1. GUIDELINES FOR THE MANAGEMENT OF AGITATION IN ADVANCED CANCER

1.1 GENERAL PRINCIPLES

➢ There are many causes of agitation in palliative care patients, which makes recommendations for treatment difficult.¹

➢ Agitation in the dying phase is well recognised but poorly defined and management can be very difficult. Reversible causes should be corrected where possible. The aim of treatment should always be to control the agitation or restlessness.²,³,⁴,⁵

➢ Management of a patient who is agitated may include non-pharmacological and pharmacological measures.¹

➢ Medication used should be titrated to control the agitation and not with the intention of sedation. Medication can be administered intermittently or via a continuous infusion. The effect of sedating medication on the conscious level will vary between individual patients.⁶,⁷

➢ Sedation can be defined as: “A medical procedure used to palliate symptoms refractory to standard treatment by intentionally diminishing the conscious level.”⁸

1.2 GUIDELINES

➢ It may be difficult to differentiate between delirium and agitation. Delirium should be excluded by using the DSM IV criteria for the diagnosis of delirium (see Guidelines for the Management of Delirium in Advanced Cancer).⁹ [Level 4]

➢ Common causes of agitation in palliative care patients are listed in Table 1.1

<table>
<thead>
<tr>
<th>Table 1.1 Causes of agitation¹,¹⁰ [Level 4]</th>
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<tbody>
<tr>
<td>Anxiety</td>
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<tr>
<td>Biochemical abnormalities</td>
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<tr>
<td>Cerebral tumour</td>
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<tr>
<td>Constipation</td>
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<tr>
<td>Depression</td>
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<tr>
<td>Drugs</td>
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</table>

➢ Drugs are a common cause of agitation and include: corticosteroids; benzodiazepines (paradoxical agitation) and opioids. Dopamine antagonists such as haloperidol, levomepromazine and olanzapine (akathisia) may also cause cognitive decline and dementia due to the acetylcholine effects.¹ [Level 4]

➢ If a patient is agitated it is important to exclude reversible causes and treat where appropriate.⁴,⁵ [Level 4]
Non-pharmacological measures are important in the management of an agitated patient. These may include reassurance, presence of familiar faces and use of a well-lit and quiet room. Psychological and spiritual support should be offered where appropriate. [Level 4]

Nicotine replacement therapy may be used where agitation is secondary to nicotine withdrawal. [Level 4]

Midazolam is the drug of choice for the management of agitation or restlessness at the end of life. [Level 3]

The intention of treatment should be to control the symptom of agitation or restlessness. However, at times this may result in a decreased level of consciousness. The drug doses should be titrated to achieve symptom control of the agitation. [Level 4]

The aim of treatment, and any expected change in level of consciousness, should be discussed with the patient, relatives and multi-disciplinary team where possible. [Level 4]

The aim of treatment, and any expected change in the level of consciousness, should be documented in the case notes. [Level 4]

Where treatment of agitation results in continuous sedation, the underlying disease process should be advanced and irreversible, and death expected in hours to days. [Level 2++]

Table 1.2 lists the pharmacological options for the symptomatic management of agitation. [Level 4]

Figure 1.1 illustrates a suggested approach to the pharmacological management of terminal agitation. [Level 4]

Where the patient is shown to lack the capacity to consent to treatment, the Mental Capacity Act 2005 must be followed. The Lasting Power of Attorney, Advance Decisions and Independent Mental Capacity Advocates should be utilised where appropriate. [Level 4]
Figure 1.1 Pharmacological management of terminal agitation in advanced cancer $^4$ [Level 4]

Agitated patient in the terminal phase. Review the medication and check for reversible causes.

Is the patient able to swallow?

**YES**
Prescribe diazepam 2mg-15mg orally daily in divided doses or lorazepam 500μg-1mg bd and/or prn sublingually.
Review patient on a four hourly basis. If patient remains agitated, may need to convert to parenteral medication.

**NO**
Prescribe midazolam 2.5mg-5mg subcutaneously prn as bolus injection.
Consider starting subcutaneous infusion of midazolam via a syringe driver over 24 hours.
Starting dose: 10mg (see Table 1.2)
Seek specialist advice if dose > 30mg is considered

Assess response 4 hourly.
Clinical condition will determine if drugs need reducing and/or stopping.

**COMPLETE RESPONSE**
Continue regimen.

**PARTIAL RESPONSE**
Add second line agent. Use Levomepromazine.
Dose range: 25mg-200mg subcutaneously via syringe driver over 24 hours.
Prescribe subcutaneous stats of 12.5mg-25mg as breakthrough medication.

**NO RESPONSE**
Switch to Levomepromazine.
Dose range: 25mg-200mg subcutaneously via syringe driver over 24 hours.
Prescribe subcutaneous stats of 12.5mg-25mg as breakthrough medication.
NB In patients with cerebral tumours/history of seizures, midazolam should be continued (see Table 1.2).

**PARTIAL / NO RESPONSE**

**NO RESPONSE**
Change to Phenobarbital.
Give 100mg-200mg bolus intramuscular injections. Start continuous infusion: 600mg-1200mg subcutaneously via a syringe driver over 24 hours.

ALL DRUGS SHOULD BE TITRATED ACCORDING TO CLINICAL NEED AND RESPONSE.
<table>
<thead>
<tr>
<th>Name of drug / Class of drug</th>
<th>Dose and route of administration</th>
<th>Side effects</th>
<th>Comments</th>
</tr>
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<tbody>
<tr>
<td><strong>Lorazepam</strong> &lt;br&gt; <em>Short acting</em> &lt;br&gt; benzodiazepine</td>
<td>500 microgram-1mg bd and prn sublingually. Maximum dose is 4mg per 24 hours.</td>
<td>Possible risk of paradoxical agitation.</td>
<td>Not for use in syringe driver. Can develop tolerance.</td>
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<tr>
<td><strong>Diazepam</strong> &lt;br&gt; <em>Long acting</em> &lt;br&gt; benzodiazepine</td>
<td>2mg-5mg tds and prn orally. 10mg via rectal route prn. 2mg-10mg via intravenous route prn.</td>
<td>Possible risk of paradoxical agitation.</td>
<td>Not for use in syringe driver. Can develop tolerance.</td>
</tr>
<tr>
<td><strong>Midazolam</strong> &lt;br&gt; <em>Short acting</em> &lt;br&gt; benzodiazepine</td>
<td>2.5mg-10mg prn via subcutaneous route. 10mg-30mg ** subcutaneously via syringe driver over 24 hours.</td>
<td>Possible risk of paradoxical agitation.</td>
<td>Will not improve cognition in delirium. Can develop tolerance. Flumazenil is the reversing agent. **If a dose &gt; 30mg / 24 hours is being considered, seek specialist palliative care advice. Doses of up to 100mg / 24 hours have been used but only when the addition of an antipsychotic such as levomepromazine is inappropriate. If patient has received an enzyme inducer such as carbamazepine or phenytoin the dose may need reducing after 3-5 days as the enzyme induction wears off.</td>
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<tr>
<td><strong>Levomepromazine</strong> &lt;br&gt; <em>Long acting</em> &lt;br&gt; phenothiazine</td>
<td>12.5mg-200mg subcutaneously over 24 hours for management of agitation. Stat doses can vary between 12.5mg-50mg subcutaneously. Can also use orally for the control of agitation.</td>
<td>High doses may precipitate seizures.</td>
<td>May lower the threshold for seizures. Therefore in patients with a history of seizure / cerebral tumours consider the addition of midazolam in a CSCI.</td>
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<tr>
<td><strong>Phenobarbital</strong> &lt;br&gt; <em>Long acting</em> &lt;br&gt; barbiturate</td>
<td>Usually given via parenteral route in this situation. Use 100mg-200mg intramuscular stat injections. Can use 600mg-2400mg subcutaneously via syringe driver over 24 hours.</td>
<td></td>
<td>Use intramuscular injections for breakthrough medication. Do not mix with other drugs in a syringe driver. There is anecdotal evidence that get fewer site reactions if use sodium chloride 0.9% as diluent, although water can be used. Can be given intravenously.</td>
</tr>
</tbody>
</table>
1.3 STANDARDS

1. Reversible causes of agitation should be treated where appropriate.\(^4,5\) [Grade D]

2. All patients should have a clinical examination at the initial assessment of agitation.\(^4,5\) [Grade D]

3. All patients should have a review of medication at the initial assessment of agitation.\(^4,5\) [Grade D]

4. The reason for the use of psychotropic medication should be documented in the case notes.\(^7\) [Grade D]

5. Patients should be reviewed every four hours to ensure adequate symptom control.\(^7\) [Grade D]

6. If a health care professional feels they may be shortening life by the use of sedation they should contact senior / specialist help for advice.\(^7,13\) [Grade D]

1.4 REFERENCES


1.5 **CONTRIBUTORS**

**Lead Contributors**

Dr C Finnegan  
Specialist Registrar in Palliative Medicine  
St John’s Hospice  
Wirral

Dr F Ahmad  
Specialty Registrar in Palliative Medicine  
Loros Hospice  
Leicester

Dr K Marley  
Specialty Registrar in Palliative Medicine  
Marie Curie Hospice  
Liverpool

Dr Cathy Lewis-Jones  
Consultant in Palliative Medicine/Medical Director  
St John’s Hospice  
Wirral  
and  
Wirral University Teaching Hospital NHS Foundation Trust  
Wirral

Dr Averil Fountain  
Consultant in Palliative Medicine  
Halton and St Helens Primary Care Trust  
Halton

Dr Lisa Beddows  
Consultant in Old Age Psychiatry  
The Stein Centre  
St Catherines’s Hospital  
Wirral

**External Reviewer**

Dr A Thorns  
Consultant in Palliative Medicine  
St Pilgrims Hospice in Thanet  
Margate