Delirium and sleep disturbances in critical care — pharmacological management

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Acknowledgements - Dr. R Bourne (Clinical pharmacist, STH NHS Foundation trust)
(Elements of this guideline are derived from STH NHS Foundation trust guidelines.)
Pharmacological management of delirium

Background

Delirium is acute brain failure in critical care patients secondary to systemic disease. It is very common, occurring in up to 80% of mechanically ventilated patients during the course of their illness. It contributes to increased patient morbidity and mortality, which persists even after patients have been discharged from hospital. Three motor subtypes exist - hypoactive, hyperactive and mixed types. The hypoactive form is the most common subtype and is often missed, or misdiagnosed.

All patients in ICU are at a high risk of developing delirium and therefore should be screened for delirium frequently (once every shift, or sooner if suspected). A daily checklist should be filled out to address all the precipitating and augmenting factors. In addition to prevention and non-pharmacological techniques appropriate drug management is an important adjunct in management of patients with delirium. Drug treatment should be considered when other non-pharmacological measures have failed or patient has distressing symptoms. Patients may be screened for the presence of delirium using tools such as the Confusion Assessment Method (CAM), a specific screening tool has been developed for use on critical care which is called CAM ICU. NICE recommend the use of CAM ICU, the flow chart can been found at: www.icudelirium.org. Nursing staff on critical care will be trained in the use of CAM ICU and will assess all patients daily. It should be noted that CAM-ICU is only 70% sensitive and delirium is fluctuant so that even patients with troublesome delirium can have lucid intervals. Therefore screening should be carried out several times a day, but a clinical suspicion of delirium should be trusted more than a single test which is known to have a significant false negative rate.

Regular drug treatment should be commenced for patients who are CAM ICU positive and reviewed daily for efficacy and adverse effects. When delirium symptoms resolve, antipsychotic medication can be withdrawn over 48 to 72 hours. Only short treatment courses (less than a week) should be used.

The incidence of delirium is higher if benzodiazepines are used for sedation, and therefore their primary indication is treatment of withdrawal delirium e.g. alcohol withdrawal. However, they remain a treatment option in patients with severe hyperactive delirium who pose a risk to themselves and/or staff.

Sleep disturbances are often regarded as a precipitating factor for causing delirium, the cause and effect relationship is not straightforward and therefore delirium status should be accounted for when attempting to improve nocturnal sleep quantity in critical care patients. For this reason guidelines on the pharmacological management of delirium and sleep disorders are included in the same document.

Further information on the pharmacological management of delirium is also available from the following links:

NICE CG 103, Delirium- diagnosis, prevention and management
Vanderbilt University Medical Center delirium resource website
UK delirium resource website
CRITICAL CARE CLINICAL GUIDELINE

MANAGEMENT OF DELIRIUM

This guideline is a summary, full details are available from the SPC www.emc.medicines.org.uk

CAM-ICU Delirium Positive

- Review drug chart, try to minimise exposure to medication associated with delirium. Ensure all doses appropriate (e.g. penicillins reduce dose in renal failure). Prescribe alternative agents where possible to minimise anti-cholinergic activity.
- Treat pain, hypoxia, constipation, pyrexia. Correct sleep/wake cycle; avoid lights at night ensure light in day.
- Provide usual glasses, hearing aids, dentures if needed.
- Review environment: avoid excessive noise, consistency with designated nurse, familiar items from home, access to a clock, involve familiar to maximise feelings of security, optimise room temperature.
- Communicate clearly to patients: orientate patients to time, remind of day and location.

Hyperactive Delirium

First Line:
Haloperidol 1 to 2.5mg qds iv
Or
Haloperidol 2.5 to 5mg qds po AND PRN
Haloperidol 1 to 2.5mg to max total daily dose (including regular and PRN doses) of 30mg daily
Second Line:
Olanzapine 5mg nocte

Consider in addition if severe agitation (especially if poses risk to self or others).
Clonidine
Or
Benzodiazepine
Or
Low dose propofol

Hypoactive Delirium

First Line:
Haloperidol 0.5mg tds iv

Nicotine Withdrawal
- If clear symptoms of nicotine withdrawal consider starting NRT as per hospital guideline
- First choice NRT on critical care are nicotine patches.
- Start:
  - 25mg patch over 16 hours if smoke over 20 cigarettes per day
  - 15mg patch over 16 hours for patients who smoke under 20 cigarettes per day.
Patches should be applied at 6am and removed at 10pm
- 24 hour patches should be avoided where possible due to a higher incidence of delirium.
- Consider clonidine or haloperidol if severe agitation (especially if poses risk to self or others).

Withdrawal Delirium

Alcohol Withdrawal
- Chlordiazepoxide as per hospital pathway (not needed if on propofol)
- Pabrinex® 2 pairs tds for 72 hours
- Consider clonidine or haloperidol if severe agitation (especially if poses risk to self or others). Note clonidine will not prevent alcohol withdrawal seizures.

General Notes:
- All prescriptions for antipsychotics should be endorsed ‘delirium’ to aid review of therapy.
- Antipsychotics should be gradually withdrawn over 2 to 3 days when the patient is negative for delirium.
- Benzodiazepines are associated with delirium and so should be used as a last resort except in alcohol withdrawal.
- Risperidone may be considered third line if haloperidol and olanzapine have been tried unsuccessfully.
- Antipsychotics should be discontinued if a patient is fully sedated.
- Patients should not be prescribed more than one antipsychotic concomitantly.

References
www.emc.medicines.org.uk accessed 01/02/12

Delirium and Sleep Disturbances in Critical Care – Clinical Guideline V1. Principal author: Ms D Hughes (Pharmacist) Dr P Prashast (Consultant Intensivist)
Approved by Medicine Clinical Guidance Subcommittee Date: June 2012 Review Date: June 2015 Page 3 of 16
### Table 1: Drugs commonly associated with delirium

<table>
<thead>
<tr>
<th>Medication</th>
<th>Comments</th>
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</table>
| Anti-parkinsonian medication                    | • Review for excess anticholinergic/ dopamine activity  
  *e.g.* benztropine;  
  co-careldopa (Sinemet®);  
  rotigotine                                                                                     |
|                                                | • Discuss with neuromedical/ geriatric team acute management and consider benefits of temporarily reducing anticholinergic and dopaminergic medication |
| Benzodiazepines                                 | • When possible limit benzodiazepine use to cover benzodiazepine or alcohol withdrawal  
  • Review use as night-time sleep aid and consider trazodone/ mirtazapine (see Management of Sleep Disturbances section) |
| Beta-lactams                                    | • Review dose in severe renal dysfunction                                                       |
| *e.g.* meropenem; benzylpenicillin; Tazocin® (piperacillin-tazobactam) |                                                                                                  |
| Corticosteroids                                 | • Use lowest effective dose and discontinue as soon as clinically appropriate                   |
| Digoxin                                         | • Consider withholding digoxin, or alternative medication for heart rate control *e.g.* β-blocker/amiodarone |
| Lithium                                         | • Maintain plasma levels within lowest effective range.  
  • Maintain plasma levels within lowest effective range.                                          |
| Opioids                                         | • Attempt to optimise pain control with adjunctive opioid sparing agents  
  *e.g.* paracetamol; gabapentin; local anaesthetics; ketamine (low dose)  
  • Avoid accumulation of neurotoxic metabolites in patients with severe renal failure *e.g.* (morphine-3-glucuronide; norpethidine)  
  • Tramadol has significant serotonin activity, therefore review appropriateness of continued/ new therapy and consider alternative analgesia/ opioids |
| Phenobarbitone                                  | Maintain plasma levels within the therapeutic range                                               |
| Phenytoin                                       | Maintain plasma levels within the therapeutic range (account for albumin and “free drug” concentrations) |
| Quinolone antibiotics                           | • Review dose in severe renal dysfunction  
  *e.g.* ciprofloxacin                                                                 |• Discuss with microbiology if alternative antibiotic appropriate |
| Selective serotonin reuptake inhibitors (SSRIs) | • Review for other drugs with serotonin activity and risk of “serotonin syndrome”  
  *e.g.* fluoxetine; paroxetine                                                                 |• Consider withholding depending on clinical circumstances, balancing risk of withdrawal versus toxicity |

### Table 2: Commonly used medications with moderate to high anticholinergic activity

<table>
<thead>
<tr>
<th>Medication</th>
<th>Alternative</th>
</tr>
</thead>
</table>

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Amitriptyline
Chlorphenamine PO/ NG
Cyclizine IV
Digoxin
Hyoscine IV/ PO/ NG
Oxybutynin PO/ NG
Ranitidine IV/ PO/ NG
Trazodone / mirtazapine
Cetirizine PO/ NG
Ondansetron IV
Atenolol
Glycopyrrolate IV; Propantheline PO/ NG
Tolterodine PO/ NG
Pantoprazole IV; Lansoprazole PO/ NG

Pharmacological management of sleep disturbances

Background
Sleep disturbances in critical care patients are characterised by sleep fragmentation. Patients are often sleep deprived, the sleep tends to be fragmented. It is a problem of sleep continuity and results in reduced quantities of deeper sleep phases, such as slow wave sleep (SWS) and rapid eye movement sleep (REM). Sleep disturbances may contribute to patient morbidity including adverse consequences on respiratory, cardiac, neurological and immunological function.

Causes of sleep disturbances in critical care patients are multi-factorial and include: the environment (e.g. noise, light), pain, ventilator dys-synchrony, delirium, circadian rhythm disturbances and medication (e.g. opioids, benzodiazepines).

Treatment of sleep disturbances therefore should not solely rely on pharmacological treatment, but seek to identify sleep disturbing factors (e.g. pain) and correct them if possible. Sleep hygiene should be encouraged and targeted drug treatment employed only if necessary.

All new prescriptions for acute treatment should be endorsed “short-term sleep-aid” and reviewed prior to discharge for critical care.

Sleep hygiene
Sleep hygiene refers to attempts to make conditions suitable for sleep to occur.

- Encourage the patient to be active during the day, e.g. early morning physiotherapy, sitting out of bed, range of motion exercises. Try to avoid long naps later in the day as these reduce the normal sleep drive and reduce nocturnal sleep quality.
- Avoid caffeinated drinks (tea/ coffee) after 1800hours.
- Try to re-enforce a day-night cycle with bright lights during the day and lights off during the night.
CRITICAL CARE CLINICAL GUIDELINE

MANAGEMENT OF SLEEP DISTURBANCE

This guideline is a summary, full details are available from the SPC www.emc.medicines.org.uk

Review all patients who have inadequate sleep (less than 4 hours of continuous sleep or inability to sleep at night and excessive daytime drowsiness).

- **Reinforce sleep hygiene and sleep wake cycle**
  - Control excess noise at night
  - Bright light in daytime, darkness at night
  - Encourage regular morning wake up time
  - Control environmental temperature
  - Encourage range of motion exercises and activity e.g. patient sitting out
  - Ensure comfortable position
  - Avoid caffeine intake by patients in the evening

- **Review current medication.** Reduce/minimise disruptive medication. Consider withdrawal reactions

- **Review pain control.** Optimise non-opioid analgesia

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**Pharmacological Management**

**Delirium Status**

Following CAM-ICU Screening

- **Delirium Positive**
  - Treat according to delirium guidelines
  - If sleep disturbance still present
  - Trazodone 50mg nocte
  - Mirtazapine 15mg nocte is an alternative agent if not responding to trazodone

- **Delirium Negative**
  - Zopiclone 3.75mg to 7.5mg nocte
  - Trazodone 50mg nocte

**If the patient has a disruption in normal circadian rhythm and is falling asleep during the day but is awake at night consider starting Melatonin MR 2mg nocte**

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**References**

www.emc.medicines.org.uk accessed 01/02/12


(Consultant Intensivist)
References

HALOPERIDOL

1. Indication
Haloperidol is a 'typical' (butyrophenone) antipsychotic with predominantly dopamine antagonist activity. It is used first line for the treatment of hyperactive delirium and at low dose for the treatment of hypoactive delirium.

2. Presentation
Intravenous Injection 5mg/ml amps
Oral 500microgram capsules
Nasogastric Oral solution 2mg/ml

3. Dose
Hyperactive delirium
1 to 2.5mg qds intravenously OR 2.5 to 5mg orally
Depending on the severity of symptoms. Prescribe additional PRN doses of 1 to 2.5mg.

Maximum daily dose 30mg.
Intravenous doses above 20mg daily should not routinely be used due to an increase in side effects and lack of increase in clinical efficacy.

Hypoactive delirium
Start with lower doses such as 0.5mg tds intravenously

4. Common Side Effects
Risk of QT prolongation (especially with intravenous administration or with concurrent medication known to cause QT prolongation e.g. clarithromycin)
Ventricular arrhythmias
Increase in cerebrovascular events (mechanism unknown)
Neuroleptic malignant syndrome. Symptoms include: hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. This is a medical emergency requiring prompt treatment and withdrawal of the antipsychotic.
Extrapyramidal side effects (consider therapy with procyclidine)

5. Contraindications
Parkinson’s disease, known hypersensitivity to haloperidol, comatose states.

6. Notes
- Consider lower doses in hepatic impairment and in elderly patients.
- The oral bioavailability is 60%, therefore oral and parenteral doses are not equivalent.
- ECG monitoring is required when haloperidol is given intravenously. Discontinue haloperidol if QTc longer than 500ms.
- Avoid concomitant use of other antipsychotics

7. References
www.emc.medicines.org.uk accessed 01/02/12
BNF edition 61 March 2011
CRITICAL CARE CLINICAL GUIDELINE

OLANZAPINE

This guideline is a summary, full details are available from the SPC www.emc.medicines.org.uk

1. Indication
Second line for treatment of hyperactive and hypoactive delirium. It is an atypical antipsychotic with greater anti serotonin versus dopamine activity. Delirium is an unlicensed indication.

2. Presentation
Orodispersible tablets: 5mg and 10mg which may be administered via NG tube. Tablets: 2.5mg, 5mg, 7.5mg and 10mg
Intramuscular injection: 10mg (or subcutaneously, note this route is unlicensed).

3. Dose
Oral. Starting dose 5mg to 10mg daily (best given at night time due to sedative effects) Consider using lower doses in older patients and in renal hepatic impairment.
Intramuscular/subcutaneous. Starting dose of 10mg
Maximum dose 20mg daily by oral/parenteral route.

4. Administration
Intramuscular injection should be reconstituted with 2.1ml water for injection to produce a 5mg/ml solution.

5. Common Side Effects
Risk of QT prolongation (especially with intravenous administration or with concurrent medication known to cause QT prolongation e.g. clarithromycin). Ventricular arrhythmias. Hyperglycaemia (sometimes associated with diabetic ketoacidosis). Increase in cerebrovascular events. Extrapyramidal side effects (consider therapy with procyclidine). Olanzapine has anticholinergic activity so may be associated with constipation and other related side effects. Deranged LFTs. Consider dosage reduction is patients with raised AST or ALT. In the event of hepatocellular injury or cholestatic injury, olanzapine should be discontinued. Neutropenia (more common when olanzapine given with valproate). Olanzapine may lower seizure threshold in patients who have previously had seizures. Hypotension.
Neuroleptic malignant syndrome. Symptoms include: hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. This is a medical emergency requiring prompt treatment and withdrawal of the antipsychotic.

6. Contraindications
Parkinson’s disease, known hypersensitivity to olanzapine, comatose states.

7. Notes
- Doses over 5mg are associated with a greater incidence of extra pyramidal side effects.
- Olanzapine is well absorbed orally.
- Oral and intramuscular/subcutaneous olanzapine should not be used concomitantly.

8. References
www.emc.medicines.org.uk accessed 08/02/12
BNF edition 61 March 2011
1. Indication
Treatment of hypoactive delirium, this is an unlicensed indication. Risperidone is an atypical antipsychotic.

2. Presentation
500microgram tablets
1mg/ml oral solution.

3. Dose
Starting dose in hypoactive delirium 500micrograms bd
In severe renal or hepatic impairment reduce dose to 250micrograms bd
Doses in the region of 250micrograms to 1.5mg daily in divided doses may be used.

4. Common Side Effects
Risk of QT prolongation (especially with intravenous administration or with concurrent medication known to cause QT prolongation e.g. clarithromycin)
Ventricular arrhythmias
Hyperglycaemia (sometimes associated with diabetic ketoacidosis).
Increase in cerebrovascular events (mechanism unknown), avoid using in patients with risk factors for stroke.
Neuroleptic malignant syndrome. Symptoms include: hyperthermia, generalised muscle rigidity, autonomic instability, altered consciousness. This is a medical emergency requiring prompt treatment and withdrawal of the antipsychotic.
Extrapyramidal side effects (consider therapy with procyclidine).
Deranged LFTs. Consider dosage reduction is patients with raised AST or ALT. Jaundice
Neutropenia (more common when olanzapine given with valproate).
Hypotension, tachycardia.
Anemia, thrombocytopenia
Dyspnoea, blurred vision, constipation, abdominal discomfort, vomiting.
Rash, erythema.

5. Contraindications
Parkinson’s disease
Known hypersensitivity to risperidone
Comatose states
Patients with dementia (high risk of stroke)

6. Notes
• Some trials using risperidone noted a higher mortality in patients also receiving furosemide, no mechanism for this has been found.

7. References
www.emc.medicines.org.uk accessed 08/02/12
BNF edition 61 March 2011
CRITICAL CARE CLINICAL GUIDELINE

CLONIDINE

This guideline is a summary, full details are available from the SPC www.emc.medicines.org.uk

1. **Indication**
   Sedation and analgesia in adult patients

Clonidine is a centrally acting antihypertensive agent. It is an $\alpha_2$-agonist producing sedation and analgesia with minimal effect on respiratory function. Clonidine is of value when opioid or benzodiazepine requirements are increasing. Clonidine may be used to treat patients withdrawing from drugs or alcohol, note it has no effect on convulsions so should not be used as sole therapy for alcohol withdrawal.

Continuous infusion of clonidene for sedation is an unlicensed method of administration.

2. **Presentation**
   150 microgram /mL injection

3. **Dose**
   **Intermittent infusion**
   Doses of 50 to 400micrograms TDS or QDS have been used

**Continuous Infusion**
Doses in the range of 1 to 4microgram/kg/hour have been used. Using ideal body weight. The normal dose range is 1 to 2 microgram /kg /hour. Doses should normally start at around 2 microgram /kg/hour for an hour and the rate is titrated to sedative effect.

4. **Administration**

<table>
<thead>
<tr>
<th>Route</th>
<th>Drug</th>
<th>Volume</th>
<th>Fluid</th>
<th>Concentration</th>
<th>Initial Rate*</th>
<th>Maximum Rate*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Central or Peripheral</td>
<td>750 microgram (5 x 150 microgram amps)</td>
<td>Made up to 50ml</td>
<td>Sodium Chloride 0.9% or Glucose 5%</td>
<td>15 microgram /ml</td>
<td>9ml/hour</td>
<td>18ml/hour</td>
</tr>
</tbody>
</table>

*Infusion rates are based on a 70kg patient.
Use a lower starting rate if blood pressure is compromised.

5. **Common Side Effects**
Hypotension and bradycardia (especially after prolonged administration >7-10 days), may potentiate, or cause sinus bradycardia and AV block.
Hyperglycaemia
Acute colonic pseudo-obstruction has been reported at high doses
Constipation, nausea, vomiting and headache
Rash, itching
Rarely fluid retention and abnormal LFTs.
Dry mucous membranes
6. Contraindications
Known hypersensitivity to the active ingredient or other components of the product
Severe bradycardia resulting from either sick sinus syndrome or AV block of 2nd or
3rd degree.

Clonidine should only be used with caution in patients with depression, with Raynaud's
disease or other peripheral vascular occlusive disease. As with other antihypertensive
drugs, treatment in patients with heart failure should be carefully monitored.

7. Y site compatibility
Compatible with:
Aminophylline, fentanyl, heparin, midazolam, morphine and potassium chloride.

Amiodarone and dobutamine if clonidine made up with glucose 5%.

8. Notes
Tolerance /tachyphylaxis occurs within 7 days of starting therapy
• Withdrawal of clonidine should be gradual due to risk of rebound hypertension,
tachycardia and agitation. Advise reduce over several days if on infusion over 2 days.
• pH 5-7
• The blood pressure lowering effect of clonidine may be exacerbated by other
hypotensive agents including other sedative drugs, diuretics, vasodilators.
• 30-40% protein bound
• t½ 10-20 hours - mean 13 hours (extended to up to 41 hours in severe renal
impairment)
• 60% renally excreted as unchanged drug. The remaining 40% is metabolised by
oxidation to metabolite, p-hydroxyclonidine, which is pharmacologically inactive.
• Clearance is reduced in renal impairment
• Should not be administered concomitantly with methylphenidate, cases of severe
adverse effects including sudden death have been reported.
• Drugs with α2- adrenoceptor antagonist properties such as Mirtazapine may reduce the
effectiveness of clonidine.
• High intravenous doses of clonidine may increase the arrhythmogenic effect/QT
prolongation of haloperidol.
• Clonidine can aid mild/moderate symptoms of alcohol withdrawal although has no effect
on convulsions so should not be used as sole therapy.

9. References
www.uk CPA.org.uk accessed
www.emc.medicines.org.uk accessed 31/10/11
www.medicinescomplete.com accessed 31/10/11
http://medusa.wales.nhs.uk Medusa medicines guide accessed 31/10/11
• Hall, JE et al. Sedative, analgesic and cognitive effects of clonidine infusions in humans.
1. Indication
Short term treatment of insomnia in delirium negative patients.
All prescriptions should be endorsed 'short term sleep aid'.

Zopiclone is a non-benzodiazepine GABA-minergic hypnotic agent. It has less disruptive effects on normal sleep architecture compared to benzodiazepines such as temazepam, which are not recommended.

2. Presentation
3.75mg tablets
7.5mg tablets

3. Dose
Starting dose 7.5mg nocte
Use lower dose 3.75mg nocte in elderly patients and in renal/hepatic impairment.

4. Common Side Effects
Delirium.
Bitter/metallic after taste

5. Contraindications
Myasthenia gravis
Severe hepatic insufficiency
Known hypersensitivity to zopiclone or any other ingredient in the product

6. Notes
- Due to the risk of dependence it is advised that treatment is not continued beyond 4 weeks.
- Rebound insomnia can occur on discontinuation.
- Drugs which inhibit cytochrome P450 enzymes such as erythromycin may potentiate the effect of zopiclone.

7. References
www.emc.medicines.org.uk accessed 13/02/12
BNF edition 61 March 2011
1. **Indication**
Short term treatment of insomnia in both delirium positive and delirium negative patients. All prescriptions should be endorsed ‘short term sleep aid’.

Trazodone is a non-tricyclic antidepressant with sedative effects. It has limited antimuscarinic activity and therefore minimal adverse effects on the normal sleep cycle.

2. **Presentation**
- 50mg and 100mg capsules
- 50mg/5ml syrup for nasogastic administration

3. **Dose**
Starting dose 50mg nocte
Dose may be increased to 100mg nocte if necessary.

4. **Common Side Effects**
- Hypotension, tachycardia
- Priapism (discontinue trazodone)
- Deranged LFTs including jaundice and hepatocellular damage (discontinue trazodone)
- Blood dyscrasias including thrombocytopenia and agranulocytosis.
- Rarely QT prolongation
- Rarely neuroleptic malignant syndrome or serotonin syndrome

5. **Contraindications**
Hypersensitivity to trazodone or any ingredients

6. **Notes**
- Potent inhibitors of cytochrome P450 enzymes may potentiate the effects of trazodone.
- Concomitant treatment with trazodone may result in elevated levels of digoxin and phenytoin.

7. **References**
www.emc.medicines.org.uk accessed 13/02/12
BNF edition 61 March 2011