Management of Pain, Agitation and Delirium

	PAIN	AGITATION	DELIRIUM
ASSESS	Assess pain 4 hourly unless intervention is required. Then prn. Use: • Patient able to self-report - Numeric Pain Rating Score (NRS) (0-10) (Figure 1) • Unable to report Critical-Care Pain Observation Tool (CPOT) (0-8) (Table 1) Patient is in significant pain if NRS >3 or CPOT >2	Assess agitation and sedation hourly using Richmond Agitation and Sedation Scale (RASS) (Table 2)	Assess delirium once per shift using CAM-ICU Score. (Table 3) Delirium present if CAM-ICU is positive
TREAT	Treat pain rapidly then reassess: • Non-pharmacological treatment- relaxation therapy • Pharmacological treatment: - Non-neuropathic pain use iv opioids +/- non-opioid analgesics - Neuropathic pain gabapentin or pregabalin + iv opioids - Post-op, rib fractures, consider thoracic epidural	Targeted sedation with SATs (Goal RASS -2 to 0). ***Unless contraindicated e.g.*** Neuro ICU patients NMB used e.g. ARDS • If under sedated (RASS >0) assess/treat pain then give a small bolus of sedation and increase rate. • If over sedated (RASS <-2) hold sedation until at target then restart at 50% of previous dose	• Treat pain first • Reorientate patient; familiarize surroundings; use glasses and hearing aids • Pharmacological treatment of delirium - Screen for alcohol or drug dependency and treat (Appx 2) - First line haloperidol - Consider atypical antipsychotic - Avoid antipsychotic drugs if prolonged QT
PREVENT	• Administer pre-procedural analgesia and/or non-pharmacological interventions • TREAT PAIN FIRST, then sedate	• Consider daily SBT, early mobility and exercise when patients are at goal sedation, unless contra-indicated • Consider use of brain function monitoring/ EEG if: - Using NMBs - Risk of seizures - Elevated ICP	• Identify delirium risk factors: dementia, HTN, ETOH & drug abuse, severe illness, • Avoid benzodiazepines or zopiclone use in those with risk factors • Mobilize and exercise patients daily • Promote sleep using day/night bundle (Appx 1) • Restart baseline psychiatric meds if indicated

PAIN

Figure 1: Numerical Rating Scale

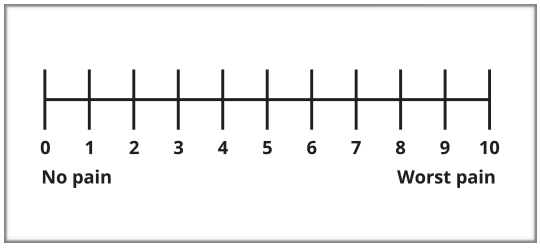


Table 1: Critical Care Pain Observation Tool

Indicator	Description	Score
Facial expression	No tension Frowning, brow lowering, orbit tightening, levator contraction All of the above plus eyelids tightly closed	Relaxed 0 Tense 1 Grimacing 2
Body movements	No movement Slow movement or rubbing pain site, seeking attention through movements Pulling tube, attempting to sit up, thrashing, not following commands, striking staff, trying to climb out of bed	Absence of movements 0 Protection 1 Restless 2
Muscle tension Evaluation by passive flexion and extension of arms	No resistance to passive movements Resistance to passive movements Strong resistance: unable to complete passive movements	Relaxed 0 Tense, rigid 1 Very tense or rigid
Ventilator compliance **OR** **Vocalisation**	Alarms not active easy ventilation Alarms stop spontaneously Asynchrony; blocking ventilation, alarms frequently activated Talking in normal tone, no sound Sighing, moaning Crying out, sobbing	Tolerating ventilator 0 Coughing 1 Fighting ventilator 2 Talking, no sound 0 Sighing, moaning 1 Crying out, sobbing 2
Total score range		0-8

Drugs

- The unit standard for intravenous infusion for analgesia is fentanyl as it has no active metabolites
- Morphine is first line for PCA and as an oral opiate in patients with adequate renal function
- Remifentanil should be reserved for selected patients requiring rapid reassessment or weaning and must be agreed with the Consultant on call. See Unit Remifentanil Guidelines on ICU website.
- Ensure regular paracetamol is prescribed and consider Trust Acute Pain Guidelines

AGITATION

Table 2: Richmond Agitation and Sedation Scale (RASS scoring)

Score	Term	Description
+4	Combative	Overly combative, violent, immediate danger to staff
+3	Very agitated	Pulls or removes tube(s) or catheter(s); aggressive
+2	Agitated	Frequent non-purposeful movement, fights ventilator
+1	Restless	Anxious but movements not aggressive or vigorous
0	Alert & calm	
-1	Drowsy	Not fully alert, but sustained awakening (eye opening/ eye contact to **voice** >10 secs)
-2	Light sedation	Briefly awakens with eye contact to **voice** (<10 seconds)
-3	Moderate sedation	Movement or eye opening to **voice** (but no eye contact)
-4	Deep sedation	No response to voice, but movement or eye opening to **physical** stimulation
-5	Unarousable	No response to voice or physical stimulation

Consider non-pharmacological methods

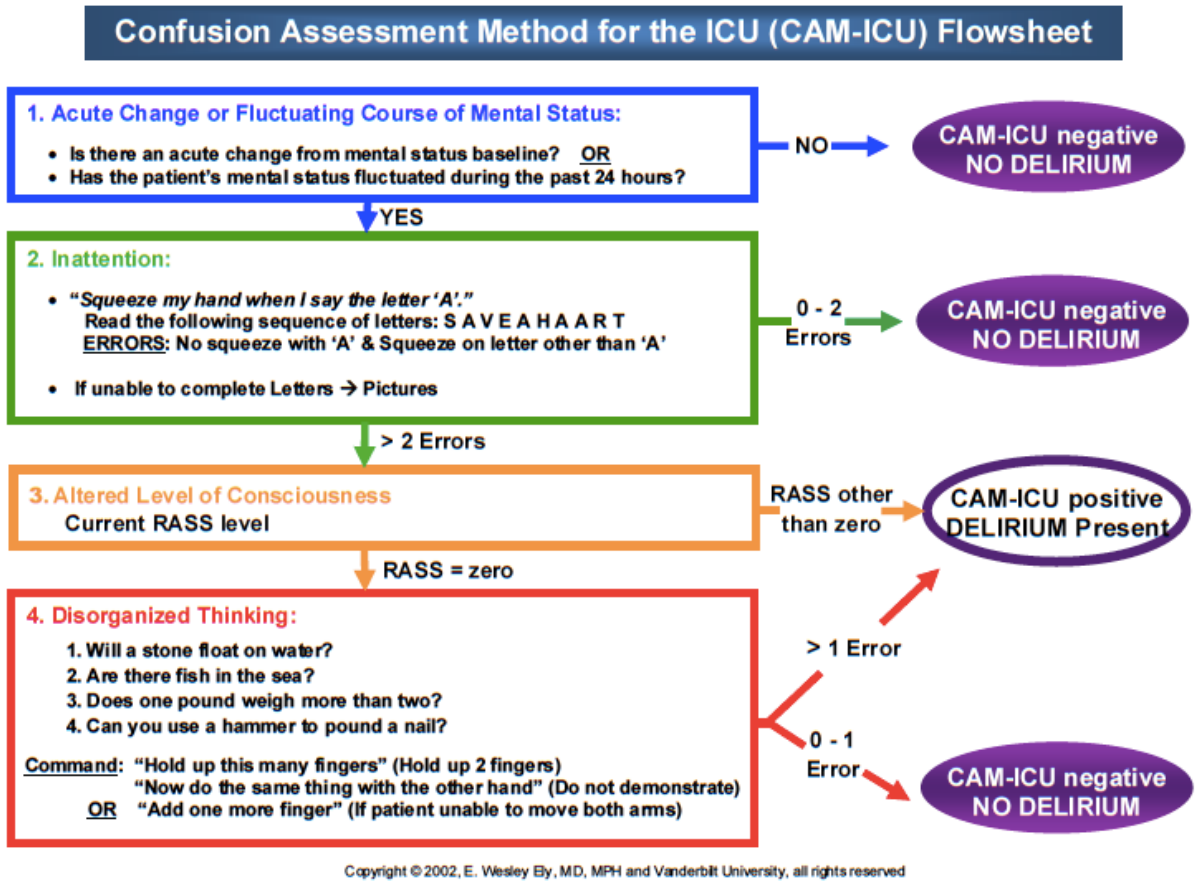
Physical	Psychological
Reduce noise	Regular orientation and reassurance
Regular repositioning	Relaxation tapes/apps
Massage	Maintain Day/Night cycle (Appendix 2)
Use of communication aids	Music

Drugs

- Propofol is the first-line agent for continuous infusion in ventilated patients except in patients with:
  - high dose inotropes or cardiovascular instability
  - with known allergy or nut allergy
  - at risk of propofol infusion syndrome (Propofol >3-4 mg/kg/hr, metabolic acidosis & cardiac dysfunction +/- raised CK or renal failure)
- Midazolam is an alternative but should be carefully titrated to RASS and used with caution in patients with renal dysfunction
- Clonidine may be helpful in patients who are tachycardic and hypertensive either IV or enterally.

DELIRIUM

Table 3: CAM-ICU Score



Treat potential causes of delirium

- Stop deliriogenic drugs
- Hypoxia & Hypercapnia
- Hypoglycaemia
- Sepsis & hypotension
- Drug, alcohol & nicotine withdrawal
- Use non pharmacological methods as for agitation

Drugs

Haloperidol (short term use only and only for delirium with agitation)
- Standard first-line antipsychotic for ICU delirium, although evidence very limited.
- Contraindicated if risk of Torsades des Pointes (long QTc, other QTc-prolonging drugs, history of Torsades des Pointes). Patient should have cardiac monitoring and daily ECGs.
- **Benzodiazepines** (Lorazepam / Midazolam)
- 2nd line, eg if Haloperidol contraindicated or ineffective despite adequate dose.
- May be required for short-term patient safety but can contribute to worsening delirium

Atypical antipsychotics
- Quetiapine first line in hypoactive delirium but also consider IM Olanzapine if enteral route unavailable.
- Quetiapine again prolongs the QTc and should be monitored with daily ECGs. Olanzapine does not.

1. INTRODUCTION

Analgesia, sedation and delirium are important but easily overlooked aspects of critical care medicine. Pain, over-sedation and delirium are significant problems amongst patients on an ICU and its treatment has become a priority. Analgesia based sedation is now advocated by many of the critical care societies across the world including the ICS and the SCCM. Regular assessment of pain, conscious level and delirium is essential necessary to guide treatment effectively. The aim of this guideline is to ensure patients are comfortable and calm in ICU, improving their experience and clinical outcomes.

2. **PROCESS (Recommendations & Justification)**

Pain, sedation and delirium should be assessed regularly

Recommendation (Action)	Justification (Rationale)
Pain should be assessed every 4 hours, or more frequently if severe.	Pain is common in ICU patients. Multiple factors such as the disease process, surgery or injuries as well as the interventions done to them such as endotracheal intubation, mechanical ventilation, vascular access and invasive monitoring can result in pain and discomfort. In one study, over 60% of patients on a mixed medical-surgical ICU were found to have moderate to severe pain. Pain assessment in ICU is difficult due to confounding factors such as sedative drugs and mechanical ventilation. The consequence of pain experienced in ICU continues after discharge, with many patients reporting the memory of pain during their time on the ICU. This can result in chronic psychological and physical disturbances. Regular pain assessments in ICU are associated with improved clinical outcomes. Pain assessment, especially if protocolised, has been associated with significantly reduced in the use of analgesic medications, ICU length of stay (LOS), and duration of mechanical ventilation. Regular pain assessment is essential to direct appropriate treatment and is strongly recommended by the Society of Critical Care Medicine in their 2013 guidelines.
Sedation should be assessed hourly	Regular assessment of sedation is necessary to sedative drugs are used in a balanced and appropriate. Sedation using drugs is often necessary to reduce stress and agitation, and to facilitate therapies such as mechanical ventilation. Excess use of sedative drugs has been shown to worsen outcome including length of stay, length of mechanical ventilation and rates of nosocomial infections. A balance must be struck between the need for sedation in certain circumstances and the risks of oversedation.

Recommendation (Action)	Justification (Rationale)
The presence of delirium should be tested for every 12 hours.	Delirium is an important problem in ICU. Potentially reversible problems such as sepsis, pain, hypoxia, electrolyte or metabolic disturbance can manifest as delirium. Delirium can interfere with other care in ICU and can result in adverse events such as unplanned removal of medical devices. The presence of delirium is an independent risk factor for morbidity and mortality in ICU. Delirium may not be apparent unless specifically tested for. Regular testing is needed to ensure that delirium is recognised and managed appropriately.

Pain and sedation should be controlled whilst optimising non-drug measures

Recommendation (Action)	Justification (Rationale)
Control pain first	As described above, pain is a common problem in ICU. Effective management of agitation and delirium is very difficult without effective pain control. Analgesia-based sedation is recommended by the UK Intensive Care Society (UK) and the Society of Critical Care Medicine (US). Analgesia should be used pre-emptively when potentially painful procedures are planned.
Use the minimum sedation necessary	Excessive sedation reduces patients' ability to communicate andand cooperate with care, and can increase the duration of mechanical ventilation, rates of nosocomial infections and ICU length of stay. Use of the minimum dose of a drug necessary to achieve a clinical goal is a widely-accepted principle in clinical practice.
Optimise non-drug measures	Many factors contribute to discomfort in ICU. Simple measures such as positioning, orientation and minimising and or grouping interventions helps to reduce the need for sedative drugs.

Pain assessment and management

Recommendation (Action)	Justification (Rationale)
Use of self reported pain score	Pain is a subjective symptom (see definition) that is best assessed by asking a conscious patient to describe their own pain. The use of a NRS simplifies this process and produces a score with is validated and intuitive.
Use of Critical care Pain Score	The CPOT is validated for the assessment of pain in patients unable to communicate compared to other non-communicative pain scoring systems. CPOT showed good psychometric properties in terms of: inter- rater reliability, discriminant validity and criterion validity in a range of ICU patients including medical and post surgical patients. A CPOT cutoff score >2 yields a sensitivity of 86% and specificity of 78%. Pain assessment is difficult when patients are unable to communicate verbally but the CPOT appears to be the best tool currently available.
Opioid analgesia should be given for pain in addition to nonopioid analgesia	As discussed above, moderate to severe pain is a common problem in ICU. All opioids drugs have similar efficacy when titrated to response. If there is significant renal dysfunction (eg calculated GFR<20ml/min), Fentanyl should be used as it has no active metabolites that are excreted in the urine and no histamine-releasing properties. Non-opioid adjunct analgesia such as paracetamol, non steroidal anti-inflammatory drugs, and local or regional analgesia should also be considered. These may reduce the dose of opioids needed but will usually be insufficient on their own in patients who are mechanically ventilated. Neuropathic pain (eg. following amputation) may be treated with atypical drugs such as gabapentin and amitriptyline.

Sedation assessment and management

Use of Richmond Agitation and Sedation Score (RASS)	The RASS is the best-validated tool for clinical assessment of sedation and agitation in ICU. It has good inter-rater reliability and has been studied in the greatest number of patients over a range of different clinical situations. RASS may be used in goal-directed protocols for titration of intravenous sedation.

Use daily sedation breaks unless contraindicated	Daily breaks from continuous IV sedation reduce the duration of mechanical ventilation, ICU length of stay and requirement for neurological imaging with no increase in adverse events.
Propofol is the first-line drug for intravenous sedation	Propofol has been used extensively for sedation on ICUs throughout the world. It has a short duration of action and permits relatively rapid emergence but can accumulate when given as a continuous infusion. The results of studies comparing propofol with benzodiazepines for intravenous sedation are conflicting. One metaanalysis suggests that the duration of mechanical ventilation is reduced when propofol is used instead of benzodiazepines for sedation, although this may not reduce ICU length of stay. A more recent meta-analysis found a slight decrease in ICU length of stay with propofol. Propofol also has a more favourable pharmacokinetic profile compared to midazolam in patients with hepatic and renal dysfunction and probably does not accumulate to the same extent. However, there is some evidence to suggest greater cardiovascular instability with propofol compared to midazolam. There is an association with benzodiazepines and delirium.However, when rates of delirium with midazolam and propofol were compared, there were no statistically significant differences between the two groups. Whilst a recent RCT comparing propofol to dexmetetomidine showed improved communication and reduced rates of delirium in patients receiving dexmetetomidine, the duration of mechanical ventilation and ICU length of stay were the same. Although dexmedetomidine may offer some small advantages over propofol, there is less clinical experience of this drug and it is considerably more expensive. On balance, propofol currently seems to offer the best combination of cost-effectiveness and clinical effectiveness for routine use in ICU. Clonidine is sometimes used as an alternative, although it produces more hypotension and bradycardia. See Unit Clonidine Policy.

Recommendation (Action)	Justification (Rationale)
Use of CAM-ICU scoring system for the assessment of delirium.	CAM-ICU demonstrates good validity and reliability when assessing for the presence of delirium. It has high levels of sensitivity and specificity when compared to the American Psychiatric Association's criteria for delirium and is specifically designed or use in the ICU. The implementation of screening for delirium using this tool has been successful in many centres throughout the world CAMICU has been translated for use in over 20 languages. The presence of delirium, as assessed by CAM-ICU, is associated with increased morbidity and mortality.
If delirium present address underlying causes.	An exhaustive list of causes of delirium is beyond the scope of this text. However, detection of delirium using CAM-ICU should trigger an investigation and management of the potential causes. Causes of delirium can be classified into modifiable and nonmodifiable. Modifiable causes include hypoxia, sepsis, electrolyte disturbance, hypercarbia, medications, sleep deprivation and disturbance of the sleep-wake cycle. Non-modifiable causes include illness severity, alcohol abuse, pre-existing dementia, CNS disease and old age. Common causes of delirium include drug or alcohol withdrawal. These causes have specific treatments, (See Appendix B) for example, benzodiazepines are used for the management of alcohol withdrawal.
If delirium is present despite attention to non-drug measures and the patient is unsafe, haloperidol is the first-line drug.	There is no evidence to support the prophylactic use of haloperidol or other antipsychotics in the prevention of ICU delirium. Haloperidol is not a substitute for proper attention to underlying causes of delirium and should only be used for short-term management of refractory hyperactive delirium, based on an individual risk benefit analysis. This includes balancing the risk of increasing cerebrovascular adverse events against the severe distress or immediate risk of harm to the patient or others. Special care should be taken to avoid or minimise the use of haloperidol in patients at risk of dementia. When treatment is necessary for the patient safety reasons haloperidol is the first-line drug.Haloperidol is not proven to reduce the duration of delirium but reduces agitation and aggressive behaviour. Doses should start at 1-2mg and if the patient is still unsafe after 30 minutes, the dose may be doubled.Continuous cardiac monitoring should be used where feasible as haloperidol can prolong the QT_c interval and precipitate fatal dysrhythmias. Haloperidol is contraindicated in patients with aprolonged QTc, who are on other QTc-prolonging drugs, or who have a history of torsades-des-pointes VT.

Recommendation (Action)	Justification (Rationale)
There is limited evidence for other antipsychotics	Other antipsychotics have been used in small clinical trials but these drugs are no more effective than haloperidol, may only be given enterally or have worse side-effect profiles. NICE guidelines recommend olanzapine as an alternative agent although there is more evidence for quetiapine.
If patient with delirium remains unsafe despite use of haloperidol, consider the use of benzodiazepine.	Benzodiazepines have a role in the treatment of specific withdrawal syndromes, such as alcohol. In other circumstances, the use of benzodiazepines should be avoided in delirium as they may worsen or prolong the problem. In certain circumstances (eg patients who are a danger to themselves or staff, and where haloperidol has failed) gaining control outweighs the risks of increasing the duration of delirium. Haloperidol should be continued during this period and the benzodiazepine should be stopped at the earliest opportunity.

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4 ONLINE RESOURES

www.icudelirium.org

http://www.ics.ac.uk/ics-homepage/guidelines-and-standards/

http://www.learnicu.org/SiteCollectionDocuments/Pain,%20Agitation,%20Delirium.pdf

Video of CAM ICU scoring: https://youtu.be/6WyJ0zL7VkI

http://www.drugscience.org.uk

Appendix 1 Day/Night Bundle

ABCDEF

Delirium Prevention Strategies

A. Assess and Treat Pain

B. Breathing Trials – SAT and SBT

C. Choose the Right Sedation

D. Delirium Assessment & Management

E. Early Exercise

F. Family Communication & Involvement

Sleep Bundle – SSH

Seeing, Sensing, Hearing.
Protecting sleep between 23:00-07:00

Seeing:

- Dim main lights where possible, use bedside lighting for patient care.
- Offer eye-mask if appropriate.

Sensing:

- Group care procedures where possible.
- Consider patient comfort e.g. positioning, analgesia.
- Complete care procedures before 23:00 or delay until after 07:00 where possible.
- Orientate patients (time, place, person) every 8 hours.

Hearing:

- Close doors/curtains where possible
- No non-clinical discussions around patients' bed spaces; staff and visitors to speak quietly
- Remove unnecessary monitoring and use 'night mode' on equipment where possible.
- Use appropriate alarm settings to avoid unnecessary alarms.
- Offer earplugs if appropriate.

Appendix 2 Drug Withdrawal

Drug	Dependence	Withdrawal	Management of withdrawal
Gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL)	Regular prolonged use of GHB/GBL can lead to physiological dependence. Users will become tolerant, consuming GHB/GBL at regular intervals during the day and at night, sometimes as often as every 1–3 hours 'around the clock' in order to avoid withdrawal. Also at risk are patient consuming more than 30g (15 teaspoons) of GHB per day, and those with concurrent alcohol or benzodiazepine dependence.	Dependent users will develop withdrawal symptoms on reduction or cessation of use, which can be severe and life threatening. It has been suggested that all cases of GHB withdrawal delirium be considered medical emergencies and be managed in critical care settings. Withdrawal syndrome is similar to that of benzodiazepines and alcohol. Problems relating to the identification of GHB/GBL withdrawal are linked to these similarities. Withdrawal has a quick onset typically a few hours after the last dose but may be within 30mins. Delirium can evolve rapidly. Mean duration of withdrawal symptoms is 9 days (range 3 - 21 days). Early symptoms: • insomnia • tremor • confusion • nausea & vomiting Over the next 12-48 hrs • tachycardia • hypertension • agitation • seizures or myoclonic jerks • hallucinations Severe withdrawal: • Delirium • Seizures (may be life threatening) • Psychosis • Withdrawal mimicking schizophrenia • Rhabdomyolysis	Management is symptomatic and requires large doses of benzodiazepines. Patients may need 150 – 200mg diazepam equivalents (or higher) in the first 24 hours. Suggested starting dose of Diazepam 20mg qds, plus 10-20mg 4 – 6 hourly prn. Benzodiazepine dose will need to be individually titrated. Ensure close observation and availability of flumazenil. Antipsychotics should be used with caution due to the risk of neuroleptic malignant syndrome and seizures.
Ketamine and Methoxetamine (ketamine analogue)	There are reports of ketamine dependence but the incidence is not known. Frequent use is associated with physical tolerance. There have been no reports of methoxetamine dependence.	Clinical experience suggests that ketamine withdrawal has symptoms of: • 'Chills' • Autonomic arousal • Lacrimation • Restlessness • Nightmares • Psychological craving • Anxiety • Shaking • Sweating • Palpitations • Tiredness • Low appetite • Low mood	1 case report describes successful elective ketamine detox with 3 day reducing course of diazepam. There are no studies to support the use of any other agents. For methoxetamine suggest using diazepam as with ketamine.
Nitrous Oxide	There are no reports of nitrous oxide dependence in the literature. There is anecdotal evidence of psychological dependence. Heavy users can suffer from vitamin B12 depletion causing: • Psychosis • Paralysis • Parasthesiae • Myelopathy • Polyneuropathy • Peripheral neuropathyThese can respond to B12 replacement. Consider B12 deficiency in patients who present with psychiatric manifestations and report nitrous oxide exposure	There are no specific withdrawal symptoms.	There are no specific withdrawal symptoms.
Cocaine	Cocaine use is associated with dependence but there is no pharmacological treatment of proven efficacy despite several Cochrane reviews.	Due to the short half-life of 90 minutes, withdrawal symptoms may occur within a few hours of the last dose. • dysphoric mood • fatigue • insomnia or hypersomnia • psychomotor agitation or retardation • increased appetite • vivid, unpleasant dreams	Medication to provide symptomatic relief when indicated on an individual basis.
Amphetamine Sulphate	Regular usage will lead to tolerance and physical and psychological dependence leading to • Serious sleeping problems • Poor nutrition and anorexia • Anhedonia • Severe effects on quality of life	As for Cocaine (above).	Medication to provide symptomatic relief when indicated on an individual basis.

Drug	Dependence	Withdrawal	Management of withdrawal
Methamphetamine	The risk of dependence with methamphetamine is high and tolerance will develop with frequent use. Dependant users show:	There is a psychological (rather than physical) withdrawal syndrome which can occur within 24 hours of the last dose. Acute withdrawal phase lasts 7 – 10 days and includes: • Severe dysphoria • Irritability • Melancholia • Anxiety • Hypersomnia and marked fatigue • Intense craving • Paranoia • Suicidal ideation • Akathisia	Pharmacological management of withdrawal is an adjunct to psychosocial therapies. Mirtazepine may have potential to lessen many symptoms of withdrawal.
Mephedrone and other Synthetic Cathinones	Mephedrone has a dependence potential due to its similarity to amphetamine. Tolerance to mephedrone develops quickly and users will consume higher doses more frequently.	Symptoms reported include: • Tiredness • Insomnia • Nasal congestion • Impaired concentration • Depression • Anxiety • Increased appetite • Irritability • Cravings to use again • Increased muscle tone alleviated by constant movement (reported by 1 heavy user)	There are no established regimens to manage withdrawal. Reports suggest that benzodiazepines may alleviate agitation and paranoia. One report describes the use of olanzapine for psychotic symptoms. Another describes the use of risperidone for symptoms of disorganisation, delusions and hallucinations.
Ecstasy (MDMA) and related drugs with similar effects	While ecstasy has some potential for dependence use is usually self-limiting, perhaps due to the long recovery period after one dose.	Withdrawal has been described, although there are wide variations in the reported incidence. This may reflect the application of withdrawal criteria to the 'come down' which may be regarded as a usual effect following usage. The post usage period is characterised by a dysphoric 'crash', and then in chronic users an extended withdrawal with anhedonia and a lack of energy.	The primary treatment for harmful chronic ecstasy usage is psychosocial. No pharmacological treatments are reported for dependence or withdrawal.
Benzofurans (Benzofury)	No information	No information	No information
Pipradrols and pipradrol derivatives e.g."Ivory Wave "or "Head Candy"	Prolonged use of D2PM can cause craving further doses. No further information on the long term effects of usage.	No information	No information
Hallucinogens	LSD and other 'classic hallucinogens' do not lead to dependence or compulsive usage.	LSD and other 'classic hallucinogens' do not lead to a withdrawal syndrome.	LSD and other 'classic hallucinogens' do not lead to a withdrawal syndrome.
Synthetic Cannabinoids (SCs)*	Long term effects of SCs are not known. Some users report features of dependence. Frequent users have reported psychosis that may last for weeks after last use and may be accompanied by depression and suicidal ideation. Symptoms may be managed with benzodiazepines and antidepressants in cases of concurrent depression or atypical antipsychotics for psychotic disorders.	Reported withdrawal symptoms are rare but include: • Headaches • Anxiety/nervousness • Insomnia/sleep disturbance • Anger/irritability • Impatience • Difficulty concentrating • Restlessness • Nausea • Depression	No information

* Sold as 'Spice'. Spice is also used as a generic term for all SCs. There are over 80 different SC compounds. The active ingredient in products of the same brand can vary and there may be more than one active ingredient in each product. Conversely, products marketed under different brand names may contain the same active ingredient(s). The concentration of active ingredient in products (even of the same brand) can vary wildly. It is therefore very difficult to predict the pharmacology of an individual product. SCs have also started to appear in cannabis resin and herbal cannabis samples, perhaps to increase the potency of weak cannabis.