Intensive Care Society Review of Best Practice for Analgesia and Sedation in the Critical Care

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1 Disclaimer

This review was produced on behalf of the Intensive Care Society, with input from subspecialist surgical and medical departments. Where possible we have achieved consensus between practicing clinicians. The review does not however necessarily represent the views of all the contributing clinicians.

The recommendations contained in this review do not indicate an exclusive course of action, or serve as a standard of medical care. Variations, taking individual circumstances into account, may be appropriate.

The authors of this review have made considerable efforts to ensure the information upon which they are based is accurate and up to date. Users of the review are strongly recommended to confirm that the information contained within them, especially drug doses, is correct by way of independent sources. The authors accept no responsibility for any inaccuracies, information perceived as misleading, or the success of any treatment regimen detailed in the review.

Should you find any errors in this document, they should be reported to the Intensive Care Society.
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4 Abbreviations

ALF  Acute Liver Failure
BD   Twice a day
dB   Decibel
ETT  Endotracheal Tube
GABA Gamma-Amino Butyric Acid
ICP  Intra-cerebral pressure
ICU  Intensive Care Unit / Critical Care Unit
IM   Intra-Muscular
IV   Intravenous
NSAID Non-Steroid Anti-Inflammatory Drug
PCA  Patient-controlled analgesia
PTSD Post-Traumatic Stress Disorder
PO   Orally
QDS  Four times per day
TDS  Three times per day
TIVA Total Intravenous Anaesthesia
5 Introduction

This review has been prepared to assist the multidisciplinary Intensive Care (ICU) team determine the best sedative regimen for their patients. Sedation has been a ubiquitous and essential component of critical care since its beginnings and plays a cardinal role in allowing therapies to be undertaken whilst minimising patient distress. Sedation requirements vary widely between patients and at different times of their illness. Being ill in an ICU is nearly always very frightening and may require a number of painful or uncomfortable procedures. The sedative regimen must be tailored to the individual patient, necessitating a multimodal and multidisciplinary approach and does not simply involve the use of drugs. Adequate analgesia should be a fundamental part of this approach; sedation should never be given as a substitute for analgesia.

The term ‘sedation’ has become a catch-all phrase to describe everything from anxiolysis – ‘a little something to help you sleep’ – to a state of unresponsiveness that mimics general anaesthesia. This imprecision in terminology emphasises the need to define precisely our aims when the decision to ‘sedate’ is made. In principle, the medical and nursing teams should always strive to use the minimum dose of sedation to achieve the desired effects without compromising patient comfort and safety. There may, however, be situations where high doses of drugs are necessary to induce deep sedation verging on general anaesthesia. Indications for the use of sedative drugs in the ICU include:

- To alleviate pain
- To facilitate the use of an otherwise distressing treatment and minimize discomfort e.g., tolerance of endotracheal tubes and ventilation
- To augment the effectiveness of a treatment e.g., inverse ratio ventilation
- As a treatment in its own right e.g., seizure control or management of intracranial pressure
- To reduce anxiety
- To control agitation
- For amnesia during neuromuscular blockade
A variety of medications may be used for sedation. These include opioids, benzodiazepines, intravenous and inhaled general anaesthetic agents, neuroleptic drugs, phencyclidine derivatives, phenothiazines, α-agonists and barbiturates. While these drugs are used to help the patient, they carry with them the potential for harm. Those who sedate patients in the ICU should be fully informed of the benefits and problems associated with each drug they use and be fully appreciative of possible adjuncts to pharmacological sedation.

High quality care does not solely rest on the judicious use of drugs but also requires an understanding of the causes of the distress and the creation of an environment that reduces stress. The ICU patient may have a limited number of ways to express themselves and a patient who is pulling at monitoring lines may be distressed, in pain, delirious or a combination of all three.

Prolonged sedation is an intervention whose adverse effects are often underestimated. Over-sedation may be responsible for prolongation of artificial ventilation (1), hypotension and under-perfusion, prolonged recovery and increased need for tracheostomy, delay in weaning from respiratory support, critical illness myopathy and muscle wasting, an increase in delirium, immunosuppression, ileus of the gastro-intestinal tract, thrombosis and DVT, with down regulation of receptors and increased risk of nosocomial pneumonia (2). Conversely, under-sedation not only causes generalised discomfort and tracheal tube intolerance but also hypercatabolism (3), increased sympathetic activity leading to hypertension, tachycardia, increased oxygen consumption, myocardial ischaemia, atelectasis, infection (4) and psychological trauma (5). However, the perception that by sedating our patients we are protecting them from an unpleasant experience is probably not entirely correct. Patients who can only recall delusional memories are more likely to develop anxiety and post-traumatic stress disorder (PTSD) following discharge (6).

This document is not meant to be a rigid framework but provides information around which clinicians may build their own sedation protocols. It is intended for all groups of ICU patients, including specific patient groups such as neurological injury, burns, cardiac patients and liver patients.
1. Develop a multi-disciplinary, structured approach for managing sedation and analgesia in the ICU

2. Perform patient assessment and optimize the ICU environment
   A. Identify predisposing and precipitating factors; manage treatable factors
   B. Identify outpatient medications (medication reconciliation), particularly psychiatric and pain medications; restart medications as appropriate
   C. Optimize patient comfort and tolerance of the ICU environment
   D. Optimize MV settings for patient/ventilator synchrony

3. Regularly perform and document structured patient evaluation and monitoring
   A. Establish and communicate treatment goals
   B. Assess presence and severity of pain, as well as response to therapy
   C. Assess level of sedation using a validated sedation scale, as well as response to therapy
   D. Assess presence and severity of agitation using a validated agitation scale
   E. Identify delirium, and consider regular assessment of delirium, using a validated delirium assessment instrument

4. Implement a structured patient-focused management strategy
   A. Select analgesic and sedative drugs based upon patient needs, drug allergies, organ dysfunction (particularly renal or hepatic dysfunction), need for rapid onset and/or offset of action, anticipated duration of therapy, and prior response to therapy
   B. Focus first on analgesia, then sedation
   C. Titrate analgesic and sedative drugs to a defined target, using the lowest effective dose
   D. Implement a structured strategy to avoid accumulation of medications/metabolites: utilize scheduled interruption, or intermittent dosing of analgesic and sedative drugs
   E. Evaluate and manage severe agitation, including search for causative factors, and perform rapid tranquilization
   F. Identify delirium, correct precipitating factors, and treat when appropriate after withdrawing all precipitating causes
   G. Avoid potential adverse effects of analgesic and sedative drugs; quickly identify and manage adverse effects that occur

5. Recognize and take steps to ameliorate analgesic and sedative drug withdrawal during de-escalation of therapy.

Modified from Sessler C and Varney K (7)

Table 1 - Key Concepts for Management of Sedation and Analgesia
6 Factors that affect the requirement for sedation in the ICU

6.1 Facilitation of mechanical ventilation and endotracheal tube (ETT) tolerance

Sedation should be administered so that a patient may tolerate an endotracheal tube. Modern ICU ventilators are now equipped with a wide range of modes which allow synchronisation of ventilation with the patient’s own breathing without the need for deep sedation in most cases.

Patient-ventilator dysynchrony or “fighting the ventilator” is a complex problem which is influenced by both ventilator performance and the patient. The ventilator’s work should match patient demand and this interaction will depend on the patient’s effort and the ventilator’s performance. If these do not match then dysynchrony will occur (8). It is associated with adverse effects including increased work of breathing, patient discomfort, increased need for sedation, difficulties in weaning, prolongation of mechanical ventilation, longer stay in ICU and an increase in mortality (9), (10).

Respiratory distress and ventilator dysynchrony may be caused by a number of problems.

Table 2: Causes of Respiratory Distress and Ventilator Dysynchrony

<table>
<thead>
<tr>
<th>Patient Related Causes</th>
<th>Ventilator Related Causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Airway patency</td>
<td>Ventilator malfunction</td>
</tr>
<tr>
<td>Bronchospasm / Asthma / Tracheomalacia. Prolonged expiratory time.</td>
<td>Circuit leaking. Check for cuff leak and then check rest of system.</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>------------------</td>
<td>------------------------</td>
</tr>
<tr>
<td>Excessive secretions</td>
<td>Trigger sensitivity incorrect.</td>
</tr>
<tr>
<td>Pulmonary Oedema</td>
<td>Incorrect ventilator support</td>
</tr>
<tr>
<td>Pneumothorax</td>
<td>Low FIO2</td>
</tr>
<tr>
<td>Pain/Anxiety</td>
<td>“Stacking”/auto-PEEP. Excess intrinsic PEEP</td>
</tr>
<tr>
<td>Abdominal distension. Body posture. Pain may splint the diaphragm.</td>
<td>Increased dead space in system may cause increased work of breathing.</td>
</tr>
<tr>
<td>Factors increasing respiratory drive (hypoxia, hypercarbia, increased metabolic states, acidosis, sepsis, burns, trauma.) Underlying lung disease.</td>
<td>Ventilator disconnection</td>
</tr>
<tr>
<td>Prolonged patient inspiratory time.</td>
<td></td>
</tr>
</tbody>
</table>

Sedation is a common solution for managing patients who “fight” the ventilator but it may not always be the best answer. Coughing and gagging are very deep reflexes and are used in the brain stem death testing. **The presence of a cough reflex should not be used to assess the depth of sedation.** If coughing is interfering with ventilation and the patient is already deeply sedated, then muscle relaxants should be considered. Clinicians should identify the cause of dysynchrony rather than reaching for the sedative syringe. Sometimes increased sedation will improve patient tolerance of the ETT or reduce anxiety to allow ventilator synchrony.

### 6.2 Pain and discomfort
Patients in ICU often experience pain as a consequence of recent surgery, trauma, invasive procedures and immobilisation (11). Pain may also be caused by devices, such as an ETT, but also monitoring such as urinary catheters and lines. Routine
medical and nursing care such as wound dressing, tracheal suctioning and physiotherapy also cause pain and discomfort.

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. Furthermore, sleep disruption, sleep deprivation and anxiety increase the perception of pain. Pain is commonly reported when ITU patients are reviewed following ICU discharge (12), (13). In multicentre studies 50 – 65% of patients complained that they suffered severe pain in ICU; 15% were unhappy with the pain management they received.

In addition to being humane, ensuring that a patient is pain free can facilitate sedation. A recent study suggested that the use of morphine alone reduced ventilated days when compared with sedation and morphine (14). Assessment of a patient’s pain is easier when the nursing and medical teams are able to communicate with the patient, adding an extra reason for minimising sedation whenever possible. Analgesia should always be considered in conjunction with sedation.

6.3 Control of ‘agitation’
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. Agitation is common in ICU patients who are not receiving mechanical ventilation. It 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. Risk factors for the development of agitation are shown in the table below.
Table 3: Independent Risk factors for the Development of Agitation (15)

<table>
<thead>
<tr>
<th>Predictive Risk Factors</th>
<th>Odds ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age 65&gt;</td>
<td>2.21</td>
<td>0.83 – 5.93</td>
</tr>
<tr>
<td>Medical cause for ICU admission</td>
<td>3.04</td>
<td>0.85 – 10.54</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>2.61</td>
<td>1.03 – 6.58</td>
</tr>
<tr>
<td>Use of sedatives in 48 hours before onset of agitation</td>
<td>4.03</td>
<td>1.62 – 10.4</td>
</tr>
<tr>
<td>Body temperature &gt; 380c</td>
<td>4.52</td>
<td>1.8 – 11.49</td>
</tr>
<tr>
<td>Sodium level &lt; 134 mmol/L</td>
<td>4.87</td>
<td>1.58 – 14.99</td>
</tr>
<tr>
<td>Sodium level &gt; 143 mmol/L</td>
<td>4.95</td>
<td>1.95 – 12.54</td>
</tr>
<tr>
<td>Long term psychoactive drug user</td>
<td>5.63</td>
<td>1.32 – 23.70</td>
</tr>
</tbody>
</table>

It is important not to confuse agitation with delirium. Delirium is defined as an acute change in mental status, or a fluctuation of mood, associated with impaired attention, disorganized thinking, confusion and an altered level of consciousness. Delirium differs from agitation because it may be either hypoactive (not agitated), hyperactive or mixed. Typically, this cognitive alteration varies throughout the day, and achieves peak intensity during the night. This symptom is usually reversible within a period of days or weeks, although some patients progress to permanent brain failure. Delusions and hallucinations may also occur.

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. A thorough assessment of the possible causes of the agitation should be sought before prescribing sedation. It must also be remembered the importance of talking to patients and explaining everything that is happening to them. One of the benefits of one-to-one nursing that is common in the UK for critically ill patients is the ability of
nursing staff to be able to communicate with their patients and ensure a resolution of the situation without physical or chemical restraint.

6.4  Anxiety

Nearly all severely ill patients will suffer some form of anxiety, distress or agitation during their stay in ICU (16), (17), (18). Anxiety and stress in critically ill patients is almost always multifactorial. Sleep deprivation (19), (20), physical environment of the unit (21), (22), (23), anxiety felt by the patient due to their insight of the situation (20), (24), (25), delirium, adverse drug effects, pain (26), (27), (28), (4), (29), (30) and inability to communicate with the ICU team may all contribute to the patient's distress. The stress response to critical illness may increase catecholamines, growth hormone, prolactin, vasopressin, cortisol, glucagon, fatty acids, protein catabolism and sympathetic tone (4), (31), (32). To our knowledge, there are no data suggesting benefit from manipulation of the stress response but at the very least it is humane to provide anxiolysis, analgesia, sedation and comfort at a time of critical illness.

Simple measures such as providing compassionate and considerate care are essential. Patients report many recollections from their critical care experience which can be both positive and negative. In one study, 66% of patients ventilated in ICU could remember being ventilated and most of those patients remembered the endotracheal tube and the IPPV and found it “moderately to extremely bothersome” (33). Stressful experiences associated with the endotracheal tube were strongly associated with subjects experiencing periods of terror, feeling nervous when left alone and poor sleeping patterns. This suggests the potential for improved symptom management, which could contribute to a less stressful intensive care unit stay and improved patient outcomes.

Patients who have been treated with muscle relaxants and paralysed have varying levels and types of memories; unfortunately most of these are distressing. Ballard et al (33) identified a total of 4 themes and 3 subthemes:
● A feeling of going back and forth between reality and the unreal, between life and death
● The subtheme was having bizarre dreams
● Loss of control;
  ● The 2 subthemes were:
    ● fighting or being tied down
    ● being scared
● Almost dying
● Feeling cared for

Anxiety is also brought about by continuous noise within ICU such as monitoring machines, telephones, pagers, other patients, medical and nursing staff. (19), (20). Sleep deprivation that is a consequence of this noise (see Section 8.6 Avoiding Sleep deprivation). 24 hour lighting also contributes to anxiety (34).

Figure 1 - Interactions between Patient and Sedative Manoeuvres

6.5 Using Sedation to Combat Insomnia
Sleep deprivation is a common occurrence in the critically ill. Its cause is often multifactorial. Sleep in ICU patients is characterized by prolonged sleep latencies, sleep fragmentation, decreased sleep efficiency, frequent arousals, a predominance of stage 1 and 2 non-REM sleep, decreased or absent stage 3 and 4 non-REM sleep, and decreased or absent REM sleep (35), (36), (37). Being a patient in ICU is very psychologically stressful. In addition, patients may be experiencing pain from recent surgery or trauma. Insomnia may be due to medical conditions (such as heart disease, COPD, asthma, Alzheimer’s, Parkinson’s disease, hyperthyroidism, arthritis) or prescription medication (e.g., anti-epileptics, beta-blockers, HRT, NSAID’s and beta-stimulants such as salbutamol, salmeterol and theophylline). Insomnia may be linked to an underlying psychiatric problem or absence of usual non-prescription drugs such as alcohol and nicotine. Patients in ICU may also suffer from insomnia caused by a loss of normal melatonin secretion (34).

However the primary factor causing sleep disruption is thought to be the ICU environment. Noise from various sources including ventilators, monitor alarms, phones, pagers and general noise of movements and personnel in the unit have all been reported to disrupt sleep (38). Several studies have demonstrated peak noise levels well in excess of the Environmental Protection Agency recommendations (38), (39), (19), (40). Some studies have suggested the use of ear plugs and head phones to improve sleep as measured by increased REM duration and decreased wakenings (41), (42). In addition to noise, light has also been proposed as a source of sleep disruption but it may be not as disturbing to sleep patterns as noise or nursing procedures (43).

Sedative drugs are often used to treat insomnia in the ICU. They may have negative effects by altering the characteristics of normal sleep but do increase the total sleep time and its continuity. Similarities and differences between normal sleep and sedation are shown in the Table 4.

<table>
<thead>
<tr>
<th>Similarities</th>
<th>Differences</th>
</tr>
</thead>
</table>

Table 4: Similarities and differences between normal sleep and sedation
<table>
<thead>
<tr>
<th>Overlapping neurophysiological pathways</th>
<th>Sleep is circadian: Sedation is not</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature deregulation</td>
<td>Sleep is completely reversible with external stimulation</td>
</tr>
<tr>
<td>REM (Rapid Eye Movement)</td>
<td>Sleep is associated with decrease in release of nor epinephrine from the locus coeruleus</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>Sleep has cyclic progression of EEG stages. There is less variability in EEG under sedation (44)</td>
</tr>
<tr>
<td>Muscle hypotonia</td>
<td>Sedation will variably alter normal sleep architecture and patterns.</td>
</tr>
<tr>
<td>Altered sensation and mentation</td>
<td></td>
</tr>
</tbody>
</table>

Before resorting to sedation, other measures to reduce sleep deprivation should be considered e.g., noise reduction, clustering interventions to avoid unnecessary disruptions, minimization of sleep-inhibiting drugs, considering withdrawal symptoms from non-prescription drugs, controlling light exposure and ensuring temperature regulation.

6.6 Presence of pharmacological withdrawal syndromes

Some critically ill patients will be dependent on other substances. The commonest substance addictions associated with withdrawal syndromes are alcohol, nicotine and opioids. Alcohol withdrawal may cause a set of symptoms mainly affecting the central nervous system causing a hyper-excitabile state, seizures, delirium and excite-neurotoxicity and can be fatal (45). Tobacco addiction may also lead to agitation and the use of nicotine patches may reduce cravings.
When patients have been sedated or given analgesia for prolonged periods in ICU then withdrawal symptoms may appear. The most significant of these is withdrawal from benzodiazepines. Benzodiazepine withdrawal is similar to alcohol withdrawal syndrome and barbiturate withdrawal syndrome and can, in severe cases, provoke life threatening withdrawal symptoms such as seizures. An abrupt discontinuation of benzodiazepines may result in a serious and very unpleasant withdrawal syndrome that may additionally result in delirium, convulsions, catatonia or hyperthermia (46), (47), (48). A protracted withdrawal syndrome may develop in some individuals with symptoms such as anxiety, irritability, insomnia and sensory disturbances. In a small number of people it can be severe and resemble serious psychiatric and medical conditions such as schizophrenia and seizure disorders. Withdrawal symptoms may persist for weeks or months after cessation of benzodiazepines. In a smaller subset of patients withdrawal symptoms may continue at a sub-acute level for many months or even years (49).

6.7 Perceived need for amnesia in the ICU patient

There is a perception among ICU staff that by sedating patients and thus ensuring amnesia of the events that we are somehow protecting them from memory of terrible events. This may be a serious misconception. Illness and its treatments have a dampening effect on memory in the critically ill. Many patients have absolutely no recall of their time in ICU and when they do have recall, they have no accurate recollections tending to remember nightmares, delusions and hallucinations rather than actual events.

It is thought that in addition to the illness and treatments, other factors such as delirium and sleep disturbance have a profound effect on memory perception from a stay in ICU. Furthermore the treatment given to provide sedation and analgesia (opiates, benzodiazepines and general anaesthetic agents) may be contributing to this memory loss. This in addition to the social isolation that patients feel when in ICU and effects memory negatively and may help to explain why ICU patients have such poor memory of the events. Patients find that their delusional memories are
much more prominent and they describe these as vivid and they describe hallucinations and nightmares. The absence of “real” memories compounds their discomfort and may predispose to post ICU PTSD. (6).

6.8 Sedation as a Treatment

6.8.1 Myocardial Protection
Myocardial dysfunction is a common problem for ICU patients. Suboptimal analgesia and sedation may trigger a stress response which can lead to myocardial ischaemia and an increase in cardiac workload, increased myocardial oxygen consumption and increased incidence of arrhythmias. Preventing further myocardial dysfunction in the critically ill patient is paramount and this can in part be achieved by optimising the patient’s sedation. Studies have demonstrated that most analgesics and sedatives agents (propofol, midazolam, clonidine, dexmedetomidine, opioids) can reduce the stress response to major surgery and decrease haemodynamic complications (50), (51), (52).

In cardiac surgery patients there is evidence supporting the use of intra-operative volatile agents for their direct myocardial protective properties and their use has been shown to reduce cardiac morbidity and mortality (53). Although there are reports of volatile agents being safely used in ICU there is currently no evidence that they provide any additional cardiac protective benefits or improved haemodynamic stability (54).

6.8.2 Neurological/neurosurgery
Sedation in NeuroICU is not just to facilitate mechanical ventilation but also has a neuroprotective role. The mantra of managing patients with primary neurological pathology is to prevent secondary injury from cerebral ischaemia. Secondary brain injury may be caused by factors causing a reduction in cerebral perfusion pressure
(CPP), factors that cause an increase in intracranial pressure (ICP) and the metabolic demands of the brain.

Sedative agents can alleviate agitation, pain and anxiety and terminate seizure activity and reduce the cerebral metabolic rate and oxygen consumption. Despite its benefits, the use of sedation in neuro-critical care must be balanced by the drawbacks of over-sedation precluding neurological assessment, prolonging ICU stay and adverse hemodynamic effects from some of the sedative agents (55). Dexmedetomidine has shown promise in several animal studies displaying a neuroprotective effect although the benefits of this have yet to be seen in clinical practice (56).

Sedatives (benzodiazepines, barbiturates and propofol) are indicated in the treatment of status epilepticus. In refractory status epilepticus, therapy is titrated against a burst suppression pattern on the EEG. There are no randomised control trials to say which agent is superior but since propofol has a much quicker clearance and elimination time than the barbiturates and benzodiazepines, its use has gained popularity (57).

### 7 Pharmacological Measures to Induce Analgo-Sedation

The 'Ideal Sedative Agent' should possess the following qualities

- Sedative, analgesic and anxiolytic properties
- Minimal cardiovascular and respiratory side-effects
- Rapid onset and offset of action
- No accumulation in renal/hepatic dysfunction
- Inactive metabolites
- No interactions with other drugs
- Cheap
The ideal sedative does not exist, and consequently a large number of drugs and combinations have been used. The most commonly used agents are intravenous anaesthetic agents or benzodiazepines, often in combination with opioids. Other options to control agitation, delirium and pain in the ICU include alpha 2 agonists such as clonidine and dexmedetomidine, ketamine, non-opioid analgesics and anti-psychotic agents. There is insufficient evidence to recommend one regimen over another, and so the agents chosen should be individualized to the patient’s requirements, characteristics and the clinical situation. However, the current literature supports modest benefits in outcomes with non-benzodiazepine-based sedation versus benzodiazepines (58).

The most common cause of restlessness and agitation in ICU patients is pain. Pain has consequences in the critically ill patient that can lead to clinically significant physiological responses such as tachycardia, increased myocardial oxygen consumption, hypercoagulability, immunosuppression, and persistent catabolism (4). Management of pain must take precedence over sedation, although both are often be attended to simultaneously. It is for this reason that we include analgesic agents in this section. Management of pain, however, consists of providing analgesia both pharmacological and non-pharmacologically e.g., ensuring proper attention to positioning, stabilisation of fractures and physiotherapy to avoid joint pain and muscle contractures. Whilst opioids will provide the majority of the pharmacologically provided analgesia provided in the ICU, it should be remembered that augmentation with other analgesia is important. In the absence of contraindications, they should be considered in all ICU patients.

As has already been mentioned, one study by Strom and colleagues suggested that the use of morphine alone reduced ventilated days when compared with sedation and morphine (14). Detailed study of this paper reveals that the patients in the ‘no sedation’ group did indeed receive both opioid analgesia with morphine and a sedative drug; it is unlikely that the use of morphine alone is feasible in the majority of ICU patients. Further study is required to demonstrate whether Strom’s findings are more than a statistical blip but the principle that patients require more analgesia than sedation is probably not a bad starting point.
7.1 Intravenous anaesthetic agents

7.1.1 Propofol

Propofol is an intravenous general anaesthetic agent that has sedative, hypnotic, anxiolytic and anterograde amnesic properties at sub-anaesthetic doses but no analgesic activity. It is an α-amino butyric acid (GABA) agonist and is a short acting agent owing to its relatively rapid onset and clearance. It has been used for sedation in ICU since the 1980s (59) and has a broad experience base. Propofol has a wide array of benefits including anxiolysis, anticonvulsant activity (60), (61), anti-emesis (62), (63) and an ability to reduce intracranial pressure (64). Following cessation of a prolonged propofol infusion there is a rapid fall in plasma concentration (65); following an infusion of mean duration 85.6 hours studied in 12 ITU patients, a 50% decrease in plasma concentration occurred in 10mins (66). This rapid onset and offset is a specific feature of propofol when compared with other commonly used ICU sedatives (66), (67).

Propofol is a lipid soluble compound and its half-life, the distribution of the drug from the blood to the tissues after intravenous administration, is very short at only 2 to 3 minutes. The $\beta$ half-life of the drug, which is basically the elimination half-life, ranges from 30 to 60 minutes. The terminal half-life, during which the drug is eliminated from the third compartment or tissue fat, ranges from 300 to 700 minutes (68), (69).

The most important side effect of propofol is hypotension due to peripheral vasodilation and negative inotropic and chronotropic effects. Hypotension is more pronounced in patients with intravascular depletion, compromised myocardial function or abnormally low vascular tone (e.g. sepsis) or when propofol is administered in combination with other sedative and opioid medication. Propofol also causes a dose-dependent respiratory depression, with other side-effects including hypertriglycerideremia, acute pancreatitis and myoclonus.

Propofol infusion syndrome (PRIS) is a rare but serious adverse drug reaction associated with high doses (>4mg/kg/hr) and long-term use (>48 hrs) of propofol.
PRIS is characterised by progressive cardiac dysfunction (bradyarrhythmia, cardiac failure and specific electrocardiograph changes), severe metabolic acidosis, hyperkalaemia, hyperlipidaemia, acute renal failure and rhabdomyolysis (71). Although the precise causes of PRIS are unknown, clinical and experimental evidence exists suggesting propofol triggers a dysfunctioning of the mitochondrial respiratory chain disrupting fatty acid oxidation. This causes reduced ATP production and cellular hypoxia in tissues leading to cytolysis of these cells with accumulation of free fatty acids (72), (73). Supportive therapy is the mainstay of treatment. The propofol infusion should be discontinued and an alternative sedative commenced. Haemodialysis or haemofiltration is recommended for elimination of propofol and its toxic metabolites. The associated bradycardia may be resistant to catecholamines and external pacing; extracorporeal membrane oxygenation has been used effectively (74).

### 7.1.2 Propofol Dosing

For intubated, mechanically ventilated adult patients, propofol should be initiated slowly with a continuous infusion in order to titrate to desired clinical effect and minimize hypotension. The infusion rate should begin at 5 µg/kg/min (0.3 mg/kg/h) and increased by increments of 5 to 10 µg/kg/min (0.3 to 0.6 mg/kg/h) until the desired level of sedation is achieved. A minimum period of 5 minutes between adjustments should be allowed for onset of peak drug effect. Most adult patients require maintenance rates of 5 to 50 µg/kg/min (0.3 to 3 mg/kg/h) or higher. Bolus administration of 10 or 20 mg should only be used to rapidly increase depth of sedation in patients where hypotension is not likely to occur.

### 7.2 Benzodiazepines

Benzodiazepines are commonly used for sedation in the critically ill. They bind to the GABA receptor complex modulating GABA release in the CNS causing down-regulation of neuronal excitation. This causes sedation, anxiolysis or hypnosis depending on the doses used and the number of receptors occupied. They do not cause general anaesthesia, but will depress the respiratory centre and cause cardiovascular depression. They are bound to plasma proteins and are not removed by dialysis.
7.2.1 Midazolam

Midazolam is a short-acting, water-soluble benzodiazepine that becomes lipophilic in the blood and rapidly enters the CNS. Anterograde amnesia occurs almost immediately after intravenous administration and usually persists for 20–40 min after a single dose. Midazolam is hydroxylated by CYP3A4 and its metabolism can therefore be affected by hepatic function, blood flow and administration of other drugs (e.g., diltiazem, macrolides, cimetidine and ranitidine) (75). Midazolam has an active metabolite, α1-hydroxymidazolam, which accumulates in renal failure. Consequently midazolam has a large variability in its elimination half-life (76) and an unpredictable offset of action following prolonged administration. A wide inter-patient variability in the pharmacokinetic properties of midazolam in critically ill patients with multiple organ failure has been reported (77), which can lead to prolonged sedation after midazolam therapy is stopped. Unpredictable awakening times and prolonged extubation times have been reported when midazolam is administered by infusion for longer than 72 hours (11). Tolerance and tachyphylaxis may occur, particularly with longer-term infusions (>= 3 days). Benzodiazepine withdrawal syndrome has also been associated with high dose/long-term midazolam infusions. Compared with propofol infusions, midazolam infusions have been associated with a decreased occurrence of hypotension but a more variable time course for recovery of function after the cessation of the infusion.

7.2.1.1 Midazolam Dosing

Midazolam is most commonly administered via a continuous infusion titrated between 0.25 and 1.0 μg/kg/min. Sedation holds should be used in patients not requiring deep sedation to ensure optimal wake up times. One review suggested that bolus administration may be used as an alternative to infusion, reducing mechanical ventilation duration and ICU length of stay (78). Doses of 0.5–2 mg IV every 5–10 minutes can be administered as needed.
7.2.2 Lorazepam

Lorazepam is a long acting benzodiazepine with a relatively low lipid solubility and slow onset of action, making it a poor choice for rapid control of agitation. It is metabolised by glucuronidation to inactive metabolites, and has a long elimination half-life of 10-30 hours (76), (79). The long context sensitive half-life when administered by infusion causes accumulation and very prolonged sedation. These characteristics make it a better agent for bolus administration than for infusion. The solvents used in the preparation of lorazepam (polyethylene glycol and propylene glycol) have been implicated in causing hyperosmolar states, lactic acidosis and renal tubular acidosis when given as a prolonged or high dose infusion (80); they may also cause diarrhoea when given in large doses orally (11).

For sedation, 0.25–0.5 mg IV every 2–4 h is commonly sufficient, and 1–2 mg IV bolus will provide moderately deep sedation for 4–8 h.

7.2.3 Other Benzodiazepines

Diazepam is used less often to sedate patients in the ICU and can only be administered intravenously by intermittent infusion due to a long elimination half-life of 30-60 hours. The active metabolites can accumulate with prolonged administration, especially in the context of renal dysfunction. A loading dose of 5-10mg is recommended with maintenance doses of 0.03-0.1mg/kg every 30 minutes to 6 hours.
7.3 Barbiturates

7.3.1 Thiopentone

The barbiturates are still occasionally used in ICU. Deep sedation with thiopentone can be used for burst suppression in management of status epilepticus, but propofol is now more commonly used. Thiopentone is immunosuppressive in inhibiting neutrophil activity in a dose dependent manner at clinically relevant dose concentrations (82). There are also numerous reports of serum potassium dysfunction associated with the use of thiopentone-induced barbiturate coma. Serum potassium concentrations should be monitored regularly if this technique is used to terminate seizures (83). For convulsive status epilepticus, administer an IV loading dose of 15–20 mg/kg over 10–15 min, with subsequent dosing based on continuous EEG monitoring. The half-life is 53–120 h.
7.4 Alpha2 agonists

7.4.1 Dexmedetomidine

Dexmedetomidine is a newer α2-agonist with analgesic, sedative, sympatholytic and anxiolytic properties. It demonstrates a much higher affinity to the alpha2 receptor than clonidine (84), (85) which makes its sedative effects much more prominent than clonidine. Sedation by α2-agonists appears to be unique in that patients can be roused readily and performance on psychomotor tests is reasonably well preserved (86). Consequently, patients sedated with α2-agonists may be more cooperative and communicative than patients sedated with other drugs in the intensive care setting. Dexmedetomidine depresses the gag reflex and improves endotracheal tube tolerance when compared with other sedatives (87), (88).

The cardiovascular effects should not be under emphasised however. Boluses of dexmedetomidine result in a biphasic response; there is an initial peripheral effect causing vasoconstriction resulting in hypertension and a reflex bradycardia and ultimately, a central effect causing vasodilation, bradycardia and hypotension. Arrhythmias and sinus arrest have both been reported (89). Boluses of Dexmedetomidine are not recommended.

Dexmedetomidine decreases the duration of mechanical ventilation when compared to benzodiazepines but not when compared to propofol (90), (91). The MIDEX trial demonstrated a shorter duration of mechanical ventilation compared to midazolam (123 versus 164 hours) but no difference in ICU length of stay, hospital length of stay or mortality. The PRODEX trial showed no benefit of dexmedetomidine over propofol in duration of mechanical ventilation, ICU length of stay, hospital length of stay or mortality (90). The ability to have an awake, comfortable and ETT-tolerant patient without respiratory depression makes Dexmedetomidine close to the ideal sedative.
7.4.1.1  Dexmedetomidine Dosing

Following infusion, dexmedetomidine exhibits a rapid distribution phase with a half-life of about 6 minutes. A loading infusion of 1 mcg/kg over a 10-minute period provides clinically effective onset of sedation generally within 10 to 15 minutes. Maintenance doses of 0.2-0.7mcg/kg/hr can be titrated to achieve the target level of sedation. For patients being converted from alternate sedative therapy, a loading dose may not be required. The terminal elimination half-life of dexmedetomidine is approximately 2 hours. Dose reductions should be considered in the elderly and those with renal or hepatic impairment, and it should be used with caution in patients with any form of heart block. Co-administration of dexmedetomidine with anaesthetics, sedatives, hypnotics and opioids enhances their clinical effects and reduces the doses required (92) (93) (94) (95).

7.4.2  Clonidine

Clonidine was initially marketed as an antihypertensive agent but was noted to be associated with drowsiness following initiation of therapy. It is a centrally acting alpha2-agonist which reduces blood pressure and slows heart rate by reducing sympathetic stimulation. Clonidine provides sedation with minimal respiratory depression and preserved arousability, and has analgesic properties at higher doses with opiate sparing effects (96). It also reduces cerebral blood flow and cerebral metabolic rate of oxygen consumption. In doses used for sedation clonidine decreases REM sleep in healthy volunteers (97), (98). The half-life is 6-24 hours, and 40-60% is excreted renally unchanged, with up to 40% metabolized to an inactive metabolite.

Clonidine is often used as a second-line sedative agent with good effect on controlling hypertension and tachycardia associated with emerging from sedation. It is also effective in controlling delirium and withdrawal syndromes from opioids, benzodiazepines, alcohol and nicotine (99). The usual dose by IV infusion is 0.5-2mcg/kg/hr, although doses up to 4mcg/kg/hr are well tolerated. Caution should be used in patients with a low cardiac output or impaired ventricular function, and accumulation occurs in renal failure. Withdrawal should be gradual over several
hours as sudden cessation can cause agitation, sweating and hypertension (100). Oral and transdermal preparations are also available.

Evidence to support the use of clonidine comes from small, often non-randomised studies. In a cohort study of 30 ventilated ICU patients with withdrawal syndrome after abrupt sedation interruption, clonidine decreased haemodynamic, metabolic and respiratory demands and facilitated patient coordination with the ventilator and early weaning. However there was no randomisation, study wasn’t blinded and 5 clonidine non-responders were excluded (101). A retrospective study showed decreased need for opioids and benzodiazepines in 13 ICU patients who received boluses of clonidine (102). Clonidine shortened the weaning process, decreased incidence of delirium, and decreased total ICU stay in patients after surgical correction of acute type A aortic dissection. A double-blind randomised study of 30 patients compared clonidine with placebo. There was no difference in mortality between the groups (103).

7.5 Opioids
Opioids such as morphine, fentanyl, alfentanil and remifentanil are the mainstays of the treatment of pain in the ICU. They are central nervous system μ receptor agonists that invoke analgesia, sedation, respiratory depression, constipation, urinary retention, nausea, and confusion. When administered parenterally in equivalent doses, there are no differences in analgesic effect, but pharmacokinetics, metabolism and side effects vary. The choice of agent therefore depends on the desired onset and duration of action and the potential adverse effects of the agent. In order to cross the blood brain barrier an opioid needs to be lipid soluble. Consequently when given as a bolus dose, duration of action of many opioids tends to be short due to redistribution into the large volume of fat stores; following infusion this compartment can become saturated and the effect substantially prolonged. There are few trials comparing the various opioids to each other in critically ill patients. There are no dosing recommendations given in this document as doses need to be titrated to the needs of each individual.
7.5.1 Morphine
Morphine is metabolised by the liver to the highly active metabolite morphine-6-glucuronide. The clearance of morphine-6-glucuronide is significantly less than that of morphine and its transfer across the blood brain barrier is slower, (104) potentially contributing to a prolonged duration of action. Morphine-6-glucuronide is excreted via the kidneys so renal impairment can further prolong duration of action (105).

7.5.2 Fentanyl
Fentanyl is a synthetic opioid agonist, approximately 100 times more potent than morphine. The pharmacokinetic constants reported for fentanyl are extremely inconsistent even in healthy volunteers (106). Estimates of apparent volume of distribution range from around 60L to over 300L, estimates of terminal half-life range from about 1.5 to 6 hours (15 hours in geriatric patients) and total body clearance ranges from 0.4 to over 1.5 L/min. Renal excretion accounts for up to 10% of the dose. It may accumulate during prolonged infusion.

7.5.3 Alfentanil
Alfentanil is an analogue of fentanyl with around one-tenth the potency of fentanyl but with a shorter duration of action following a single dose. The pharmacokinetics of alfentanil can be described by a three-compartment model with sequential distribution half-lives of 1 and 14 minutes; and a terminal elimination half-life of 90-111 minutes. It is mainly metabolised in the liver. Alfentanil has a small volume of distribution (between 0.4-1 L/kg). Only 1.0% of the dose is excreted as unchanged drug; urinary excretion is the major route of elimination of metabolites.

7.5.4 Remifentanil
Remifentanil is a newer agent whose metabolism is not dependant on organ function (107) displaying a “context sensitive” half-life. Studies have suggested a better quality of sedation, hypnotic sparing effect and shorter time to extubation (107), (108), (109), (110), (111), (112). Remifentanil is significantly more expensive than morphine, but it may be that the shorter time to extubation may offset these costs (112). If using remifentanil it is important that medical and nursing staff are aware of its differing qualities; specifically bolus administration is unnecessary and potentially hazardous because of bradycardia and hypotension. Rapid onset of withdrawal and pain should be considered pre-emptively when stopping an infusion (111), (113).

Meticulous titration of opioid infusions helps to minimise any differences in pharmacokinetics. A double blind RCT comparing remifentanil and fentanyl has demonstrated similar times to extubation, the authors speculating that frequent monitoring and adjustment prevented over sedation in the fentanyl group (111).

7.6 Ketamine

Ketamine is an NMDA receptor antagonist and can be used for induction and maintenance of anaesthesia as well as sedation on the ICU. It induces a state referred to as “dissociative anaesthesia” and is also used as a recreational drug. In some respects, ketamine would be the ideal sedative agent as it has sedative, analgesic, cardiovascular stability and bronchodilator properties. Ketamine is a core medicine in the World Health Organization’s “Essential Drugs List” and is used widely in third world countries and field anaesthesia situations. However its association with hallucinations prohibits its use in the ICU as a single agent.

Ketamine is useful for facilitating painful procedures within critical care, particularly in the paediatric and burns population (114), (115), (116). Ketamine is also useful in the trauma patient as airway tone and reflexes are maintained, and it is not associated with reduction in vasomotor tone or respiratory depression (117). It is being increasingly used in the pre-hospital setting (118), (119) and is a useful adjunct in the management of post-operative pain to reduce opioid related adverse events (120). Ketamine was traditionally regarded as being contraindicated in the setting of
raised intracranial pressure. However, the evidence in head injury is conflicting and inconclusive, and if there is a risk of haemodynamic instability on induction then ketamine may still be a useful agent (121), (122).

Ketamine may be considered in cases of severe bronchospasm and in conjunction with a benzodiazepine sedative but the bronchodilatory effect is minimal. Volatile anaesthetic agents are better bronchodilators than ketamine.

7.7 Volatile anaesthetic agents

7.7.1 Isoflurane, Sevoflurane, Desflurane
Difficulties in delivery and scavenging combined with concerns over fluoride accumulation and the dependency with ventilation limit the use of volatile anaesthetic agents on the ICU. Delivery devices such as the Anaesthetic Conserving Device (AnaConDa®) and scavenging systems such as the Aldasorber® make administering isoflurane and sevoflurane on the intensive care unit safer for the staff. Isoflurane has shown safe, effective sedation for up to 96 hours in small studies, with faster awakening than midazolam (123) and a similar awakening to propofol but with an increase in the number of patients suffering from delirium (124). For short term post-operative sedation (<12hrs) desflurane has demonstrated faster awakening and faster mental recovery when compared with propofol (125). Isoflurane is a potent bronchodilator and offers a valuable treatment in status asthmaticus (126).

7.8 Tranquilisers / antipsychotics
Neuroleptics are indicated for the treatment of agitation due to hyperactive delirium, with options including haloperidol and oral antipsychotics such as chlorpromazine, olanzapine, quetiapine and risperidone. Haloperidol is used most often as it has few cardiovascular side effects and can be given intravenously. (11), (127). It is a butyrophenone that works by blocking D2 receptors probably in the mesolimbic region (128). Its side effects include extapyramidal symptoms, and rarely, the
neuroleptic malignant syndrome (129). The patient should be monitored for precipitation of arrhythmias such as torsade de pointes (130) and haloperidol should be used with caution in patients with a QTc interval of over 450 msec. The optimal dosing regimen is not clear and should be assessed on an individual patient basis. A starting dose is 2-10 mgs intravenously depending on the severity of the agitation, repeating every 20-30 minutes titrating to effect. While a patient continues to suffer episodes of delirium, regular haloperidol can be prescribed 2-5 mgs 4 to 6 hourly and reviewed on a daily basis.

There is a paucity of evidence comparing the antipsychotics to haloperidol and to one another in critically ill patients, although olanzapine has been shown to be as effective as haloperidol in critical care patients (131). A small randomized double blind placebo controlled study of 36 patients indicated that quetiapine may reduce the duration of delirium in ICU patients (132). National guidelines for the management of delirium recommend short term haloperidol or olanzapine if non-pharmacological measures are not effective (NICE guideline 103). Levomepromazine is increasing in popularity, although data about its use in ICU is limited.

7.8.1 Haloperidol Dosing
The optimal dosing regimen is not clear and should be assessed on an individual patient basis. A starting dose is 2-10 mgs intravenously depending on the severity of the agitation, repeating every 20-30 minutes titrating to effect. While a patient continues to suffer episodes of delirium, regular haloperidol can be prescribed 2-5 mgs 4 to 6 hourly and reviewed on a daily basis.

7.9 Non-Opioid Analgesics

7.9.1 Paracetamol
Paracetamol is an antagonist of the cyclooxygenase system that inhibits the production of thromboxane in the pain pathway. It is available in enteral and
intravenous forms. It also possesses potent antipyretic properties. The regular administration of paracetamol may reduce the requirement for opioids in post-operative pain (133), (134).

### 7.9.2 Non-Steroidal Analgesics (NSAIDS)

NSAIDS such as ibuprofen, diclofenac and ketoprofen non-selectively inhibit cyclooxygenase and may be used as adjuncts to opioid therapy in selected patients in the ICU. They should be used with caution as they may cause acute kidney injury and gastric erosion through their action on renal production of prostacyclin. They also carry an increased risk of cardiovascular events including myocardial infarction and stroke (135).

### 7.9.3 Tramadol

Tramadol is a centrally acting synthetic opioid developed in the late 1970’s. It is a weak agonist at the µ-opioid receptor, releases serotonin and inhibits the re-uptake of norepinephrine. It is a synthetic analogue of codeine and is converted in the liver to O-desmethyltramadol which is a potent µ-opioid agonist. Tramadol is used in a similar way to codeine to treat moderate pain and is pharmacologically similar to levorphanol as it is an NMDA-antagonist and molecularly similar to venlafaxine.

There are more potent and effective opioid analgesics than tramadol that can be administered safely in critical care because of the ability to monitor potential respiratory depression easily in a well-staffed critical care area. It can cause reduction in seizure threshold. When combined with tricyclic antidepressant can reduce seizure threshold even further. There have been rare cases of patients having grand mal seizures on doses as low as 100 – 400mg orally (136), (137).

### 7.9.4 Analgesia for neuropathic pain
Gabapentin, pregabalin, and tricyclic antidepressants such as amitriptyline are useful adjuncts in the treatment of neuropathic pain in patients who can tolerate enteral administration. Gabapentin and pregabalin are GABA analogues that inhibit neurotransmitter release by binding to voltage-gated calcium channels at the alpha 2-delta subunit, with pregabalin being the more potent derivative. In small studies of neuropathic pain in Guillain Barre patients on the ITU, use of gabapentin reduced the need for rescue opioid (138), (139). Gabapentin is renally excreted, and accumulation can occur in severe renal failure so dose adjustment is needed. Side effects include sedation, confusion, dizziness and ataxia. The dose of gabapentin should be commenced at 100mg three times daily, increasing slowly to maximum of 3600mg daily in 3 divided doses.

Pregabalin and amitriptyline (non-licensed indication) are recommended as first line agents for the treatment of neuropathic pain (NICE guideline 96). Pregabalin should be started at 75mg twice daily and increased to a maximum dose of 300mg twice daily. Amitriptyline is commenced at a dose of 10mg/day and titrated as required to a maximum dose of 75mg/day.

7.10 Local anaesthetics / Regional Nerve Blocks

Regional anaesthesia is an attractive option in the ICU, and is most commonly utilized in post-operative and trauma patients. It is often employed by anaesthetists in the perioperative period to provide post-operative analgesia, reduce the stress response from surgery, reduce the depth of general anaesthesia required, or to allow surgery for patients in whom general anaesthesia is contraindicated. These advantages are also applicable to critical care, where the requirement for sedation may be reduced by the addition of regional techniques. Contradictions to regional anaesthesia in ICU patients include spinal injury, acute neurological injury and coagulopathy.

Patients who have undergone laparotomy (both elective and emergency) represent a large cohort of critical care patients. A Cochrane systematic review in 2005 suggested that continuous epidural analgesia provided superior pain relief for 72
hours following laparotomy when compared to opioid-based patient-controlled analgesia (PCA), but had a higher incidence of pruritus. There was no statistically significant difference in other comparative factors (140). The MASTER trial also showed improved analgesia with epidural when compared with PCA, along with a reduction in pulmonary and thrombo-embolic complications. It did not show a difference in overall mortality (141).

Trauma patients may also benefit from regional anaesthesia. Patients with chest trauma and rib fractures may benefit from epidural rather than systemic opioid-based analgesia as there is evidence that these patients have lower pain scores and improved forced expiratory volumes (142), reduced incidence of pneumonia and shorter duration of mechanical ventilation (143). The growing interest and use of ultrasound-guided regional anaesthesia may permit an expansion of techniques available, particularly the insertion of nerve plexus/TAP catheters to prolong the duration of effective regional anaesthesia. There is also increasing use of regional anaesthesia in military trauma patients. The first use of continuous peripheral nerve blockade in the management of traumatic amputation from blast injury was described in 2005 (144). These techniques are becoming more prevalent in injured soldiers and, in combination with early commencement of anti-depressant and anti-epileptic chronic pain drugs, may reduce the incidence of chronic pain.

8 Non Pharmacological Measures

Prior to instigating sedative medication, it is important to consider the many, often simple, factors which may reduce or even remove the requirement for pharmacological intervention.

8.1.1 Use of Sedation Breaks

This is examined more closely in Section 10.2.1 but it is important to understand that avoiding the complications of sedation is as important as pharmacological sedation.
There is a recognition that sedation scores may adequately assess a patient who is able to communicate, but once the patient is not moving in bed, it is impossible to know whether the patient will take minutes or days to rouse.

8.2 Correction of underlying pathophysiology
Hypoxaemia, hypercarbia and hypotension can all cause confusion and agitation. Simple measures such as providing supplemental oxygen, assisting ventilation to remove excess carbon dioxide, and generating an arterial blood pressure sufficient to allow adequate cerebral perfusion can all improve conscious level. Outlined below are some specific scenarios where the requirement for sedation can be reduced by treating the underlying cause of confusion.

8.2.1 Treatment of the Underlying Cause (e.g., sepsis)
The examples outlined below are for guidance only and is not an exhaustive list:

Intensive care physicians are well accustomed to treating patients who are confused, agitated or drowsy because of Multi-Organ Dysfunction Syndrome. Patients should be managed according to the 2012 Surviving Sepsis Campaign (145).

Similarly, patients with acute intra-cranial pathology, such as sub-dural haematomas, should be referred to a neurosurgical unit for guidance as to appropriate management.

8.2.2 Treat alcohol/drug withdrawal
Alcohol withdrawal syndrome (AWS), sometimes known as delirium tremens or “DTs”, is characterised by anxiety and agitation, which may progress to delirium, hallucinations and seizures. Withdrawal symptoms may begin from 6 hours and up to 5 days after cessation of alcohol intake. Symptom severity may be reduced by
prophylactic treatment (146). Individual centres often create their own guidelines, but first line prophylaxis and treatment is usually with a benzodiazepine, which promotes anxiolysis and raises the seizure threshold. Commonly used agents are the long-acting benzodiazepines; diazepam and chlordiazepoxide, or more short-acting lorazepam. Doses should be titrated to effect and reduced, and may be high in the early stages of AWS.

Non-benzodiazepine agents are often used in conjunction with benzodiazepines for symptom control, but should not be used as monotherapy. β-adrenergic antagonists and α2-adrenergic agonists (e.g., clonidine, dexmedetomidine) may provide additional anxiolysis. Acute delirium and hallucinations can be treated with haloperidol, although this drug can increase the incidence of seizures (147). It should be remembered that compared with neuroleptic drugs, sedative-hypnotic agents (benzodiazepines and barbiturates) reduce mortality, reduce the durations of symptoms and are associated with fewer complications (147). Currently, there is no evidence to support the use of one particular sedative hypnotic, or to switch between agents. Clinicians should consider the therapeutic/toxic effect index of each drug, the onset of action required, and the potential consequences of instigating longer acting sedation.

In addition to pharmacological management, many experts recommend various supportive care measures; the use of a quiet, well-lit room, reassurance and reorientation, frequent monitoring of vital signs and restraints as required. Correction of dehydration and any underlying electrolyte abnormalities are also recommended although the use of magnesium for symptom control has not been shown to be beneficial (147).

Future management of the neurological complications of AWS may include the use of anticonvulsant medication such as carbamazepine, valproate and topirimate, and centrally-acting natriuretic peptides (148).
8.2.3 Treating uraemia
Uraemia, if severe enough, may present with encephalopathy and seizures. The requirement for sedation can be decreased by treating the uraemia, and the underlying cause of the raised urea. “Overt uraemia” is often cited as a trigger, but there are no universally accepted levels which mandate renal replacement therapy (149).

8.3 The Role of Medical and Nursing staff
The place of human contact and reassurance are important in the frightening and unfamiliar surroundings of the ICU. The manner, behaviour and communication skills of medical and nursing staff can provide anxiolysis and reduce the requirement for sedatives. In particular, patients benefit from regular reassurance and explanations prior to procedures. Agitation may arise from a critically ill patient's inability to perform basic bodily functions, so management of basic thirst, hunger, constipation and full bladder are essential. Attention must also be paid to minimising pain, nausea and vomiting.

8.4 The Role of Relatives
The place of simple hand holding and hearing the voice of trusted relatives or reassurance from a friendly voice cannot be underestimated.

8.5 ITU designs
ICUs should be designed in a way which minimises stress for patients and staff. The environment should be comfortable, with appropriate temperature, humidity and lighting. Wherever possible, bed spaces should be close to windows to provide natural light, reduce sensory deprivation, and allow diurnal variation. Diurnal variation can be reinforced by appropriate activities such as eating, washing, shaving.
and brushing teeth, and by visits from relatives. Sensory orientation may be further improved by clocks, calendars and access to radio/TV.

Patient privacy and dignity must be maintained wherever possible. Further information on ICU designs is provided by the Society of Critical Care Medicine (150).

8.5.1 Noise

Noise can be particularly stressful, and ICUs should be designed to minimise noise pollution. Excessive environmental noise affects people both psychologically and physically (151). Unwanted negative effects in critically ill patients may include cardiovascular stimulation (152) suppression of the immune response to infection (153) and sleep disruption (38). This includes monitor alarms, and closing mechanisms for doors and waste bins.

In a study published in 1993 from an ICU built in the 1960s (154), noise did not change between day and night, with average background sounds of between 60-65 dB and peaks up to 96 dB. Most alarms reached 60-70 dB, but some exceed 80 dB. A similar study reported ranges from 50 dB to 75 dB with peaks of up to 85 dB (155). To put these into context, a busy office usually measures at 70 dB, noise on busy urban street is generally quoted as 80-90 dB, a vacuum cleaner 70 dB and a washing machine 65 dB (a bedroom is usually around 40 dB). These exceed guidance published by the World Health Organisation (WHO) which states that in rooms where patients are being treated or observed sound levels should not exceed 35 dB (156).

Noise may be a necessary for the normal working of equipment (e.g. High Frequency Oscillatory Ventilation) or for alarms to assure patient safety. However human behaviour such as loud talking and noisy bin lids is modifiable (40).
Undue noise is associated with greater requirements for sedation and analgesia in critically ill patients and therefore noise should be minimised. Introduction of guidelines to reduce noise in the critical care area can be effective. In particular a decrease in the number of alarms from haemodynamic monitoring (without affecting patient safety). In a study in from Geneva by Walder and colleagues (42) were able to show significant noise reduction (particularly at night) and particularly the peak noise levels following the implementation of guidelines aimed at reducing noise levels although they were not able to eliminate the background noise levels.

A recent quality improvement (QI) project undertaken to improve the quality of sleep for patients in the ICU at Johns Hopkins Hospital (157), demonstrated significant improvements in perceived night time noise, incidence of delirium / coma, and daily delirium / coma-free status during a three phase introduction of various interventions. Interventions to decrease sleep disruptions included, minimizing loudspeaker announcements, turning off patient televisions, dimming hallway lights, and grouping care activities. Daytime interventions were used to promote normal circadian rhythms included raising window blinds, preventing excessive napping, encouraging mobilization, and minimizing pre-bedtime caffeine. Non-pharmacological sleep aids such as earplugs, eye masks and soothing music were introduced for the non-delirious and a pharmacologic guideline introduced. This guideline discouraged the use of commonly prescribed sedating medications known to alter sleep and precipitate delirium (i.e., benzodiazepines, opiates, diphenhydramine), and recommended readily available alternatives: zolpidem for patients without delirium, and haloperidol or an atypical antipsychotic for patients with delirium (157).

8.5.1.1 Music

A recent study published in JAMA demonstrated that in patients who were able to request listening to music resulted in greater reduction in anxiety compared with usual care, but not compared with noise cancelling headphones. Music also resulted in greater reduction in sedation frequency compared with usual care or noise cancelling headphones, and greater reduction in sedation intensity compared with usual care, but not compared with headphones (158).
8.6 Avoiding Sleep deprivation

Sleep disturbances in ICU are caused by multiple factors: critical illness itself; drugs; ventilator asynchrony; environment of ICU with its 24hr care (excessive noise and lighting); stress and anxiety associated with an admission to ICU; withdrawal reaction.

Sleep disruption can induce sympathetic activation and elevation of blood pressure which possibly contributes to patient morbidity. It may also contribute to delirium and agitation (159). Furthermore there is a significant correlation between sleep deprivation and delirium characterised by confusion, agitation, and psychosis. Abnormal sleep patterns in ICU may predispose to posttraumatic stress disorder after discharge (160), (161).

Sleep deprivation is perceived as one of the most stressful components of patients’ time in the ICU. Total sleep time is often decreased with almost half of the total sleep time occurring during the daytime. Polysomnographic studies performed on mechanically ventilated ICU patients have demonstrated an increase in sleep fragmentation, and changes in architecture of sleep pattern (162). REM sleep and slow wave sleep (the most refreshing phases) are disproportionately decreased.

Sleep deprivation has been linked to the development of ICU delirium. Although direct causal effect has not been demonstrated (insomnia may follow the onset of delirium), it is plausible that both conditions are related and sleep deprivation is a potential risk factor for development of delirium. Clinical features common to both conditions include inattention, fluctuating mental status, and cognitive dysfunction. Both conditions have similar risk factors (pain, stress, sepsis) as well as pathophysiological changes (dopaminergic excess, cholinergic deficiency, regions of CNS involved) (163).
Delirious patients are often agitated; they try to remove catheters and tubes and often need to be sedated to prevent this. Sedative drugs interfere with normal sleep pattern; sleep deprivation potentiates development of delirium and agitation (159). The vicious circle is closed.

The consequences of sleep deprivation (immunological dysfunction (164), prevalence of catabolic state (165), psychological disturbances (166), (167)) are well researched in healthy individuals but not so in critically ill.

The majority of drugs used to sedate ICU patients cause sleep disturbances. Benzodiazepines, although often used to initiate sleep, decrease total sleep time and REM phase (168). Opiates increase the number of arousals during the night and increase stage 1 (non-REM sleep) as well as decrease in total sleep time and REM sleep (161). Propofol increases total sleep time without enhancing REM sleep or slow wave sleep (169).

Non-pharmacological interventions such as day and night variation, noise limitation, relaxing environment, use of ear plugs and eye masks can considerably help in promoting good sleep. Efforts should be made to achieve maximum patient-ventilator synchrony (170).

Patients on midazolam infusion with regular sedation breaks have shown to have longer REM stage but more arousals and shorter total sleep time (171).

Pharmacological interventions are limited. Melatonin maintains normal sleep architecture (161) and promotes sleep without increasing sedation in normal subjects. In a small study of critically ill it showed to increase sleep by an hour (2.5 hrs in placebo group vs 3.5 hrs when used 10 mg of melatonin) (172). Zopiclone does not suppress slow wave sleep (173).
8.7 Ensuring patient comfort by using different types of ventilation modes

Patient-ventilator asynchrony (PVA) is a frequently encountered problem in mechanically ventilated patients. It causes patient discomfort (174) and is associated with longer duration of mechanical ventilation and lower rates of successful weaning (175), (176).

Increased sedation is often used to facilitate mechanical ventilation and to promote patient-ventilator synchrony (177), (178). However, increased sedation leads to further decrease in respiratory effort and increase in patient ventilator asynchrony. As sedated patients appear calm, the asynchrony is less frequently diagnosed. Patient agitation due to asynchrony is often treated with sedative medications that cause further respiratory depression which may then lead to increased PVA (179).

The most common type of asynchrony is ineffective triggering. This is characterised by increase in diaphragmatic pressure that does not result in a machine delivered breath. Other types of patient-ventilator asynchrony include delayed triggering, auto-triggering, double triggering (breath-stacking), premature cycling, delayed cycling and flow asynchrony (9).

The ventilation mode is one of the factors that can influence the prevalence of patient-ventilator asynchrony. Patients on pressure support ventilation and volume controlled CMV have higher asynchrony rates than patients on neutrally adjusted ventilation assist (NAVA) and proportional assist ventilation (PAV) (180), (181). Improved synchrony with NAVA probably relates to using the diaphragmatic electromyographic signal to trigger and cycle the ventilation and hence decreasing the delay between the patient triggering and machine delivered breath.

Use of biphasic intermittent positive airway pressure (BiPAP) ventilation when compared with controlled mandatory ventilation (CMV) and intermittent mandatory
ventilation (IMV) reduced the consumption of analgesics and sedatives, and the duration of intubation. The possibility of unrestricted spontaneous breathing in all phases of the respiratory cycle was considered to be the reason (182).

The mode of ventilation is not the only factor; degree of ventilatory support and how the mode is applied both play the role in patient-ventilator interactions. Higher degree of ventilatory support may cause ineffective triggering in patients with air-flow obstruction as a result of worsening dynamic hyperinflation. Low degree of respiratory support will cause double triggering (breath stacking) in patients with acute lung injury with an increased air hunger (183).

Asynchrony can also be detected in patients receiving NIV. The magnitude of mask leak and higher pressure-support levels are the most common causes (174).

Quality of sleep is adversely affected by patient-ventilator asynchrony. Ventilatory settings adjusted for awake patients may become larger than required during sleep, as patients' ventilatory demand is reduced while sleeping (184). Excessive respiratory support during sleep may cause hypocapnia and central apnoea which then cause increased rate of arousals (185). Studies on mechanically ventilated patients comparing pressure support ventilation with NAVA (170) and with assist ventilation (185) demonstrated improved patient ventilator synchrony, decreased frequency of central apnoea, decreased frequency of arousals and improved REM sleep.

In summary, selecting the correct mode of ventilation as well as the correct settings for particular patient will help to reduce the patient-ventilator asynchrony and decrease the need for sedation. A patient's needs and responses to the ventilator may change rapidly depending on the progression of the disease, and also whether they are awake or asleep. Frequent assessment and adjustment based on patient observation and ventilator graphics assessment may be necessary. Patient-ventilator asynchrony should not be treated with increased sedation as this further
decreases respiratory effort and worsens the interactions between patient and ventilator.

8.8 Tracheostomy v ETT

There are several potential benefits of ventilation via a tracheostomy compared with an ETT; the airway dead-space and resistance are decreased (reducing the work of breathing), it is easier to provide airway toilet via the shorter device, and importantly, sedation requirements can be reduced. An oral/nasal ETT passes via the oropharynx and laryngopharynx, and stimulates the gag and cough reflexes which require more heavy sedation to suppress. These reflexes are less readily stimulated by tracheostomy tubes.

The optimum timing for tracheostomy is still unknown. Although a meta-analysis has found decreased mortality associated with the placement of ‘early’ tracheostomies (186), this has not been borne out by some recent trials. A recent randomised-controlled trial designed to detect a reduction in ventilator-free days in cardiac surgery patients did not show any difference between those with early tracheostomies and those with long-term intubation. However, it did show statistically significant reductions in mean duration of IV sedation, mean doses of sedatives and increased number of sedation-free days in those patients with tracheostomies (187). The same research group had previously demonstrated, in an observational study, that when compared to ETT’s, critically ill patients with tracheostomies again required lower total doses of sedatives, spent a shorter time under “heavy” sedation and achieved more autonomy earlier (188). This trend is expected to be replicated in the results of the TracMan study in the UK. The primary endpoint for this study is 30 day mortality following randomisation to early or late tracheostomy, but the number of days of receiving sedative medication is a secondary endpoint. [http://www.controlled-trials.com/mrct/trial/486617/tracman, accessed 08/05/11]. At the study’s presentation, at the 29th International Symposium of Intensive Care and Emergency Medicine in Brussels (March 2009), the lead author stated the following: "If you had 100 patients requiring tracheostomy, doing it early results in 2.4 days less sedation overall, but you would perform 48
more, with 3 more procedural complications and no effect on mortality or ICU length of stay."

9 Methods for assessing sedation

Many tools exist for evaluating depth of sedation; however without a gold standard against which to evaluate, it is difficult to establish which is optimal. Broadly speaking we can use subjective clinical sedation scales or objective physiological tools – in everyday practice however, clinical sedation scores are the most useful.

9.1 Desired level of sedation

The desired level of sedation depends on the clinical circumstances for which it is required. In highly specialised circumstances (such as NeuroICU), deep levels of sedation will be required. The desired score depends on the sedation scale in use in your unit. Evidence suggests that using a sedation scale is better than not using one but there is no ‘best’ sedation scale. For the general ICU patient, sedating the patient so that he or she remains in verbal contact with those caring for them is the best balance between anxiety and sedation that is too deep.

9.2 Clinical Sedation Scales

In order to improve our sedation practices it is necessary to measure and target a sedation depth in a reproducible manner, various validated scales allow us to do this; and several studies have successfully demonstrated a number of clinical outcome improvements in clinical care by using them (1), (189), (190), (191), (192), (193), (194), (195). The first sedation scoring system was proposed by Ramsay nearly 35 years ago (196) and remains the basis of the most widely used scoring system in the UK (197). A systematic review by De Jonghe and colleagues identified a further 24 scales (198), and additional scales have been developed since. There are more
detailed scales which can still be performed rapidly, but it is unclear whether gathering additional information relates to an improved level of care. The choice of sedation scale is probably less important than a unit familiarising itself with a validated sedation scale, using it regularly and auditing its use. Depth of sedation should be regularly assessed. There are no data on how frequently this should be performed.

With so many scales at our disposal, it is likely that none are superior. The majority of these scales have not been validated, and generally those that have, have been validated against each other. Many scales are versions of existing scales. Three of the commonest scales are given below. They have been chosen because they are versions of the commonest in use in the UK (197).

The advantages of introducing a sedation protocol have not been demonstrated universally. Whilst MacLaren’s study demonstrated improved pain scores and pharmacy costs, patients spent longer ventilated probably negating any cost savings (199). An Australian study (200) showed a significant prolongation in duration of mechanical ventilation following a change in a previously successful protocol.

The presence of cough upon suctioning is not a good method of assessing depth of sedation. A study in mechanically ventilated ICU patients with non-neurological conditions assessed while under sedation has shown that the absence of cough reflex is independently associated with increased 28-day mortality and that the absence of the oculocephalic response is independently associated with the occurrence of altered mental status (201).

9.3 Commonly Used Sedation Scales

9.3.1 Ramsay Sedation Scale (RSS)
The Ramsay Sedation Scale (196) was the first scale to be defined for sedated patients and was designed as a test of reusability in six different levels. It is an
intuitive scale and therefore lends itself to universal use wherever sedative drugs or narcotics are given (including beyond the ICU).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Patient is anxious and agitated or restless, or both</td>
</tr>
<tr>
<td>2</td>
<td>Patient is cooperative, oriented and tranquil</td>
</tr>
<tr>
<td>3</td>
<td>Patient responds to commands only</td>
</tr>
<tr>
<td>4</td>
<td>Patient exhibits brisk response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>5</td>
<td>Patient exhibits a sluggish response to light glabellar tap or loud auditory stimulus</td>
</tr>
<tr>
<td>6</td>
<td>Patient exhibits no response</td>
</tr>
</tbody>
</table>

The RSS may be used in conjunction with a pain score.

**9.3.2 The Richmond Agitation Sedation Score (RASS)**

The Richmond Agitation Sedation Score (RASS) is a ten point scale that assesses both degrees of agitation and sedation. When assessing sedation it differentiates between verbal and physical stimulation; it also makes a basic assessment of attention, providing a possible indicator of delirium (202), (203). This tool has also been validated against BIS index and drug doses, it also integrates with the Confusion Assessment Method for the ICU (CAM-ICU, See below) for assessing delirium (204).

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+4</td>
<td>Combative, violent, danger to staff</td>
</tr>
<tr>
<td>+3</td>
<td>Pulls or removes tube(s) or catheters; aggressive</td>
</tr>
<tr>
<td>Score</td>
<td>Term</td>
</tr>
<tr>
<td>-------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>7</td>
<td>Dangerous Agitation</td>
</tr>
<tr>
<td>6</td>
<td>Very Agitated</td>
</tr>
<tr>
<td>5</td>
<td>Agitated</td>
</tr>
<tr>
<td>4</td>
<td>Calm and Cooperative</td>
</tr>
<tr>
<td>3</td>
<td>Sedated</td>
</tr>
<tr>
<td>2</td>
<td>Very Sedated</td>
</tr>
</tbody>
</table>

### 9.3.3 Riker Sedation-Agitation Scale (SAS)

Frequent non-purposeful movement, fights ventilator
Anxious, apprehensive, but not aggressive
Alert and calm
Awakens to voice (eye opening/contact) >10 sec
Light sedation, briefly awakens to voice (eye opening/contact) <10 sec
Moderate sedation, movement or eye opening. No eye contact
Deep sedation, no response to voice, but movement or eye opening to physical stimulation
Unarousable, no response to voice or physical stimulation
not communicate or follow commands, may move spontaneously

1 | Unarousable | Minimal or no response to noxious stimuli, does not communicate or follow commands

Guidelines for SAS Assessment

1. Agitated patients are scored by their most severe degree of agitation as described.

2. If patient is awake or awakens easily to voice ("awaken" means responds with voice or head shaking to a question or follows commands), that’s a SAS 4 (same as calm and appropriate – might even be napping).

3. If more stimuli such as shaking is required but patient eventually does awaken, that’s SAS 3.

4. If patient arouses to stronger physical stimuli (may be noxious) but never awakens to the point of responding yes/no or following commands, that’s a SAS 2.

5. Little or no response to noxious physical stimuli represents a SAS 1. This helps separate sedated patients into those you can eventually wake up (SAS 3), those you can't awaken but can arouse (SAS 2), and those you can’t arouse (SAS 1).

9.3.4 Motor Activity Assessment Scale (MAAS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Unresponsive</td>
</tr>
<tr>
<td></td>
<td>Does not move with noxious stimuli</td>
</tr>
<tr>
<td>1</td>
<td>Responsive only to noxious</td>
</tr>
<tr>
<td></td>
<td>Opens eyes or raises eyebrows or turns head toward stimulus or moves</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td><strong>stimuli.</strong></td>
<td>limbs with noxious stimuli</td>
</tr>
<tr>
<td>2</td>
<td>Responsive to touch or name.</td>
</tr>
<tr>
<td>3</td>
<td>Calm and cooperative.</td>
</tr>
<tr>
<td>4</td>
<td>Restless and cooperative.</td>
</tr>
<tr>
<td>5</td>
<td>Agitated.</td>
</tr>
<tr>
<td>6</td>
<td>Dangerously agitated, uncooperative.</td>
</tr>
</tbody>
</table>

**9.3.5 Physiological Sedation Measurements**

Sedation scales that measure the clinical response of a patient cannot differentiate depths of sedation in patients who are already heavily sedated and therefore unresponsive to stimuli (205), (206). Various physiological methods have been
employed including heart rate variability, evoked potentials and interpretations of the electroencephalogram (EEG) (206). Of these probably the most developed are those that provide a simplified interpretation of a processed EEG, such as BIS, BIS-XP and entropy.

Whilst many studies have demonstrated a correlation between sedation score and BIS or BIS-XP, the correlation is not strong enough nor sufficiently reproducible to suggest its use as a replacement to sedation scoring (202), (207), (208), (209). Additionally, processed EEG interpretation will not measure degrees of agitation (in fact electromyographic interference in more awake patients is a major limitation). EEG simplification was designed for use with general anaesthesia and its place in ICU practise in the UK has yet to be established.

These techniques should not be used as a replacement for a clinical sedation scale. However this remains a developing field, with ongoing improvements in hardware and software demonstrating more reliable results (210). They may prove to be a useful adjunct especially in quantifying depths of sedation beyond a clinical score of “does not respond to pain”. It may also be of use in paralysed patients, where clinical scales are not possible and awareness should be avoided if at all possible; an additional advantages with this technique is that electromyographic interference is minimal. There remains a significant number of factors that can affect results of processed EEG including critical illness encephalopathy, focal and diffuse neurological injury, sleep, temperature and a variety of drugs (notably neuromuscular blockers and ketamine (211)). As with all monitors of physiology, results should be interpreted within the clinical context.

9.3.6 Assessing Pain

In addition to being humane, ensuring that a patient is pain free can facilitate sedation. Painful procedures, such as mobilisation and airway suctioning, are common on the critical care unit; the presence of catheters, drains and endotracheal tubes can be a continual source of discomfort. Pain has been associated with detrimental effects on sleep, agitation and a stress response.
Pain is commonly reported when ITU patients are followed up (12), (13), it is also recognised that subjective evaluations underestimate pain compared with the patient’s own assessment (212). The tools at our disposal in the ICU are far from adequate but pain assessment can be carried out as outlined below.

### 9.3.7 Conscious Communication

Pain is a subjective experience therefore patients’ self-report of pain remains the gold standard; unfortunately the presence of tracheal tubes limits this method. The use of a visual pain scale may help to quantify the level of pain, however in practice critical care patients may struggle to use these scales (213), using closed questions may prove more productive. Numerical rating and visual analogue scales correlate with each other and can provide a sensitive linear assessment (214), (215), (216), (217).

### 9.3.8 Behavioural Pain Scales

These rely on assessing a combination of domains, such as facial expression, body movements, compliance with ventilation and muscle tension (218). The Behavioural Pain Score (BPS) (219), (220), (221) and Critical Care Pain Observation Tool (CPOT) (213) have both been validated. Unsurprisingly pain scores tend to correlate with sedation scores; pain scores becoming less sensitive as patients become more sedated. This may lead to the inappropriate use of sedatives to treat pain.

Using the BPS with the RASS, to assess pain and agitation respectively, has been demonstrated to decrease the incidence of pain and agitation and reduces the duration of mechanical ventilation and incidence of nosocomial infections (194).
10 Problems Associated with Sedation

10.1 Introduction: Newly recognised adverse effects of sedation

Sub-optimal use of sedation is associated with a number of adverse ICU outcomes. All pharmacological agents are associated with side effects as described above and prolonged over sedation is associated with hypotension, bradycardia, respiratory depression, failure to cough, venothromboembolism and accumulation of the sedative agent. Several retrospective and prospective observational studies have reported a relationship between sedation and ICU-acquired infections (222). Oversedation prolongs exposure to risk factors for infection by prolonging duration of mechanical ventilation and length of stay in the ICU (223).

10.1.1 Immunomodulation by Sedatives

Sedative agents may also have direct immunomodulatory effects. Midazolam and thiopentone have been found to impair neutrophil function (82) and benzodiazepines inhibit cytokine production by macrophages (224). Propofol exhibits anti-inflammatory effects in vitro and in vivo animal models that may be related to antioxidant properties (225) (226) whereas opioids have significant effects on lymphocytes, inducing a potentially deleterious shift to Th2 cytokine predominance (227). Compared with the other sedative agents, dexmedetomidine possesses superior anti-inflammatory effects, improved macrophage function and anti-apoptotic activity (227) and is potentially beneficial in septic patients.

10.1.2 Post-traumatic stress disorder (PTSD)

In recent years, it has become apparent that PTSD occurs in a significant number of ICU survivors. Estimates of the prevalence of PTSD following critical care vary between 3% and 59% (5), (6), (228), (229), (230), depending on the diagnostic group. PTSD is characterised by intrusive memories, flashbacks, insomnia, anxiety, depression and avoidance of reminders and triggers. Avoidance of hospitals and medical professionals probably hides the true extent of the problem. PTSD is likely
to be a factor contributing to the poor health related quality of life experienced by many critical care survivors (231), (232).

PTSD may arise from the inability of patient to rationalise what is happening to them. The presence of factual memories may provide some protection (5), (233); the recall of delusional memories, prolonged sedation, and physical restraint with no sedation increase the risk of PTSD (228). Daily interruption of sedation is not detrimental and probably beneficial to psychological outcome (234).

Interestingly, there may also be physiological and pharmacology changes may influence the development of PTSD. One study suggested that patients with better memory consolidation had higher doses of cortisol administered (229) whilst another by the same author in patients having cardiac surgery, suggested that patients who were given higher stress doses of hydrocortisone during the peri-operative period showed lower chronic stress and PTSD six months after surgery (235).

### 10.2 Managing the problems with sedation

#### 10.2.1 Sedation breaks

The optimal sedation level varies between the patients; depends on co-morbidities, illness severity and type of treatment. Optimally sedated patients should be awake, calm and co-operative. This is often difficult to achieve.

Interrupting continuous sedation with regular daily breaks, together with assessing the level of sedation, allows clinicians and nurses to target the minimal sedation necessary to keep the patient comfortable. A recent systematic review found a strong association between interventions designed to optimise sedation and reduced duration of mechanical ventilation and length ICU stay (236). Interventions included regular assessment of the level of sedation, choice of sedative drugs and daily sedation breaks. Three studies including two RCTs (1), (223), (237) looked specifically at sedation breaks. Weaning time, ICU and hospital length of stay were
significantly lower in the groups with sedation holds. 28-day mortality was reduced but not significantly. In one study (237), one-year mortality was also significantly reduced in the sedation hold arm. In another, there was a trend towards reduction of nosocomial pneumonia (1). Complications were not increased as a result of sedation breaks. The practise of sedation breaks can considerably decrease the cost of analgesic and sedative drugs (238).

Regular sedation breaks should be implemented where appropriate. Exceptions should be made for patients in whom deep sedation is necessary, such as patients with increased intracranial pressure, or patients in whom optimal ventilation is difficult to achieve.

10.2.2 Adverse effects of opioids
Non-opioid analgesia should also be considered as it may avoid or reduce the need for opioids and hence their side effects (e.g. constipation, urinary retention, respiratory depression). In post-operative patient, using patient controlled epidural analgesia as opposed to patient controlled intravenous analgesia can improve pain scores (239). Because of the risk renal injury, non-steroidal anti-inflammatory drugs used be used with extreme caution.

10.2.3 Confusion/Delirium/Psychosis
Virtually all of the drugs used for sedation and analgesia in the ICU have the ability to induce delirium (Table 5). The presence of delirium has been shown to predict increased ICU mortality (240). Several studies (1), (2), (191) have suggested that attention to detail and balancing sedation correctly reduces length of ICU stay, hospital stay and delirium. The perception that by sedating our patients we are protecting them from an unpleasant experience is probably not entirely correct. In addition to increasing ICU stay, the truth may be that we are transitioning some patients from an unpleasant reality to a terrifying delusion by undermining their ability
to rationalise these thoughts as unreal. Patients who can only recall delusional memories are more likely to develop anxiety and post-traumatic stress disorder (PTSD) following discharge (6).

**Table 5 - Deliriogenic Drugs**

<table>
<thead>
<tr>
<th>Analgesics</th>
<th>Codeine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fentanyl</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
</tr>
<tr>
<td></td>
<td>Pethidine</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline</td>
</tr>
<tr>
<td></td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>Chlorphenamine</td>
</tr>
<tr>
<td></td>
<td>Promethazine</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Prochlorperazine</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Midazolam</td>
</tr>
<tr>
<td></td>
<td>Lorazepam</td>
</tr>
<tr>
<td>Cardiovascular agents</td>
<td>Atenolol</td>
</tr>
<tr>
<td></td>
<td>Dopamine</td>
</tr>
<tr>
<td></td>
<td>Digoxin</td>
</tr>
<tr>
<td>Other agents</td>
<td>Lidocaine</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids</td>
</tr>
<tr>
<td></td>
<td>Furosemide</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
</tr>
</tbody>
</table>
Delirium is a common and under rated organ dysfunction associated with poor outcomes. It encompasses a range of diagnoses previously referred to as ICU psychosis, ICU syndrome, acute confusional state, septic encephalopathy and acute brain failure (241). Delirium is a strong predictor of mortality with a threefold increase in risk of death after pre-existing co-morbidities, severity of illness, coma and use of sedatives and analgesics are controlled for (240), (242), (243). It is associated with increased risk of long-term accelerated cognitive decline, prolonged hospital stay, institutionalization and cost (244). Delirium risks are cumulative, each additional day spent in delirium is associated with a 20% increased risk of prolonged hospitalization and a 10% increased risk of death (240).

The pathophysiology of delirium remains poorly understood, however evidence supports the role of cholinergic deficiency, with dopamine excess as a contributory factor (245). Additionally, almost all sedative drugs disrupt normal REM sleep pattern and sleep deprivation may also contribute to ICU delirium although pro-inflammatory cytokines are produced in the central nervous system that can also contribute to neuronal cell death. In patients who died from septic shock examination of brain tissue has demonstrated apoptosis associated with high endothelial iNOS expression (246). These structural changes may be responsible for a disruption in the balance of neurotransmission (6), (247).

11 Sedation in practice

11.1 A generic sedation framework

There has been a shift in the emphasis of sedation practice away from the use of large doses of sedatives to the idea of analgo-sedation. This is in recognition that pain in ICU patients is frequently under recognised. Furthermore, the association of sedative agents with the onset of delirium and the deleterious outcomes associated with developing delirium have led to the idea that non-pharmacological manoeuvres should be tried before going to the drug cupboard.
Below is a generic framework for providing analgesia and sedation to ICU patients. The ICU should be an environment that is calm and as quiet as possible. Diurnal variations should be observed and lighting at night should be kept to the minimum necessary to ensure patient safety. Clocks should be pointing at the patients (not at the staff) and relatives should be encouraged to assist with care and perhaps bring in the patient’s own music or tune to their favourite radio station (although the noise from this should be kept to a minimum). The use of eyepads and ear plugs should be considered but staff should remember that critically ill patients may not be able to alert carers when they wake up. Patients should receive explanations of everything that is happening to them during their stay.

Patients should have their sedation status regularly assessed (although it would be inappropriate to wake patients who are asleep), pain should be addressed by consideration of adjunctive analgesia, appropriate positioning and nerve blocks. The patient should undergo an assessment of their mental state before receiving sedative drugs.

Figure 3 - A general framework for Analgo-Sedation in ICU (the list of drugs used is not exhaustive)
11.2 A framework for the management of delirium

There is little known about the best way to manage patients who develop delirium. A recent study of 141 UK ICU patients (71 of whom received haloperidol) suggested that the pre-emptive use of haloperidol was not helpful to stave off the onset of delirium (248). A Chinese group have reported however that elderly patients admitted to intensive care unit after non-cardiac surgery, short-term prophylactic administration of low-dose intravenous haloperidol significantly decreased the incidence of postoperative delirium (249). Wang’s study was larger (229 received haloperidol and 228 placebo) and this does raise the question of race and age differences in the development of delirium. The routine use of antipsychotic medication cannot be recommended.

Figure 4 outlines a generic framework for the management of the patient with delirium. ICU staff should bear in mind that the intubated patient has a limited number of ways that they may express themselves and that signs such as headshaking, moving in bed or pulling at lines and tubes could be a sign of constipation, agitation, pain or all three.

![Figure 4 - A suggested framework for the management of delirium](image-url)
12 References

Sedation Guidance from other International Societies

SCCM Sedation Guidance (58):


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