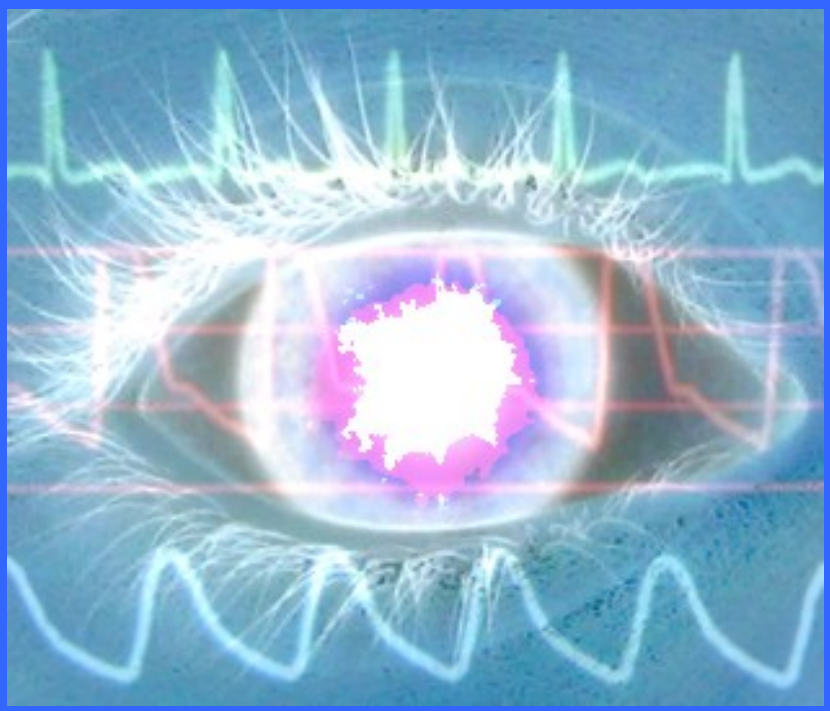
Detection, Prevention and Treatment of Delirium in Critically Ill Patients



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Introduction

The management of delirium is an important and challenging facet of therapy when dealing with critically ill patients. Delirium has recently been shown to be an independent predictor of increased mortality at 6 months and longer length of stay in ventilated intensive care patients[1]. It is also associated with increased length of hospital stay[2] and may predispose patients to prolonged neuropsychological disturbances after they leave intensive care[3]. These factors contribute to the greater intensive care and hospital costs attributed to patients with delirium[4].

This resource was assembled because of the frequent correspondence between critical care pharmacists via the UKCPA newsgroups, requesting help to manage agitated or delirious patients, and because the various responses generated tended to encompass a variety of approaches which appeared to be rooted in local practice or anecdote.

The aim of this resource is to provide a toolkit, which facilitates the practitioner in getting to grips with the various aspects of delirium management.

Overview of Delirium

Delirium has been defined as "an acute, reversible organic mental syndrome with disorders of attention and cognitive function, increased or decreased psychomotor activity and a disordered sleep-wake cycle". It is commonly found in the critically ill (i.e. not always in ICU) with a reported incidence of 15-80% [1,2,5,6]. The term ICU psychosis is old fashioned, inaccurate and not appropriate.

Three delirium subtypes have been characterised[7]:

Hyperactive - Agitated, paranoid.
Hypoactive - Withdrawn, quiet, paranoid.
Mixed - Combination of hyperactive and hypoactive

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

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

It is worth noting that schizophrenic patients do not have cognitive defects and tend to have auditory, rather than visual hallucinations. The delirious patient may perceive the environment as hostile and try to escape, sometimes employing violence against staff or visitors[5].

The hypoactive form is often not well recognised and inappropriate therapy may be started if the patient is misdiagnosed as being depressed[8]. Disorientation is common in delirium, but this is not a feature of depression[5].

The behaviour of the delirious patient can change dramatically over hours or even minutes, giving rise to confusion amongst caregivers about the patient's actual mental state[9].

The active use of an intervention program has been shown to reduce the incidence of delirium in non critically ill elderly patients and also reduced overall hospital length of stay by 4 days. The same study showed a reduction in hospital length of stay by 10 days in the sub group of delirious patients[10]. An intriguing retrospective study in critically ill patients found that those patients who had received haloperidol during their intensive care stay exhibited a reduction in mortality when compared with patients who never received haloperidol (20.5% vs. 36.1%, p=0.004)[11], although the reason for this finding is unclear and several explanations are possible.

There are many predisposing factors for the development of delirium, that include[5]: -

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

It is worth bearing in mind that there is a long list of differential diagnoses that include pain (acute or pre-existing chronic), non-clinical seizure activity, undetected intracerebral bleed and hypertensive encephalopathy[5].

Delirium can be mistaken for, or found in combination with other forms of mental illness. Table 1. summarises the features of various forms of mental illness[12].

Table 1. Features of four types of mental illness (Adapted from reference 12)

	Delirium	Dementia	Depression	Psychosis
Onset	Acute	Insidious	Variable	Variable
Reversibility	Quick and fluctuating	Slow and constantly progressive	Variation during the day	Variable
Level of consciousness and orientation	Clouded, disorientated	Lucid until the last stages	Generally Normal	Intact, although the patient may be perplexed in the acute stage
Attention and memory	Poor short term memory and constant inattention	Poor short term memory, without inattention	Poor attention, but intact memory	Poor attention, but intact memory
Cognition	Focal cognitive failure	Global cognitive failure	Cognition intact	Variable
Psychotic symptoms	Frequent; psychotic ideation is usually brief and non-elaborated, however ICU patients may exhibit more complex paranoid symptoms[13]	Less frequent	Rare; psychotic ideation is complex and related to the mood of the patient	Frequent; psychotic symptoms are complex and often paranoid
EEG	Abnormalities in 80-90% (most frequent: generalised diffuse slowing)	Abnormalities in 80-90% (most frequent: generalised diffuse slowing)	Normal	Normal

Detection of Delirium

Delirium is under recognised in the critically ill. The agitated patient is easily identified, but there are other differential diagnoses that may confuse the picture along with the fluctuating nature of the condition.

An important step in the prevention of delirium in critically ill patients is the avoidance of either excessive or inadequate use of sedative and analgesic therapy. The use of validated sedation scoring systems is recommended when titrating sedative agents to the appropriate sedation level for each patient.

There are three validated scoring systems that can be used in critically ill patients to monitor sedation and agitation. They are the Sedation Agitation Scale (SAS)[14], the Richmond Agitation Sedation Scale (RASS)[15] and the Motor Activity Assessment Scale (MAAS)[16]. These scales are 7 point (10 in case of RASS) scoring systems ranging from dangerously agitated to unrousable, with an aware and calm score in between. These scales go some way to identifying delirious patients as they can indicate a number of levels of agitation. The locally adopted scoring system should be used in all critically ill patients irrespective of their current sedative status. This continuous monitoring records the fluctuations in the patient's level of consciousness throughout their critical care stay. However, these scores are unable to identify all delirious patients and must be used in conjunction with specific delirium tests.

Three delirium-screening tools have been validated in critically ill patients. The Intensive Care Delirium Screening Checklist (ICDSC)[17] and the Delirium Detection Score (DDS)[18] use an eight-feature checklist, while the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU)[19] uses a four feature score. These tools aim to identify inattention, the single most important feature of delirium. When the CAM-ICU tool is used in conjunction with a sedation-agitation scoring system, two of the 4 features are already scored enabling rapid completion. This in turn increases the likelihood that the tool will be routinely accepted into clinical practice.

The CAM-ICU tool can be found in the Appendix and supporting training material can found at the following URL: www.icudelirium.org

Prevention of Delirium

Prevention is more effective than treatment.

Non-Pharmacological Interventions

The importance of using non-pharmacological interventions that encourage the orientation of the patient to their surroundings cannot be over stated[20]. Maintaining normal physiological function is also very important.

Providing support and orientation

- Communicate clearly and concisely; give repeated verbal reminders of the day, time, location, and identity of key individuals, such as members of the multidisciplinary team and relatives.
- Provide clear signposts to patient's location including a clock, calendar, and chart with the day's schedule.
- Have familiar objects from the patient's home in the room/ by the bed.
- Attempt consistency in nursing staff (e.g. named nurse).
- Use television or radio for relaxation and to help the patient maintain contact with the outside world. Some discretion is required as patients may build events from television programs or radio into delusions[21]
- Involve family and caregivers to encourage feelings of security and orientation.

Providing an unambiguous environment

- Attempt to create a day / night cycle with lights off at night but on all day with appropriate day time stimulation. Pharmacological sleep aids are a last resort.
- Control sources of excess noise (such as staff, equipment, visitors).
- Keep room temperature between 21.1°C to 23.8°C

Maintaining competence

- Identify and correct sensory impairments; ensure patients have their glasses, hearing aid, and dentures. Consider whether an interpreter is needed.
- Encourage self-care and participation in treatment (e.g. have patient give feedback on pain).
- Arrange treatments to allow maximum periods of uninterrupted sleep.
- Maintain activity levels: non-ambulatory patients should undergo a full range of movements for 15 minutes, three times a day if possible.

Remove potential organic drivers

- Identify and correct/treat organic causes such as hypoxia, pain, acidosis, haemodynamic instability and infection.

Pharmacological Interventions

Drug therapy can contribute to the development of delirium. Prompt cessation of medication that is no longer required can help minimise the occurrence of delirium.

Directly deliriogenic drugs

Drugs that exhibit antimuscarinic or dopaminergic activity are particularly associated with the development of delirium (see Table 2.[22-25]). Increased plasma concentrations and / or increased blood brain barrier permeability (e.g. in renal failure) may make patients particularly prone to the deliriogenic effects of some drugs (e.g. penicillins, quinolones, opioids and linezolid[25])

Table 2. Drugs commonly used in critical care that have been shown to be deliriogenic

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

Drugs affecting sleep

Establishing a regular day-night cycle is widely held to be important and many drugs are known to adversely affect normal sleep patterns. Prescribers should be familiar with the range of agents that affect sleep, and specifically how each drug may affect sleep architecture. A summary can be found in Table 3 [24].

Table 3. Drugs commonly used in critical care and their affect on sleep patterns (adapted from reference 24)

Drug Class or Individual Drug	Sleep Disorder Induced or Reported
Benzodiazepines	↓ REM, ↓ SWS
Opioids	↓ REM, ↓ SWS
Clonidine	↓ REM
Non steroidal anti-inflammatory drugs	↓ TST, ↓ SE
Norepinephrine/ Epinephrine	Insomnia, ↓ REM, ↓ SWS
Dopamine	Insomnia, ↓ REM, ↓ SWS
β-Blockers	Insomnia, ↓ REM, Nightmares
Amiodarone	Nightmares
Corticosteroids	Insomnia, ↓ REM, ↓ SWS
Aminophylline	Insomnia,↓ REM, ↓ SWS, ↓ TST, ↓ SE
Quinolones	Insomnia
Tricyclic antidepressants	↓ REM
Selective Serotonin Reuptake Inhibitors	↓ REM, ↓ TST, ↓ SE
Phenytoin	↑ Sleep Fragmentation
Phenobarbital	↓ REM
Carbamazepine	↓ REM

REM: rapid eye movement, SWS: slow wave sleep, TST: total sleep time, SE: sleep efficiency.

Patients who have had significant suppression of REM sleep by pharmacological agents are at risk of REM rebound upon withdrawal of the drug. REM rebound is characterised by tachycardia, hypertension, apnoeas, ventilatory depression and nightmares. Critically ill patients weaning from mechanical ventilation may be particularly prone to the adverse effects of REM rebound. Consideration of the acute withdrawal effects of commonly used drugs such as benzodiazepines and opioids is necessary (See pages 13-21). Avoid abrupt discontinuation of drugs known to suppress REM sleep where possible.

Treatment of Delirium

If all preventative measures fail and no organic cause can be identified and treated, active delirium treatment should be instigated. Delirium is thought to be predominantly due to an excess of dopaminergic activity and/or inadequacy of brain muscarinic activity. Pharmacological therapy is aimed at correcting this imbalance. In some patients, consideration of the use of physical restraints may be necessary in dangerously agitated patients unsatisfactorily controlled by sedatives or neuroleptics, or without a protected airway[26].

Hyperactive / Mixed Delirium

Butyrophenone antipsychotics

Haloperidol is the agent of choice[5]. The haloperidol dose depends on the patient's level of disturbance, age and cardiovascular status and is usually between 0.5 – 10 mg haloperidol enterally or intravenously.

A typical starting dose is 1-2mg by intravenous injection every 2-4 hours in the general population[27]. The enteral route can be used for less severely disturbed patients identified early through delirium screening. Patients identified later are likely to require larger initial doses. Lower initial doses should be considered for elderly patients. Large initial doses may be required for severely agitated patients.

If the patient remains unmanageable after 20-30 minutes after an intravenous dose and is not exhibiting adverse side effects, double the haloperidol dose[20, 25]. This cycle should be repeated until the patient is manageable.

There has been no daily maximum safe dose of haloperidol established. Exceptionally large doses have been reported, but QT prolongation may occur[5]. Such high doses are probably not necessary. High levels of D_2-receptor occupancy with haloperidol are more effective than low levels when treating psychosis. High levels of D_2-receptor occupancy have been found with the enteral administration of only 2mg/day of haloperidol in a group of schizophrenics, although this dose had been given for 2 weeks before measuring occupancy rates[28]. Very high D_2-receptor occupancy rates are also associated with extrapyramidal side effects[29].

Once control is achieved, a regular dose can be prescribed four-six hourly, either intravenously or enterally. The dose can be reduced and discontinued over several days.

Continuous infusions of haloperidol may be needed rarely in some patients who have received multiple bolus doses (eg more than 8 doses of 10mg in 24 hours, or more than 10mg an hour for 5 hours). Some sources describe treatment with a 10mg intravenous bolus of haloperidol followed by continuous infusion 5-10mg/hour in critically ill patients[30, 31]. This regime is not licensed and should be used with caution. Discontinue haloperidol if extrapyramidal symptoms develop.

Cardiac monitoring may be required with high doses due to the risk of QT prolongation. Appropriate plasma potassium and magnesium monitoring and replacement are recommended. Reduce the haloperidol dose or discontinue if QT prolongation occurs (QTc>450msec or 25% greater than previous ECG readings)[30].

Procyclidine may be required to treat extra-pyramidal side effects. Give 2.5mg procyclidine enterally three times daily, titrating up by 2.5mg daily according to response. The usual daily dose is 10-20mg. In an emergency, 5-10mg of procyclidine may be given by intravenous injection and usually provides relief within 5 to 10 minutes[32].

Phenothiazine antipsychotics

Phenothiazines such as chlorpromazine are not specifically recommended. While there is no direct evidence to recommend butyrophenones over phenothiazines on the grounds of efficacy, the side effect profile of haloperidol is more favourable than for phenothiazines. In a study that compares the agents for delirium, chlorpromazine and haloperidol were found to be equally efficacious in terminally ill AIDS patients, but there was a trend towards decreased cognitive function in the chlorpromazine group[33]. Phenothiazines exhibit greater anticholinergic activity than butyrophenones and this increases the risk of hypotension, tachycardias and cardiac arrhythmias, although butyrophenones carry a greater risk of extra-pyramidal side effects[34, 35]. The anticholinergic activity of neuroleptic agents as well as non-neuroleptic agents are implicated in the development of delirium in stroke and some have

advocated caution in using such agents in patients with acute stroke[36]. Chlorpromazine and other low potency typical antipsychotics have been shown to posses the greatest effect on lowering seizure threshold when compared with other neuroleptics[37]. Chlorpromazine is specifically not recommended for rapid tranquilisation in other clinical areas such as the Emergency Department[38] and until a well powered study is conducted that shows superiority of chlorpromazine over haloperidol in the treatment of delirium, the most cost effective agent with the cleanest side effect profile is recommended.

Atypical antipsychotics

There is very little evidence regarding the use of atypical antipsychotics for delirium treatment in the critical care setting where published data is limited to one prospective randomised trial and a case report[39, 40].

Olanzapine 5mg daily was found to be as effective as 2.5mg-5mg haloperidol enterally three times daily in a randomised group of critically ill patients who were screened for delirium. Rescue haloperidol use in both groups was similar.

Enteral olanzapine may therefore be useful in patients who do not tolerate haloperidol due to extra-pyramidal side effects. Recent advice from the Committee on Safety of Medicines regarding the increased risk of stroke in patients with dementia who are treated with olanzapine in the general population should also be borne in mind[41], particularly as dementia is a risk factor for the development of delirium. The orodispersible formulation is not absorbed sublingually, although may be dispersed in water to facilitate administration through enteral feeding tubes.

There is no reported experience with using parenteral atypical antipsychotics agents in critically ill patients. Intramuscular olanzapine should only be used as an alternative to intravenous haloperidol where side effects are particularly troublesome (e.g. in Parkinson's disease) and the enteral route is not available. Risperidone is presented as a depot injection for chronic schizophrenia and cannot be recommended.

Benzodiazepines

Benzodiazepines should be used to manage specific delirium syndromes such as alcohol or benzodiazepine withdrawal syndromes (see pages 13 and 18).

Otherwise benzodiazepines should generally be avoided, as there is evidence to show that they contribute to the development of delirium[42], and that they are ineffective in treating delirium[33]. The contribution to delirium is particularly evident with high doses of benzodiazepine or when using benzodiazepines with a long half-life.

Benzodiazepines may be used as rescue therapy for rapid tranquillisation if haloperidol therapy (or equivalent) is failing and the patient poses a danger to themselves or attending staff or visitors. Clearly in such cases the increased risk of worsening delirium is outweighed by the need to gain control of the situation. It is important to remember that the benzodiazepine use does not treat delirium, and additional therapy with haloperidol is required.

In such situations, use a short acting benzodiazepine to calm the patient sufficiently in order to gain control of the situation. There are no clinical trials to guide practice from the critical care literature. A recent study in the emergency department found that an intramuscular injection of 5mg midazolam was as effective as an intramuscular injection of 2mg lorazepam in controlling severe agitation, however midazolam had a significantly faster onset of action (18.5 mins ± 14mins vs. 32.2 mins ± 20mins) [43]. Time to arousal with midazolam was 81.9 minutes compared with 217.2 minutes with lorazepam.

The commencing dose depends on level of disturbance, age and tolerance to benzodiazepines. Given that intravenous access is usually already established in critically ill patients, a starting dose of 5-10mg midazolam should be given intravenously every 2 minutes until the patient is manageable (with close monitoring in an appropriate setting). Where the intravenous route is not available, give 5mg by intramuscular injection, repeating every 15 minutes until the patient is manageable. Lorazepam is also widely used in this situation at a dose of 1-2mg either intramuscularly or intravenously. The onset of action of intravenous lorazepam (5 mins) is slower than that of midazolam and intravenous doses must be diluted before use. Lorazepam is metabolised by the liver to inactive metabolites which may influence the choice of agent used in patients with severe renal impairment[44].

Hypoactive Delirium

There are no published data in the critical care literature regarding the treatment of this form of delirium. Available data stems from the palliative and elderly care populations. Hypoactive delirium appears to be associated with a worse outcome, although this point is debated and lack of recognition of the condition may explain this finding[45].

Antipsychotics

Olanzapine has been used in an open trial for the treatment of delirium in cancer patients[46]. Only patients who could take the drug enterally were included in the study. There was no placebo group and outcomes were measured using a scoring system (Memorial Delirium Assessment Scale - MDAS). Olanzapine dose was titrated according to clinical judgement and side effects. Overall MDAS scores improved, but a number of factors predicted a poor response to treatment from a logistic-regression analysis. These were: age > 70 years old, CNS spread of cancer disease and hypoactive delirium. Additionally, χ^2 analysis identified hypoxia, history of dementia and worse delirium severity as predictive of a poor response to olanzapine.

Stimulants

Methylphenidate has been used in cancer patients with hypoactive delirium in a small trial[47]. Cognitive scores significantly improved in all patients as measured by Mini-Mental State Examination. The majority of patients required 20-30mg methylphenidate a day. Up to 50mg a day was required by some patients, larger doses than this did not appear to improve symptoms but did cause more side effects.

There are no good data to inform a decision on choice of agent to treat hypoactive delirium. It is therefore suggested that management should be as for hyperactive / mixed delirium, although methylphenidate may be useful where such treatment fails.

Night Sedation

No ideal hypnotic agent exists. Although benzodiazepines are often used for acute insomnias, their use in patients at high risk of delirium requires careful consideration because of the established association with the formation of delirium[42]. Benzodiazepines also suppress REM sleep and this should be avoided in this group of patients where possible[24]. Night sedation with benzodiazepines (and other GABA agonists) should be limited to those delirious patients specifically requiring benzodiazepine therapy such as in alcohol and benzodiazepine withdrawal (See pages 13 and 18). The use of Zaleplon, Zolpidem or Zopiclone are not recommended substitutes for short acting benzodiazepines[48].

Trazodone

Trazodone is a tricyclic-related antidepressant and is not normally the agent of choice in non-depressed patients suffering from sleep disorders such as insomnia. However, in patients who are at high risk of delirium or already delirious, it offers potential advantages over GABA agonist drugs, other tricyclic antidepressants and related substances. Trazodone exhibits 5-HT_2 antagonism, minimal antimuscarinic activity and reduced adverse effects on the normal sleep cycle in healthy adults[49]. Tolerance usually develops within a week, so trazodone should only be for short term use. Priapism is a rare potential problem requiring immediate discontinuation. The dose is 50mg trazodone enterally at night for a maximum of seven days. Use of Trazodone in this situation is unlicensed.

Haloperidol

If the enteral route is not available, intravenous haloperidol, 2–5mg intravenously at night may be used[50]. The dose should be reviewed if the patient is also requiring haloperidol for control of hyperactive delirium/ agitation.

Treatment of Withdrawal Syndromes

Benzodiazepine withdrawal

Benzodiazepine withdrawal syndromes are common in the critically ill and though particularly prevalent in patients who have required long periods of sedation, can also occur with just a few days therapy[51]. One study has shown that a third of patients with a length of stay greater than 7 days exhibit withdrawal syndromes from analgesic or sedative agents. Such patients tend to have been treated for adult respiratory distress syndrome or require the use of neuromuscular blocking agents during their treatment[52]. Patients may also have a history of benzodiazepine use or misuse prior to their intensive care admission.

An acute withdrawal reaction typically last for 1-2 weeks and is followed by a prolonged period (months) of gradually decreasing somatic and psychiatric symptoms (Table 4.)[5, 53]

Table 4. Features of benzodiazepine withdrawal

Psychiatric symptoms	Somatic symptoms
Acute anxiety states	Parasthesia
Phobias	Tremors
Perceptual disorders	Muscle pains
Irritability	Blurred vision
Aggression	Seizures
	Ataxia

Where it is anticipated that patients will require sedation for a long period of time, consideration of the following factors may reduce the amount of sedation required and/or the intensity of the withdrawal syndromes experienced by the patient.

- Titrate sedatives to sedation scores and re-assess parameters on a daily basis. In the majority of cases critically ill patients should be kept awake and comfortable not unresponsive and unrousable. The use of sedation breaks is strongly recommended when possible.
- Continuing or re-commencing the patients normal antipsychotics or long term antidepressants may assist in the transition phase (especially if patient has a long psychiatric history)
- Always give consideration to other factors exacerbating withdrawal syndromes (e.g. alcohol, nicotine) and treat if appropriate.

Withdrawal can be achieved by reducing the administration of benzodiazepine over a period of many days to weeks. This can be facilitated by changing to a longer acting agent such as lorazepam, which has the additional advantage of allowing enteral administration or sublingual administration. Adaptation of protocols to individual circumstances is required due to wide variation in response between patients.

Example withdrawal regime using lorazepam (this is from the paediatric literature, but still forms a useful guide for the adult population)[54]: -

- Calculate the daily infused dose of midazolam and divide by 12 to give an approximate total daily dose of lorazepam
- Prescribe one quarter of the daily dose of lorazepam at a frequency of six hourly, rounding down to a convenient dosage unit
- After the second oral dose of lorazepam, reduce the midazolam infusion by 50%
- After the third oral dose of lorazepam, reduce the midazolam infusion by a further 50%
- After the fourth oral dose of lorazepam, discontinue the midazolam infusion
- Reduce daily lorazepam intake by 500micrograms-1mg a day until weaned completely.
- Haloperidol may also be required. Titrate the amount required in aliquots of 1-10mg, then administer as a regular dose every 4-6 hours. Wean the haloperidol on a daily basis along with the lorazepam.

A body of literature exists surrounding the use of diazepam to manage benzodiazepine withdrawal in patients with long term benzodiazepine addiction. Some clinicians may prefer to utilise diazepam rather than lorazepam for benzodiazepine withdrawal in critically ill patients, on the grounds of familiarity with the agent and local availability. Where diazepam is used for this purpose, clinicians should be alert to the association of the formation of delirium with long acting benzodiazepines and the difficulties in establishing a baseline dose for diazepam. Production and accumulation of active

metabolites in the first few days of therapy may cause increasing sedation without an increase in diazepam dose. This may pose a particular hazard where patients are discharged to normal ward care shortly after commencing regular diazepam.

Example withdrawal regime using diazepam[55]:-

- Calculate the daily infused quantity of Midazolam (day 0).
- Reduce the infusion rate by 20% on day 1.
- Reduce the infusion rate by 10% of the original dose on a daily basis until the equivalent of 80mg/day midazolam has been reached.
- Convert 80mg/day midazolam to 10mg diazepam four times a day.
- Reduce daily diazepam intake by 10mg/day until weaned completely.
- Haloperidol may also be required. Titrate the amount required in aliquots of 1-10mg, then administer as a regular dose every 4-6 hours. Wean the haloperidol on a daily basis along with the diazepam.

An alternative approach is to prescribe small doses of lorazepam (e.g. 500micrograms) or diazepam (e.g. 1-5milligrams), which can be given as often as needed during the first few days after the cessation of benzodiazepine infusion. This can be used to calculate a regular baseline dose which can then be tailed off over several days to weeks. The onset of sedative action of oral or sublingual lorazepam is approximately 20 to 30 minutes and for oral diazepam is approximately 30 minutes[56].

In all cases there is the potential need to reduce the benzodiazepine dose in a far slower fashion. This will be particularly evident in patients with an antecedent history of benzodiazepine abuse. Such patients will require dose reduction from their baseline requirement over a period of many weeks to months, not days to weeks. This scenario is beyond the scope of this document and specific advice should be sought from a local addiction centre if required.

The following information on the management of other conditions that emerge on benzodiazepine withdrawal is drawn from the management of withdrawal in the community due to the lack of published data in the critical care literature[57]:

- Anxiety is a common additional complication that will require management primarily through non-pharmacologic methods. Simple encouragement is all that is required in many cases, though cognitive and behavioural therapy may be required in resistant cases.
- Insomnia can be countered by providing a larger benzodiazepine dose at night or through the use of adjuvant sedatives
- Panic attacks can complicate withdrawal and non-pharmacological interventions are recommended for dealing with these (e.g. counselling, breathing exercises, relaxation techniques, etc).

Benzodiazepine withdrawal in head injured patients

Head injured can be very difficult to manage for the following reasons: -

- Patients can be heavily sedated +/- paralysed for a long period of time (sometimes weeks) to maintain stable ICPs and CPPs.
- Large doses of hypnotics are required to achieve the desired level of sedation. Tolerance can quickly occurs, resulting in rapid dose escalation followed by a pronounced withdrawal syndrome.
- Once the neurological parameters are stable, there is often pressure to completely stop sedation to facilitate neurological assessment.
- It can be difficult to assess which symptoms are due to drug withdrawal and which are due to the sequelae of the patients' original injury.

Use the minimum amount of sedative agents as possible, and wean slowly such as in the schedules on pages 13 and 14.

Patients requiring a prolonged respiratory wean

Patients with acute lung injury sometimes require prolonged periods of analgesia and sedation to facilitate ventilation. Early tracheostomy formation may be useful but any clinical advantage is as yet unproven. The following factors should be borne in mind when dealing with patients requiring a prolonged respiratory wean:

- This group of patients are often over-sedated. Meticulous adherence to the prescribed target sedation scores is important. Targets should be reviewed on a daily basis and sedation breaks employed.
- Restart regular anti-depressants or anti-psychotics in the early phase of admission where these agents are part of the patient's drug history.
- This group of patients are prone to day-night cycle irregularities. Use of non-pharmacological delirium prevention strategies is particularly important.

Opioid withdrawal

Opioid withdrawal reactions can occur as a result of prolonged opioid infusions whilst critically ill, or because of a prior history of opioid use or abuse. Withdrawal reactions can occur with all opioids and are characterised by adrenergic excitation and exaggerated nociceptor responses due to hyperactivity of cells within the locus caeruleus (Table 5.).

Table 5. Features of opioid withdrawal (Adapted from Reference 53)

Signs and Symptoms	
Sweating	Restlessness
Rhinorhoea	Irritability
Lacrimation	Abdominal cramps
Yawning	Nausea
Tremor	Vomiting
Weakness	Diarrhoea
Insomnia	Mydriasis
Feeling hot and cold	Tachycardia
Flushing	Piloerection

Where it is anticipated that patients will require an opioid for a long period of time, consideration of the following factors may reduce the amount of opioid required and/or the intensity of the withdrawal syndromes experienced by the patient.

- Titrate analgesics using scoring systems and re-assess parameters on a daily basis.
- Use regular paracetamol where possible to reduce the opioid load.
- Not all pain is relieved by opioids. For example vascular patients, and patients with syndromes such as Guillain Barré may require adjunct therapies (e.g. gabapentin).

Where opioid dependence has become an issue, withdrawal can be achieved by reducing the total daily dose of opioid over a period of many days to weeks. The daily opioid requirement can be met through the enteral route, using a morphine sulphate solution or by changing to a long acting agent such as methadone. The conversion of daily opioid requirements to methadone is not straightforward.

Example withdrawal regime (opioid infusion tailing): -

- Calculate the daily infused quantity of opioid (day 0).
- Reduce the infusion rate by 20% on day 1.
- Reduce the infusion rate by 10% of the original dose on a daily basis until weaned completely. Pragmatic rounding off of doses will be required to allow appropriate prescribing and administration.

Example withdrawal regime (converting to methadone)[58]: -

- Calculate the daily infused quantity of opioid (day 0) and calculate from this the equivalent 24 hour oral morphine dose.
- On day 1, prescribe the oral methadone dose as 1/10th of the 24 hour oral morphine dose at a frequency of 3 hourly when required (maximum 30mg 3 hourly) and stop the opioid infusion.
- Allow the patient to have the dose 3 hourly when required. Where the patient is unconscious or unable to indicate the need for a dose, bedside staff must assess the patient according to symptoms and administer doses when required.
- On day 6, note the previous 48 hours intake and convert to a regular 12 hour dose, with a similar or smaller dose prescribed when required. Because of the long half life of methadone, it takes this long to establish a baseline.
- Wean the methadone off over several days to weeks

Where the patient is transferred from critical care to normal ward care, or between critical care units, care must be taken to ensure that the opioid reduction program continues. Where methadone is being used, it must be made clear that its use is to facilitate withdrawal from an iatrogenic dependence and that the ultimate aim is discontinue completely before the patient goes home, if appropriate.

Clonidine blocks pre-synaptic α-receptors in the caeruleus locus and has been used to blunt the symptoms of opioid withdrawal, with or without reducing doses of opioid.

Start at 50-100mcg enterally three times a day, and wean slowly in conjunction with the opioid. Higher doses may be required initially (up to 1mg over 24 hours has been used). Clonidine is not thought to be superior to slow weaning of opioids. Some studies show a faster wean, but with a tendency towards more severe withdrawal symptoms and more adverse effects (principally hypotension) although none of these data were gathered from a critically ill population[59].

Antidepressant withdrawal

Withdrawal reactions from tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRI's) and serotonin and noradrenaline reuptake inhibitors (SNRI's) are well described in the literature[60].

Table 6. Features of antidepressant withdrawal (Adapted from Reference 60)

Tricyclic antidepressants	SSRI's / SNRI's antidepressants
Abdominal Pain	Dizziness
Nausea and vomiting	Nausea
Diarrhoea	Lethargy
'Flu-like symptoms	Headache
Fatigue	Anxiety
Anxiety	'Electric shock-like' sensations
Agitation	Balance problems
Nightmares	Tremor
Sleep disturbance	Sweating
Movement disorders	Insomnia
	Nightmares

Symptoms occur typically within a few days of cessation of therapy and last a few weeks, or longer.

Prompt continuation of antidepressant therapy is important. Where enteral absorption is problematic, alternative methods of administration for some agents can be attempted. Where antidepressants cannot be continued, treatment is supportive. Anticholinergics have been given for tricyclic antidepressant withdrawal[61,62].

Tricyclic antidepressants

Amitriptyline has been given to a patient with short gut syndrome[63]. The patient was instructed to crush the tablets and let them dissolve in the mouth to facilitate buccal absorption, although there may also have been some absorption from the short gastro-intestinal tract when saliva was swallowed. The dose given was guided by therapeutic drug monitoring and was quite variable. Monitoring is unlikely to be available in many centres, but where withdrawal reactions are severe, consideration could be given to buccal dosing.

Amitriptyline has also been given rectally (50mg twice daily in a cocoa butter vehicle) with clinical improvement, but without serum monitoring[64].

Selective serotonin reuptake inhibitors (SSRI's)

SSRI's with short half-lives (such as paroxetine) appear to generate more severe withdrawal symptoms and with a higher incidence than SSRI's with long half-lives (such as fluoxetine). The emergence of withdrawal reactions may be delayed in patients receiving SSRI's with long half-lives.

Risk of bleeding is higher in patients receiving SSRI's both in terms of increased incidence of gastro-intestinal bleeding and through a probable anticoagulant effect via platelet inhibition[65, 66]. Such risks must be balanced against the potential for withdrawal reactions when considering ongoing therapy.

Citalopram infusion is available on mainland Europe and licensed within the UK. It can be obtained directly from the manufacturer, with a few days lead-time.

Fluoxetine capsules have been administered to healthy volunteers via the rectal route. In the study, fluoxetine capsules given rectally were found to have approximately 15% of the bioavailability of capsule given orally[67].

Monoamine oxidase inhibitors

Monoamine oxidase inhibitor withdrawal is treated symptomatically with an antipsychotic such as haloperidol[68].

Alcohol withdrawal delirium

Alcohol dependence is relatively common and patients presenting to critical care may experience alcohol withdrawal syndromes, including alcohol withdrawal delirium. Such syndromes may substantially complicate the management of critically ill patients. Symptoms of alcohol withdrawal delirium can occur rapidly after cessation of alcohol intake, but typically take two to three days to develop and last for a further two to three days or occasionally longer. Diagnostic criteria have been published to aid the diagnosis of Alcohol Withdrawal and Alcohol Withdrawal Delirium[37]

Table 7. DSM-IV Diagnostic criteria for alcohol withdrawal and alcohol withdrawal delirium (Adapted from reference 37)

	Alcohol Withdrawal
A	Cessation of (or reduction in) alcohol use that has been heavy and prolonged
B	Two (or more) of the following developing within several hours to a few days after criterion A: 1. Autonomic hyperactivity (eg sweating or pulse rate >100/min) 2. Increased hand tremor 3. Insomnia 4. Nausea or vomiting 5. Transient visual, tactile, or auditory hallucinations or illusions 6. Psychomotor agitation 7. Anxiety 8. Grand mal seizures
C	The symptoms in criterion B cause clinically significant distress or impairment in social, occupational or other important areas of function
D	The symptoms are not due to a general medical condition and are not better accounted for by another mental disorder
	Alcohol Withdrawal Delirium
A	Disturbances of consciousness (reduced clarity of awareness of environment), with reduced ability to focus, sustain or shift attention
B	A change in cognition (such as memory deficit, disorientation or language disturbance) or the development of a perceptual disturbance that is not better accounted for by a pre-existing, established or evolving dementia
C	The disturbance develops in a short period (usually hours to days) and tends to fluctuate during the day
D	There is evidence from the history, physical examination or laboratory findings that the symptoms in criteria A and B developed during or shortly after a withdrawal syndrome

Treatment of alcohol withdrawal delirium should be primarily with sedative hypnotics. In both alcohol withdrawal and alcohol withdrawal delirium, treatment with sedative hypnotics is associated with improved outcome in terms of mortality, duration of symptoms and complication rates when compared with other treatment options, such as neuroleptics[37, 69].

There is no evidence of superiority of one particular sedative-hypnotic over any other. There are case reports that show switching sedative-hypnotic class can be beneficial when patient's symptoms are refractory to treatment with large sedative doses. Differences in the mechanism of action of benzodiazepines, barbiturates and propofol may explain this.

In alcohol withdrawal, shorter acting agents are associated with a higher incidence of rebound effects when compared with longer acting agents, although no evidence is available to show whether the same is true for alcohol withdrawal delirium.

A variety of withdrawal regimes based on enteral or parenteral benzodiazepine administration exist. In general, all benzodiazepines appear to be equally efficacious in the treatment of alcohol withdrawal. Longer acting agents are non-significantly more efficacious in preventing seizures and shorter acting agents are thought to be associated with less oversedation[69]. Additional considerations for the critically ill population include the requirement for a variety of presentations to cater for the available administration routes. The potential of benzodiazepines to contribute to the formation of delirium has not been studied in this group of patients, but given the association of diazepam and chlordiazepoxide with the formation of delirium (See table 2), the use of lorazepam in patients deemed to be at high risk of delirium seems reasonable.

Lorazepam (Parenteral) [37]
Lorazepam 1-4mg intravenously every 5 to 15 minutes until calm (or 1-4mg intramuscularly every 30 to 60 minutes until calm), then every hour to maintain light somnolence.

Lorazepam (Enteral) [69]
Lorazepam 2mg every six hours for 4 doses, then 1mg every 6 hours for 8 doses. Additional doses can be given when required if needed for poorly controlled symptoms

Alternative sedatives such as propofol and barbiturates may be beneficial if the patient remains refractory to treatment.

Adjuncts
Neuroleptic agents are not recommended as the sole pharmacological agent for the treatment of alcohol withdrawal delirium. They may be useful as adjunct therapy when agitation, perceptual disturbances or disturbed thinking are not adequately controlled by sedative hypnotics.

Example neuroleptic regimes: -
Haloperidol 0.5 to 5mg intravenously/intramuscularly every 30 to 60 minutes as required
Haloperidol 0.5 to 5mg orally every 4 hours as required

Thiamine 100mg orally or intravenously should be given daily for at least three days to prevent the development of Wernicke-Korsakoff syndrome. Pabrinex is often used and contains 250mg thiamine per dose. Higher doses are needed in established Wernicke's encephalopathy.

Other therapies such as propranolol, magnesium, ethanol and clonidine have little evidence base with respect to alcohol withdrawal delirium and are not recommended[37]. Clonidine may still have a role in alcohol withdrawal without delirium.

Nicotine withdrawal

Sudden abstinence from tobacco can result in a variety of physiological and psychological symptoms that may tax the resolve of the most committed smoking quitter and the major features of this are summarised in Table 8[70-72].

Table 8. Features of tobacco withdrawal

Signs and Symptoms	
Bradycardia	Anger
Irritability	Difficulty concentrating
Anxiety	Increased appetite
Dysphoria	Impatience
Depressed mood	Craving
Slowed cognition	Constipation
Sleep disruption	Increased sensitivity to pain

Enforced tobacco abstinence as a result of a hospital admission may result in withdrawal reactions, the severity of which is related to the patient's usual level of tobacco use. The commonest form of tobacco use is through smoking, although other methods of use, known generically as “smokeless tobacco”, may also have been employed (e.g. snorting snuff and chewing leaf tobacco).

Nicotine replacement

A large evidence base exists supporting the use of nicotine substitutes to help patients to stop smoking. A mainstay of this approach is the active participation of the patient who must be committed to the goal of quitting. Some evidence exists that following up patients who are forced to quit because of an intensive care admission helps to maintain tobacco abstinence[73].

The evidence base for the use of nicotine replacement therapy on the critical care unit is extremely limited. A case series from a neuro-intensive care unit describes 5 patients with a history of tobacco use who developed delirium refractory to usual therapy[74]. Delirium resolved in all cases within 6 hours of the application of a 21mg nicotine patch. The authors call for a larger trial to demonstrate the efficacy and safety of the approach, specifically noting that nicotine (separate from smoking) has been shown to increase the thrombogenic potential of the cerebral endothelium. An additional study confirming the thrombogenic effect of nicotine and its metabolites has also been reported[75].

One further case report has been published outlining the use of a nicotine patch in an agitated patient with a strong history of smoking and alcohol intake, although the simultaneous commencement of intravenous multivitamins may have contributed to the patients improvement[76].

Given the clear somatic symptoms experienced by patients with a strong history of smoking in the context of a poor evidence base, it is prudent to consider nicotine replacement therapy after all other potential factors have been either identified and treated or discounted, and where the thrombosis risk is accepted.

A variety of nicotine presentations are available, patches are the most appropriate form to use in critically ill patients. Typically higher strength patches should be used, reflecting the probability of heavy smokers being more likely to be treated following a robust selection process. Consideration should be given as to how the patient will be managed when they leave critical care.

Clonidine

Oral or transdermal clonidine has been used in several studies examining its effect on smoking cessation rates. These have been reviewed by the Cochrane Collaboration, which recommends clonidine as a second line agent after nicotine predominantly because of the side effect profile of the drug[77]. The review finds that clonidine may be useful where it can treat more than one condition, or where the withdrawal from nicotine is intense. It may be particularly useful if the smoker experiences extreme agitation or anxiety unrelieved by nicotine replacement therapy, and the review suggests that clonidine can be substituted for or added to nicotine replacement therapy in this situation. The use of intravenous clonidine has not been studied for this indication.

100 micrograms of clonidine should be given enterally twice daily, titrating up to 400micrograms per day as tolerated. Transdermal clonidine is available on a named patient basis. Clonidine may be

required for several days to four weeks. The dose should be tapered off slowly over several days at the end of treatment to avoid rebound effects on blood pressure and glycaemic control. Treatment should not extend beyond about 4 weeks, as this is the recognised limit of acute nicotine withdrawal syndromes.

Withdrawal from recreational drugs.

The critically ill patient may have been taking recreational agents prior to their hospital admission. Sudden cessation of these agents can precipitate withdrawal reactions and may be the primary reason for the patient's state of delirium in critical care. There is a range of recreational drugs available and these may be classified under eight subgroups (Table 9.)[78].

Table 9. Recreational drugs by subgroup

- *Anticholinergics*
  - -Hyoscine
  - -Diphenhydramine
  - -Hydroxyzine
- *Psychedelics*
  - -3,4-methylenedioxy-methamphetamine (MDMA, ecstasy, adam)
  - -Lysergic acid diethylamide (LSD, blotter)
  - -Psilocybin (magic mushrooms)
- *Stimulants*
  - -Amphetamine (hearts, speed, crystal)
  - -Cocaine (crack, coke)
  - -Methylphenidate (White dragon)
- *Cannabinoids*
  - -Marijuana
  - -Hashish (hash, grass)
- *Opioids /Narcotics*
  - -Heroin (china cat, skag)
  - -Fentanyl (STP, six pack)
  - -Methadone (orange barrel, dolphin)
  - -Opium (dust)
- *Mixtures*
  - -Amphetamine + barbiturates (French blue)
  - -Cocaine + heroin (Speed ball)
  - -Cocaine + phencyclidine (Space base)
  - -Opioid + marijuana (PJ)
- *Dissociatives*
  - -Ketamine (K-hole, vitamin K)
  - -Phencyclidine (PCP, angel)
- *Sedative hypnotics*
  - -Alcohol
  - -Barbiturates (ace, yellow jackets)
  - -Benzodiazepines (Pumpkin seeds, roches)
  - -Rohypnol (rib, date pill)

The general consensus from the literature suggests treatment as follows[27, 53, 79-83]:

Anticholinergics: No adjuncts available, treatment is supportive.
Cannabinoids: No adjuncts available, treatment is supportive.
Dissociatives: Try benzodiazepines and wean as necessary. Avoid phenothiazines, but may try olanzapine.
Psychedelics: Psychological dependence may result in insomnia and so may require treatment with benzodiazepines, weaning as necessary.
Sedative hypnotics: See page 13.
Opioids / Narcotics: See page 14.
Stimulants: Major physical withdrawal reactions are unlikely. Try benzodiazepines for insomnia and wean as necessary. Other strategies include the use of tricyclic antidepressants, clonidine, carbamazepine, bromocriptine and amantadine, however there is no evidence supporting the use of any of these.

There are only very limited references to the treatment of psychosis as a result of withdrawal to these drugs in the critical care setting. As a result the majority of references used are from general medical and psychiatry journals and do not consider psychoses in the critically ill. In fact the vast majority of withdrawal programmes depend purely on counselling.

Consensus of clinical opinion would suggest weaning with benzodiazepines, and adding in adjunctive clonidine where recreational drugs are suspected. This may be done as an infusion of 0-90micrograms/hour (unlicensed), titrated on an individual patient basis in increments of 15-30micrograms/hour. Higher infusion rates may be occasionally required, although hypotension frequently limits usefulness.

Treatment Summary

All Patients

Use a delirium screening tool

Use a delirium screening tool in all patients throughout their critical care stay in addition to other routine monitoring (such as sedation score, pain score, etc).

Maintain a high index of suspicion for delirium.

Rule out differential diagnoses.

Treat contributing factors.

Prevention is better than cure

Provide the following in all patients: -

Non-pharmacologic interventions

Psychological support and orientation
Unambiguous environment
Maintain competence.
Remove potential organic drivers

Pharmacologic interventions

Avoid drugs with antimuscarinic activity wherever possible.
Avoid drugs that affect sleep patterns wherever possible.
Alleviate predisposing factors for delirium.

Delirious Patients

General Delirium

Mild Symptoms

1st Line
Haloperidol 2-5mg enterally three to four times daily, titrating to symptoms.

2nd Line
Olanzapine 5mg enterally daily in patients unable to tolerate haloperidol (e.g. Parkinson's Disease).

Moderate-Severe Symptoms

1st Line
Haloperidol 0.5mg-10mg intravenously (dose depending on clinical parameters). Double the dose if the patient remains unmanageable after 20-30 minutes with no adverse effects, repeating as necessary. Convert to a regular dosing schedule when control is established.

2nd Line
Continuous infusions of Haloperidol 5-10mg/hour may be required in extreme circumstances.

3rd Line
Olanzapine 2.5-10mg intramuscular injection, repeated after 2 hours if necessary in patients unable to tolerate haloperidol (e.g. Parkinson's Disease).

Adjunct Therapies

Dangerous Motor Activity
Midazolam 5-10mg intravenously every 2-3 minutes until the patient is calm (or 5mg intramuscularly every 15 minutes if the intravenous route is not available). Titrate the dose as required.

Hypoactive Delirium
Consider 10-30mg methylphenidate daily in divided doses in addition to normal therapy if not responding.
Titrate to maximum 50mg daily in divided doses if required.

Night Sedation
50mg trazadone enterally at night for seven days
or
2-5mg haloperidol intravenously at night

Withdrawal Delirium

Benzodiazepines
Start a benzodiazepine and titrate to the minimum effective dose given by an appropriate route of administration. Taper the dose over days to weeks. Long acting benzodiazepines such as lorazepam can be utilised to facilitate tapering regimes.

Opioids
Start an opioid and titrate to the minimum effective dose given by an appropriate route of administration. Taper the dose over days to weeks. Long acting opioids such as methadone can be utilised to facilitate tapering regimes.
Clonidine has also been used, although side effects may limit usefulness.

Antidepressants
Restart usual medication as soon as possible.
Where this is not possible, consider using the intravenous, buccal or rectal routes if available.
Treat symptomatically if no alternative route available.

Ethanol
Use a benzodiazepine first line titrating to the minimum effective dose. Taper the dose over several days.
Clonidine cannot be recommended, as there is no evidence to support its use in alcohol withdrawal delirium.

Nicotine
Weak evidence exists for the use of nicotine replacement therapy given as a patch where the patient has a history of heavy tobacco use.
Enteral clonidine has some evidence base for treating nicotine withdrawal. Clonidine and nicotine replacement may be used together if the withdrawal reaction is particularly intense.

Other Illicit Drugs
Consensus suggests weaning with benzodiazepines with an adjunctive clonidine infusion where necessary. Where the drug of abuse is known, specific advice may be found in the main text.

References

1. Ely EW et al. Delirium as a predictor of mortality in mechanically ventilated patients in the intensive care unit. JAMA 2004; 291: 1753-62.
2. Ely EW et al. The impact of delirium in the intensive care unit on hospital length of stay. Intensive Care Med 2001; 27:1892-1900.
3. Jackson JC et al. Six month neuropsychological outcome of medical intensive care patients. Crit Care Med 2003; 31: 1226-34.
4. Milbrandt EB et al. Costs Associated with Delirium in Mechanically Ventilated Patients. Crit Care Med 2004; 32: 955-962, 2004.
5. Management of the agitated intensive care unit patient. Critical Care Medicine 2002 30(1 2)(Suppl): S97-S123
6. Jacobi J et al. Clinical practice guidelines for the sustained use of sedatives and analgesics in the critically ill adult. Crit Care Med 2002; 30: 119-41
7. Meagher DJ, Trzepacz PT Motoric Subtypes of Delirium Semin Clin Neuropsychiatry 2000; **5** (2): 75-85
8. Nicholas LM, Lindsey BA Delirium presenting with symptoms of depression Psychosomatics 1995 36: 471-479
9. Justic M Does “ICU psychosis” really exist? Crit Care Nurse 2000; 20:28-37
10. Lundstrom M, Edlund A, Karlsson S *et al* A multifactorial intervention program reduces the duration of delirium, length of hospitalisation and mortality in delirious patients J Am Geriatr Soc 2005; 53: 622-628
11. Milbrandt EB, Kersten A, Kong L *et al* Haloperidol use is associated with lower hospital mortality in mechanically ventilated patients Crit Care Med 2005; 33(1): 226 – 229
12. Centeno C, Sanz A, Bruera E Delirium in advanced cancer patients Palliative Medicine 2004; 18: 184-194
13. Jones C, Griffiths RD, Humphris G Disturbed memory and amnesia related to intensive care. Memory 2000, 8(2): 79-94
14. Riker RR, Picard JT, Fraser GL Prospective evaluation of the Sedation-Agitation Scale for adult critically ill patients Crit Care Med 1999; 27: 1325-1329
15. Sessler CN *et al*. The Richmond Agitation-Sedation Scale: validity and reliability in adult intensive care patients. Am J Respir Crit Care Med 2002; 166: 1338-1344
16. Devlin JW, Boleski G, Mlynarek M *et al* Motor activity assessment scale: A valid and reliable sedation scale for use with mechanically ventilated patients in an adult surgical intensive care unit Crit Care Med 1999; 27: 1271-1275
17. Bergeron N *et al*. Intensive Care Delirium Screening Checklist: evaluation of a new screening tool. Intensive Care Med 1993; 60: 356-60
18. Otter H, Martin J, Basell K *et al* Validity and reliability of the DDS for severity of delirium in the ICU Neurocritical Care 2005; 2: 150-158
19. Ely EW *et al*. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA 2001; 286: 2701-2710
20. Meagher DJ. Delirium: optimising management. BMJ 2001; 322: 144-9
21. P. Skirrow, C. Jones, Griffiths RD, Kaney S. The impact of current media events on hallucinatory content: The experience of the intensive care unit (ICU) patient. British Journal of Clinical Psychology 2002;41:87-91
22. Tune LE and Bylsma FW. Benzodiazepine-induced and anticholinergic-induced delirium in the elderly. Int Psychogeriatrics 1991; 3: 397-408
23. Han L *et al*. Use of medications with anticholinergic effect predicts clinical severity of delirium symptoms in older medical inpatients. Arch Intern Med 2001; 161: 1099-1105
24. Bourne RS and Mills GH. Sleep disruption in critically ill patients - pharmacological considerations. Anaesthesia 2004; 59: 374-84
25. Brown TM. Drug-induced delirium. Sem Clin Neuropsychiatry 2000; 5: 113-24.
26. Bray K, Hill K, Robson W *et* al British Association of Critical Care Nurses position statement on the use of restraint in adult critical care units Nursing in critical care 2004; 9: 199-211
27. Practice guideline for the treatment of patients with delirium Am J Psychiatry 1999; 156: 1-20
28. Kapur S, Remington G, Jones C *et al* High levels of Dopamine D_2 receptor occupancy with low-dose haloperidol treatment: A PET study Am J Psychiatry 1996; 153 (7): 948-950

29. Farde L, Nordstrom AL, Weisel FA *et al* Positron emission tomographic analysis of central D_1 and D_2 dopamine receptor occupancy in patients treated with classical neuroleptics and clozapine: Relation to extrapyramidal side effects Arch Gen Psychiatry 1992; 49: 538-544
30. Practice guideline for the treatment of patients with delirium Am J Psychiatry 1999; 156: 1-20
31. Seneff MG, Mathews RA Use of haloperidol infusions to control delirium in critically ill adults Ann Pharmacother 1995; 29: 690-693
32. Procyclidine Hydrochloride, Martindale 34th Edition, p488. Pharmaceutical Press 2005 ISBN 0-85369-550-4
33. Breitbart W, Marotta R, MM Platt *et al* A double blind trial of haloperidol, chlorpromazine and lorazepam in the treatment of delirium in hospitalized AIDS patients Am J Psychiatry 1996; 153: 231-237
34. AHFS drug information 2006 28:16.08.25 p2393, ISBN 1-58528-142-5
35. Martindale 34th edition, 2005 Pharmaceutical Press, p701.3, ISBN 0-85369-550-4
36. L Caeiro; JM Ferro; MI Claro; J *et al* Delirium in acute stroke: a preliminary study of the role of anticholinergic medications European Journal of Neurology 2004 11: 699-704
37. Mayo-Smith MF, Beecher LH, Fischer TL *et al* Management of Alcohol Withdrawal Delirium: An evidence based practice guideline Arch Intern Med 2004; 164: 1405-1412
38. Violence: The short-term management of disturbed/violent behaviour in psychiatric in-patient settings and emergency departments, Clinical Guideline 25, 2005 National Institute for Clinical Excellance
39. Skrobik Y, Bergeron N, Dumont M, Gottfried S Olanzapine vs Haloperidol: treating delirium in a critical care setting Intensive Care Med 2004; 30:444-449
40. Anand HS Olanzapine in an intensive care unit Canadian Journal of Psychiatry 1999; 44 (4): 397
41. Chairman - Committee on Safety of Medicines (2004) "Atypical antipsychotic drugs and stroke" CEM/CMO/2004/1, http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/antipsystoke_9304.pdf (accessed 27/08/2004)
42. Marcantonio ER, Juarez G, Goldman L *et al* The relationship of postoperative- delirium with psychoactive medications JAMA 1994; 272: 1518-1522
43. Nobay F, Simon BC, Levitt MA A prospective, double-blind randomised trial of midazolam versus haloperidol versus lorazepam in the chemical restraint of violent and severely agitated patients Academic Emergency Medicine 2004; 11: 744-749
44. Gehlbach, BK; Kress JP Sedation in the intensive care unit. Current Opinion in Critical Care 2002; 8: 290-298
45. Andrew MK, Freter SH, Rockwood K Incomplete functional recovery after delirium in elderly people: a prospective cohort study. BMC Geriatrics 2005; 5: 5
46. Breitbart W, Tremblay A, Gibson C An open trial of olanzapine for the treatment of delirium in hospitalized cancer patients Psychosomatics 2002; 43: 175-182
47. Gagnon B, Low G, Schreier G Methylphenidate hydrochloride improves cognitive function in patients with advanced cancer and hypoactive delirium: a prospective clinical study Rev Psychiatr Neurosci 2005, 30: 100-107
48. Technology Appraisal 77 Guidance on the use of zaleplon, zolpidem and zopiclone for the short-term management of insomnia. National Institute for Clinical Excellence, April 2004
49. Ware C, Pittard J Increased deep sleep after trazodone use: a double-blind placebo-controlled study in healthy young adults. Journal of Clinical Psychiatry 1990; 51, 18-22
50. Yamashita H *et al*. Effect of risperidone on sleep in schizophrenia: a comparison with haloperidol. Psychiatry Research 2002; 109: 137-42
51. Zapantis A and Leung S Tolerance and withdrawal issues with sedation Crit Care Nurs Clin N Am 2005, 17: 211-223
52. Cammarano WB, Pittet JF, Weitz S *et al* Acute withdrawal syndrome related to the administration of analgesic and sedative medications in adult intensive care patients Critical Care Medicine 1998; 26(4): 676-684
53. CR81. Substance misuse detainees in police custody The Royal College of Psychiatrists 2001, URL: http://www.rcpsych.ac.uk/publications/cr/council/cr81.pdf (accessed 05/09/2005)
54. Tobias JD Tolerance, withdrawal and physical dependency after long term sedation and analgesia of children in the paediatric intensive care unit Crit Care Med 2000; 28: 2122-2132
55. Dunne T, Egan A Local ICU protocol for sedation weaning in difficult patients, Manchester Royal Infirmary, Manchester
56. Gelman CR, Rumack BH, Hess AJ (eds) Drugdex, Micromedex Inc, Englewood, Colorado, USA. Vol 128 (Expires June 2006)

57. Ashton CH, The treatment of benzodiazepine dependence. Addiction 1994; 89: 1535-1541
58. Morley J and Makin M The use of methadone in cancer pain poorly responsive to other opioids Pain Reviews 1998; 5: 51-58
59. Gowing OL, Farrell M, Ali R, White J Alpha2 adrenergic agonists for the management of opioid withdrawal. The Cochrane Database of Systematic Reviews 2004, Issue 4 Art. No.: CD002024.pub2.
60. Withdrawing patients from antidepressants Drug and Therapeutics Bulletin 1999; 37: 49-52
61. Dilsaver SC, Feinberg M, Greden JF Antidepressant withdrawal symptoms treated with anticholinergic agents Am J Psychiatry 1983; 140 (2): 249-251
62. Dilsaver SC, Kronfol Z, Greden JF *et al* Antidepressant withdrawal syndromes: Evidences supporting the cholinergic overdrive hypothesis J Clin Psychopharmacol 1983; 3:157-164
63. Robbins B, Reiss RA Amitriptyline absorption in a patient with short bowel syndrome Am J Gastroenterol 1999 Aug; 94 (8): 2302-2304
64. Adams F Amitriptyline Suppositories NEJM 1982; 306: 996
65. Do SSRI's cause gastrointestinal bleeding? Drug and Therapeutics Bulletin 2004; 42: 17-18
66. Movig KL, Janssen MW, de Waal Malefijt J Relationship of serotonergic antidepressants and need for blood transfusion in orthopaedic surgical patients Arch Intern Med. 2003 Oct 27;163(19):2354-8
67. Teter CJ, Phan KL, Cameron OG *et al* Relative rectal bioavailability of fluoxetine in normal volunteers Journal of Clinical Psychopharmacology 2005; 25: 74-78
68. Haddad P Antidepressant discontinuation syndromes: Clinical relevance, prevention and management Drug Safety 2001; 24: 183-197
69. American Society of Addiction Medicine Working Group on Pharmacological Management of Alcohol Withdrawal Mayo-Smith MF, Cushman P, Hill AJ, *et al* Pharmacological management of alcohol withdrawal: A meta-analysis and evidence based guideline JAMA 1997; 278: 144-151
70. Hughes JR, Gust SW, Skoog K *et al* Symptoms of tobacco withdrawal: a replication and extension Arch Gen Psychiatry 1991; 48: 52-59
71. Creekmore FM, Lugo RA, Weiland KJ Postoperative opiate requirements of smokers and nonsmokers Ann Pharmacother 2004; 38: 949-953
72. Hajek P, Gillison F, McRobbie H Stopping smoking can cause constipation Addiction 2003; 98: 1563
73. Jones C, Griffiths RD, Skirrow P, Humphris G Smoking cessation through comprehensive critical care Intensive Care Med 2001 27; 1547-1549
74. Mayer SA, Chong JY, Ridgeway E *et al* Delirium from nicotine withdrawal in neuro-ICU patients Neurology 2001; 57: 551-553
75. Hioki Y, Aoki N, Kawano K *et al* Acute effects of cigarette smoking on platelet-dependant thrombin generation Eur Heart J 2001; 22: 56-61
76. Honisett TD Nicotine replacement therapy for smokers admitted to intensive care Intensive and Critical Care Nursing 2001; 17: 318-321
77. Gourley SG, Stead LF, Benowitz NL Clonidine for smoking cessation (Review) 2004 The Cochrane Database of Systematic Reviews Issue 3. Art. No.:CD000058.pub2
78. Alberta college of paramedics 2001 URL: http://www.collegeofparamedics.org/con_ed/2001/streetdrugs.htm (accessed 05/09/2005)
79. Zimmerman JL Poisonings and overdoses in the intensive care unit: General and specific management issues Crit Care Med 2003; 31(12) 2794-2801
80. Thompson JP Acute effects of drugs of abuse Clin Med 2003; 3: 123-126
81. Giannini AJ An approach to drug abuse, intoxication and withdrawal American Family Physician 2000 May 1; 61: 2763-2774
82. Khouzam HR Helping your patients beat cocaine addiction: The four dimensions of treatment Postgraduate Medicine 1999;105(3): 185-191
83. Substance Use Related Disorders and Treatment URL: http://www.psychiacomp.com/didactic/substance-treatment.php (accessed 01/02/2005)

Appendix

CAM-ICU Delirium Screening Tool [19]

Linking Sedation and Delirium Monitoring: A Two Step Approach to Assess Consciousness

Step One: Sedation Assessment

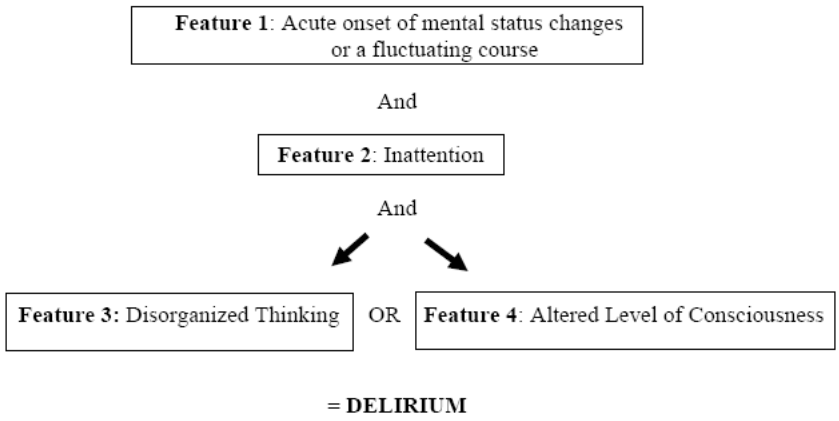
The Richmond Agitation and Sedation Scale: The RASS*

Score	Term	Description	
+4	Combative	Overtly 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 vigorous	
0	Alert and calm		
-1	Drowsy	Not fully alert, but has sustained awakening (eye-opening/eye contact) to *voice* **(≥10 seconds)**	Verbal Stimulation
-2	Light sedation	Briefly awakens with eye contact to *voice* **(<10 seconds)**	Verbal Stimulation
-3	Moderate sedation	Movement or eye opening to *voice* **(but no eye contact)**	Verbal Stimulation
-4	Deep sedation	No response to voice, but movement or eye opening to *physical* stimulation	Physical Stimulation
-5	Unarousable	No response to *voice or physical* stimulation	Physical Stimulation

If RASS is -4 or -5, then **Stop** and **Reassess** patient at later time
If RASS is above - 4 (-3 through +4) then **Proceed to Step 2**

*Sessler, et al. AJRCCM 2002; 166:1338-1344.
*Ely, et al. JAMA 2003; 289:2983-2991.

Step Two: Delirium Assessment



CAM-ICU Features and Descriptions

1. Acute Onset or Fluctuating Course	Absent	Present

A. Is there evidence of an acute change in mental status from the baseline?

OR

B. Did the (abnormal) behavior fluctuate during the past 24 hours, that is, tend to come and go, or increase and decrease in severity as evidenced by fluctuation on a sedation scale (e.g. RASS), GCS, or previous delirium assessment?

2. Inattention	Absent	Present

Did the patient have difficulty focusing attention as evidenced by **scores *less than 8*** on either the auditory or visual component of the **Attention Screening Examination (ASE)**? (Instructions on next page).

3. Disorganized Thinking	Absent	Present

Is there evidence of disorganized or incoherent thinking as evidenced by **incorrect answers to 2 or more of the 4 questions and/or inability to follow the commands**?

Questions (Alternate Set A and Set B):

Set A	Set B
1. Will a stone float on water?	1. Will a leaf float on water?
2. Are there fish in the sea?	2. Are there elephants in the sea?
3. Does one pound weigh more than two pounds?	3. Do two pounds weigh more than one pound?
4. Can you use a hammer to pound a nail?	4. Can you use a hammer to cut wood?

Other:

1. Are you having any unclear thinking?
2. Hold up this many fingers. (Examiner holds two fingers in front of patient)
3. Now do the same thing with the other hand. (Not repeating the number of fingers)

4. Altered Level of Consciousness	Absent	Present

Is the patient's level of consciousness anything *other than alert* such as vigilant, lethargic, or stupor? (e.g., RASS other than "0" at time of assessment)

Alert	spontaneously fully aware of environment and interacts appropriately
Vigilant	hyperalert
Lethargic	drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
Stupor	becomes incompletely aware when prodded strongly; can be aroused only by vigorous and repeated stimuli, and as soon as the stimulus ceases, stuporous subject lapse back into the unresponsive state

Overall CAM-ICU (Features 1 and 2 and either Feature 3 or 4):	Yes	No

The Attention Screening Examination (ASE) – Auditory and Visual

A. Auditory (Letter) ASE

Directions: Say to the patient, "I am going to read you a series of 10 letters. Whenever you hear the letter 'A,' indicate by squeezing my hand." Read the following 10 letters in a normal tone (loud enough to be heard over the noise of the ICU) at a rate of one letter per second.

S A H E V A A R A T

Scoring: Errors are counted when patient fails to squeeze on the letter "A" and when the patient squeezes on any letter other than "A."

B. Visual (Picture) ASE

*** * See following Picture Packets (A and B) * ***

Step 1: 5 pictures

Directions: Say to the patient, "Mr. or Mrs. _____, I am going to show you pictures of some common objects. Watch carefully and try to remember each picture because I will ask what pictures you have seen." Then show Step 1 of either Packet A or Packet B, alternating daily if repeat measures are taken. Show the first 5 pictures for 3 seconds each.

Step 2: 10 pictures

Directions: Say to the patient, "Now I am going to show you some more pictures. Some of these you have already seen and some are new. Let me know whether or not you saw the picture before by nodding your head yes (demonstrate) or no (demonstrate)." Then show 10 pictures (5 new 5 repeat) for 3 seconds each (Step 2 of Packet A or B, depending upon which form was used in Step 1 above).

Scoring: This test is scored by the number of correct "yes" or "no" answers during the second step (out of a possible 10). In order to improve the visibility for elderly patients, the images are printed on 6"x10" buff colored paper and laminated with a matte finish.

Note: If a patient wears glasses make sure he/she has them on when attempting the Visual ASE.

References:

Ely, E.W., Inouye, S., Bernard G., Gordon, S., Francis, J., May, L., Truman, B., Speroff, T., Gautam, S., Margolin, R, Dittus, R. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). JAMA; 286, 2703-2710, 2001.

Ely, E.W., Margolin, R., Francis, J., May, L., Truman, B., Dittus, B., Speroff, T., Gautam, S., Bernard, G., Inouye, S. Evaluation of delirium in critically ill patients: Validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). Critical Care Medicine. 29:1370-1379, 2001.

Visual ASE - Packet A

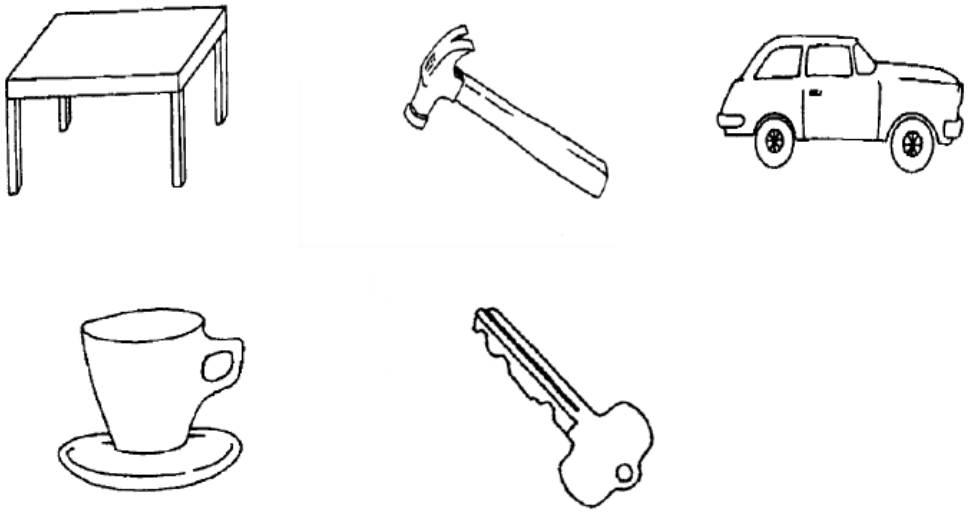
Step 1

Visual ASE - Packet A

Step 2

Visual ASE - Packet B

Step 1



Visual ASE - Packet B

Step 2