# Symptom Control Medication & the Dying Person

## Summary of Main Recommendations

### Recognising the Likelihood of Dying, Medication Review, Anticipatory Prescribing & Decision Making

- The recognition that someone is possibly or likely to be dying is crucial to facilitate good symptom control.\(^4\) [Level 4]
- When the likelihood of dying is recognised, all medication should be reviewed with the dying person and those important to them by the responsible clinician or an appointed delegate. An individualised care plan should be co-created detailing which medications are to continue, be commenced and the role of anticipatory prescribing.\(^4\) [Level 4]

### Routes of Administration

- Routes of administration should be reviewed to reduce the risk of failed administration of medication. The subcutaneous route is recommended for parenteral use in the dying because it has fewer complications compared with intravenous use.\(^10\) [Level 2+]

### Symptoms

- For all symptoms
  - Construct the individualised care plan using the principles outlined in Sections 4.1.4.4 [\(^\checkmark\)]
  - Review the role of non-pharmacological approaches to managing symptoms [\(^\checkmark\)]
  - Assess the likely cause of symptoms to guide management [\(^\checkmark\)]
  - After administration of medication, review efficacy and amend the individualised care plan as needed, involving the dying person and those important to them wherever possible [\(^\checkmark\)]

### Pain: Medication Review

- Existing analgesia should be reviewed; this may need to be administered by a different route.\(^10\) [Level 2+]

### Pain: Anticipatory Prescribing

- If the dying person is already taking regular analgesia, doses of additional analgesia to be used should take this into account.\(^7,\,8,\,12,\,19\) [Level 4]
- If the dying person is not using strong opioids consider prescribing:
  - Morphine sulphate 1.25mg – 2.5mg subcutaneously up to 2-4 hourly PRN.\(^7,\,8,\,22\) [Level 4]
  - Midazolam 2.5mg – 5mg subcutaneously up to 2-4 hourly PRN.\(^7,\,8,\,22\) [Level 2+]
- If the dying person is allergic or intolerant of morphine, or if the eGFR is <30mls/min an alternative opioid should be prescribed (e.g. oxycodone 1mg to 3mg subcutaneously up to 2-4 hourly).\(^1,\,28\) [Level 4]

### Pain: Continuing Review

- If two or more “as required” doses of strong opioid are needed over 24 hours, a continuous subcutaneous infusion (CSCI) should be considered, if not already in being used.\(^8,\,22\) [Level 4]

### Breathlessness: Medication Review

- Existing medication for breathlessness should be reviewed; this may need to be administered by a different route.\(^6,\,22\) [Level 4]

### Breathlessness: Anticipatory Prescribing

- Morphine sulphate 1.25mg – 2.5mg subcutaneously up to 2-4 hourly PRN.\(^7,\,8,\,22\) [Level 2+]
- Midazolam 2.5mg – 5mg subcutaneously up to 2-4 hourly PRN.\(^7,\,8,\,22\) [Level 2+]

### Breathlessness: Continuing Review

- If two or more “as required” doses of strong opioid or benzodiazepine are needed over 24 hours, a continuous subcutaneous infusion (CSCI) should be considered, if not already in place.\(^6,\,22\) [Level 4]
Excessive Respiratory Tract Secretions: Medication Review

- Explanation of these symptoms to those important to the dying person and non-pharmacological measures are an important part of the management of respiratory tract secretions. [7, 40] [Level 4]

Excessive Respiratory Tract Secretions: Anticipatory Prescribing

- Hyoscine hydrobromide 400 microgram subcutaneously PRN or glycopyrronium 200 microgram subcutaneously PRN or hyoscine butylbromide 20 mg subcutaneously PRN. [32, 32-40] [Level 3]

Excessive Respiratory Tract Secretions: Continuing Review

- Regular administration of a CSCI should be considered as soon as possible if respiratory tract secretions develop. [5] [Level 4]
- Consider changing or stopping medication if secretions are still present, they have not improved despite a switch to alternative anticholinergic agents or unacceptable anti-cholinergic side effects occur despite treatment to relieve these issues. [32, 32-40] [Level 4]

Restlessness and Agitation: Medication Review

- Possible reversible causes of the agitation should be sought and managed appropriately. Examples include urinary retention, opioid toxicity, nicotine withdrawal, constipation and noise. [5, 7] [Level 4]

Restlessness and Agitation: Anticipatory Prescribing

- Midazolam 2.5mg – 5mg SC up to 2-4 hourly PRN. [7, 8, 22]
- The dying person with an eGFR of <30mls/min should be prescribed a reduced dose of midazolam e.g. midazolam 1mg subcutaneously “as required.” [22, 44]
- Patients who show signs of delirium may require haloperidol 500 microgram subcutaneously 2 hourly as required and should be monitored for the development of extra pyramidal side effects. [22, 44]

Restlessness and Agitation: Continuing Review

- If a reversible cause for the agitation is found and managed, the patient should continue to be monitored for any further agitation and additional “as required” doses of midazolam administered as needed. It may not be necessary to commence a CSCI of midazolam at this stage. [5, 8] [Level 4]
- If restlessness and agitation is not responding to these measures, specialist palliative care advice should be sought. [5] [Level 4]

Nausea and Vomiting: Medication Review

- Those who have previously been nauseated and who are established on anti-emetic medication should continue on an anti-emetic. This should be converted to an appropriate equivalent and be prescribed for regular administration and to be given via the parenteral route. [5, 7, 8] [Level 4]

Nausea and Vomiting: Anticipatory Prescribing

- For the dying person who becomes nauseated or is vomiting, levomepromazine 2.5mg to 6.25mg subcutaneously 4-hourly may be the most effective anti-emetic to prescribe due to its multiple modes of action. [7, 8, 30] [Level 3]
- Cyclizine may theoretically exacerbate symptoms of severe heart failure and should be used with caution in patients with this condition. [31] [Level 3]

Nausea and Vomiting: Continuing Review

- If the dying person requires two or more doses of an antiemetic medication the patient may benefit from the drug being administered via a CSCI. [8] [Level 4]

Other symptoms

- Some dying people will have other symptoms not covered in this guidance (e.g. sweating, pyrexia and itch). Individualized care plans should be in place to manage these symptoms and consider obtaining specialist palliative care advice. [✓]
Section 1: Introduction

- The control of symptoms in the dying is a key aspect of high quality palliative care.
- Many people fear that they will die in pain.\(^1\) Symptom control in the last days of life is assessed annually in the VOICES survey.\(^2\) The 2013 survey found bereaved carers reported pain control to be only “fair” or “poor” in 20% of deaths with the figure rising to 26% for other symptoms.\(^2\) This survey also showed variation in the perceived success of symptom control between care settings (home, hospital, care home and hospice).\(^2\) The majority of people die in the hospital setting but have worse reported outcome measures compared to those who die elsewhere.\(^2\)
- Symptoms that may be experienced by dying people include:\(^3\)
  - Pain
  - Breathlessness
  - Excessive respiratory tract secretions
  - Restlessness and agitation
  - Nausea and vomiting
- The Leadership Alliance for Care of Dying People has identified symptom control as one of the Five Priorities for Care.\(^4\) It recommends:

  “An individual plan of care, which includes food and drink, symptom control and psychological, social and spiritual support, is agreed, co-ordinated and delivered with compassion.”\(^4\)
Section 2: Scope and Purpose

- The following guideline is an update of Guidelines for the Use of Drugs in the Last Hours and Days of Life developed in 2006 and updated in 2009.5
- This guideline aims to support healthcare professionals to develop an individual plan of care for the use of symptom control medication in a dying person.
- This guideline may be used by practitioners who care for dying people in all care settings including doctors, nurses and pharmacists. It is also a source of information for people with a life-limiting illness and those important to them.
- Table 1 summarises the scope and purpose of this guideline.

<table>
<thead>
<tr>
<th>Table 1: Scope of guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Population</strong></td>
</tr>
<tr>
<td><strong>Populations not covered</strong></td>
</tr>
</tbody>
</table>
| **Healthcare setting**     | People in their usual place of residence  
                             | Primary and community care  
                             | Secondary and tertiary care including acute hospital and mental health trusts  
                             | Hospice care |
| **Topics**                 | Common symptoms experienced by dying people  
                             | Medication used to support symptoms in the dying person  
                             | Routes of administration of medication used to control these symptoms |
| **Topics not covered**     | Other aspects of care of the dying e.g. organisation of care, management of other domains of care including skin integrity, clinically assisted nutrition and hydration |
Section 3: Methods

- The guideline is based on the AGREE II criteria which may be found in detail in the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group (CMPCNAG) Guideline Development Manual.6

3.1 Clinical Questions & Interventions

- Clinical questions were derived from the previous guidance published in 2006 and reviewed in 2009. The questions were initially framed by delegates attending the CMPCNAG Review meeting on 6th March 2014 and refined at a meeting of the Guideline Development Group on 29th April 2014. The clinical question used to guide the literature review in PICO (Patient, Intervention, Control, and Outcome) format is:
  - What medication is effective in controlling symptoms (pain, dyspnoea, nausea and vomiting, agitation and secretions) in adult people who are dying?

3.1.1 Outcomes

- To provide safe, timely and effective medication to improve the symptoms experienced by dying people through:
  - appropriate review and cessation of non-essential medications
  - appropriate prescription of as required medications
  - evaluation and facilitation of the most appropriate route for medication administration on an individualised basis
  - ongoing review, communication and documentation of the treatment plan

3.2 Literature Search

- Systematic electronic database searches were done to find potentially relevant articles. PubMed, EMBASE (Scopus), CINAHL and Cochrane databases were searched in July 2014. A full explanation of the search strategy, results and appraisal of evidence may be found on the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group website. Grading of level of evidence and recommendations follows the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group Guideline Development Manual and uses SIGN criteria.6
Section 4 Guideline Recommendations

4.1 Recognising the Likelihood of Dying

- Symptom control in a dying person – as in any other situation – requires an holistic assessment, considered intervention and a review of the effectiveness of interventions made. What may make the care of the dying person different are the presence of new symptoms such as respiratory tract secretions, the loss of the oral route for administration of medication and the need to achieve rapid symptom control at a potentially uncertain, unstable and emotionally charged time. Therefore, the recognition that someone is possibly or thought likely to be dying is crucial. [Level 4]

- Care and symptom control in a dying person is a continuous process, meaning there should be continual assessment of the condition, needs and wishes of the dying person with an appropriate response. [Level 4]

- Further guidance is available in the Leadership Alliance for the Care of the Dying People Report “One Chance to Get It Right”.

4.2 Medication Review and Anticipatory Prescribing

- When the likelihood of dying is recognised, all medication should be reviewed by the responsible clinician or an appointed delegate. [Level 4]

- This review should consider:
  - current and anticipated symptom burden [Level 4]
  - available routes of administration of medications and how these may change as someone dies; that is potential loss of oral route and/or venous access [Level 4]
  - current and anticipated organ function; i.e. such as a clinically significant risk of renal or hepatic impairment? [Level 4]
  - the dying person’s diseases and medications used in their therapy [Level 4]

- This review should result in individualised, documented decisions regarding which current medications are considered essential and those considered not essential for symptom control in the dying phase. This should be communicated following the principles of Decision Making in Section 4.3. [Level 4]

- Medication to control symptoms that can occur in dying people should be prescribed using an individualised approach in anticipation of the symptoms occurring. [Level 4]

- The timing of this prescription will vary depending on the preference of the dying person, care setting and the clinical course of illness. It should be individualised and consider:
  - the likelihood of dying occurring and the risks of sudden deterioration needing urgent symptom control [Level 4]
  - discussion with the person and those important to them about the likelihood of symptoms occurring [Level 4]
- the benefit and harms of prescribing or not prescribing anticipatory medication [4, 7, 8] [Level 4]
- logistics (e.g. the expiry date of medication and renewal of stock, time taken to have medication prescribed, obtained and administered). [4, 7, 8] [Level 4]

When anticipatory medication is used, the efficacy and side effects should be monitored and reviewed at least daily and these assessments used to inform the daily review of the individualised care plan. The frequency of review will to some extent be dependent on the care setting. [4] [Level 4]

4.3 Decision Making

The recognition that dying may occur – and how an individual should be supported through this – may have been identified through advance care planning. This is a voluntary process and it may be that this did not or could not take place, for example a catastrophic cerebral haemorrhage. As an ongoing process the dying person should be involved as much as they want to be in decisions about:

- the reason for the prescription of medication to relieve symptoms [4, 7, 8] [Level 4]

- the choice – if available – between different types of medication available to relieve the symptom in question [4, 7, 8] [Level 4]

- the route of administration of symptom control medications in the dying phase [4, 7, 8] [Level 4]

If a decision-specific capacity assessment shows they are unable to be involved in treatment decisions in accordance with the Mental Capacity Act 2005, any available advance care plans, Advance Decisions to Refuse Treatment and Lasting Power of Attorney for Health and Welfare should be consulted. [4] [Level 4]

In addition to this, and especially if these measures are not in place, those important to the dying person should be involved in the dying person’s care. Their ongoing involvement entails considering what the wishes of the dying person would be in decisions around the reason, choice and route of symptom control medications in the dying phase. [4] [Level 4]

All of these discussions should be documented in the clinical record. [4] [Level 4]

4.4 Routes of Administration

The process of dying is often characterised by the unreliability or loss of the oral route for medicine administration. An alternative route is therefore needed. The subcutaneous route is recommended for parenteral use in the dying because it has fewer complications compared with intravenous administration. [10] [Level 2+]

A medication review should take place in all dying patients. The specialist palliative care team should be contacted to provide support as necessary. [✓]
A subcutaneous access port should be sited to avoid repeated skin puncture. A “safer sharp” needle or system should be used to reduce risk of needlestick injury. [Level 4]

If regular administration of medicines is needed, a continuous subcutaneous infusion (CSCI) should be used which may be delivered through use of a syringe pump. [Level 4]

If a syringe pump is not available to administer a CSCI, it may be necessary to prescribe regular subcutaneous injections to cover the 24 hour dose. [Level 4]

Increasingly, long term medication delivery routes (e.g. percutaneous enterostomy or a peripherally inserted central catheter (PICC)) are being used to deliver medications to people with advanced illness. If present in the dying phase these routes should be evaluated on an individual basis to determine whether they are appropriate to be used to deliver medications for specific problems. This may be favoured in certain instances (e.g. to control seizures with a specific intravenous antiepileptic). [✓]

4.5 Symptoms

Symptom control in a dying person – as in any other situation – requires holistic assessment, considered intervention and a review of the effectiveness of any intervention made. These key principles are reviewed in depth in each of the Network’s guidelines. In this section we pull together the main considerations faced when caring for someone who is dying.

4.5.1 Pain

Pain should be managed promptly and include an assessment for potentially reversible causes e.g. urinary retention. Further information on managing pain in palliative care is available in the following Cheshire and Merseyside Palliative and End of Life Care Strategic Clinical Network Guidelines: Cancer-Related Breakthrough Pain, Corticosteroids, Ketamine, Methadone, Neuropathic Pain, Non-Steroidal Anti-Inflammatory Drugs, Opioid Substitution, and Substance Misuse.

4.5.1.1 Pain: Medication Review

If the dying person regularly uses an oral strong opioid:
- this should be converted to a CSCI using the principles in Guidelines for Opioid Substitution. [Level 4]

If the dying person regularly uses a transdermal strong opioid:
- this should be continued in the dying phase with no further titrations in patch dose [Level 4]
- If two “as required” doses of strong opioid are needed in a 24-hour period a continuous subcutaneous infusion of strong opioid should be commenced in addition to the transdermal strong opioid patch [Level 4]
- The starting dose of the opioid in the continuous subcutaneous infusion (CSCI) should be equivalent to the “as required” doses used in the last 24 hours, excluding those used to manage incident pain [23][Level 4]
- The CSCI and corresponding “as required” doses of SC strong opioid should be titrated according to “as required” use and the patch changed as usual, again with no further titrations in patch dose [23][Level 4]

- If the dying person regularly uses methadone as opioid substitute maintenance therapy:
  - Administer via a separate CSCI to avoid the symptoms of withdrawal and do not alter the dose [5, 23][Level 4]
- If the dying person regularly uses methadone or ketamine as analgesia the specialist palliative care team should be contacted to provide support. [15, 16][✓]
- If the dying person regularly uses an oral adjuvant analgesia without a subcutaneous equivalent (e.g. amitriptyline, gabapentin or pregabalin)
  - the impact of this stopping due to loss of the oral route should be assessed [8, 22][Level 4]
  - There is insufficient evidence to recommend the use of other subcutaneous medication to replace the loss of oral adjuvant analgesia without a subcutaneous equivalent. In practice, clonazepam has been used and its use as a substitute adjuvant analgesic should be discussed with Specialist Palliative Care [✓]

- If the dying person regularly uses corticosteroids:
  - it is usually appropriate to discontinue these in the dying phase unless they have been necessary in achieving good symptom control e.g. managing headaches and cancer pain [5, 14, 22][Level 4]
  - for patients unable to take oral dexamethasone, doses less than or equal to 8mg may be given by daily bolus subcutaneous injection [5, 14, 22][Level 4]
  - if a CSCI is necessary, dexamethasone should be administered via a separate syringe pump to prevent precipitation [5, 12, 14, 22][Level 4]

- The specialist palliative care team should be contacted to provide support if the dying person is prescribed several medications, has significant multimorbidity or there is uncertainty about appropriate medication management. [✓]

4.5.1.2 Pain: Anticipatory Prescribing

Following discussions with the dying person and those important to them outlined in Section 4.2 about prescription of anticipatory medication for pain:

- If the dying person already takes oral strong opioids for breakthrough pain:
  - this should be prescribed as a subcutaneous dose using the principles in Guidelines for Opioid Substitution [7, 8, 19, 22][Level 4]
- If the dying person uses rapid onset transmucosal fentanyl citrate for breakthrough pain:
This should continue to be prescribed and administered as tolerated and in accordance with the brand-specific guidance (see Guidelines for Cancer-Related Breakthrough Pain)\textsuperscript{15} [Level 4]

- Transmucosal fentanyl brands should not be switched to offer a different route of administration (e.g. from a sublingual preparation to a nasal preparation) as they are not the same formulation and so doses are not equivalent\textsuperscript{13, 24} [Level 4]

- An appropriate subcutaneous dose of an injectable opioid should be prescribed based on the background strong opioid dose using the principles in Guidelines for Opioid Substitution\textsuperscript{7, 8, 19, 22} [Level 4]

- If the dying person is not using strong opioids:
  - Morphine is the subcutaneous analgesia of choice in the dying phase and should be prescribed 2.5mg – 5mg subcutaneously up to 2-4 hourly PRN\textsuperscript{7, 8, 22} [Level 4]
  - If the dying person is allergic or intolerant of morphine, or if the eGFR is <30mls/min an alternative opioid should be prescribed (e.g. oxycodone 1mg to 3mg subcutaneously up to 2-4 hourly)\textsuperscript{5, 25} [Level 4]

- Anticipatory prescriptions for CSCIs may be appropriate in some settings; however, this requires training and locally agreed policy. [✓]

4.5.1.3 Pain: Continuing Review

- The effectiveness of the use of “as required” doses of analgesia should be recorded, and this information used to review:
  - The dose used\textsuperscript{8} [Level 4]
  - The need to increase background analgesia via a CSCI\textsuperscript{8} [Level 4]

- If two or more “as required” doses of strong opioid are needed over 24 hours, a continuous subcutaneous infusion (CSCI) should be considered, if not already in place.\textsuperscript{8} [Level 4]

- Doses used to manage predictable incident pain should not be included when calculating an increase in CSCI opioid.\textsuperscript{5} [✓]

- If a syringe pump is not available to administer a CSCI, it may be necessary to prescribe the subcutaneous opioid every 4 hours to cover the 24 hour dose.\textsuperscript{8} [Level 4]

4.5.2 Breathlessness

Breathlessness management uses a multi-modal approach including functional changes, the use of relaxation therapies as well as the use of medication. Further information on managing breathlessness in palliative care is available in the following Cheshire and Merseyside Palliative and End of Life Care Strategic Clinical Network Guidelines: Breathlessness\textsuperscript{26}, Oxygen\textsuperscript{27}, Pleural Effusions.\textsuperscript{28}

4.5.2.1 Breathlessness: Medication Review

- If the dying person regularly uses an oral strong opioid for breathlessness:
- this should be converted to a CSCI/24hrs using the principles in *Guidelines for Opioid Substitution*.7, 8, 12, 22 [Level 4]

- If the dying person regularly uses an **oral or sublingual benzodiazepine** for breathlessness:
  - this should be converted to a CSCI over 24hrs of midazolam considering the oral dose of benzodiazepines used.7, 8 Guidance on what may be considered to be equivalent doses can be found in the Palliative Care Formulary 22 [Level 4]

### 4.5.2.2 Breathlessness: Anticipatory Prescribing

Following discussions with the dying person and those important to them outlined in Section 4.2 about prescription of anticipatory medication for breathlessness:

- Review the use of non-pharmacological approaches to breathlessness management.26 [Level 4]

- Strong opioids and benzodiazepines are the drugs of choice in the management of breathlessness in the dying person.29 [Level 2+]

- The dying person who is breathless and already established on a long-acting opioid may benefit from an “as required” dose of opioid that is lower than the usual one sixth of the total daily dose of opioid.30 [Level 2+]

- Immediate release opioids may be more helpful than long-acting opioids in relieving breathlessness.29, 30 [Level 3]

- Morphine is the first line parenteral strong opioid for patients with breathlessness.
  - In opioid naïve patients the appropriate “as required” dose is 1.25mg–2.5mg subcutaneously prescribed 2-4 hourly.7, 8, 22, 29, 30 [Level 4]

- Midazolam is the benzodiazepine of choice for breathlessness associated with anxiety in the dying person.
  - The “as required” dose of midazolam is 2.5mg subcutaneously. A CSCI may be required. The starting dose should be titrated according to need.7, 8 [Level 4]
  - The dying person with an eGFR of <30mls/min should be prescribed a reduced dose of midazolam i.e. a starting dose from 1mg subcutaneously 5, 22, 31 [Level 4]

- It may be helpful to prescribe and record “as required” doses of opioids for pain and breathlessness separately for those patients who require “as required” doses for both symptoms. This may be useful when titrating the prescribed regular dose of opioids. [✓]

### 4.5.2.3 Breathlessness: Continuing Review

- If opioids and/or benzodiazepines are effective, a CSCI should be considered incorporating the dose needed over the previous 24 hours.7, 8 [Level 4]
4.5.3 Excessive Respiratory Tract Secretions

- Inability to clear secretions from the oropharynx and trachea often results in noisy respiration as the secretions oscillate with expiration and inspiration. Assess the effect of this symptom on the dying person and those important to them.\(^7,\,8,\,32\) [Level 4]

- Non-pharmacological measures are an important part of the management of respiratory tract secretions and may simply include a change of position.\(^7,\,33\) [Level 4]

4.5.3.1 Excessive Respiratory Tract Secretions: Medication Review

- Early use of anti-cholinergic agents may be helpful in dying people with disease known to be associated with an increased incidence of respiratory tract secretions. Examples include primary malignancy of the lung or brain, severe heart failure and non-cancer respiratory disease.\(^34\) [Level 4]

4.5.3.2 Excessive Respiratory Tract Secretions: Anticipatory Prescribing

Following discussions with the dying person and those important to them outlined in Section 4.2 about prescription of anticipatory medication for excessive respiratory tract secretions:

- Prescribe hyoscine hydrobromide, glycopyrronium or hyoscine butylbromide which are all available for the management of excessive respiratory tract secretions.\(^13\) There is no conclusive evidence to favour one drug over another and therefore anticholinergic side effects such as dry mouth, urinary retention or worsening delirium should be monitored.\(^32-40\) [Level 2+]

- Table 2 gives further details of clinical situations where a particular drug may be selected e.g. renal impairment.

- Pulmonary oedema may be the cause of excessive respiratory tract secretions. Consider the use of parenteral furosemide under the guidance of specialist palliative care.\(^7\) [Level 4]

4.5.3.3 Excessive Respiratory Tract Secretions: Continuing Review

- It is important to talk to those important to the dying person and give explanations and reassurance, as this symptom may cause considerable distress to the family whilst not causing distress to the dying person.\(^7,\,33,\,35\) [Level 4]

- An “as required” dose of an anti-cholinergic drug should be given as soon as respiratory tract secretions develop as they do not always relieve symptoms secondary to secretions that are already in place.\(^35\) Regular administration of a CSCI should be started as soon as possible.\(^7\) [Level 4]

- If side effects of dry mouth occur, treat this with frequent mouth care which may include artificial saliva replacement gels or sprays.\(^22\) [Level 4]

- Consider changing or stopping medication if secretions are still present, they have not improved despite a switch to alternative anticholinergic agents or unacceptable anti-cholinergic side effects occur.\(^22,\,32-40\) [Level 4]
4.5.4 Restlessness and Agitation

- Further information on managing restlessness and agitation in palliative care is available in the following Cheshire and Merseyside Palliative and End of Life Care Strategic Clinical Network Guidelines: *Agitation* 41, *Delirium* 42, *Spiritual Care*. 43

### 4.5.4.1 Restlessness and Agitation: Medication Review

- Possible reversible causes of the agitation should be sought and managed appropriately. Examples include urinary retention, opioid toxicity, nicotine withdrawal, constipation and noise. 5, 7, 42, 43 [Level 4]

### 4.5.4.2 Restlessness and Agitation: Anticipatory Prescribing

Following discussions with the dying person and those important to them outlined in Section 4.2 about prescription of anticipatory medication for restless and agitation:

<table>
<thead>
<tr>
<th>Table 2 Anticholinergic drugs used in the management of respiratory tract secretions 22, 32-40 [Level 2+]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Hyoscine Hydrobromide</td>
</tr>
<tr>
<td>Glycopyrronium</td>
</tr>
<tr>
<td>Hyoscine Butylbromide</td>
</tr>
</tbody>
</table>
- Midazolam 2.5mg–5mg subcutaneously up to 2 to 4 hourly as required should be prescribed and administered subcutaneously if a patient is, or may become agitated.\(^5, 7, 8, 42\) [Level 4]
- The dying person with an eGFR of <30mls/min should be prescribed a reduced dose of midazolam. A suitable starting dose would be 1 mg midazolam "as required" subcutaneously.\(^22\) [Level 4]
- Patients who are paranoid and / or hallucinating may require haloperidol 500 microgram 2 hourly as required subcutaneously and should be monitored for the development of extra pyramidal side effects.\(^22, 44\) [Level 3]

4.5.4.3 Restlessness and Agitation: Continuing Review

- If a reversible cause for the agitation is found, the patient should continue to be monitored for any further agitation and additional "as required" doses of midazolam administered as needed. It may not be necessary to commence a CSCI of midazolam at this stage.\(^5, 8\) [Level 4]
- If a CSCI is required it should be commenced according to the number of "as required" doses of midazolam or haloperidol given in the last 24 hours.\(^5, 7, 12, 41, 44\) [Level 4]
- If the patient is still agitated at a dose of 30mg of midazolam over 24 hours via a CSCI, specialist palliative care advice should be sought.\(^5, 41\) [Level 4]
- Agitated patients who do not respond fully to midazolam or haloperidol may benefit from the addition of levomepromazine.\(^5, 22, 41\) [Level 4]
- In severe cases, phenobarbital may be used for the management of agitation in the last days/hours of life but should only be administered under the guidance of specialist palliative care.\(^41, 45\) [Level 3]

4.5.5 Nausea and Vomiting

- Nausea should be managed promptly and include an assessment for the likely underlying cause in order to guide management. Further information on managing nausea and vomiting in palliative care is available in the following Cheshire and Merseyside Palliative and End of Life Care Strategic Clinical Network Guidelines: Bowel Obstruction, Nausea and Vomiting.\(^46, 47\)

4.5.5.1 Nausea and Vomiting: Medication Review

- Those who have previously been nauseated and who are established on anti-emetic medication should continue on an anti-emetic. This should be converted to an appropriate equivalent and be prescribed regularly and parenterally. The subcutaneous route is recommended.\(^5, 7, 8, 22, 47\) [Level 4]

4.5.5.2 Nausea and Vomiting: Anticipatory Prescribing

Following discussions with the dying person and those important to them outlined in Section 4.2 about prescription of anticipatory medication for nausea and vomiting:

- Review the role of non-pharmacological approaches to nausea.\(^47\) [Level 4]
- An anti-emetic should be prescribed as required in the event of nausea or vomiting developing in the last days / hours of life.\(^7, 8, 22\) [Level 4]
For the dying person who becomes nauseated or is vomiting, levomepromazine 2.5mg to 6.25mg subcutaneously 4-6 hourly may be the most effective anti-emetic to prescribe due to its multiple modes of action.[7, 8, 22, 46, 48] [Level 3]

Cyclizine may theoretically exacerbate symptoms of severe heart failure and should be used with caution in patients with this condition.[49] [Level 3]

4.5.5.3 Nausea and Vomiting: Continuing Review

If the dying person requires two or more doses of antiemetic medication they may benefit from a CSCI administration of antiemetic medications. This should be reviewed and prescribed as appropriate according the specific needs of the individual.[8, 22, 46, 47] [Level 4]

4.5.6 Other symptoms

Some dying people will have other symptoms not covered in this guidance (for example sweating, pyrexia and itch). Individualized care plans should be place to manage these symptoms and advice sought from Specialist Palliative Care Teams.[✓]
Section 5: Standards

1. Documented discussions about the use of medications for symptom control should be conducted with the dying person, and those important to them, at the earliest possible opportunity. [Grade D]

2. When dying is recognised all medication should be reviewed for its role in providing symptom control. [Grade D]

3. Available medication routes (which may include intravenous and gastrostomy access) should be reviewed with a documented plan about their suitability for drug administration in the dying phase. [Grade D]

4. Medications should be prescribed for administration by the most reliably accessible route. [Grade B]

5. Use an individualised approach to prescribe as required medications for the following symptoms: [Grade D]
   - Pain
   - Breathlessness
   - Excessive respiratory tract secretions
   - Restlessness and agitation
   - Nausea and vomiting

6. Each specialist palliative care service should have a policy or standard operating procedure describing how syringe pumps for continuous subcutaneous infusion:
   - are accessed
   - are used safely
   - And how staff are supported in developing and maintaining competency in their use. [Grade D]

7. Medication should be administered by the most appropriate route if a CSCI cannot be used because of patient preference, non-availability or patient safety. [Grade D]

8. The efficacy of medication used to support the care of the dying person should be reviewed daily. [Grade D]

Applications and Implications

There is limited economic modelling of the impacts of the use of symptom control medication in the dying. One cohort study of 191 participants examined the cost effectiveness of use of hyoscine hydrobromide compared with glycopyrronium to improve respiratory tract secretions, finding a potential saving of £1.53 per patient with glycopyrronium. The authors themselves recognised the significant limitations of the methodology given the difficulties of studies in people with palliative care needs, commenting “to prove null hypothesis that both drugs are equally efficacious in 30 bedded unit would take 12 years or a multi-centre study.”
The majority of drugs used are generic in formulation. The guidelines do not suggest significant changes in comparison with existing clinical practice, therefore implementation of this guideline is likely to be cost neutral.

The greatest impact will be in improving quality of care as outlined in the introduction through improved symptom control and satisfaction with care.


Recommendations for research and service improvement include:

- Comparison of subcutaneous and buccal midazolam in the management of agitation in the dying.
- Use of CSCI Levetiracetam versus CSCI midazolam for the management of seizures in the dying.
- Comparison of patient outcomes (e.g. symptom control, site reactions) for 24hr and 48hr CSCI medication delivery in the dying.
- Comparison of subcutaneous analgesic requirements on account of adiposity (e.g. BMI >30 vs BMI<30) in the dying phase.
- Evaluation of the use of NSAIDs (e.g. ketorolac, diclofenac) to manage sweats and pyrexia in the dying.

**Acknowledgments and Declarations of Interest**

We acknowledge the work of the following in supporting these guidelines.

**Development, Public Participation and External Peer Review**

- Dr R Isherwood (Consultant in Palliative Medicine, Strathcarron Hospice, Scotland), Dr A Dickman (Consultant Pharmacist, Blackpool Teaching Hospitals NHS Trust), Dr M Brooks (Medical Director, St Rocco’s Hospice, Warrington), Dr K Groves (Medical Director, Southport, West Lancashire and Formby Integrated Specialist Palliative Care Service), Ms H Ferguson (Clinical Nurse Specialist in Palliative Care, Royal Liverpool and Broadgreen University Hospitals NHS Trust) and Dr I Back (retired Consultant in Palliative Medicine) who developed the previous guidelines in 2006
- Christine Riley our patient, carer and public representative who reviewed and influenced the development of the guidelines and our audit questionnaire
- Dr Aruna Hodgson, Consultant in Palliative Medicine, Wrightington, Wigan and Leigh Foundation NHS Trust who acted as the External Peer Reviewer
- Dr Helen Bonwick for kindly proof reading the final draft.
- The authors contributed as follows. Literature Review: CR, AN, AK. Audit Tools: AF, AK, AN, CR, DJ, MW, PG, RC. Updating Guidance and Grading Recommendations: AF, AK, AN, CR, DJ, MW, PG, RC. Standards: AF, AK, AN, CR, DJ, MW, PG, RC. Final writing of manuscript of guidelines: AK, AN, CR

**Funding**

The guidelines were funded through the use of supporting professional activity time facilitated by the employing organisations of the authors.
Conflicts of Interests
The authors and reviewers have declared no conflicts of interest.

Review Date
The guidelines will be reviewed three years after publication as outlined in the Cheshire and Merseyside Palliative and End of Life Care Network Audit Group Guideline Development Manual.
References


15. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Ketamine. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2014 [Link]

16. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Methadone. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2014 [Link]

17. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Neuropathic Pain. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]

18. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Non-Steroidal Anti-Inflammatory Drugs. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]
19. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. *Opioid Substitution*. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]

20. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. *Substance Misuse*. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]


27. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. *Oxygen*. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2014 [Link]


Guidelines for the use of Symptom Control Medication & the Dying Person
Date of Production: October 2015
Date of Review: October 2018


41. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Agitation. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]

42. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Delirium. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]

43. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Spiritual Care. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]


46. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Bowel Obstruction. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]

47. Cheshire and Merseyside Palliative and End of Life Care Network Audit Group. Nausea and Vomiting. Liverpool: Cheshire and Merseyside Palliative and End of Life Care Network Audit Group; 2010 [Link]


Appendix 1: Systematic Review Summary Form

Guideline Title: Guidelines for using Symptom Control Medication in the Dying Person

Reviewers: Amara Nwosu, Claire Robinson, Andrew Khodabukus