th>
<th>12 h prior to dex</th>
<th>12 h post-dex</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Extubation after dex initiation</strong></td>
<td></td>
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<td></td>
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<tr>
<td>≤ 24 h [n(%)]</td>
<td></td>
<td>13 (65)</td>
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<td></td>
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<tr>
<td>&gt; 24 h [n(%)]</td>
<td></td>
<td>1 (5)</td>
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<td></td>
</tr>
<tr>
<td><strong>Total</strong> [n(%)]</td>
<td></td>
<td>14 (70)</td>
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*a One patient re-intubated within 48 h of extubation

<table>
<thead>
<tr>
<th></th>
<th>Additional sedative and analgesic use</th>
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<tbody>
<tr>
<td></td>
<td>12 h prior to dex</td>
<td>12 h post-dex</td>
<td>P value</td>
<td></td>
</tr>
<tr>
<td>Propofol (mg/h)*; n = 15</td>
<td>146 ± 90</td>
<td>70 ± 77</td>
<td>&lt; 0.001</td>
<td></td>
</tr>
<tr>
<td>Morphine equivalent (mg/h)*; n = 12</td>
<td>20 ± 27</td>
<td>13 ± 22</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>Midazolam (mg/h)*; n = 5</td>
<td>5 ± 4</td>
<td>1.7 ± 1.7</td>
<td>0.19</td>
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</tr>
</tbody>
</table>

*a Six patients weaned off propofol after dex

*b Two patients weaned off analgesics or midazolam after dex

- HR at 12 & 24 h after dex significantly lower than prior to dex (P < 0.05 and P < 0.01, respectively)
- Dex associated with minimal changes in MAP (P = NS)
- One patient initiated on vasopressor therapy after administration of dex
- Mean oxygen saturation for all patients was 97% at dex initiation and 2 h after

**Conclusions**

In mechanically ventilated patients who failed previous attempts at weaning and extubation secondary to agitation, dexmedetomidine allowed for successful extubation in 65% of patients within 24 h of initiation and was associated with a reduction in concomitant sedative and analgesic use with minimal adverse effects.

**Strengths**

- Validated scales used for assessment of agitation
- Heterogeneous patient population

**Limitations**

- Small patient population
- Observational analysis with no control group and open label dex administration
- Limited baseline characteristics provided
- No predefined criteria for patient-ventilator dyssynchrony or prolonged need for intubation
- No protocol for dosing or titration of dex
- No systematic collection of sedation scores prior to dex or target sedation score
- Delirium not evaluated as a possible cause of agitation

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate effects of dex on resolution of agitation during weaning from MV of critically ill patients who failed conventional therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Design</td>
<td>Prospective, open-label, observational cohort study performed in tertiary medical/surgical intensive care units in two Australian hospitals</td>
</tr>
</tbody>
</table>
| Population | Inclusion  
> Age ≥ 18 years, MV > 24 h, sedatives &/or opioids > 24 h, development of agitation &/or delirium upon weaning from sedation &/or opioids and failure to achieve extubation with conventional therapy and weaning as assessed by intensivist  
> Exclusion  
> Dex allergy, pregnancy or lactation, SBP < 90 mmHg &/or HR < 55 BPM, likely to die &/or withdrawal of therapy within 24 h, long-term α2 agonist or antipsychotic use, opiate or benzodiazepine dependence or chronic pain or detoxification treatment within 6 months, dementia, parkinsonism, chronic epilepsy, recent cerebrovascular surgery or surgery involving a free arterial flap, recent severe traumatic brain injury (TBI), hepatic encephalopathy within 14 d, recent drug overdose or carbon monoxide poisoning |
| Methods   | Ventilation strategy  
> Standardized criteria utilized for consideration of extubation  
> Assessment  
> Agitation assessed at 0, 6, and 12 h using Motor Activity Assessment Scale (MAAS) with target score of 2 to 4 [Appendix E]  
> Intervention  
> Conventional sedation and analgesia running for ≤ 48 h prior to enrollment and preferentially weaned 2 h after dex initiation  
> Initial dex infusion 0.4 mcg/kg/h with titration of 0.2 mcg/kg/h every 30 min to a maximum dose of 1 mcg/kg/h to achieve target MAAS score  
> Rescue sedation of midazolam 1 mg &/or propofol given for MAAS scores of 5 to 6  
> Additional analgesia with morphine 1-2 mg or fentanyl 10-20 mcg if required  
> Dex discontinued once no longer required, at discretion of intensivist, or after 14 days |
| Outcomes  | Primary outcome  
> Percentage achieving target MAAS score at 6 and 12 h following dex  
> Secondary outcomes  
> Hours of ventilation  
> Number extubated  
> Additional sedatives and analgesics after dex |
| Statistics | Categorical variables presented as percentages  
> Continuous variables presented as median and interquartile range (IQR)  
> Fisher’s exact test performed to compare proportion of patients in target MAAS category at baseline and at 6 and 12 h after initiation of dex  
> P value < 0.05 considered statistically significant |
Results

- 28 patients were enrolled with a total of 30 episodes occurring

<table>
<thead>
<tr>
<th>Baseline characteristics (n = 30)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>70.5 (51 – 76)*</td>
<td></td>
</tr>
<tr>
<td>Males (%)</td>
<td>96.7</td>
<td></td>
</tr>
<tr>
<td>Ventilation time prior to dex (h)</td>
<td>115 (87 – 263)*</td>
<td></td>
</tr>
<tr>
<td>APACHE II score</td>
<td>18 (15 – 27)*</td>
<td></td>
</tr>
<tr>
<td>Dobutamine</td>
<td>9 (30)*</td>
<td></td>
</tr>
<tr>
<td>Noradrenaline or adrenaline</td>
<td>10 (33)*</td>
<td></td>
</tr>
</tbody>
</table>

* Expressed as median (IQR)

<table>
<thead>
<tr>
<th>Dex infusion details</th>
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</thead>
<tbody>
<tr>
<td>Maximum dex infusion rate (mcg/kg/h)</td>
<td>0.7 (0.7-1)*</td>
<td></td>
</tr>
<tr>
<td>Dex infusion time (h)</td>
<td>62 (24-252)*</td>
<td></td>
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</table>

* Expressed as median (IQR)

<table>
<thead>
<tr>
<th>Primary outcome: Achievement of target MAAS score</th>
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<tbody>
<tr>
<td>MAAS score within target range</td>
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<td></td>
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</tr>
<tr>
<td>Prior to dex</td>
<td>7 (23)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 h post-dex</td>
<td>28 (93)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 h post-dex</td>
<td>26 (87)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td>&lt; 0.001†</td>
<td>&lt; 0.001†</td>
</tr>
</tbody>
</table>

* Expressed as number (%)
† P value calculated for 6 & 12 h post-dex scores compared with score prior to dex

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Post – dex ventilation time (h)</td>
<td>70 (28-96)*</td>
<td></td>
</tr>
<tr>
<td>Successful extubation</td>
<td>10 (33)*</td>
<td></td>
</tr>
<tr>
<td>Additional sedatives &amp; analgesics (up to 72 h post – dex)</td>
<td>18 (60)*</td>
<td></td>
</tr>
</tbody>
</table>

* Expressed as median (IQR)
† Expressed as number (%)

- Adverse events
  - Hemodynamic instability (n = 2), elevated LFTs (n = 1)
    - One episode of hemodynamic instability resulted from sepsis, and one episode required moderate increase in noradrenaline and dobutamine dosage at 12 h
  - Self – extubation occurred in one patient
  - Dex discontinued in 6 patients due to unrelated clinical deterioration

Conclusions

Dexmedetomidine can be used successfully to treat emergence agitation in mechanically ventilated medical/surgical ICU patients undergoing weaning.

Strengths

- Prospective trial
- Generalizable due to heterogeneous patient population (medical & surgical ICU population)

Limitations

- Observational study
- Small patient population
- Unable to assess individual analgesic and sedative use
- Unable to quantify effect of dex on ventilation time and length of ICU stay due to prolonged ventilation and ICU stay prior to dex therapy
Objective: Feasibility of trial design and safety of haloperidol and dexmedetomidine.

Design: Randomized, open-label, parallel-group pilot trial in a medical and surgical ICU at a single center in Australia.

Population:
- Inclusion: MV due to agitation (RASS ≥ 2) requiring large sedative doses such that extubation not possible.
- Exclusion: Not eligible for extubation (e.g., high-dose opioids, returning to OR, airway protection or ventilator support necessary), previous adverse reaction to haloperidol or α2 agonists.

Methods:
- Patients randomized using computer-generated random-number sequence:
  - Dex (n = 10)
  - Haloperidol (n = 10)
- Assessment:
  - Agitation assessed using RASS every 4 h with target score of 0 (Appendix C).
  - Delirium assessed using Intensive Care Delirium Screening Checklist (ICDSC) (Appendix F).
- Intervention:
  - Dex
    - Infusion of 0.2 – 0.7 mcg/kg/h for as long as deemed necessary by physician.
    - Optional loading dose of 1 mcg/kg.
  - Haloperidol
    - Infusion of 0.5 – 2 mg/h for as long as deemed necessary by physician.
    - Optional loading dose of 2.5 mg.
  - Once dex discontinued, could not be re-initiated.
  - Haloperidol could be continued by infusion or bolus without restriction.
  - Infusion titration adjusted by nurse as necessary to achieve target RASS score.

Outcomes:
- Primary outcome: Time from study drug initiation to extubation.
- Secondary efficacy outcomes:
  - Time from study drug initiation to ICU discharge.
  - Time to achieve a satisfactory sedation score.
  - Need for supplemental sedative and analgesic medication.
- Secondary safety outcomes:
  - Change in QTc interval.
  - Duration and rate of vasopressor or inotropic support.
  - Requirement for re-intubation.

Statistics:
- Power analysis: 20 patients required for 80% power of detecting difference in time to extubation of 24 h in treatment group with 95% certainty.
- Categorical baseline and outcome data compared using chi-squared tests.
- Continuous data assessed graphically & compared using Mann-Whitney U or Student’s t tests.
- Univariate survival analysis of time to extubation performed using log-rank test.
- Cox proportional hazards model of time to extubation constructed using backward elimination with initial model incorporating all listed baseline data and final model being displayed as best fit.

Results: Baseline characteristics (n = 20)

<table>
<thead>
<tr>
<th></th>
<th>Dex (n = 10)</th>
<th>Haloperidol (n = 10)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>52 (42-69)*</td>
<td>68.5 (43-78)</td>
<td>NS</td>
</tr>
<tr>
<td>APACHE II (≤ 24 h of enrollment)</td>
<td>13.3 (10-18)*</td>
<td>15.5 (11-19)*</td>
<td>NS</td>
</tr>
<tr>
<td>Physical restraint prior to enrollment</td>
<td>8 (80)†</td>
<td>5 (50)†</td>
<td>NS</td>
</tr>
<tr>
<td>Ventilation time (h) prior to randomization</td>
<td>45 (34.5-73.3)*</td>
<td>65.2 (28-87)*</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Expressed as median (IQR); † Expressed as number (%)
## Results, cont.

### Intervention details

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loading dose given</strong></td>
<td>8 (80)*</td>
<td>6 (60)*</td>
<td>NS</td>
</tr>
<tr>
<td><strong>Infusion rate</strong></td>
<td>0.47 (0.33-0.62) mcg/kg/h $^\dagger$</td>
<td>1.43 (0.96-1.9) mg/h $^\dagger$</td>
<td>--</td>
</tr>
</tbody>
</table>

* Expressed as number (%)
$^\dagger$ Expressed as mean (95% confidence interval)

### Primary outcome

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to extubation (h)</strong></td>
<td>19.9 (7.3-24)*</td>
<td>42.5 (23.2-117.8)*</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Requiring tracheostomy (n)</strong></td>
<td>0</td>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td><strong>Time to extubation (h) excluding patients requiring tracheostomy</strong></td>
<td>19.9 (7.3-24)*</td>
<td>49.8 (23.2-117.8)*</td>
<td>0.0147</td>
</tr>
</tbody>
</table>

* Expressed as median (IQR)

### Secondary efficacy outcomes

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time to ICU discharge (days)</strong></td>
<td>1.5 (1-3)*</td>
<td>6.5 (4-9)*</td>
<td>0.0039</td>
</tr>
<tr>
<td><strong>Time to satisfactory RASS score (-2 to 1) (h)</strong></td>
<td>4 (0-7)*</td>
<td>18 (9-22)*</td>
<td>0.071</td>
</tr>
</tbody>
</table>

### Additional sedatives

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Propofol (%)</strong></td>
<td>60</td>
<td>80</td>
<td>0.33</td>
</tr>
<tr>
<td><strong>Midazolam (%)</strong></td>
<td>20</td>
<td>10</td>
<td>0.53</td>
</tr>
</tbody>
</table>

### Additional analgesia (morphine) (%)

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Additional analgesia (morphine) (%)</strong></td>
<td>30</td>
<td>40</td>
<td>0.64</td>
</tr>
</tbody>
</table>

* Expressed as median (IQR)

### Secondary safety outcomes

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in QTc interval</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>QTc interval prior to study drug</td>
<td>0.411 (0.384-0.438)*</td>
<td>0.426 (0.395-0.457)*</td>
<td>0.41</td>
</tr>
<tr>
<td>QTc interval while on study drug</td>
<td>0.395 (0.365-0.425)*</td>
<td>0.446 (0.423-0.457)*</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Proportion with QTc interval &gt; baseline (%)</td>
<td>30</td>
<td>70</td>
<td>0.07</td>
</tr>
</tbody>
</table>

### Duration & rate of vasopressor support

<table>
<thead>
<tr>
<th></th>
<th>Dex</th>
<th>Haloperidol</th>
<th>$P$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion requiring 20% dose increase or newly requiring norepinephrine (NE)$^b$ (%)</td>
<td>20</td>
<td>20</td>
<td>1.00</td>
</tr>
<tr>
<td>Time NE required$^a$ (h)</td>
<td>59.8 (17.9-100)*</td>
<td>34.4 (0.0-87.1)</td>
<td>0.37</td>
</tr>
<tr>
<td>NE infusion rate$^a$ (mcg/min)</td>
<td>2.51 (0.07-4.90)*</td>
<td>3.97 (0.00-11.07)</td>
<td>0.55</td>
</tr>
<tr>
<td>Requirement for re-intubation (n)</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* Expressed as mean (95% confidence interval)
$^a$ While on study drug
$^b$ Within 8 h after commencement of study drug

### Adverse events

- 1 receiving haloperidol experienced QTc interval prolongation requiring drug discontinuation

### Conclusions

Dexmedetomidine may be more efficacious for the treatment of agitated delirium in intubated patients than haloperidol and appears to have a better side effect profile.

### Strengths

- Randomized, comparator trial
- Validated scales used for assessment of agitation and delirium

### Limitations

- Unblinded study
- Small patient population
- Lack of routine delirium assessment
- Inadequate dosing of dex
- Unconventional administration of haloperidol
IX. Economic Data
   a. Pandharipande et al. – 2007\textsuperscript{22}
      1. Median calculated cost for study drug: dex - $4675 vs. lorazepam - $2335

<table>
<thead>
<tr>
<th></th>
<th>Total Cost</th>
<th>Dex (n = 45)</th>
<th>Lorazepam (n = 45)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacy</td>
<td>$27460 ($15710-46430)</td>
<td>$20660 ($9840-42270)</td>
<td></td>
<td>0.15</td>
</tr>
<tr>
<td>Respiratory care</td>
<td>$3530 ($2170-6940)</td>
<td>$2920 ($2070-5830)</td>
<td></td>
<td>0.35</td>
</tr>
<tr>
<td>Intensive care unit</td>
<td>$61400 ($37300-108200)</td>
<td>$59500 ($35900-83000)</td>
<td></td>
<td>0.32</td>
</tr>
<tr>
<td>Hospital</td>
<td>$101400 ($64500-148900)</td>
<td>$78900 ($44000-124600)</td>
<td></td>
<td>0.18</td>
</tr>
</tbody>
</table>

Data presented as median (IQR)

b. Maldonado et al. - 2009\textsuperscript{24}
   1. Average total cost for postoperative care
      i. Dex group: $7025
      ii. Propofol group: $9875 (vs. dex, \( P = 0.12 \))
      iii. Midazolam group: $9570 (vs. dex, \( P = 0.07 \))
   2. Average cost for all patients who developed delirium vs. average cost for all patients who never developed delirium: $12965 vs. $6763 (\( P = 0.004 \))

X. Conclusions
   a. Dexmedetomidine provides adequate sedation compared with benzodiazepines and propofol in mechanically ventilated patients at doses ranging from 0.2-1.5 mcg/kg/h
   b. Dexmedetomidine may facilitate extubation by reducing opioid requirements thereby causing less respiratory depression and incidence of delirium
   c. Insufficient data available to recommend dexmedetomidine use routinely for weaning from mechanical ventilation
   d. Patients who should get dexmedetomidine
      1. Difficulty weaning from MV due to:
         i. Agitation or delirium
         ii. Excessive sedative and/or analgesic use with GABA receptor agonists (BDZ or propofol) or opioids
   e. Patients who should not get dexmedetomidine
      1. Hypovolemia or hypotension
      2. Previous history of cardiac arrhythmias
APPENDICES

APPENDIX A: Modes of MV

<table>
<thead>
<tr>
<th>Mode</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Assist-control ventilation (ACV)</td>
<td>• Delivers set volume of air upon patient initiated breath^7</td>
</tr>
<tr>
<td></td>
<td>• Controls breath at predetermined frequency and tidal volume (TV) if patient breath not initiated^7</td>
</tr>
<tr>
<td></td>
<td>• Most common initial mode of MV used in ICUs^6,7</td>
</tr>
<tr>
<td>Pressure-support ventilation (PSV)</td>
<td>• Supports patient breathing by delivering air at predetermined pressure^7</td>
</tr>
<tr>
<td></td>
<td>• Adjunctive positive end-expiratory pressure (PEEP): constant pressure applied to maintain functional residual capacity &amp; aid gas exchange^7</td>
</tr>
<tr>
<td>Synchronized intermittent mandatory ventilation (SIMV)</td>
<td>• Intermittently supplies mandatory frequency of breaths at predetermined volume or pressure that is synchronized with patient breathing efforts^7</td>
</tr>
<tr>
<td></td>
<td>• Commonly used in conjunction with PSV during weaning process^6,7</td>
</tr>
<tr>
<td>Continuous positive airway pressure (CPAP)</td>
<td>• Description: constant pressure maintained above atmospheric pressure throughout respiratory cycle^8</td>
</tr>
<tr>
<td></td>
<td>• Commonly used during spontaneous breathing trials (SBT)^8</td>
</tr>
</tbody>
</table>

APPENDIX B: Criteria for Weaning from MV^7,32

<table>
<thead>
<tr>
<th>Method of Assessment</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vital capacity</td>
<td>10 mL/kg</td>
</tr>
<tr>
<td>Tidal volume</td>
<td>&gt; 4 mL/kg</td>
</tr>
<tr>
<td>Minute ventilation</td>
<td>&lt; 101 breaths/min</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>&lt; 38 breaths/min</td>
</tr>
<tr>
<td>Dynamic compliance</td>
<td>&gt; 22 mL/cm H₂O</td>
</tr>
<tr>
<td>Static compliance</td>
<td>&gt; 33 mL/cm H₂O</td>
</tr>
<tr>
<td>PaO₂/FiO₂ ratio</td>
<td>&gt; 0.35</td>
</tr>
<tr>
<td>Negative inspiratory force (NIF)</td>
<td>20-30 cm H₂O</td>
</tr>
<tr>
<td>Dead space to tidal volume ratio</td>
<td>0.6</td>
</tr>
<tr>
<td>Rapid shallow breathing index (RSBI)</td>
<td>&lt; 105 breaths/min/L</td>
</tr>
<tr>
<td>Crop index</td>
<td>&gt; 13 mL/breath/min</td>
</tr>
</tbody>
</table>

APPENDIX C: Richmond Agitation-Sedation Scale (RASS)^33,34

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ 4</td>
<td>Combative</td>
<td>Overtly combative or violent; immediate danger to staff</td>
</tr>
<tr>
<td>+ 3</td>
<td>Very agitated</td>
<td>Pulls on or removes tube(s) or catheter(s) or has aggressive behavior toward staff</td>
</tr>
<tr>
<td>+ 2</td>
<td>Agitated</td>
<td>Frequent nonpurposeful movement or patient-ventilator dyssynchrony</td>
</tr>
<tr>
<td>+ 1</td>
<td>Restless</td>
<td>Anxious or apprehensive but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>0</td>
<td>Alert and calm</td>
<td>Not fully alert, but has sustained (&gt; 10 seconds) awakening, with eye contact, to voice</td>
</tr>
<tr>
<td>- 1</td>
<td>Drowsy</td>
<td>Not fully alert, but has sustained (&gt; 10 seconds) awakening, with eye contact, to voice</td>
</tr>
<tr>
<td>- 2</td>
<td>Light sedation</td>
<td>Briefly (&lt; 10 seconds) awakens with eye contact to voice</td>
</tr>
<tr>
<td>- 3</td>
<td>Moderate sedation</td>
<td>Any movement (but no eye contact) to voice</td>
</tr>
<tr>
<td>- 4</td>
<td>Deep sedation</td>
<td>No response to voice, but any movement to physical stimulation</td>
</tr>
<tr>
<td>- 5</td>
<td>Unarousable</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>
**APPENDIX D: Riker Sedation-Agitation Scale (SAS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Term</th>
<th>Descriptor</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Dangerous agitation</td>
<td>Pulling at endotracheal (ET) tube, trying to remove catheters, climbing</td>
</tr>
<tr>
<td></td>
<td></td>
<td>over bedrail, striking at staff, thrashing side-to-side</td>
</tr>
<tr>
<td>6</td>
<td>Very agitated</td>
<td>Requiring restraint and frequent verbal reminding of limits, biting ET tube</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>Anxious or physically agitated, calms to verbal instructions</td>
</tr>
<tr>
<td>4</td>
<td>Calm and cooperative</td>
<td>Calm, easily arousable, follows commands</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
<td>Difficult to arouse but awakens to verbal stimuli or gentle shaking,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>follows simple commands but drifts off again</td>
</tr>
<tr>
<td>2</td>
<td>Very sedated</td>
<td>Aroused to physical stimuli but does not communicate or follow commands,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>may move spontaneously</td>
</tr>
<tr>
<td>1</td>
<td>Unarousable</td>
<td>Minimal or no response to noxious stimuli, does not communicate or follow</td>
</tr>
<tr>
<td></td>
<td></td>
<td>commands</td>
</tr>
</tbody>
</table>

**APPENDIX E: Motor Activity Assessment Scale (MAAS)**

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unresponsive</td>
<td>Does not move with noxious stimulus</td>
</tr>
<tr>
<td>1</td>
<td>Responsive only to noxious stimuli</td>
<td>Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs with noxious stimulus</td>
</tr>
<tr>
<td>2</td>
<td>Responsive to touch or name</td>
<td>Opens eyes OR raises eyebrows OR turns head toward stimulus OR moves limbs with when touched or name is loudly spoken</td>
</tr>
<tr>
<td>3</td>
<td>Calm and cooperative</td>
<td>No external stimulus is required to elicit movement AND patient is adjusting sheets or clothes purposefully and follows commands</td>
</tr>
<tr>
<td>4</td>
<td>Restless and cooperative</td>
<td>No external stimulus is required to elicit movement AND patient is picking at sheets or tubes OR uncovering self and follows commands</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
<td>No external stimulus is required to elicit movement AND attempting to sit up OR moves limbs out of bed AND does not consistently follow commands</td>
</tr>
<tr>
<td>6</td>
<td>Dangerously agitated, uncooperative</td>
<td>No external stimulus is required to elicit movement AND patient is pulling at tubes or catheters OR thashing side to side OR striking at staff OR trying to climb out of bed AND does not calm down when asked</td>
</tr>
</tbody>
</table>

* Noxious stimulus, suctioning OR five seconds of vigorous orbital, sternal, or nail bed pressure

**APPENDIX F: Intensive Care Delirium Screening Checklist (ICDSC)**

<table>
<thead>
<tr>
<th>Patient Evaluation</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Altered level of consciousness* (A-E)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inattention</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disorientation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucination-delusion-psychosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychomotor agitation or retardation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inappropriate speech or mood</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep/wake cycle disturbance</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptom fluctuation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score (0-8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Level of consciousness:
  A: No response, score: None
  B: Response to intense and repeated stimulation (loud voice and pain), score: None
  C: Response to mild or moderate stimulation, score: 1
  D: Normal wakefulness, score: 0
  E: Exaggerated response to normal stimulation, score: 1