1. Introduction & Scope

The management of analgesia and sedation is pivotal to the care of critically ill patients, but can be challenging, and adversely affect other aspects of patient care. Poor management of Pain, Agitation & Delirium (PAD) may be detrimental to patient outcome \[^{[1]}\]

Part A of this guideline covers the structured assessment and management of pain and sedation.

Part B focuses on the assessment and management of agitation and delirium.

Part C is a summary of PAD specific to extracorporeal membrane oxygenation (ECMO)

This document sets standards for the safe and effective provision of analgesia, sedation and delirium in critically ill adult patients in critical care.

This document does not provide guidance for the management of patients who are sedated by anaesthetists in perioperative/pre-procedural medicine.

PAD management therapies should be delivered in a holistic & timely manner with the aim of improving the quality of care and patient experience, decreasing the patient’s length of mechanical ventilation, ICU stay and associated morbidity; and the appropriate use of Trust resources.

All patients should have a clear plan documented for the management of PAD in their notes. This should be reviewed daily or more frequently if the clinical situation dictates.

This document provides evidence based advice and expert opinion relating to the management of PAD in critical care to:

- Minimise or treat pain
- Provide anxiolysis, somnolence and if necessary amnesia
- Allow ventilator synchronicity
- Reduce cough and improve tube tolerance
- Minimise time on mechanical ventilation
- Facilitate weaning from ventilatory support
- Reduce the incidence of critical care delirium

The guidance set out in this document applies to the management of PAD by Intensivists, Advanced Critical Care Practitioners, Nurses, Pharmacists, Anaesthetists and other physicians in the critical care units within University Hospitals of Leicester.

For the management of delirium **outside of critical care**, please refer to the local guidelines or practice.
**UHL Critical Care: Pain, Agitation and Delirium (PAD) Summary Guideline**

This is the working summary guideline for the assessment, treatment and prevention of pain, anxiety and delirium (PAD); if further information is required please refer to the full guideline below.

<table>
<thead>
<tr>
<th>Pain</th>
<th>Agitation</th>
<th>Delirium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Assessment</strong></td>
<td><strong>Assessment</strong></td>
<td><strong>Assessment</strong></td>
</tr>
<tr>
<td>Assess pain when doing observations, or when clinical situation dictates. Use NPRS or CCPOT. Patient is in moderate (or greater) pain if NRS/VAS $&gt; 5$ or CPOT $&gt; 3$ If new or changing pain consider the cause.</td>
<td>Assess agitation when doing observations or when clinical situation dictates. Use the RASS. If agitated consider the cause: Pain, Anxiety, Delirium Please see full guideline for other causes which include bowel discomfort/constipation, sleep deprivation and lack of homeostasis.</td>
<td>Assess delirium twice per shift or as clinical situation dictates. Use CAM-ICU If CAM-ICU positive consider the cause. Consider delirium if patient has a fluctuating, conscious level, agitation or is not interactive.</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
<td><strong>Treatment</strong></td>
</tr>
<tr>
<td>Treat pain according to type, see below, and reassess within 30 minutes. Non-neuropathic pain: Local anaesthetic / regional blocks (if applicable). Simple analgesics: paracetamol and NSAIDs (if appropriate) Opiates: morphine bolus (+/- infusion or PCA) or remifentanil infusion.</td>
<td>If over sedated: hold sedation until at RASS target (normal target $-2$ to $0$) and then restart at half rate. If agitated treat cause, treat pain first then exclude other causes. Pharmacological treatment: RASS $+1$ or $+2$: Haloperidol or alpha 2 agonist (e.g. clonidine) if required RASS $+3$ or $+4$: Propofol or other sedative</td>
<td>If CAM-ICU positive assess for cause of delirium. Treat pain (if applicable). Reassure and orientate to time, place and person. Provide glasses and/or hearing aids. Pharmacological treatment: Use haloperidol or alpha 2 agonist. Avoid benzodiazepines, whenever possible, unless specifically indicated.</td>
</tr>
<tr>
<td><strong>Prevention</strong></td>
<td><strong>Prevention</strong></td>
<td><strong>Prevention</strong></td>
</tr>
<tr>
<td>Prevent pain by ensuring: The patients’ regular analgesics (or equivalent) are prescribed. Prophylactic analgesics are used pre-procedure (including local anaesthesia where applicable).</td>
<td>RASS target to be $-2$ to $0$ unless otherwise clinically indicated. Daily sedation holds: to occur unless clinical decision to the contrary: If at RASS $-3$ then sedation to be halved. If RASS $&lt;-4$ sedation to be held until at target and then restarted at half rate.</td>
<td>Identify risk factors: Examples include dementia, excess alcohol intake and severity of illness - see full guideline for more information Avoid benzodiazepines. Mobilise. Communication aids. Prescribe/provide regular medication.</td>
</tr>
<tr>
<td><strong>Sleep</strong></td>
<td><strong>Sleep</strong></td>
<td><strong>Sleep</strong></td>
</tr>
<tr>
<td>Sleep is integral to the prevention of delirium and for recovery Promote sleep by controlling light and noise; clustering patient care activities to reduce awakening; providing day / night differentiation. Pharmacological treatment: Melatonin modified release (start at 2mg at night 2 hours before bedtime, increase to 4mg dose if needed); avoid zopiclone; if a benzodiazepine must be used then lorazepam is first line.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Pain

**Pain**

Instruction: Ask patient to “please indicate the intensity of their current pain level using a scale of 0 (no pain) to 10 (worst pain imaginable)”

<table>
<thead>
<tr>
<th>Description</th>
<th>Indicator</th>
<th>Facial Expressions</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>None</td>
<td>None</td>
<td>0</td>
</tr>
<tr>
<td>Mild</td>
<td>None</td>
<td>None</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>None</td>
<td>None</td>
<td>2</td>
</tr>
<tr>
<td>Severe</td>
<td>None</td>
<td>None</td>
<td>3</td>
</tr>
</tbody>
</table>

**Table:**

- **Facial Expressions:**
  - None
  - None
  - None
  - None

- **Score:**
  - 0
  - 1
  - 2
  - 3

**Diagram:**

- **Pain:**
  - Instruction: Ask patient to “please indicate the intensity of their current pain level using a scale of 0 (no pain) to 10 (worst pain imaginable)”

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**Delirium - CAM-ICU**

- Instruction: "When assessing for delirium, use the CAM-ICU tool.

**Agitation - RASS**

- Instruction: "Use the RASS scale to assess agitation.

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**Acknowledgment:**

April 2018

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**Reference:**

Adult Critical Care Pain, Agitation and Delirium (PAD) Guideline Approved at ITAPS Core Group Meeting on 6th Trust Ref: C24/2018 Next Review Date: October 2019
A.1: Definitions

Pain: an unpleasant sensory or emotional experience associated with tissue damage or described in terms of tissue damage. It is a spectrum and patients have variable tolerance.\(^3\)

Analgesia is the control of pain. Appropriate analgesia should be administered if a patient is suspected to be in pain. Sedation alone is NOT a substitute for appropriate analgesia.

Agitation is a psychomotor disturbance characterized by a marked increase in both motor and psychological activities, often accompanied by a loss of control of action and a disorganization of thought.

Anxiety: nearly all severely ill patients will suffer some form of anxiety, distress or agitation during their stay in ICU. Anxiety and stress in critically ill patients is almost always multifactorial. Sleep deprivation physical environment of the unit, anxiety felt by the patient due to their insight of the situation, delirium, adverse drug effects, pain and inability to communicate with the ICU team may all contribute to the patient’s distress.

Sedation is a continuum from the awake state. The American Society of Anesthesiologists (ASA) uses the following definitions for levels of sedation:

- **Minimal Sedation (Anxiolysis):** a drug induced state during which patients respond normally to verbal commands. Cognitive function and coordination maybe impaired, but ventilatory and cardiovascular functions are unaffected.

- **Moderate sedation:** a drug-induced depression of consciousness during which patients respond purposefully to verbal commands, either alone or accompanied by light tactile stimulation. No interventions are required to maintain an open airway and spontaneous ventilation is adequate. Cardiovascular function is maintained.

- **Deep sedation/analgesia:** a drug-induced depression of consciousness during which patients cannot easily be aroused, but respond purposefully following repeated or painful stimulation. The ability to independently maintain ventilation may be impaired.

- **General anaesthesia:** a drug-induced loss of consciousness during which patients are not rousable even by painful stimulation. The ability to maintain ventilation is frequently impaired and patients typically require assistance to maintain a patent airway.
A.2: Pain and Agitation in Critical Care

Analgesics, anxiolytics and sedatives are used in critical care medicine to provide relief from pain and anxiety to allow delivery of life-saving therapy[^4,^5].

Pain
The majority of patients treated in critical care suffer pain as part of the course of their presenting complaint, and undergo painful interventions throughout the course of their stay and therefore require analgesia[^1].
Pain perception varies according to various factors including personality, cultural background, surroundings and fear. It has been associated with detrimental effects on sleep, agitation and stress response. Failure to treat pain properly leads to an increased use of other sedative agents, increased sympathetic activity and increased oxygen consumption[^17].

Agitation
Agitation is common in ICU patients and is associated with a higher rate of self-removal of lines and catheters as well as a higher rate of nosocomial infection and a longer duration of hospital stay[^17].
Risk factors for the development of agitation include:
- Age > 65
- Alcohol Abuse
- Use of sedatives in 48 hours before onset of agitation
- Body temperature > 38°C
- Acute sodium derangement (high and low)
- Long term psychoactive drug use

It is important not to confuse agitation with delirium (see Part B). Agitation without delirium is more common and may develop simply because the patient has pain, discomfort or anxiety. Agitation does not usually require further treatment, once the disturbance has resolved compared with delirium which may not resolve without further intervention. A thorough assessment of the possible causes of the agitation should be sought before prescribing sedation.

Anxiety
Simple measures such as providing compassionate and considerate care are essential in managing anxiety. Patients report many recollections from their critical care experience which can be both positive and negative (negative examples include stressful experiences associated with the endotracheal tube). Negative experiences have been strongly associated with subjects experiencing periods of terror, feeling nervous when left alone and poor sleeping patterns.
Anxiety is also brought about by continuous noise within ICU such as monitoring machines, telephones, pagers, other patients, medical and nursing staff. Sleep deprivation can be a consequence of this noise whilst 24 hour lighting also contributes to anxiety.
Patients who have been treated with muscle relaxants and paralysed have varying levels
and types of memories; unfortunately most of these are distressing.$^{[17]}$
**Analgesia and Sedation**

Therapy can be administered to facilitate patient cooperation with organ support. Agitated patients have higher basal metabolic rates and increased oxygen consumption, which interferes with and reduces the efficiency of organ support. There is an increasing body of evidence demonstrating that over use of these therapies, either as sole agents or in combination, is associated with increased mortality, increased duration of mechanical ventilation and increased length of ICU stay amongst other detrimental outcomes [1,6,7,8]. The following issues may occur with both analgesic and sedative agents, especially when used in combination [9,10].

<table>
<thead>
<tr>
<th>Inadequate-analgesia / Under-sedation</th>
<th>Over-analgesia / Over-sedation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilator dysynchrony with VQ mismatch due to effects on pulmonary vasculature, resulting in increased ventilator support, cough reflex suppression &amp; reduced secretion clearance</td>
<td>Accumulation [6]</td>
</tr>
<tr>
<td>Inadvertent self-extubation and subsequent injury</td>
<td>Tolerance and tachyphylaxis</td>
</tr>
<tr>
<td>Inadvertent displacement of lines/cannulas, enteral tubes</td>
<td>Withdrawal</td>
</tr>
<tr>
<td>Cardiovascular stress response, increased inotrope/vasopressor requirements and ischemia</td>
<td>Prolonged ventilation and subsequent VAP/VILI</td>
</tr>
<tr>
<td>Discomfort, anxiety, awareness, Post-Traumatic Stress Disorder (PTSD)</td>
<td>Cardiovascular depression</td>
</tr>
<tr>
<td></td>
<td>More diagnostic tests for “slow to wake” patients</td>
</tr>
<tr>
<td></td>
<td>REM sleep deprivation contributing to delirium [11]</td>
</tr>
<tr>
<td></td>
<td>Delayed GI motility, poor enteral feeding, and constipation.</td>
</tr>
</tbody>
</table>

Daily interruptions of sedation have been proven to reduce ventilator days and inappropriate diagnostic studies to investigate unexplained altered mental status [7]. The “sedation hold” has become widespread practice and has become part of the ventilator care bundle used in the High Impact Interventions as well as being incorporated into the surviving sepsis campaign guidelines [12]. A landmark paper published in the Lancet in 2008 by Girard looked at 336 critically ill patients and demonstrated that pairing the sedation hold and spontaneous breathing trials reduced the length of time on ventilation, ICU stay and mortality. The NNT for one life saved was 7 in this study [13]. It is therefore expected that all patients suitable for sedation holds should receive one. The reason for omitting a sedation hold should be documented in the medical and nursing notes.

As well as the pairing of sedation holds with spontaneous breathing trials being effective; there is emerging evidence that early mobilisation of these patients during their sedation holds improves their functional status at hospital discharge and a shorter length of delirium on the critical care unit [14]. There has recently been an increase use of analgesia based sedation within the literature improving satisfactory levels of sedation compared with hypnotics [15].

The ability of the patient to remember non-delusional aspects of their stay on ICU is protective against long-term psychological dysfunction including post-traumatic stress disorder and sedation holds have been shown to protect against this. The use of patient diaries may also assist in this.
The aims of treatment[^16]:

- **All patients should be comfortable and free from significant pain.**
  - Analgesia is thus the first aim.

- **Anxiety should be minimised.**
  - This is difficult as anxiety is an appropriate emotion. The most important way of achieving this is to provide compassionate and considerate care; communication is an essential part of this.
  - Establish a comprehensive Drug History using multiple sources, utilising your Pharmacy team accordingly. It may be that the patient usually takes antidepressants and anxiolytics and withdrawal will only add to this anxiety. It’s generally best to avoid newly starting antidepressants in patients you perceive to have become anxious or depressed since admission. These agents generally take 3-4 weeks, sometimes up to 2 months to work and in many cases actually seem to worsen symptoms in the short term.
  - Check patient’s smoking status and consider nicotine replacement therapy.

- **Patients should be calm, co-operative and able to sleep when undisturbed.**
  - This does not mean that they must be asleep at all times.

- **Patients must be able to tolerate appropriate organ system support.**
  - Thus patients with very poor gas exchange, particularly those requiring inverse I:E ratios or the initial stages of permissive hypercapnoea may need neuromuscular blockade. It is impossible to stop interbreathing with sedatives without serious overdosage. A nerve stimulator should be used to monitor the extent of neuromuscular blockade.

- **PATIENTS MUST NOT BE PARALYSED AND AWAKE**
  - This is one of the only indications for deep sedation.

In order to be able to manage analgesia and agitation safely and effectively, it is necessary to know how to correctly assess them.
A.3 Assessment of Pain

Pain Assessment

The majority of patients treated in adult ICUs have pain\textsuperscript{[18]}. Therefore all critically ill patients should have adequate analgesia\textsuperscript{[1]}. Untreated or uncontrolled pain is not only distressing for the patient but is associated with higher energy expenditure, immunodysregulation and an increased incidence of post-traumatic stress disorder\textsuperscript{[1]}.

A sedated patient’s pain assessment must include further investigation and observation to determine the presence of pain. All members of the MDT should consider if lines, drains or painful catheters can be removed or supported to minimise pain.

It can be difficult to assess pain in critically ill intubated patients as their ability to communicate is impaired. Two well-validated scales are available to assess a patient’s degree of pain. These are the non-verbal pain scale and the critical care pain observation tool (CCPOT)\textsuperscript{[19]}. The two pain scores are described below.

**FOR BOTH THE VISUAL SCORE AND THE CCPOT THE TARGET SCORE IS <2.**

The score should be recorded in the notes at the beginning of each nursing shift. Self-reporting of pain should be the default method of reporting pain, and when this is not possible the CCPOT should be used.

For the **self-reporting of pain** either the Wong-Baker faces\textsuperscript{[20]} or the 0 to 10 numeric pain scale can be used. The ventilated/sedated may find it challenging to interpret, and for these patients the Wong-Face Scale, with its visual scale, easier to follow. When assessing an awake patient; document which scale has been used in the notes.

![Wong-Baker Faces Pain Rating Scale](image1)

![0-10 Numeric Pain Rating Scale](image2)

**TARGET NON-VERBAL PAIN SCORE IS 0 TO 2**
In patients **unable to self-report pain**, the 10 point CCPOT (see below) should be used. The target score is **less than 2**. Observable behavioural/facial expressions and physiological indicators are important surrogates and indices which can be used to quantify pain.

**Instructions for completing the Critical-Care Pain Observation Tool (CCPOT):**
1. Observe the patient at rest for one minute to obtain a baseline value.
2. Observe the patient during stimulating procedures (turning, endotracheal suctioning, and wound dressing changes) to detect behaviour to pain.
3. Evaluate before and after the peak effect of an analgesic to assess effectiveness.
4. The rating should be attributed to the highest score in the observation period.

Score each element, with muscle tension assessed last, as touch and limb flexion may alter the response to the other indicators distorting the result if measured first.

<table>
<thead>
<tr>
<th>The Critical-Care Pain Observation Tool (TARGET SCORE ≤2)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Indicator</strong></td>
</tr>
<tr>
<td><strong>Facial Expression</strong></td>
</tr>
<tr>
<td>- Relaxed, neutral</td>
</tr>
<tr>
<td>- Tense</td>
</tr>
<tr>
<td>- Grimacing</td>
</tr>
<tr>
<td><strong>Body Movements</strong></td>
</tr>
<tr>
<td>- Normal position</td>
</tr>
<tr>
<td>- Protection</td>
</tr>
<tr>
<td>- Restlessness</td>
</tr>
<tr>
<td><strong>Compliance with the ventilator</strong></td>
</tr>
<tr>
<td>- Tolerating ventilator</td>
</tr>
<tr>
<td>- Coughing but tolerating</td>
</tr>
<tr>
<td>- Fighting the ventilator</td>
</tr>
<tr>
<td><strong>Muscle Tension</strong></td>
</tr>
<tr>
<td>Relaxed</td>
</tr>
<tr>
<td>Tense</td>
</tr>
<tr>
<td>Rigid</td>
</tr>
<tr>
<td><strong>Total</strong></td>
</tr>
</tbody>
</table>

*Should the patient’s score be 2 in just one indicator (e.g. restlessness) then consider other reasons for restlessness such as delirium.*
**A.4: Assessment of Agitation**

Despite perceived advantages, continuous infusions of sedative agents have been shown to increase the duration of mechanical ventilation and length of stay on intensive care [1,6]. Additionally, the weaning of patients from mechanical ventilation is often hampered by the sedation that they receive.

Every ventilated patient should have a defined sedation target documented in their notes following the Richmond Agitation and Sedation Scale (RASS). The RASS is a 10-point scale, with four levels of anxiety or agitation (+1 to +4), one level to denote a calm and alert state (0), and 5 levels of sedation (-1 to -5) culminating in unrousable (-5). The definitions of each level are listed below.

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combative +4</td>
<td>Overtly combative, violent, immediate danger to staff</td>
</tr>
<tr>
<td>Very agitated +3</td>
<td>Pulls or removes tube(s) or catheter(s), aggressive</td>
</tr>
<tr>
<td>Agitated +2</td>
<td>Frequent non-purposeful movement, fights ventilator</td>
</tr>
<tr>
<td>Restless +1</td>
<td>Anxious but movements not aggressive or vigorous</td>
</tr>
<tr>
<td>Alert and Calm 0</td>
<td></td>
</tr>
<tr>
<td>Drowsy -1</td>
<td>Not fully awake but has sustained awakening (&gt;10secs), eye-opening to contact or voice</td>
</tr>
<tr>
<td>Light sedation – 2</td>
<td>Briefly wakes with eye contact to voice (&lt;10secs)</td>
</tr>
<tr>
<td>Moderate sedation – 3</td>
<td>Movement or eye opening to voice <strong>but</strong> no eye contact</td>
</tr>
<tr>
<td>Deep sedation -4</td>
<td>No response to voice, but movement or eye opening to physical stimulation</td>
</tr>
<tr>
<td>Unarousable – 5</td>
<td>No response to voice or physical stimulation</td>
</tr>
</tbody>
</table>

**If a target RASS score is not documented in the clinical notes,**

aim for a **DEFAULT RASS of 0 to -2**
A.5: Treatment of Pain and Agitation

Individual patient circumstances, cautions, contraindications and interactions should be considered on a case by case basis when selecting therapeutic agents for a particular patient. Therefore, in this guideline revision, we are not being prescriptive in our approach by suggesting a hierarchy of agents. A comprehensive review of a patients analgesia, anti-anxiolytic and sedation needs should be performed at least daily, and should be dynamically reviewed with the availability of a more collateral history to inform decision making.

Analgesia

Paracetamol

See UHL Guideline for Oral and Intravenous Dosing of Paracetamol in ADULTS


NSAIDs

NSAIDs are effective analgesics but are insufficient alone after major surgery. Their use may reduce opioid usage (and their associated side-effects) whilst increasing quality of analgesia. However, caution is needed as they can cause GI bleeding, trigger acute kidney injury, increase risk of postoperative bleeding and possibly exacerbate bronchospasm in sensitive asthmatic patients. These agents are usually prescribed for short-term use only via oral/enteral (e.g. Ibuprofen) or rectal (e.g. Diclofenac) routes.

Tramadol

Tramadol is licensed for the treatment of moderate to severe pain and produces analgesia by two mechanisms: an opioid effect and an enhancement of the serotonergic and adrenergic pathways. It has fewer of the typical opioid side effects, e.g. less respiratory depression and constipation, but it is known to lower seizure threshold (caution needed in patients with epilepsy) and psychiatric reactions have been reported. Tramadol has the potential to produce serotonin syndrome when co-prescribed with tricyclic antidepressants or SSRIs. Tramadol can be prescribed via either injectable or oral/enteral routes.

Oral/Enteral Opioids

Morphine is the first-line oral/enteral agent and is usually prescribed in the first instance PRN as the solution form in 10mg/5ml strength. Usual starting dose range is between 2.5mg and 10mg, with a frequency between 4 to 6 hourly, both depending on the individual patient, pre-existing opioid tolerance and renal function. Higher doses and increased frequency can be prescribed as per clinical assessment and patients' analgesic requirements.

Morphine solid-dose forms are also available as either immediate release or modified release preparations but these will usually need to be ordered via pharmacy as not routinely stocked on intensive care units.

The alternative oral/enteral opioid is oxycodone which is available in solution form and both immediate release and modified release solid dose formulations. These will usually need to be ordered via pharmacy, except when used as part of specific protocols. Oxycodone mainly undergoes hepatic metabolism, however elimination via kidneys remains prolonged in renal impairment albeit to a lesser extent than morphine. Therefore cautious dosing is still recommended in patients with AKI or CKD with a gradual titration, ideally administering doses when required in the first instance, to minimise risk of accumulation.
Injectable Critical Care Therapy

Please see INsite for UHL polices that have information relating to PCA, epidural and continuous local anaesthetic infusion use. These are the most common forms of injectable analgesia delivered to patients who are not intubated on critical care.

*In an intubated and mechanically ventilated patient, when the CCPOT score > 2 and/or the numeric and facial pain score are ≥ 5, injectable forms of analgesia should be considered.*

**Morphine Sulfate**

Morphine Sulfate is an opioid analgesic which has been widely used in critical care.

It is metabolised primarily by the liver into multiple active metabolites, and is excreted by the kidneys, with an initial half-life of up to 6 hours and a long terminal half-life of up to 44 hours.

Therefore, morphine is less suitable for patients with significant hepatic and renal impairment, and in those patients where short periods of sedation are required.

**Initiating IV Infusion Morphine Analgesia**

- **Pain identified using scoring tool / expected post procedure or intervention**

- **Give 2-5mg bolus of Morphine Sulfate. If pain is still apparent after 5-10 minutes repeat bolus dose**

- **Consider starting Morphine Sulfate infusion at 1-3mg/hr if repeated bolus doses are required and/or adequate analgesia level reached**

- **If pain is still apparent after at least 15 minutes of infusion commencing then give an additional 2-5mg bolus dose and repeat as necessary**

- **If repeated bolus doses needed for adequate analgesia consider increasing infusion rate**

- **Review infusion rate vs target RASS in 30-60 minutes and action as per boxes below**

  - **RASS ≥ +1**
    - Despite bolus doses and increases in infusion rate
    - Seek ICU clinician review to discuss increasing infusion rate further, adding adjuvant or switching to alternative agent
  
  - **RASS -2 to 0**
    - MAINTAIN current rate and reassess hourly
  
  - **RASS -3**
    - HALF RATE and reassess in 1 hour
  
  - **RASS -4/-5**
    - STOP infusion. Reassess in 30 to 60 minutes
      - Once RASS -2 to 0 restart at half the previous rate and reassess hourly
**Alfentanil**

Alfentanil is an analogue of fentanyl with a clinical potency of around 10 times the potency of morphine. However it only has between one-fourth and one-tenth the clinical potency of fentanyl but with a shorter duration of action following a single dose. Alfentanil has the fastest onset to action of all the opioids (90 seconds) due to its ability to rapidly cross the blood-brain barrier. Alfentanil has a terminal elimination half-life of approximately 90 minutes which is considerably shorter than fentanyl, due to the relatively small volume of distribution. It is primarily metabolised in the liver and may be inhibited by cytochrome P450 3A4 inhibitors (e.g. fluconazole or erythromycin).

Alfentanil is licensed for analgesia and suppression of respiratory activity in mechanically ventilated patients on intensive care to aid compliance, improve tolerance of the endotracheal tube and provide analgesia during painful procedures.

Alfentanil given by infusion should only be given in areas where facilities are available to deal with respiratory depression and where continuous monitoring is undertaken. The maximum recommended licensed duration of treatment with alfentanil infusion is 4 days, and prolonged use should be reviewed and authorised by an ICU consultant. At the standard doses used within in UHL, alfentanil provides no sedative activity. Therefore supplementation with an appropriate hypnotic or sedative agent may be required and advice should be sought from an intensive care clinician.

Alfentanil is a potent opioid, and is highly likely to suppress spontaneous ventilation (more so than compared with fentanyl) and elderly patients’ are particularly sensitive so lower doses should be used. Undesirable effects include bradycardia, hypotension, nausea and vomiting, which are typical of all opioids but may be more pronounced with alfentanil. Clearance is prolonged in hepatic impairment but unaffected in renal impairment.

Initial infusion rate is usually 2mg/hour (or 30 microgram/kg/hour based on ideal body weight) with a maintenance infusion typically between 1mg and 5mg per hour. Intravenous bolus doses of 0.5mg may be used to provide additional pain relief during brief painful procedures such as physiotherapy, endotracheal suction or wound dressings.

**Fentanyl**

Fentanyl is a synthetic opioid agonist, approximately 100 times more potent than morphine. It is a µ-receptor agonist and as such shares morphine’s effects. However, it is less likely to precipitate histamine release. High doses significantly reduce or even eliminate the metabolic stress response to surgery but are associated with bradycardia and chest wall rigidity. Doses vary depending on the duration of analgesia and sedation required, lower doses are usually sufficient for analgesia whilst maintaining spontaneous ventilation (i.e. 1-2 microgram/kg/hour) whilst higher doses are indicated when opioid based analgesia and sedation required in ventilated patients.

Its onset of action is rapid following intravenous administration due to its high lipid solubility (nearly 600 times more lipid-soluble than morphine). At low doses its short duration of action is due solely to distribution. However, following prolonged infusion or high doses, the half-life increases dramatically from 30 – 60 minutes to 9–16 hours and care must be taken to adjust infusion rate with time. This prolonged context-sensitive half time has reduced the frequency of continuous infusions used within critical care, although bolus doses remain appropriately used for acute analgesia indications.
Remifentanil

Remifentanil is a fentanyl derivative that is a pure µ agonist. It has an ester linkage, which is very rapidly broken down by plasma and non-specific tissue esterases, particularly in muscle. The metabolites have minimal pharmacodynamic activity and the context-sensitive half-time of remifentanil is relatively constant. Therefore a patient may be maintained on a remifentanil infusion for a long period, without significant drug accumulation as seen with other opioids. The advantage of this pharmacokinetic profile is that a patient may be given prolonged infusions of remifentanil, with rapid offset of action when this is no longer required. Analgesic effects wear off so rapidly that pain may be a significant problem immediately post-cessation. This must be anticipated by the administration of a longer acting opioid shortly before therapy is weaned off.

Remifentanil may therefore be considered in the following cases:

- Renal or liver dysfunction
- Short intended duration of ventilation
- Endo tracheal tube intolerance
- Neurological dysfunction requiring frequent assessment (e.g. Head/Hypoxic Brain Injuries)
- Raised ICP resistant to medical management
- Sedation withdrawal after long-term sedation
- Tracheostomy and ready to wean

Remifentanil is an extremely potent opioid, and is highly likely to suppress spontaneous ventilation. Undesirable effects include bradycardia, hypotension & muscle rigidity; which resolve on discontinuation. Ideal Body Weight must be used to reduce the likelihood of these adverse effects.

**REMIFENTANIL MUST NEVER BE BOLUSED,** instead the background rate should be increased.

The default remifentanil dose range used within ICU is 0 to 2 micrograms/kg/min. The licensed maximum rate is higher than this but it is has been agreed within critical care usage to limit the upper rate maximum at 5 micrograms/kg/min (via consultant authorisation) to permit adequate analgesia without the need to add in additional agents. [21]

**Adjuvants for alternative pain relief**

In patients with inadequate pain relief (CCPOT >2, numeric pain and Wong-Baker face score score ≥5) and other reasons for severe pain, a number of strategies can be considered. The first of which would be a switch the alternative opioid agent if appropriate.

Neuropathic pain adjuvants (e.g. amitriptyline, gabapentin, pregabalin) can be considered if clinical assessment identifies an acute cause or there is a pre-existing condition present. Amitriptyline is contraindicated immediately post MI, and in arrhythmias (particularly heart block). Gabapentin and pregabalin should be dosed according to renal function to avoid over-sedation and titrated slowly to minimise adverse side-effects.

Clonidine and ketamine can also be used, on the advice of ICU consultants only, in specific scenarios where adequate pain control is not being achieved using standard agents.
Remifentanil IV Infusion Initiation Example

Commence infusion at 0.1 micrograms/kg/min

Assess RASS and pain score after 5 mins

Increase or decrease infusion rate as tolerated* by 0.015mL/kg/hr (0.025 micrograms/kg/min) increments, reassessing every 5 mins, until dose of 0.2 micrograms/kg/min (0.12mL/kg/hr) is reached, OR lower if desired RASS and adequate analgesia are achieved.

Adequate sedation at 0.2 micrograms/kg/min?

YES

Initiate an additional sedative

NO

Adequate analgesia at 0.2 mcg/kg/min?

YES

Continue at current rate, but review on-going need in line with sedation requirements.

NO

Discuss options with Consultant:

- If willing to escalate dose for additional analgesia as tolerated in increments of 0.015mL/kg/hr (0.025 micrograms/kg/min) intervals up to maximum of 0.5 micrograms/kg/min (0.3 mL/kg/hr) OR

- Add in adjunct analgesic agent OR

- Switch to alternative analgesic agent

Notes:

- Tolerance can be assessed by heart rate (can cause bradycardia), MAP and ability to spontaneously breathe.
- A new syringe must be available to change over within 3 minutes as Remifentanil as an extremely short half-life.
- Only run concomitantly with compatible infusions that will not require a bolus.
- When stopping infusion, aspirate central lines and slowly flush peripheral lines.
- 30 minutes prior to ceasing consider Morphine Sulphate IV 5-10mg bolus to avoid resurgence of pain.

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**Agitation**

If the patient remains agitated and unsettled after the administration of analgesia, then sedation should be added to therapy. The majority of ventilated patients will require both.

**Propofol**

Propofol is highly effective for short-term ventilation (≤ 5 days); reduces mean arterial pressure (MAP) by up to 30%; and reduces cardiac output. Serum triglyceride levels may be necessary in some patients, particularly after 3 days (review if >2mmol/L) [22].

*Caution*: Propofol Infusion Syndrome can occur with infusions over 48 hours. This is characterised by metabolic acidosis, hyperkalemia, rhabdomyolysis and cardiac failure [22].

*Contraindications*: hypersensitivity to soya, peanut, or eggs [22].

The flowchart below provides a guide to commencing propofol:

**Initiating Propofol for Sedation**

- Most patients will already be loaded with propofol either in theatre or during intubation on ICU
- When this doesn’t apply you can consider giving bolus dose 20mg (2mL of 1% propofol) every minute until RASS -2 to 0

Commence infusion at an agreed rate with ICU clinician

Minimum rate usually 20mg/hr (2mL/hr 1%)

- Reassess RASS in 5-10 mins

  - **RASS ≥ +1**
    - Give 20mg (2mL) bolus then increase rate by 2mL/hr. Monitor MAP and cardiac output to ensure bolus and increased rate is safely tolerated
    - Ensure adequate is analgesia provided
    - If RASS ≥ +1 after 3 repeated bolus doses / infusion rate increases within 60min discuss with ICU clinician

  - **RASS -2 to 0**
    - MAINTAIN current rate

  - **RASS -3**
    - REDUCE rate by HALF and reassess in 5-10 minutes

  - **RASS -4/-5**
    - STOP infusion and allow RASS to fall to -3

  - If RASS still hasn’t fallen to -2 to 0 in 30 minutes, further half the infusion rate. Repeat this particular step until RASS -2 to 0

  - **RASS -2 to 0** return to routine monitoring
If the required Propofol dose exceeds 4mg/kg/hour, then consider adding an adjuvant or use of an alternative agent. Adjuvants should be considered in propofol therapy when:

- Patient sedated >5 days
- Reduction in heart rate, MAP required.
- Raised serum triglycerides (>2mmol/L) /propofol intolerance, green urine and high clinical suspicion of propofol related infusion syndrome.
- Unable to sedate
- Uncontrolled agitation/delirium

Adjuncts or alternatives when sedation inadequate with propofol alone:
- alpha-2 agonists (e.g. clonidine or dexmedetomidine)
- benzodiazepines (e.g. midazolam or lorazepam)

**Clonidine**

Clonidine is a centrally acting alpha-2-agonist, which reduces blood pressure and slows heart rate by reducing sympathetic stimulation. Analgesia occurs as a result of stimulation of opiate receptors centrally and peripherally. Primary indication is as an adjunct when adequate sedation cannot be maintained using conventional agents such as propofol. In addition to sedation, clonidine has opioid sparing analgesic properties, and can aid weaning from conventional sedation when agitation secondary to alcohol and/or nicotine withdrawal reactions is problematic.

Its half-life has been variably reported between 6 to 24 hours. Fifty per cent is excreted renally, so may accumulate in renal impairment.

Clonidine may cause hypotension and bradycardia. As it is a negative chronotrope, caution should be used in patients with low cardiac output or impaired ventricular function.

Sudden withdrawal of clonidine may result in agitation, sweating and hypertension. Therefore, reduce the dose gradually, usually over several hours.

Clonidine can be used as a continuous intravenous infusion (see algorithm below) or via intermittent dosing, either IV or enteral. Intermittent doses range from 25 microgram up to 150 microgram with a frequency up to QDS. If required dose exceeds 150 microgram QDS consider switching to a continuous intravenous infusion.

When weaning from prolonged intravenous infusion use, clonidine may be switched to the enteral route if appropriate. Although the bioavailability of IV to enteral is 1:1, in clinical practice when converting to enteral dosing this ratio is not used because the intermittent doses would exceed the usual maximum. Instead the infusion rate is usually weaned down to at least 1 microgram/kg/hour before switching to intermittent enteral doses, which are usually divided into 3 daily doses up to a maximum of 150 microgram per dose. This can then be weaned gradually over the next 2-3 days (can sometimes extend to 5-7 days) by initially reducing then dose followed by reducing the frequency.

Occasionally patients with a history of chronic pain benefit from clonidine administered by the epidural route and this may be added to plain levobupivacaine epidural using a specified dose regime but should only be done in liaison with the Acute Pain Team and Pharmacy (see UHL Epidural Analgesia Post Operative Ward Based for Non Obstetric Patients UHL Anaesthesia Policy).
Clonidine IV Infusion Initiation

Commence infusion at 0.5 to 1 microgram/kg/hr

Assess MAP & Heart Rate once infusion started
If bradycardic or intolerable drop in MAP/BP then half infusion rate and reassess cardiovascular response in 30 minutes.
If tolerating, review rate according to RASS

Assess RASS

RASS ≥+1
Increase incrementally to 2 micrograms/kg/hr as tolerated
If still not adequately sedated seek authorisation from ICU consultant to increase incrementally to 4 micrograms/kg/hr
If bradycardia and/or hypotension occur, reduce back to a previously tolerated rate

RASS -2 to 0
MAINTAIN current rate and reassess RASS hourly

RASS -3
HALF RATE and reassess RASS in 30 - 60 minutes

RASS -4 /-5
STOP infusion and reassess RASS in 30 - 60 minutes
When RASS falls to -2 to 0, then restart at half rate or at a previously tolerated rate
Dexmedetomidine

Dexmedetomidine is a shorter acting alpha 2 agonist, which is used in select patients to provide rousable sedation. Has been shown to reduce the prevalence of delirium and shortened length of stay compared with midazolam. However recent studies have not demonstrated a length of stay benefit over propofol. As yet there are no direct studies of dexmedetomidine vs clonidine

Suggested uses:
- Patients who are exceptionally challenging to manage where the somnolent effects of propofol are not desired and the patients have failed a trial of clonidine.
- Predicted difficult extubation where sedation is still required.
- Patients who have a very high risk of developing critical care delirium.
- Patients who immediately require sedation who are receiving non-invasive ventilation.
- No dose adjustment is required in renal impairment

Contraindications
- Pregnancy or breastfeeding
- Grade 2 or 3 heart block unless paced
- Acute cerebrovascular conditions
- Previous allergy to Dexmedetomidine or other alpha-2 agonists
- Uncontrollable hypotension

Cautions
- End stage hepatic failure
  - manufacturer advises caution in hepatic impairment (liver metabolism); a reduced maintenance rate is advised
- Severe paralytic ileus
- Local vasoconstriction at a higher concentration may be of greater significance inpatients with ischaemic heart disease or severe cerebrovascular disease, and these patients should be monitored closely. Dose reduction or discontinuation should be considered in a patient developing signs of myocardial or cerebral ischaemia

Side Effects and Adverse Reactions
- The most frequent adverse reactions are: hypotension (25%), hypertension (15%) and bradycardia (13%)
- Common adverse reactions (1-10%) include: hyperglycaemia, hypoglycaemia, agitation, myocardial ischaemia/infarction, tachycardia, nausea, vomiting, dry mouth, withdrawal syndrome and hyperthermia

Interactions
- Co-administration with anaesthetics, sedatives, hypnotics and opioids is likely to lead to an enhancement of effects.
- Enhanced hypotensive and bradycardic effects may be seen with other drugs that have these effects e.g. beta-blockers

When switching between clonidine & dexmedetomidine, it may take longer to achieve the desired RASS due to differing half-lives and competition for the same receptor sites. If control is not achieved within 72 hours of initiation, and doses have been optimised to the maximum tolerated dose, then the choice of agent will need to be reviewed.

The flowchart below may help when initiating Dexmedetomidine in the context of pre-existing sedation and analgesia
**Initiating Dexmedetomidine for rousable sedation**

Find actual body weight to start dexmedetomidine infusion (must be diluted prior to administration) at starting rate of 0.7 microgram/kg/hour

Should be prescribed using specific ICU sticker

Run for 15 minutes then assess patient for desired level of sedation

- **RASS -2 to 0 achieved?**
  - **No**
    - Titrate infusion dose stepwise at 15 minute intervals using increases between 0.1 to 0.2 microgram/kg/hour to achieve desired RASS score within the first hour
    - Continue other sedation until dexmedetomidine dose reaches optimal infusion rate
  - **Yes**
    - Wean other sedation by 25 – 50% per hour
      - Continue cardiac monitoring
      - Reduce dexmedetomidine infusion rate if bradycardia or hypotension occur
      - Max dose 1.4 microgram/kg/hour

**If target RASS not achieved** within 72 hours of initiation, at maximum tolerated dose, seek advice from consultant and consider alternatives.

**To stop dexmedetomidine:**

Dexmedetomidine can either be stopped or if preferred the remainder of the infusion can be run until complete, reducing the dose gradually. This may be preferred especially after very prolonged treatment.

Reduce infusion rate stepwise by 0.4 microgram/kg/hour to 0.2 microgram/kg/hour increments over a few hours and run until finished.

If no adverse cardiovascular or withdrawal symptoms after reducing, simply allow infusion to run out at a low infusion rate. If possible reduce rate as to allow remainder of infusion to run over night as may help with sleep.
Benzodiazepines

Benzodiazepines are useful where sedation is complicated by alcohol withdrawal or where treatment of delirium with antipsychotics which prolong the QT interval is contraindicated, and the patient is severely or dangerously agitated, and orientation & environmental management has been unsuccessful.

**Lorazepam:**
- Doses of 0.5-1mg po/ng/iv 4 to 8 hourly may be considered, **NEVER** prescribe doses of more than 20mg per day.
- Lorazepam is almost completely absorbed from the gastrointestinal tract and peak serum levels are reached in 2 hours. It is metabolised by a simple one-step process to a pharmacologically inert glucuronide. There are no major active metabolites. The elimination half-life is about 12 hours and there is minimal risk of excessive accumulation.

**Midazolam:**
- The pharmacokinetics of midazolam are more complicated than that of Lorazepam due to the active metabolite alpha-hydroxy-midazolam.
- Bolus doses in the range of 0.5 – 5mg can be given each time the patient appears agitated or anxious. This can be in combination with an analgesic such as morphine.
- If a patient is requiring repeated bolus dosing to manage agitation and anxiety, this should be reviewed by an ICU clinician to decide on continued management.
- The decision to run an infusion of Midazolam **MUST** only be authorised by an ICU consultant as there will be an increased risk of accumulation associated with delirium and prolonged length of critical care stay.
Definition

Delirium has been defined as “an acute, reversible organic mental syndrome with disorders of attention and cognitive function, increased or decreased psychomotor activity and a disordered sleep-wake cycle”. It is commonly found in the critically ill (i.e. not always in ICU) with a reported incidence of 15-80%.

Three delirium subtypes have been characterised:

Hyperactive - Agitated, paranoid.

Hypoactive - Withdrawn, quiet, paranoid.

Mixed - Combination of hyperactive and hypoactive

The hyperactive form is usually well recognised and the patient may be labelled as being “agitated”. Such patients exhibit some or all of the following features:

- Continual movement (fidgeting, pulling at catheters or tubes, moving from side to side)
- Disorientated (in at least one aspect such as who they are or where they are)
- Commands may not be followed (complex commands followed less than simple ones)
- Patients who can communicate verbally may be unintelligible, or make inappropriate responses. The patient may shout or call out
- Pain is exaggerated
- Abnormal vital signs

It is worth noting that schizophrenic patients do not have cognitive defects and tend to have auditory, rather than visual hallucinations. The delirious patient may perceive the environment as hostile and try to escape, sometimes employing violence against staff or visitors.

The hypoactive form is often not well recognised and inappropriate therapy may be started if the patient is misdiagnosed as being depressed. Disorientation is common in delirium, but this is not a feature of depression. The behaviour of the delirious patient can change dramatically over hours or even minutes, giving rise to confusion amongst caregivers about the patient’s actual mental state.

There are many predisposing factors for the development of delirium that include:

- Failure to provide adequate pain relief
- Hypoxaemia
- Acidosis
- Severe infection
- Advancing age
- Immobilisation
- Frustration
- Patient-ventilator dysynchrony
- Metabolic and haemodynamic instability
- Cerebral illnesses (e.g. dementia, stroke, abscesses, seizures, tumours)
◆ Drug interactions
◆ Withdrawal of drugs
◆ Pre-existing alcohol/substance abuse
◆ Drug side effects (principally excess antimuscarinic and dopaminergic activity)
Assessment

It is a GPICS standard (1.3.3)\textsuperscript{10} that all critical care patients are routinely screened for delirium. Patients should be screened for delirium regularly throughout the day, at least twice per nursing shift, ideally at the beginning and middle of that shift, and when delirium status changes (e.g. positive to negative and vice versa).

The agitated patient is easily identified, but there are other differential diagnoses that may confuse the picture along with the fluctuating nature of the condition. (e.g. dementia, depression, schizophrenia, dysphasia, bipolar affective disorder, sub-clinical seizures). Patients may have delirium in addition to these with acute delirium presentation. If delirium symptoms are protracted or unusual then the differential diagnosis should be reviewed.

The UHL agreed validated score used to assess agitation is RASS, discussed earlier, and can go some way to identifying delirious patients as the score can indicate a number of levels of agitation. However this score is unable to identify all delirious patients and must be used in conjunction with specific delirium tests.

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) uses a four feature score and is the UHL agreed validated delirium-screening tool for use in critically ill patients. The tool is recommended by NICE in England\textsuperscript{11} and the Society of Critical Care Medicine (SCCM)\textsuperscript{12}. When the CAM-ICU tool is used in conjunction with a sedation-agitation scoring system, two of the four features are already scored enabling rapid completion.

The CAM-ICU tool is below and can be found on the reverse of the ICU bed-side charts. Supporting training material on using the assessment tool can be found on http://www.icudelirium.org/delirium/monitoring.html and features video examples along with PDF training manuals, worksheets and a FAQ.
Delirium Prevention

Non-Pharmacological Management

Providing support and orientation
◆ Daily routine where possible, providing clear signposts to patient's location including a clock, calendar, and chart with the day's schedule.
◆ Have familiar objects from the patient's home and photographs of patient/family/home in the room or by the bed.
◆ Communicate clearly and concisely; give repeated verbal reminders of the day, time, location, and identity of key individuals, such as members of the MDT and relatives.
◆ Attempt consistency in nursing staff (e.g. named nurse).
◆ Use television or radio for relaxation and to help the patient maintain contact with the outside world.
◆ Involve family and caregivers to encourage feelings of security and orientation.

Providing an unambiguous environment
◆ Attempt to create a day / night cycle with lights off at night but on all day with appropriate day time stimulation. Pharmacological sleep aids are a last resort.
◆ Delirious patients should be located in a quieter area of the ICU where appropriate.
◆ Control sources of excess noise (such as staff, equipment, visitors).

Maintaining competence
◆ Identify and correct sensory impairments; ensure patients have their glasses, hearing aid, and dentures. Consider whether an interpreter is needed.
◆ Encourage self-care and participation in treatment (e.g. patient gives feedback on pain).
◆ Arrange and cohort treatments to allow minimise interruptions to daily routine and sleep.
◆ Maintain activity levels in conjunction with daily physiotherapy plans.

Remove potential organic drivers
◆ Identify and correct/treat organic causes such as hypoxia, pain, acidosis and infection.

Pharmacological Interventions
Common causes of delirium include drug or alcohol withdrawal. These causes have specific treatments, for example, benzodiazepines are used for the management of alcohol withdrawal. See Alcohol Withdrawal UHL Policy [link to policy].

Pain is a modifiable risk factor for delirium and inadequate pain control is a frequent cause for agitation in the ICU. When pain is not assessed and treated, patients may be inappropriately given a sedative medication rather than an analgesic medication. In ICU populations, where opioid analgesics are used most often to treat pain, an association has been seen showing a reduced risk of delirium. Conversely, in ICU populations, where opioids are frequently used for sedation (either alone or in conjunction with other sedating medications, particularly benzodiazepines), treatment with opioid analgesics has been associated with an increased risk of delirium, especially when their use induces coma.
Drugs commonly associated with delirium

Drug therapy can contribute to the development of delirium and prompt cessation of these medications, where clinically appropriate, can help minimise the occurrence of delirium.

Several medications have been associated with delirium. With regard to sedatives, use of lorazepam and midazolam, is most strongly associated with a higher risk of delirium. Sedation with benzodiazepine infusions for mechanical ventilation, in particular, carries a higher risk of delirium compared to other sedative regimens, as will deeper levels of sedation when compared to light sedation. Additionally, medications with anticholinergic properties (e.g., diphenhydramine, promethazine) can precipitate delirium.

Dexmedetomidine may have advantages over benzodiazepines, since it produces analgesia, causes less respiratory depression, and provides rousable sedation in which patients are more interactive and so potentially better able to communicate their needs. When compared with lorazepam and midazolam (now rarely used as continuous infusions within UHL critical care settings), dexmedetomidine resulted in less delirium and a shorter duration of mechanical ventilation but no difference regarding stays in the ICU or hospital. However when two short-acting titratable drugs such as propofol and dexmedetomidine are compared, there is no significant difference with regards to delirium reduction, which reflects the indifference between the time spent at the target sedation level, duration of mechanical ventilation or ICU stay.

Drugs commonly used in critical care that have been shown to be deliriogenic

- Analgesics
  - Codeine
  - Fentanyl
  - Morphine
  - Pethidine
- Antidepressants
  - Amitriptyline
  - Paroxetine
- Anticonvulsants
  - Phenytoin
  - Phenobarbital
- Antihistamines
  - Chlorphenamine
  - Promethazine
- Antimuscarinics
  - Atropine
  - Hyoscine
- Antipsychotics
  - Chlorpromazine
- Antiemetics
  - Prochlorperazine
- Cardiovascular agents
  - Atenolol
  - Digoxin
  - Dopamine
  - Lidocaine
- Corticosteroids
  - Dexamethasone
  - Hydrocortisone
  - Prednisolone
- Hypnotic agents
  - Chloridiazepoxide
  - Chlortalidone
  - Diazepam
  - Thiopental
- Miscellaneous agents
  - Furosemide
  - Ranitidine

There is no evidence currently to support the prophylactic use of haloperidol or other antipsychotics in the prevention of ICU delirium. Other agents have also been evaluated, covering a variety of pathophysiologic pathways, and there remains a lack of evidence of their use in delirium prophylaxis. In addition, many of these agents have significant side effects, in particular the antipsychotics, which may prolong the QT interval, lead to over sedation, or cause neuroleptic malignant syndrome. This emphasises the necessity of non-pharmacologic preventative measures to improve delirium outcomes. Antipsychotics are not a substitute for proper attention to underlying causes of delirium and should only be used for short-term management of refractory delirium, based on an individual patient risk-benefit assessment.
**Delirium Treatment**

If all preventative measures fail and no organic cause can be identified and treated, delirium treatment should be considered. Delirium is thought to be predominantly due to an excess of dopaminergic activity and/or inadequacy of brain muscarinic activity that often occurs during the course of a severe acute illness. Pharmacological therapy is aimed at correcting this imbalance. Antipsychotics are currently the mainstay of pharmacotherapy for the management of delirium in most settings and fall into one of the following to groups:

**First-generation antipsychotic drugs: Haloperidol**

These act predominately by blocking dopamine D2 receptors in the brain. They are not selective for any of the four dopamine pathways in the brain and so can cause a range of side effects. High levels of D2 receptor occupancy with haloperidol are more effective than low levels when treating psychosis.

**Second-generation antipsychotic drugs: Olanzapine, Quetiapine, Risperidone**

Sometimes referred to as atypical antipsychotic drugs, these have reduced affinity for dopamine D2 receptors and a wider variety of reported affinities for serotonin, adrenergic and muscarinic receptors. They have more distinct clinical profiles, particularly with regard to side-effects. However, to date the studies evaluating these medications have been limited by small sample size.

**Antipsychotic agents**

**Haloperidol**

- Historical agent of choice however the body of evidence regarding its effective use in treating delirium remains controversial.
- Haloperidol is not proven to reduce the duration of delirium but reduces agitation and aggressive behaviour.
- Available in enteral and parenteral formulations for administration.
- Flow chart below suggests a regimen for its use within UHL critical care units.
- Less sedating and fewer antimuscarinic or hypotensive symptoms compared to other antipsychotics.
- Cautions and side-effects:
  - Cardiovascular - Prolongation of QT-interval especially with higher doses, ECG monitoring required. Avoid concomitant administration of drugs that prolong the QT-interval.
  - Extrapyramidal side-effects (EPS) – acute dystonic reactions, parkinsonian symptoms, tardive dyskinesia are more common with IM haloperidol and in antipsychotic naive patients. Atypical antipsychotics such as olanzapine/quetiapine should be prescribed if EPS are a particular concern – see below
- Contraindications: Parkinson’s disease, bradycardia, age over 80 years, post MI, post cardiothoracic surgery.
- Hepatic impairment: use with caution as can precipitate coma.
- Renal impairment: use small doses in severe renal impairment due to increased cerebral sensitivity.
- Weaning: Continue effective dose for 1-2 days, then halve dose and give 6 hourly for 1-2 days, then 8 hourly for 1-2 days and then 12 hourly (if needed) or stop/switch to PRN.
Example of Haloperidol initiation in critical care for delirium management

**Is Haloperidol appropriate?**
- **Yes**
  - Can patient safely and reliably take medicines via oral or enteral route?
    - **Yes**
      - Haloperidol PO/Enteral tube (Tablet or Liquid)
        - Dose: 5-10mg PRN 4-6 hourly (Usual max 30mg daily)
        - Older patients (> 70): 2.5-5mg PRN 4-6 hourly (Usual max 20mg daily)
    - **No**
      - Haloperidol IV
        - Dose: 2.5-5mg PRN 4-6 hourly (Usual max 20mg daily)
        - Older patients (> 70): 1.25-2.5mg PRN 4-6 hrly (Usual max 10mg daily)
  - **No**
    - **SEVERE AGITATION/ACUTE AGGRESSIVE BEHAVIOUR**

**Consider prescribing regular dose from BD to QDS once acute control achieved or delirium starts to show signs of resolving**

**If delirium still ineffectively controlled either switch to an alternative agent or consider adding in an adjunct therapy**

**Haloperidol 2.5-5mg IV is equivalent to 5-10mg PO/Enteral**

Review treatment daily; stop/wean as clinically appropriate
Olanzapine

- Useful in patients requiring night sedation
- Oral/Enteral dose using tablets/orodispersible tablets: 10mg ON with a dose range between 5-20mg daily. Maximum 20mg daily. Usually given as a once daily evening/night-time dose due to drowsiness\(^3\) but twice daily dosing can be considered if clinically appropriate for the patient\(^4\).
- IM injection dose: 5-10mg as a single dose followed by 5-10mg after 2 hours if required (use lower doses in patients over 70 years old). No more than 3 injections daily for up to 3 day duration. Maximum 20mg daily.
- Combined oral and parental maximum daily dose is 20mg in 24 hours.\(^3\)
- Cautions and side effects: Bone marrow suppression, risk of DKA in diabetic patients due to hyperglycaemia\(^3\). Use IM route with caution in septic patients with poor peripheral circulation and in haematology patients with deranged clotting.
- Contraindications with IM injection: Acute MI, bradycardia, recent heart surgery, severe hypotension, unstable angina\(^3,4\)
- Hepatic and renal impairment: consider initial dose of 5mg daily\(^3\)
- Prolonged use may require weaning: dose should be reduced in decrements of 2.5mg daily every 2-3 days\(^4\) The most common dose used is 10mg daily and so a suggested reduction strategy would be:
  - 7.5mg daily for 1-2 days
  - 5mg daily for 1-2 days
  - 2.5mg daily for 1-2 days and then stop

Risperidone

- Tablets, orodispersible tablets and solution available for oral/enteral administration\(^3\)
- Starting dose 0.5-1mg daily\(^4\) in 1-2 divided doses and can be titrated to a maximum daily dose of 4mg in 2 divided doses.
- Consider using lower doses (0.25mg) in patients over 70 years old.
- Prolonged use may require weaning: dose should be reduced in decrements of 0.25 to 0.5mg per dose over 2-3 days. The most common dose used is 0.5mg twice daily so a suggested reduction strategy would be:
  - 0.25mg bd for 1-2 days and then stop
  - 0.25mg on for 1-2 days and then stop

Quetiapine

- Only available in tablet formulation for oral route but can be crushed/dispersed in water for enteral tube administration\(^3\)
- Weak evidence and limited experience of use at UHL, particularly with dose titration.
- Starting dose 25mg bd, increased every 24 hours by 25-50mg per dose up to a maximum daily dose 200 mg bd\(^5,6,7\)
- Prolonged use may require weaning: dose should be reduced in decrements of 12.5-25mg bd over 2-3 days. For example from a 50mg twice daily dose, a suggested reduction strategy would be:
  - 25mg bd for 1-2 days
  - 25mg on for 1-2 days and then stop
Adjuvant agents

Clonidine

- First choice alpha-2 agonist.
- Target patient group: Agitated intubated patients who would benefit from lighter sedation, agitated elderly patients, patients in whom there are uncertainties about prescribing an antipsychotic or in whom opioids and benzodiazepines may present additional risk factors for the development or exacerbation of delirium.
- Contraindications: Severe heart failure, renal failure, bradycardia, paralytic ileus
- Dose 25-75 microgram 6-8 hourly IV/Oral/Enteral
- Weaning: Occasionally a mild rebound tachycardia and hypertension is observed on acute withdrawal. This typically resolves within 12 hours. If this occurs, restart at previous dose and reduce slowly over 4-6 days. A common dose used is 50 microgram qds and so suggested weaning would be:
  - 50 microgram tds for 1-2 days
  - 25 microgram tds for 1-2 days
  - 25 microgram bd for 1-2 days and then stop

Lorazepam

- Benzodiazepines should generally be avoided as there is evidence to show that they contribute to the development of delirium. However, they can be effective in the following patient groups: patients with prolonged QTc, cardiac patients with relative contraindications to antipsychotics, can be used in alcohol or benzodiazepine withdrawal syndromes, or as rescue therapy for rapid tranquillisation if haloperidol therapy (or equivalent) is failing and the patient poses a danger to themselves or others (usually given as IM injection)
- Dose oral/enteral: 0.5-1mg 4-8 hourly. Max 20mg per day
- Dose IV/IM injection: 0.5-2mg as a rescue dose, repeated if necessary but multiple repeat doses are not recommended.
- Use smaller doses in severe renal impairment and severe hepatic impairment

Weaning therapy

This is patient specific and should be reviewed daily. Agents can generally be stopped acutely if only used over short period (i.e. < 5 days) and weaned gradually when treatment period of delirium has been prolonged. Weaning over the course of a few days is usually adequate, as described in examples for individual agents, and is usually achieved within a patients’ critical care admission. Therapy commenced in a critical care setting for the management of delirium should ideally be stopped prior to discharge to a ward. On the rare occasions where this is not possible, convert parental therapy to an equivalent enteral/oral dose, ensuring a clear handover between medical and nursing teams regarding a weaning plan. Consult critical care pharmacist for advice if needed.
Part C: ECMO Summary

ECMO Sedation Guidelines

Initial assessment
- Morphine and Propofol – as intravenous infusions
- Add Midazolam as boluses if struggling for control
- May require paralytic – preference: atracurium infusion
- Aim for spontaneous breathing and responsive to voice
  (RASS 0 to -1) as soon as possible
- This is achieved by stopping paralysis & actively
  reducing morphine and midazolam

Following 48 hours
- If ongoing sedation requirements still present use:
  - Remifentanil infusion
  - Propofol infusion if hypnotic agent still required
    - ideally boluses to control dangerous agitation
  - If ongoing agitation or delirium use haloperidol regularly
  - Consider olanzapine 2nd line
  - Aim to wean propofol over 48 hours – if needed clonidine
    can be used to facilitate this

Treat Withdrawal Symptoms
- ETOH: Diazepam as per trust policy, consider lorazepam
  - opioid: Pharmacist to locate usual treatment centre & re-institute
    methadone if appropriate
  - BZ: consider lorazepam
  - Antidepressant: Recommence as soon as enteral feeding
    established, withdrawal symptoms can occur rapidly
  - Nicotine: 2mg patch for anyone smoking > moderately

Address Sleep
- Night sedation - to be given at 21:00
  - Zopiclone: 3.75 - 7.5mg
  - Melatonin: commence at 2mg
  - Attempt to maintain a day / night cycle

Difficult Agitation
- Dexmedetomidine if above techniques have failed to
  achieve awake and spontaneously breathing patient – by
  consultant initiation only
- If no improvement in 48 hours - stop dexmedetomidine
  and reconsider clonidine / remifentanil
  - Use of lorazepam (IV / NIV) - ‘cleaner’ profile

Consider Sedation Holds Daily
- Daily sedation holds ideal but not appropriate for all ECMO
  patients
- Consider halving sedation every hour until rouetable and re-
  sedate if appropriate
- Document sedation hold plan
3. Education and Training

Medical trainee education and training via ICU specific induction, and educational training programme curriculum delivery (ICU and School based teaching programmes).

ICU Nurse training via foundation programme (Justine Cadwallader, Education and Practice Development Lead, ITAPS)

ITAPS Pharmacy team training via team meeting teaching sessions, postgraduate study/qualification, UKCPA master class courses and local induction.

4. Monitoring & Compliance

<table>
<thead>
<tr>
<th>Element to be Monitored</th>
<th>Lead</th>
<th>Method</th>
<th>Frequency</th>
<th>Reporting arrangements</th>
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<tbody>
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<td>Guideline adherence</td>
<td>?</td>
<td>ITAPS audit cycle</td>
<td>2 yearly</td>
<td>ITAPS audit meeting.</td>
</tr>
</tbody>
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5. Supporting References

Sedation References (Part A)


19. Validation of the Critical-Care Pain Observation Tool in Adult PatientsCéline Gélinas, RN, PhD, Lise Fillion, RN, PhD, Kathleen A. Puntillo, RN, DNsC, Chantal Viens, RN, PhD and Martine Fortier, MPs Am J Crit Care July 2006 vol. 15 no. 4 420-427


**Delirium References (Part B)**


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7. Reade M.C.; Finfer S. Sedation and delirium in the intensive care unit. New England Journal of Medicine; 2014; vol. 370 (no. 5); p. 444-454


6. Key Words

- Pain
- Anxiety
- Agitation
- Delirium
- Sedation
- Critical Care
- CAM-ICU
- RASS
- CCPOT