Government of **Western Australia**
Department of **Health**

WA Cancer and Palliative Care Network

Evidence based clinical guidelines for adults in the terminal phase

Second Edition

Good palliative care involves anticipatory sourcing of medications and pre-emptive prescribing

The **"Evidence based clinical guidelines for adults in the terminal phase"** flipbook resource provides five evidence based protocols for palliative care:

1. Dyspnoea (Community and Inpatient)
2. Nausea and Vomiting
3. Pain
4. Respiratory Tract Secretions
5. Terminal Restlessness/Agitation.

The five protocols each have a user friendly flowchart, evidenced based summary and the full version of the evidence based clinical guidelines.

The WA Cancer and Palliative Care Network would like to thank the expert panel who developed the resources for the Palliative Care Community Medications Project:

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If you would like more information about the Palliative Care Community Medications Project or other projects developed by the WA Cancer and Palliative Care Network please visit: www.healthnetworks.health.wa.gov.au/cancer

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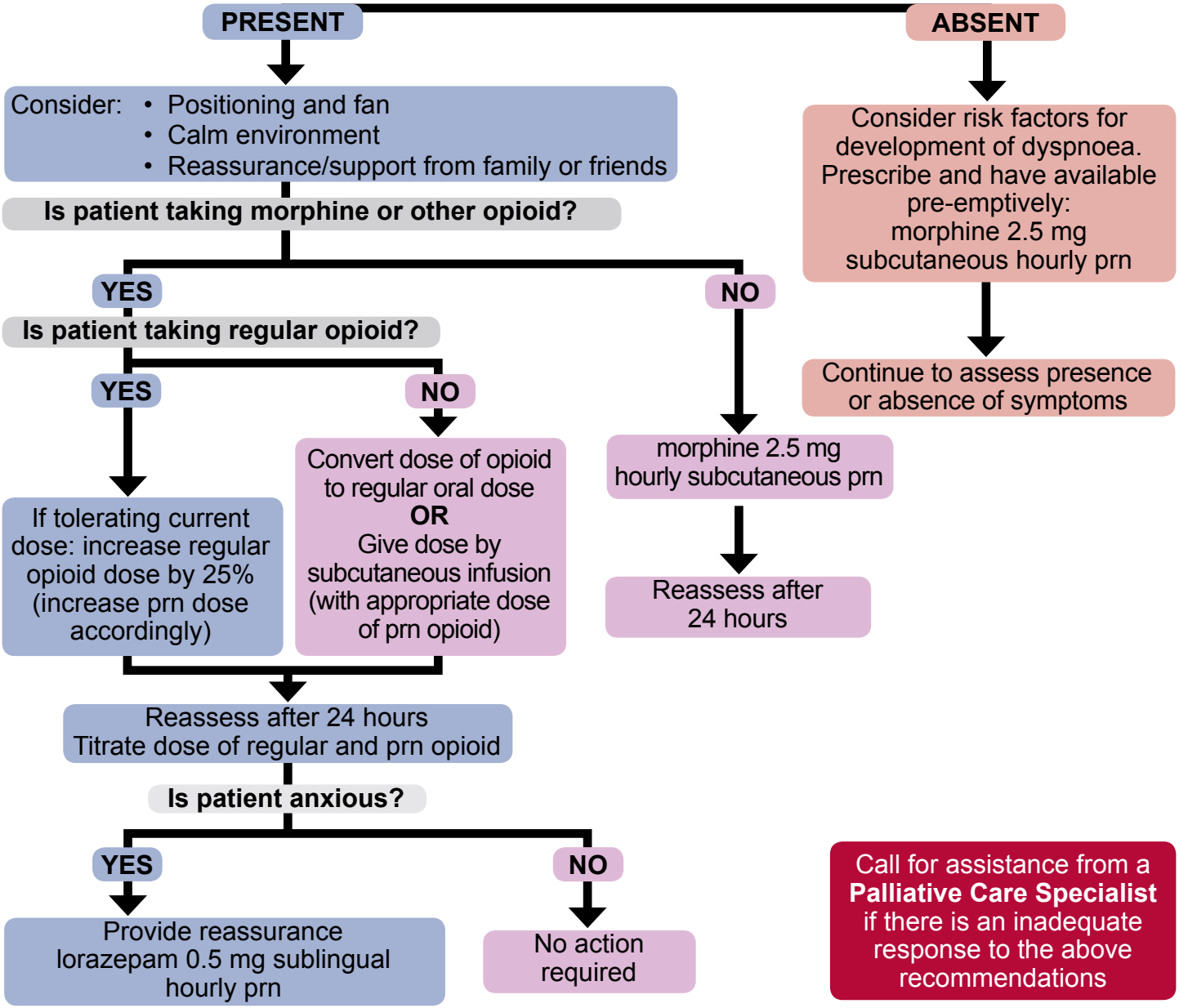
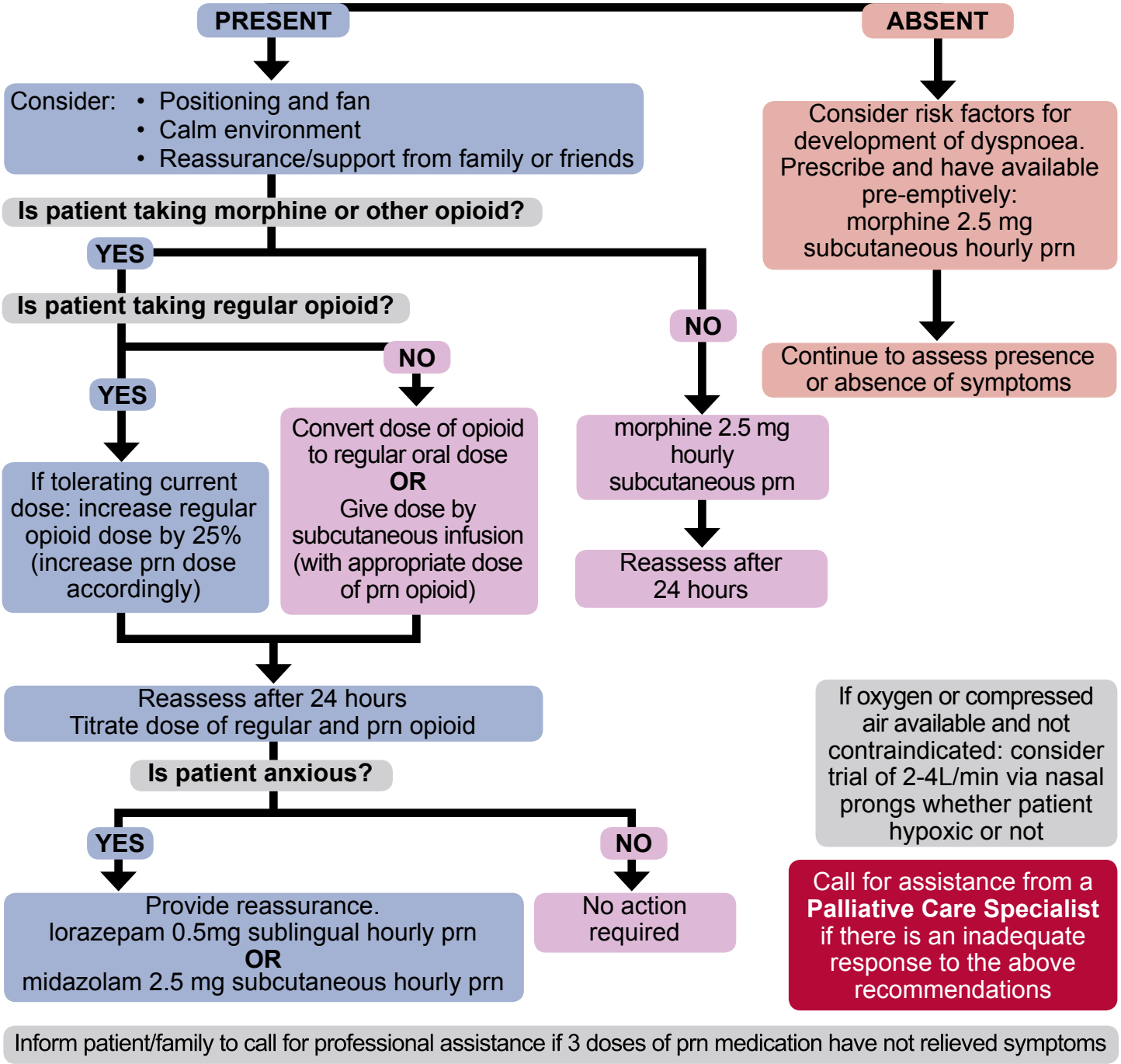
Evidence based clinical guideline for adults in the terminal phase



Management of Dyspnoea (Community)

Evidence based clinical guideline for adults in the terminal phase



Management of Dyspnoea (Inpatient)

Summary of Evidence
Evidence based clinical guidelines for adults in the terminal phase

- Dyspnoea is a subjective experience.[1,2,3 [Level V]]
- Opioids are beneficial in reducing the symptom of dyspnoea.[4 [Level I]]
- Subcutaneous or oral morphine improve the symptom of dyspnoea without a detrimental effect on respiratory function.[4 [Level I],5 [Level II],6 [Level III-2]]
- Low dose morphine is effective in relieving dyspnoea.[5,7,8 [Level II]]
- There is insufficient evidence to recommend the use of inhaled opioids.[4 [Level I]]
- Dyspnoea is significantly associated with anxiety.[9 [Level III-2],10 [Level IV]]
- The addition of a benzodiazepine (midazolam) to a baseline of regular morphine improves sensation of dyspnoea in presence of anxiety.[11 [Level II]]
- Oxygen saturation does not correlate with sensation of dyspnoea.[12 [Level II]]
- Oxygen (and air) decrease the sensation of dyspnoea at rest regardless of whether hypoxia is present.[12,13 [Level II]]
- Some patients with cancer feel better during oxygen inhalation.[14 [Level I]]
- Air flow over the face[15 [Level III]] and nasal mucosa[16 [Level II]] lessens the sensation of dyspnoea.

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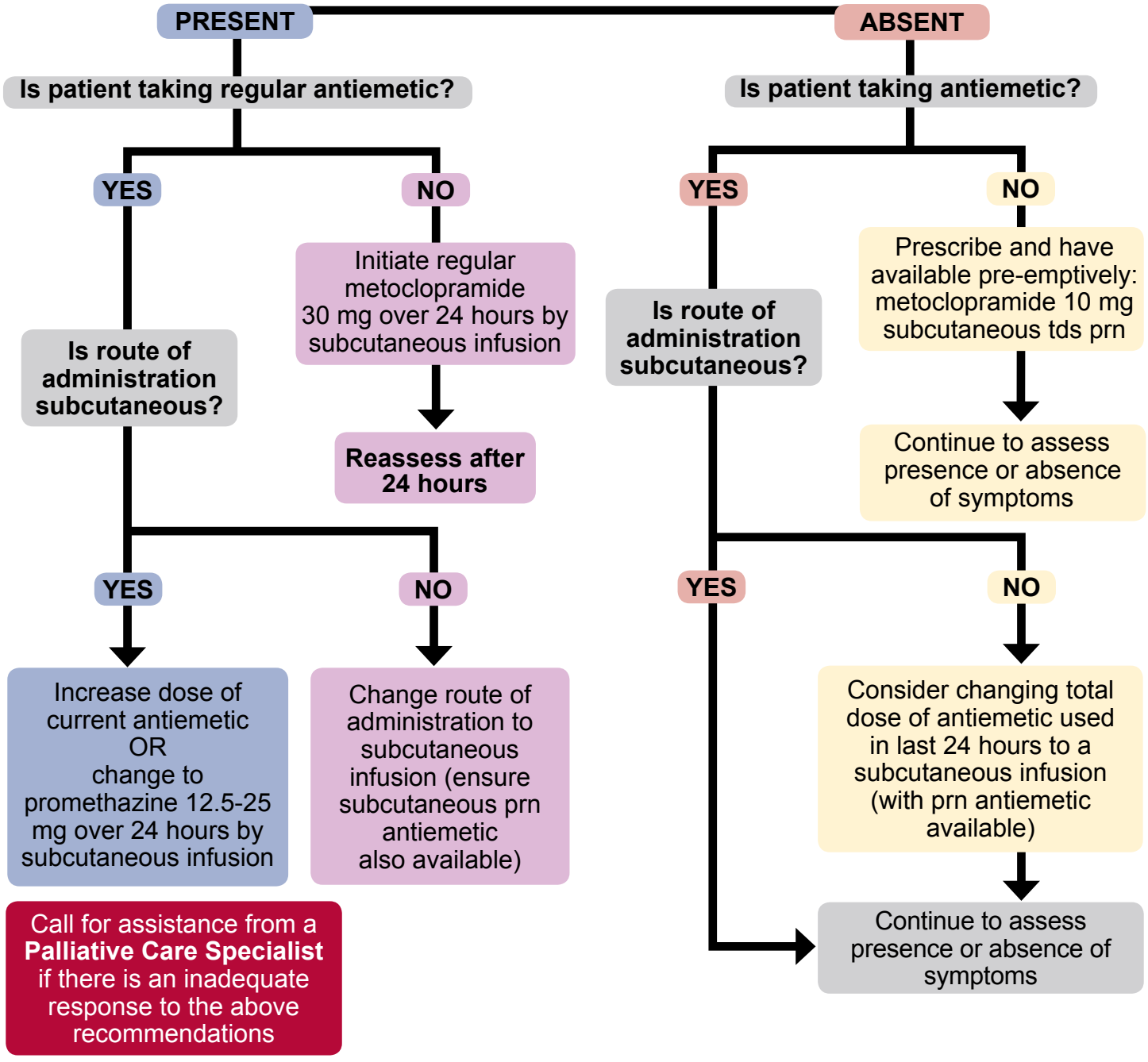

Management of Nausea and Vomiting

Summary of Evidence
Evidence based clinical guideline for adults in the terminal phase

- The rate of both nausea and vomiting generally decreases as patients enter the terminal phase of disease.[1] [Level III-3]
- The appropriate medication is usually selected dependent upon its receptor and neurotransmitter affinity, after determining the most likely cause of emesis.[2,3] [Level V]
- This mechanistic approach may not be so relevant in end of life symptom management.[2] [Level V]
- To provide continuous relief of nausea or vomiting, medications should be given regularly (that is, at regular fixed intervals or by infusion).
- If unable to swallow or vomiting, the subcutaneous route of administration is recommended.[4] [Level V]
- An appropriate first line antiemetic in the terminal phase is metoclopramide due to its prokinetic and dopamine antagonist effects.
- Metoclopramide is effective in the management of nausea and vomiting in patients with advanced cancer.[5,6,7] [Level II]
- Promethazine is an appropriate second line antiemetic in the terminal phase as it exerts its effect on histamine receptors in the vomiting centre.

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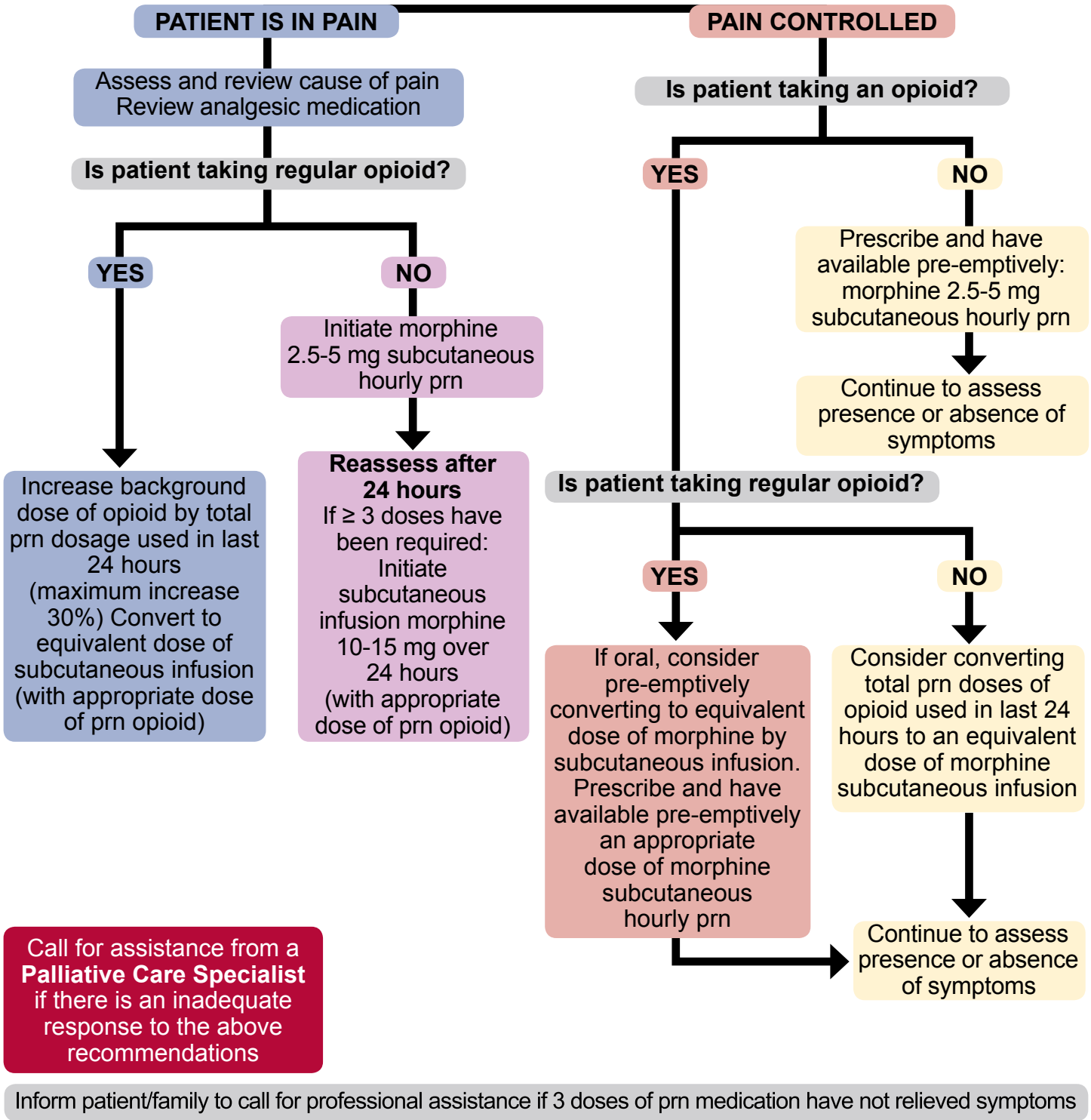
Evidence based clinical guideline for adults in the terminal phase



Summary of Evidence
Evidence based clinical guideline for adults in the terminal phase

- Morphine is the opioid of choice,[1 [Level V]] and is as effective as other opioids.[2 [Level I]]
  - If morphine is not tolerated contact a palliative care specialist for advice.
- Analgesia should be by the oral route of administration if possible.[3,4 [Level V]]
  - It is anticipated that patients will be increasingly less able to swallow as their condition deteriorates.
- If unable to swallow, the subcutaneous route of administration is recommended.[1,3 [Level V]]
  - Patients prefer administration of opioids subcutaneously compared with the intramuscular route.[6 [Level II]]
  - When changing from oral to subcutaneous morphine start with 1/3rd of the oral dose to allow for the decreased oral bioavailability.[3 [Level V]]
- To provide continuous pain relief, analgesia should be given “by the clock” (that is, at regular fixed intervals or by infusion).[4 [Level V]] This is the background dose.
  - Subcutaneous infusions of opioids are as effective as intravenous infusions.[7 [Level II]]
- Adequate dose of breakthrough opioid should be available. The dose is calculated as 1/6th or 1/12th of the daily dose.[1,2,3 [Level V]]
- Breakthrough doses of opioid should be prescribed 1 hourly ‘when required’ (prn).[2 [Level V]]
- Morphine should be prescribed with caution in renal dysfunction due to accumulation of neurotoxic metabolites.[3 [Level V]]
- Pethidine should not be used because of risk of accumulation of its toxic metabolite, norpethidine.[9,10 [Level IV]]
- Transdermal fentanyl is not appropriate to initiate in the terminal phase.

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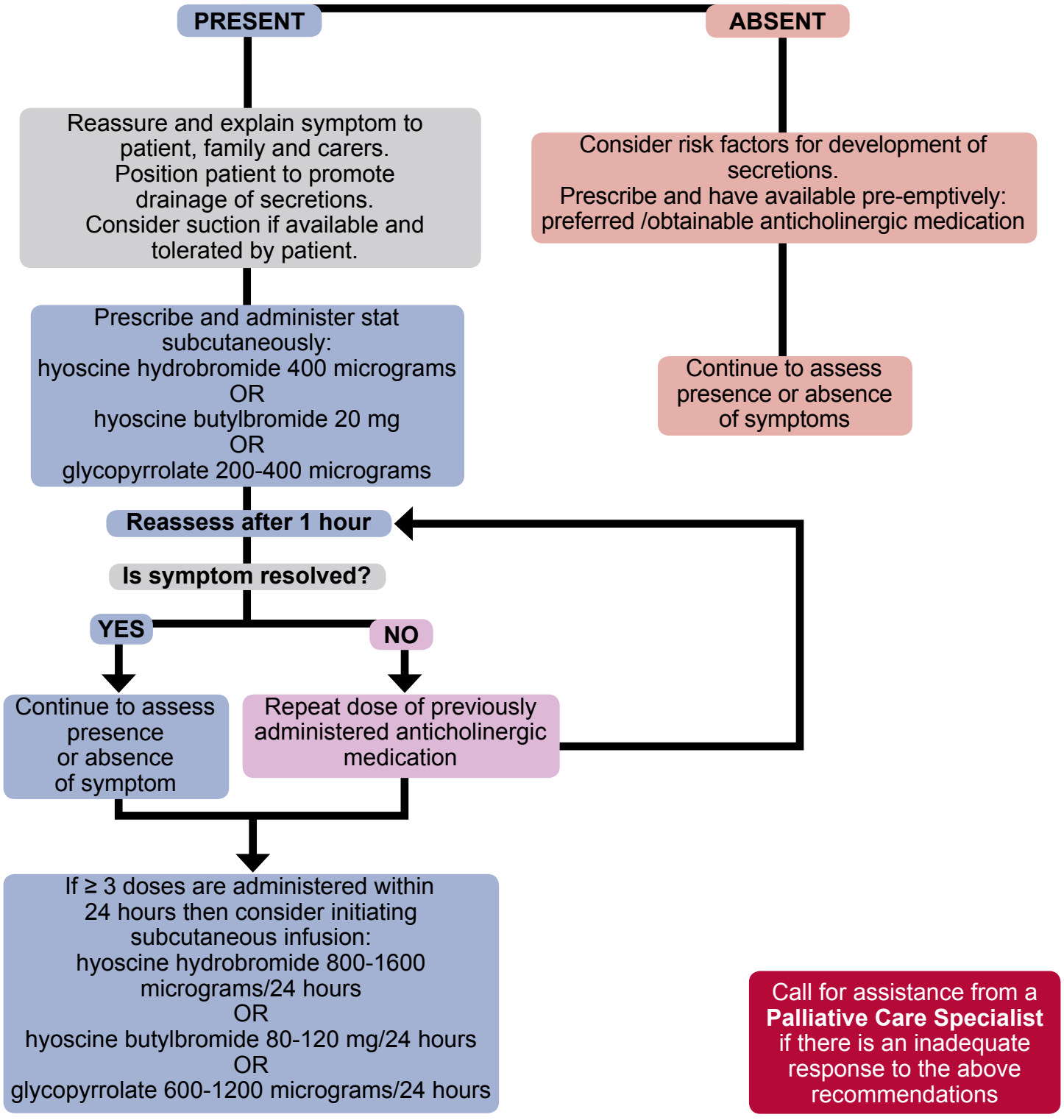

Management of Respiratory Tract Secretions

Summary of Evidence
Evidence based clinical guideline for adults in the terminal phase

- Reported incidence of terminal respiratory tract secretions ranges from 23%[1 [Level IV]] to 92%.[2 [Level III-2]] (Most studies report rates of between 30 - 56%).[3 [Level III-3], 4-7 [Level IV]]
- Incidence increases as patients are closer to death.[4 [Level IV]]
- Management is effective in approximately 40 - 70% of cases.[3,8,9 [Level III-3],6 [Level IV]]
- There is no consistent measure for terminal secretions, which may explain the variation in reported incidence and rates of effective management.
- Dehydration does not prevent the symptom of death rattle.[2 [Level III-2]]
- Family and carers distress about this symptom can be relieved with explanation of the reason for noisy breathing, and reassurance.[3 [Level III-3]]
- Positioning to promote drainage of secretions is effective.[10 [Level V]] Positioning with occasional suctioning improved symptoms without the use of medications in 31% of patients.[7 [Level IV]]
- Medications do not dry existing secretions, hence administering medication as early as possible is advantageous.[11 [Level III-2] ,9 [Level III-3],12 [Level V]]
- High incidence of symptom and the need for prompt treatment supports anticipatory prescribing to avoid delays in controlling symptom.
- There is no conclusive evidence of significant difference in efficacy of anticholinergic medications and therefore no particular medication can be recommended.[13 [Level I] ,11 [Level III-2]]
- Medication choice to be based on ease of access, cost and differing pharmacological profiles.

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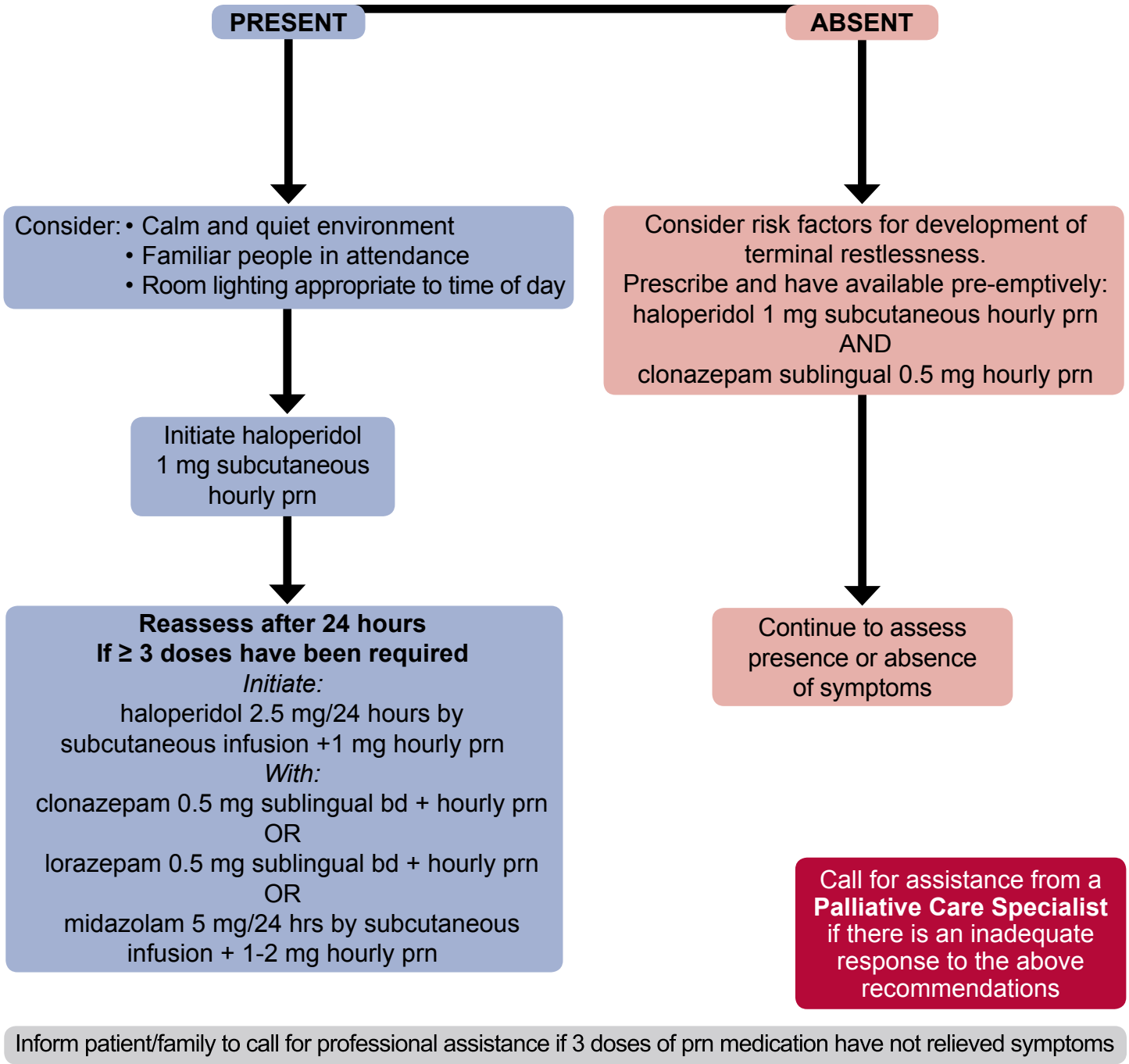

Management of Terminal Restlessness/Agitation

Summary of Evidence
Evidence based clinical guideline for adults in the terminal phase

- Terminal restlessness is an agitated delirium that occurs in some patients during the last few days of life.[1] [Level V]
- Reported incidence of terminal restlessness is 62%[2] [Level IV] - 88%.[3] [Level IV]
- Family members find terminal restlessness very distressing.[4] [Level IV]
- The development of delirium leads to increased caregivers anxiety.[5] [Level III-2]
- Non-pharmacological measures can be helpful in managing delirium.[6] [Level V]
- Where possible, any potentially reversible causes should be treated.[6] [Level V]
- Prompt pharmacological treatment is required to reduce the possibility of harm for the patient and distress for the family.[6] [Level V]
- There is limited evidence from clinical trials on the role of drug therapy for the treatment of delirium in terminally ill patients.[7] [Level I]
- Haloperidol is the drug of choice for the treatment of patients with delirium near the end of life.[7] [Level I]
- Low dose haloperidol (< 3mg per day) is effective in treating delirium with few adverse effects.[8] [Level I]
- Sedation may be necessary to complement the effect of haloperidol, and benzodiazepines are effective in this role.[6] [Level V]
- Benzodiazepines should not be used alone as they may worsen the delirium.[9] [Level II],[6]

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The levels of evidence applied to this document are those designated by the National Health and Medical Research Council of Australia (NHMRC) with the addition of a Level V.

Level V is deemed to be the opinion of specialists with experience in the field of palliative medicine.

I evidence obtained from a systematic review of all relevant randomised controlled trials.

II evidence obtained from at least one properly designed randomised controlled trial.

III-1 evidence obtained from well-designed pseudo-randomised controlled trials (alternate allocation or some other method).

III-2 evidence obtained from comparative studies with concurrent controls and allocation not randomised (cohort studies), case control studies, or interrupted time series with a control group.

III-3 evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.

IV evidence obtained from case series, either post-test or pre-test and post-test.

V specialist expert opinion.

Appendix II: Evidence based clinical guidelines

Introduction

Dyspnoea is a subjective experience of difficult, laboured and uncomfortable breathing.[1] It is a distressing symptom for the patient, their family and their carers. Patients and their families may have feelings of anxiety, fear, helplessness or panic associated with dyspnoea.[2]

It is a common symptom in the terminally ill. In the last 6 weeks of life 70% of patients suffer from dyspnoea, with the prevalence and severity increasing as death approaches.[3 [Level III]]

The risk of dyspnoea is increased in the presence of cardiac and respiratory disease.[3 [Level III]]

However, Reuben and Mor found that 24% of terminal cancer patients had no cardiopulmonary or other identifiable cause for their dyspnoea.[3 [Level III]] In terminally ill patients respiratory muscle weakness may contribute significantly to dyspnoea.[4 [Level III-2]]

Management

Early in the disease process therapy is aimed at treating any reversible causes of dyspnoea. In the terminal phase management should be focused on symptomatic relief.[2,5 [Level V]] The subjective experience does not usually correlate with objective measures.[6 [Level II]] Therefore measurements of, for example oxygen saturation, are rarely helpful at this stage of disease.[7 [Level IV]] The patient's level of distress should be the guiding factor in treatment.

Dyspnoea and pain are significantly correlated, with studies finding that the level of dyspnoea patients experienced was related to the level of pain [8 [Level III-2]], and that dyspnoea is more severe in patients with unrelieved pain.[9 [Level IV]] Therefore, pain management needs to be optimised in patients with dyspnoea.

Morphine

Morphine is beneficial in reducing the symptom of dyspnoea.[10 [Level I]] Morphine delivered subcutaneously or taken orally has been shown to improve the symptom of dyspnoea without a detrimental effect on respiratory function.[10 [Level I],11 [Level II],12 [Level III-2]]

The mechanism of action of morphine to relieve dyspnoea is not completely understood. Various mechanisms are proposed to contribute including decreased central perception, decreased respiratory rate and effort and reduction in anxiety.[16 [Level V]]

There have been no dose-finding studies to ascertain the appropriate dose of morphine for relieving dyspnoea. However, low dose morphine is effective in relieving dyspnoea.[11,13,14 [Level II]] Single subcutaneous doses of 5 mg decreased the symptom of dyspnoea for at least 3 hours in opioid naïve patients.[11 [Level II]] Slow release oral morphine 10 mg twice daily and 20 mg once daily relieved dyspnoea in opioid naïve patients.[14 [Level II],15 [Level IV]] In patients already taking regular doses of opioids for pain relief, a dose of 25% of the equivalent 4 hourly dose, may be sufficient to reduce dyspnoea for 4 hours.[13 [Level II]]

It is recommended therefore, to initiate therapy in those not previously prescribed opioids, with a small dose and to increase incrementally until dyspnoea is relieved.

If this is an acute episode of dyspnoea in an opioid naïve patient who is able to swallow then morphine mixture 5 mg (or 2.5 mg in elderly patients) is the preferred medication.[2,16 [Level IV]] This can be repeated at hourly intervals.

If breathlessness is continuous, use morphine mixture regularly 5 mg every 4 hours (or 2.5 mg every 4 hours in elderly patients). Initiating therapy with an immediate release medication will result in faster therapeutic plasma levels than a slow release preparation and therefore quicker symptom relief and the possibility of more rapid titration. A breakthrough dose (equivalent to the 4 hourly dose) should be made available and administered as required no more frequently than hourly. The dose can be titrated up if tolerated by the patient but ineffective in relieving the dyspnoea.

If the opioid naive patient is unable to swallow then a subcutaneous morphine dose of 2.5 mg (or 1 mg in elderly patients) is appropriate for acute dyspnoea.[2 [Level V]] If breathlessness is continuous use a subcutaneous infusion containing 10 mg morphine over 24 hours. A breakthrough dose (equivalent to 1/6th of the daily dose) should be made available and administered as required no more frequently than every 30 minutes. If this dose is ineffective in relieving the dyspnoea, it can be titrated up as tolerated by the patient.

Patients previously taking opioids whom have uncontrolled dyspnoea should have an increase in background opioid. There are no studies to direct the magnitude of the increase but consensus suggests a 25% - 50%.[2,16 [Level V]] An appropriate breakthrough dose should also be prescribed and given no more frequently than every 30 minutes.[2 [Level V]] The high incidence of dyspnoea in terminal patients as they approach death, and need for prompt treatment, supports anticipatory prescribing to avoid delays in controlling symptoms. A dose of morphine 2.5 mg subcutaneously 'when required' to be repeated at a maximum rate of every 30 minutes is reasonable.

Other Opioids

Opioids other than morphine do not have the data to support their use in managing this symptom. It is unclear whether they are all equally effective.[1 [Level V]] However, because the proposed mechanism of action could be attained with all opioids, it is proposed that they would have the same effect. There is no evidence that changing opioids will result in better management of dyspnoea.

Nebulised Opioids

There is insufficient evidence at present to recommend the use of inhaled opioids.[10 [Level I]]

Benzodiazepines

There is no evidence to support the use of benzodiazepines in relieving dyspnoea per se. However, dyspnoea is strongly associated with anxiety and patients with severe dyspnoea have significantly higher levels of anxiety.[9 [Level IV]] Dudgeon found a significant, although low association between breathlessness and anxiety visual analogue scores.[17 [Level III-2]]

Benzodiazepines are useful in relieving anxiety and therefore are frequently prescribed empirically for patients with an anxiety component to their dyspnoea with good effect. Alprazolam, lorazepam, clonazepam, diazepam and midazolam have been used. There have been no dose-finding studies for any benzodiazepines in the relief of dyspnoea.

Midazolam has been shown to improve the symptom of dyspnoea in anxious patients receiving regular morphine.[18 [Level II]] In that study doses of 5 mg subcutaneously every 4 hours were administered. More conservative doses of midazolam (2.5 mg subcutaneously) have been found empirically to be of assistance.[2 [Level V]] Midazolam has the advantage of having a rapid onset and a short duration of effect making it useful for relief of acute dyspnoea. It is also very sedating and

amnesic. It is however, expensive to obtain in the community setting. Alprazolam is a very effective anxiolytic with a suggested initial dosing regimen of 0.125 mg orally twice daily for relief of anxiety related to dyspnoea.[2 [Level IV]] It may also be given on an as needed basis in a dose of 0.125 mg not more frequently than 6 hourly.[2 [Level V]] It is less sedating than other benzodiazepines.

Lorazepam when given sublingually will treat acute anxiety attacks rapidly and has a shorter duration of effect than most benzodiazepines. It also has amnesic properties. If dyspnoea is continuous then ongoing therapy is needed. This can be achieved by giving the longer acting clonazepam twice daily (initial dose 0.25 mg twice daily).[2 [Level V]] Clonazepam has reliable absorption sublingually and will reach peak levels more rapidly by this route than orally.[19 [Level III-2]] Subcutaneous doses are used empirically with success. An alternative for relief of continuous breathlessness is midazolam 2.5-5 mg daily via subcutaneous infusion.[2 [Level V]] These doses may need titrating up if tolerated but not giving effective relief.

In situations where the patient is extremely distressed it may be appropriate to sedate them to make them less aware of the symptom and decrease their fear. This method of symptom control would need to be discussed with the patient and family before initiation. Increased doses of clonazepam or midazolam are effective sedatives.

Oxygen

Oxygen saturation does not correlate with sensation of dyspnoea.[6 [Level II]] Use of oxygen or air improves symptomatic feeling of dyspnoea regardless of whether the patient is hypoxic.[6,20 [Level II]]. This may in part be due to the effect of air flow over the face[21 [Level III]] and nasal mucosa.[22 [Level II]] Therefore, the use of a fan to blow air directly onto the face may be beneficial in relieving dyspnoea.

Evidence regarding the use of oxygen in palliative care is not conclusive. A recent meta-analysis found that oxygen did not relieve the symptom of dyspnoea although there was a group of patients that experienced less dyspnoea when using oxygen.[23 [Level I]] Another systematic review found that there wasn't a consistent improvement in breathlessness in patients with cancer when using oxygen compared with breathing air, with only one of four studies demonstrating an improvement in dyspnoea with oxygen inhalation.[24 [Level I]]

However, cancer participants felt better breathing oxygen.[24 [Level I]] These reviews did not include the study by Philip et al which found oxygen useful.[6 [Level II]] The use of oxygen should be individualised based on a formal assessment of benefit in the individual patient.[23 [Level I]] A trial of oxygen, delivered by nasal prongs, is reasonable in some patients, if available.[16 [Level V]]

Oxygen is not always readily available in the community and is an expensive commodity.
Use of a mask may be appropriate if the patient is comfortable with this method of administration, although many find it claustrophobic. Safety issues regarding its use need to be discussed with the patient and family.

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Evidence based clinical guideline for adults in the terminal phase

Introduction

Nausea and/or vomiting are common symptoms in palliative care patients. The prevalence of nausea is estimated to be between 6-68% across several terminal diseases.[1] [Level III-3] (AIDS 43-49%, heart disease 17-48%, renal disease 30-43%, cancer 6-68%)[1] [Level III-3]

The rate of both nausea and vomiting generally decreases as patients enter the terminal phase of disease. In a study of patients with end stage cancer, nausea decreased from a rate of 31% to 17%, and vomiting from 20 to 13% in the last one to two weeks of life.[2] [Level III-3] This decrease in symptom rate is attributed to the decrease in food intake, medications and activity by the person.

Management

There are many causes of nausea and vomiting in palliative care patients such as gastric stasis, intestinal obstruction, medications, biochemical abnormalities, raised intracranial pressure and psychological factors such as anxiety and fear.[3,4] [Level V] Ideally, reversible underlying causes of nausea and vomiting should be identified and treated.[4] [Level V] However, antiemetic medication is needed for most palliative care patients as they commonly have irreversible and multifactorial causes.[3] [Level V]

After determining the most likely cause of emesis the appropriate medication is selected dependent upon its receptor and neurotransmitter affinity.[4,5] [Level V] Often more than one neurotransmitter is involved, therefore treatment frequently requires more than one antiemetic. Up to one-third of palliative care patients will require more than one antiemetic for symptom control.[5] [Level V]

Two prospective studies that aimed to determine the relevance and efficacy of aetiology-based guidelines (otherwise named the mechanistic approach) in advanced cancer patients showed that nausea was controlled in 56%-82% of patients and vomiting in 84-89% of patients within one week.[6,7] [Level IV]

However, the mechanistic approach may not be so relevant in end of life symptom management.[4] [Level V] In the last few days of life it is generally not reasonable to investigate the many possible causes of the nausea/vomiting. The most probable causes are medications, electrolyte abnormalities or gastric stasis. The medication that will treat all these effects is metoclopramide via its dopamine antagonism and prokinetic action. An antihistamine such as promethazine is considered an appropriate second line agent due to its effect on the vomiting centre.

There are several antiemetics that may be effective in managing nausea and vomiting. If the patient is currently taking an antiemetic and symptoms are adequately controlled there is no need to change the antiemetic.

Once antiemetic therapy has commenced, the patient must be regularly re-evaluated to ensure effective symptom management. If, after optimising the regular antiemetic dose, there is still no improvement then the drug choice should be reconsidered. A second line antiemetic can be added or substituted if first line therapy is proving to be ineffective.[3,5,8] [Level V]

Antiemetics will be more effective if given on a continuous rather than ‘prn or as needed’ basis. The maintenance of adequate plasma levels of the medications will prevent nausea and/or vomiting from ongoing stimuli. An adequate dose of ‘as needed’ medication should also be available. Antiemetics should be continued, unless the cause is self-limiting.[5,8] [Level V]

The route of administration should be chosen to ensure the drug reaches the site of action. The oral route is generally not appropriate in the last few days of life as it is anticipated that patients will

be increasingly less able to swallow as their condition deteriorates. Vomiting will also decrease drug absorption. The recommended route of administration for palliative care patients is subcutaneous. [3] [Level V]

Metoclopramide

Metoclopramide is a commonly prescribed antiemetic for the management of nausea and vomiting of many causes. Metoclopramide has been found to be effective in the management of nausea and vomiting in patients with advanced cancer.[9,10,11] [Level II] The recommended initial oral dose of metoclopramide is 10 mg three to four times daily.[3,12] [Level V]

If the patient is unable to swallow or is vomiting, then metoclopramide may be administered by subcutaneous infusion. Metoclopramide given subcutaneously reaches a peak concentration comparable with intravenous and higher than intramuscular administration.[13] [Level III-2] The peak occurs at 30 minutes after subcutaneous administration (which is similar to intramuscular administration) and continues at therapeutic levels for 4 hours.[13] [Level III-2] Doses of 30-60 mg of metoclopramide by subcutaneous infusion over 24 hours are usually recommended. [3] [Level V]

Promethazine

Promethazine is a potent antihistamine with anticholinergic effects. It is commonly prescribed for the management of nausea and vomiting of various causes. It is recommended in the post-operative setting when prophylactic or first line therapy has failed.[14] [Level V] It is particularly useful to treat motion sickness and considered the most effective antihistamine in this setting.[15] [Level V]

Promethazine is an appropriate second line antiemetic in the terminal phase. However, if it is needed it should be substituted for, rather than added to, metoclopramide therapy.

Oral doses of 10-25 mg 6-8 hourly of promethazine are recommended.[16] [Level V] Smaller doses of 10 mg every 12 hours are also utilised with good effect. The higher doses commonly recommended (25 mg every 4-6 hours with a maximum of 100 mg over 24 hours) [3,12] [Level V] are not often required.

Promethazine has an oral bioavailability of approximately 25-30%[17,18] [Level III-2] and therefore by parenteral administration, smaller doses may be adequate. It has been found that 6.25 mg of intravenous promethazine will adequately treat nausea and vomiting of multiple causes.[19] [Level III-2] The usual initial dose for subcutaneous administration of promethazine is 12.5-25 mg daily by infusion.

The most common adverse effect is a dose related sedative effect. This may not be a problem in the terminal setting. The level of sedation experienced by patients using low dose promethazine was minimal and equivalent to that caused by ondansetron.[19] [Level III-2]

Promethazine is not generally recommended for subcutaneous administration because of concern regarding skin irritation.[20] [Level V] However, diluted in an adequate amount of sodium chloride 0.9% it can usually be administered over 24 hours by subcutaneous infusion without significant problems.

Conclusion

Antiemetics should be prescribed regularly and by a parenteral route to ensure adequate systemic effect. In the terminal phase metoclopramide is considered an appropriate first line medication. Promethazine may be substituted if nausea and/or vomiting continue.

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Evidence based clinical guideline for adults in the terminal phase

Introduction

Pain is a common symptom in the terminally ill and probably the symptom most feared by patients and families. It can be a major contributor to the overall suffering of the patient.

Although it is commonly recognised that pain occurs in most patients with advanced cancer (64%[1]), pain is not uncommon in other terminal diseases. In patients with AIDS 76% report pain,[2] 29% of patients with congestive cardiac failure have chest pain and 37% some type of pain.[3] In another study, 42% patients with congestive cardiac failure indicated that they had severe pain in the last three days of life.[4] Of patients with chronic obstructive pulmonary disease, 37% experience chest pain and 50% pain of some description.[4]

Pain is not just a physical experience. The emotional experience and inter-relationship with spiritual, social, and psychological factors must be considered and dealt with to facilitate good pain management.

Pain control can be achieved in the majority of patients although some may require referral for specialist management.[5 [Level V]]

Management

Opioids are the gold standard for managing pain in the terminal stages and morphine is the opioid of choice.[5,6 [Level V]] Morphine is as effective as other opioids in managing pain.[7 [Level I]] It also has the advantages of being easily accessible and available on the Pharmaceutical Benefits Scheme. It is available in parenteral form in various strengths and is licensed for subcutaneous administration. Importantly, most prescribers have some familiarity with its use.

Route of Administration

Although it is preferable to give analgesia by the oral route if possible,[5,8 [Level V]] it is anticipated that patients will be increasingly less able to swallow as their condition deteriorates. If unable to swallow, the subcutaneous route of administration is recommended.[5,6 [Level V]]

Patients prefer opioids to be administered subcutaneously compared with intramuscularly.[9 [Level II]] Intramuscular injections are usually more painful.[6 [Level V]] Nursing staff also prefer to give morphine subcutaneously (via a cannulae) rather than intramuscularly.[10 [Level IV]] The time to peak concentration after a subcutaneous injection of morphine is 16 minutes.[11 [Level IV]] The rate of absorption and variability in absorption of morphine are similar between the subcutaneous and intramuscular routes of administration.[11 [Level IV]] There is no difference in analgesic effect of morphine between these routes, and the adverse effect profile is the same.[9 [Level II]] When initiating or reviewing medications for a person who is dying it is recommended to utilise the subcutaneous route pre-empting the decreased ability to take oral medication.

Analgesia should be given ‘by the clock’ (that is, at regular fixed intervals) to give continuous pain relief.[8 [Level V]] Therefore to maintain effective analgesia, morphine injections need to be given every four hours. A continuous subcutaneous infusion will also provide continuous analgesia and represents a more practical administration method. Continuous subcutaneous infusions of opioids are as effective as continuous intravenous infusions and have a similar adverse effect profile in children and adults.[12 [Level II],13 [Level III-3]]

Doses of analgesia

It is recommended to initiate opioids with a small dose and to increase the dose incrementally each day until pain is relieved. For an opioid naive patient experiencing pain for the first time in the terminal stage of disease doses of 2.5-5 mg of morphine administered 1 hourly as required may be sufficient to manage pain. If the patient is requiring three doses or more doses of 'prn' analgesia in a 24 hour period then a subcutaneous infusion should be initiated with morphine 10-15 mg over 24 hours.[5 [Level V]]

For patients previously managed on oral opioids their current dose of medication should be converted to an equivalent dose of subcutaneous morphine by infusion. When changing from oral to subcutaneous morphine, the initial subcutaneous dose is one-third of the oral dose to allow for the decreased oral bioavailability.[5 [Level V]]

Breakthrough analgesia

In addition to the background analgesia, an adequate dose of 'prn' opioid should be prescribed for breakthrough pain.[5,6,8 [Level V]] This is given to the patient when they experience an acute episode of pain. There are no randomised controlled studies providing evidence for the best breakthrough dose. The present recommendations are based on expert opinion and provide safe guidelines for a starting breakthrough dose.[14 [Level V]] The prescribed breakthrough dose should be equivalent to one-sixth to one-twelfth of the daily dose.[5,6,8 [Level V]] Oral breakthrough doses of opioid should not be given more frequently than every 30 minutes,[5 [Level V]] and the recommended interval for prescribing is 'hourly prn'.[6 [Level V]] A dose of subcutaneous morphine will reach peak analgesic effect 50-90 minutes after administration, although peak plasma levels will be achieved more quickly.[15 [Level V]] It is therefore recommended that subcutaneous breakthrough doses are also prescribed hourly. If three consecutive breakthrough doses are taken without achieving pain relief, then a review of pain management is required. [5 [Level V]]

Increasing doses

Titration of morphine doses is dependent upon the patient's response to the previous day's morphine dose. If the patient has required two or more doses of breakthrough analgesia it is reasonable to increase the background daily dose to include the total of those doses.[5,6 [Level V]] The breakthrough dose may then need adjusting as well.

Other analgesics

Although patients experiencing pain for the first time in the terminal phase will usually have good effect from morphine, not all pain is managed by opioids. Patients who have been previously taking analgesia should continue on their current medications, which may include paracetamol, non-steroidal anti-inflammatory drugs and agents for neuropathic pain. The doses may need to be adjusted if pain is increasing or if the patient is experiencing adverse effects. Oral medication may need to be converted to a subcutaneous or rectal formulation.

Renal impairment

Most opioids are metabolised in the liver and then excreted renally. Therefore in patients with renal impairment, the opioids and their metabolites may have a prolonged effect and higher plasma levels. This may result in excessive drowsiness, confusion, respiratory depression, myoclonus or seizures.

The general recommendation is to decrease doses and increase the interval between doses of opioids in patients with mild to moderate renal impairment. In the last few days of life it is generally inappropriate to measure renal function. Therefore, dose initiation must be based on previous information (if available) and careful titration. Patients will need regular monitoring for analgesic efficacy and adverse effects.

It is generally recommended that morphine should be used with caution in patients with renal impairment. [5 [Level V]] It is not only morphine, but also the more potent and neurotoxic metabolites that may accumulate. If the creatinine clearance is less than 30mL/min the recommended initial dose is 50% of the normal dose.[16 [Level V]] That is, 2.5 mg oral morphine or 0.75 mg subcutaneous morphine every 6-8 hours. Although a subcutaneous infusion (5-7.5 mg morphine over 24 hours) may be initiated, it may be preferable to change to an alternative opioid.

The most preferable alternative opioid for use in the last few days of life is hydromorphone. This is based not only on safety, but also on the availability and low cost of the parenteral formulation. Small amounts of hydromorphone and its active metabolite are excreted renally and therefore accumulation with the expected adverse effects may occur.[5,17 [Level V]] The initial dose of hydromorphone in a renally impaired patient is 1-2 mg by subcutaneous infusion over 24 hours with a breakthrough dose of 0.2-0.4 mg hourly when required.

Oxycodone and fentanyl are considered safer in renal dysfunction than morphine. The metabolites of oxycodone are not thought to contribute significantly to its analgesic effect or cause adverse effects.[18 [Level V]] Therefore, although excretion of oxycodone and its metabolites is slowed in renal impairment, dose adjustment only needs consideration in severe renal dysfunction.[19 [Level V]] Fentanyl has no pharmacologically active metabolites [5 [Level V]] and its clearance is not greatly affected by renal impairment.[20 [Level V]] Although patients should be closely monitored, dosage adjustment is usually not required. [20 [Level V]] However, the parenteral formulation of both of these medications is currently unavailable on the Pharmaceutical Benefits Scheme.

Opioids not recommended in the terminal phase of care

Pethidine has no advantages over other opioids and its use should be discouraged. It causes more nausea and vomiting that morphine.[21 [Level III-3]] Repeated dosing of pethidine results in accumulation of its active metabolite norpethidine, causing neurotoxicity including tremor and seizures.[22, 23 [Level IV]] Since norpethidine is renally excreted toxicity is an even greater risk in the presence of renal impairment.

It is not recommended to initiate fentanyl patches in the terminal stages of disease because of their delayed effect (peak concentration reached 24-72 hours after application [24 [Level V]]) and the need for slow titration. For a patient already using transdermal fentanyl, continuing this method of analgesia through the last days of life is suitable.

Methadone may be a suitable opioid to continue in the terminal phase but assistance should be sought from a palliative care specialist if the patient is taking this medication. It has complicated pharmacokinetics and dose adjustments need to be undertaken with care. Methadone should not be started in the last few days of life.

Conclusion

Morphine is the medication of choice for patients suffering pain for the first time in the last few days of life. The dose should be administered by subcutaneous infusion and titrated carefully to provide effective pain relief. Patients who have been previously stabilised on oral opioids may need to be converted to subcutaneous morphine in the terminal stages.

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Evidence based clinical guideline for adults in the terminal phase

Introduction

Terminal respiratory tract secretions are also known as 'death rattle'. It describes the gurgling, bubbling noise made as air passes through or over accumulated secretions in the oropharynx or bronchial tree in patients close to death who are unable to clear the secretions by coughing or swallowing.[1]

The reported incidence of respiratory tract secretions ranges from 23%[2 [Level IV]] to 92%.[3 [Level III-2]] The wide range in reported incidence is possibly due to a lack of definition and objective measures of the symptom. Most studies report rates of between 30-56% (31-50%[4 [Level III-3]], 56%[5], 49%[6], 50%[7], 44%[8 [Level IV]]). The incidence increases as patients move closer to death.[6 [Level IV]]

Patients with lung or cerebral cancer have been found to have a significantly higher risk of developing death rattle.[6,8 [Level IV]] Morita et al reported that refractory symptoms are more common in the presence of lung disease, either cancer or infection and oedema.[8 [Level IV]] This association was not found in a previous study but lack of diagnostic sensitivity may have affected the likelihood of demonstrating this relationship.[3 [Level III-2]]

Previous anecdotal evidence has suggested that there is a relationship between the level of hydration and respiratory secretions. This has led to the recommendation for removal of artificial hydration in terminally ill patients to prevent death rattle. Ellershaw et al demonstrated a trend in the relationship between level of hydration and the development of respiratory tract secretions but the data was not statistically significant.[3 [Level III-2]] Furthermore, being biochemically dehydrated did not prevent the accumulation of respiratory secretions or the symptom of 'death rattle'.[3 [Level III-2]]

Management

Studies concur that the management of 'death rattle' is effective in approximately 40-70% of cases (54-65%[4], 40-57%[9 [Level III-3]], 71%[7], 58%-72%[8 [Level IV]]).

Management usually encompasses positioning and administration of anticholinergic medications. Positioning to promote drainage of secretions is effective.[10 [Level V]] Lichter and Hunt found that 31% of patients with terminal secretions were effectively managed using only nursing interventions that included change of position, reassurance and occasional suctioning.[5 [Level IV]] Removal of secretions by gentle suctioning may be useful but the benefits usually last only a few minutes.[11[Level V]]

Since anticholinergic medications are anti-secretory it is unlikely that they dry existing secretions.[1 [Level III-2], 4,12 [Level III-3]] Symptom management is not always achieved rapidly and hence early detection and prompt administration of medication is advantageous.[8 [Level IV] ,11 [Level V]]

There are three clinical studies reported in palliative patients comparing the effectiveness of anticholinergic medications. These studies do not involve large numbers of patients and are not randomised controlled trials. None of these studies found a significant difference between the medications (see Table 1 for results of two studies).

Table 1: Summary of study results

Authors	Measurement	Hyoscine butylbromide 20mg	Hyoscine hydrobromide 400 microgram	Glycopyrrolate 200 microgram
Hughes et al [4] (n=37 in each arm)[Level III-3]	% patients improved 30mins after single subcutaneous dose	54%	35%	46%
Back et al [11] (n=128 hyoscine; n= 63 glyopyrrolate) [Level III-3]	% patients improved 30mins after first dose		56%	27%
	% patients required second dose		33%	50%
	% patients improved by last measurement		51%*	42%*

* not statistically significant

The third study was conducted by Hugel et al.[9 [Level III-3]] Patients whom had received hyoscine hydrobromide (n=36) were retrospectively matched with those whom had received glycopyrrolate. The protocol involved a stat dose and then a subcutaneous infusion with dosage adjustments as required each 24 hours.

Observations were undertaken every 4 hours and resulted in no significant difference at 4 hours after the first dose. At time of death 26 (72%) of patients in the glycopyrronium group and 21 (58%) of hyoscine group were symptom free. There are no details of extra doses; however 3 patients receiving hyoscine and 7 patients receiving glycopyrrolate had their infusion dose increased.

Bee and Hillier discuss the results of another study by Likar et al (unable to be accessed and written in German) which was a small (n=31) randomised cross-over study comparing the effect of hyoscine hydrobromide to saline.[13 [level I]] The assessment was conducted on a scale of one to five, with one being noisy breathing and five being very severe rattle. The intervention group showed a non-significant reduction in death rattle over a period of 10 hours.

There appears to be great individual patient variation in the effectiveness of anticholinergic medications in drying salivary secretions.[14 [Level III-2]] No conclusive evidence of comparative efficacy has been attained and therefore no particular medication can be recommended.[1 [Level III-2] ,13 [Level I]]

It is suggested, that although there is currently no conclusive evidence to support the use of anticholinergic medication in drying terminal secretions, the practice is deeply engrained in palliative care practice and is likely to continue.[13 [Level I]] However, the prescribing of these agents should be undertaken with close monitoring for lack of therapeutic benefit and for adverse effects, with therapy discontinued in these situations.[13 [Level I]]

Family and carers are often very distressed by this symptom. Their anguish can be relieved with explanation of the reason for noisy breathing, and reassurance.[4 [Level III-2]] It has been demonstrated that distress can be relieved in about 90% of relatives by sensitive communication.[3 [Level III-2] ,15 [Level IV]]

Dose recommendations

The current dosage recommendations are listed in Table 2.

Table 2: Dose recommendations for anticholinergic medications for the management of terminal secretions [10,16 [Level V]]

Medication	Subcutaneous stat / prn dose	Subcutaneous infusion dose over 24 hours
Atropine	400-1200 microgram 4-6 hourly	1200-2000 microgram
Glycopyrrolate	200-400 microgram	600-1200 microgram
Hyoscine butylbromide	20 mg 4 hourly	20-120 mg
Hyoscine hydrobromide	400 microgram 4 hourly	800-2000 microgram

The medications have been found to have a dose-dependent effect in drying secretions.[17 [Level II] , 14 [Level III-2]]

Glycopyrrolate is considered to be 5 times more potent in its antisialogogue effect than atropine suggesting that the equivalent dose for 200 microgram of glycopyrrolate is 1 mg atropine.[17 [Level II]] Hyoscine hydrobromide 400 microgram is considered equivalent to glycopyrrolate 270 microgram.[14 [Level III-2]] Hyoscine hydrobromide is also an effective central anti-emetic.[18 [Level V]]

Adverse effects

The adverse effect profile of the various anticholinergic medications is often the determining factor in the choice of agent.

All anticholinergic medications may exacerbate oesophageal reflux, cause urinary retention, dry mouth or precipitate narrow-angle glaucoma. These medications also influence heart rate. Atropine in doses of 400-600 micrograms may cause tachycardia after an initial slowing of the heart.[18 [Level V]] This effect is dose related although not as pronounced in elderly people.[18 [Level V]] The cardiac effect of the other medications is considered minimal although variable. Glycopyrrolate has also been shown to accelerate heart rate in doses of 8 micrograms/kg.[19 [Level III-3],20 [Level IV]] Hyoscine hydrobromide may result in a slowing of heart rate after an initial increase.

Glycopyrrolate and hyoscine butylbromide do not readily cross the blood brain barrier and therefore rarely exhibit central nervous system effects. This is in contrast with the drowsiness, amnesia, fatigue and dreamless sleep that are commonly associated with the use of hyoscine hydrobromide.[18 [Level V]] These effects may however be an advantage in the terminal stages of disease.

Atropine and hyoscine hydrobromide at high dose may cause restlessness, hallucinations, excitement and delirium.[18 [Level V]] The same adverse effects may also be experienced at therapeutic doses of hyoscine hydrobromide in the presence of severe pain.[18 [level V]] However, Hugel et al found no significant difference in level of agitation between glycopyrrolate and hyoscine hydrobromide.[9 [Level III-3]] It has also been observed that there is no difference in the amount of sedative medication needed in patients taking these medications.[12 [Level III-3]]

Conclusion

The high incidence of terminal respiratory tract secretions, and need for prompt treatment, supports anticipatory prescribing to avoid delays in controlling symptoms. Differences in onset of action, adverse effects, access and cost need to be considered when choosing appropriate agent.

Table 3: Comparison of anticholinergic medications for managing terminal respiratory tract secretions

	Atropine	Hyoscine hydrobromide	Hyoscine butylbromide	Glycopyrrolate
Cost *	PBS	$55.00 (5 x 400 micrograms)	$35.00 (5 x 20 mg)	$58.20 (5 x 200 micrograms)
Equivalent dose	1 mg	400 micrograms	20 mg	200-270 micrograms
Effect on secretions (dose dependent)	(1 mg)[21]	(500 micrograms)[17]	(30 mg)[22]	(200 micrograms)[21]
Onset of action	30 mins	30 mins	15 mins	30 mins
Time to peak effect	1 hour	1 hour	15 mins	2 hours
Duration of effect	4 hours	4 hours	1 hour	4 hours
Decrease in secretions	72%	79%	25%	74%
Adverse and other effects [18-20,22]				
Sedative effects	Nil	Sedative and amnesic	Minimal sedation	Minimal sedation [4]
Other CNS effects	Restlessness, confusion	Restlessness, delirium	Nil	Nil
Heart rate (dose related)	Transient decrease and then increase[18]	Transient increase and then slowing[18]	Increase[5]	Significant increase after 60 mins [3] Significant increase 15-60 mins [4]
Antiemetic	Not reported	Yes	No	No

* March 2010 dispensed price

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Evidence based clinical guideline for adults in the terminal phase

Introduction

Terminal restlessness is an agitated delirium that occurs in some patients during the last few days of life.[1 [Level V]] The symptoms include irritability, anxiety, paranoia, distress, hallucinations and confusion.

Delirium is a common symptom in the general population occurring in up to 30% of all admissions to hospital.[2 [Level I]] In comparison, the incidence of delirium diagnosed on admission to an inpatient palliative care service is between 29% and 44%.[3, 5 [Level IV], 4 [Level III-2]]

In the last few days of life the incidence of delirium increases, with terminal restlessness reported in 62%[5 [Level IV]] to 88%[4 [Level III-2]] of patients. Most studies suggest an incidence of more than 80% (83%[6 [Level IV]], 85%[7 [Level IV]], 88%[4 [Level III-2]]).

Terminal restlessness is thought to be disturbing for patients. It has been found that 54% of cancer patients who experience delirium can recall the experience after the delirium has resolved.[8 [Level IV]]

Family members find terminal restlessness very distressing.[9 [Level IV]] When family members were asked to rate the level of distress they felt when observing the various symptoms associated with end of life delirium, the only symptom with low rates of distress was somnolence. 71-87% of family members experienced high levels of anguish from the each of the symptoms of agitation, hallucinations, inappropriate behaviours, and cognitive symptoms such as disorientation, memory disturbance and communication difficulty in their dying relative.[9 [Level IV]]

The development of delirium leads to increased anxiety in caregivers.[10 [Level III-2]] Caregivers of patients with advanced cancer who experienced delirium, were 10 times more likely to have generalised anxiety than caregivers whose family member didn't have delirium.[10 [Level III-2]]

Management

Prompt recognition and treatment of terminal restlessness is required to reduce the possibility of harm for the patient and distress for the family.[11 [Level V]] In the last few days of life relieving symptoms is paramount, and therefore treatment of delirium should not be delayed while searching for the cause.[12 [Level V]] It is usually appropriate to limit assessment to history and physical examination.[12 [Level V]]

Reversing precipitating causes

Where possible, any potentially reversible causes should be treated.[11 [Level V]] There is often more than one precipitating factor for terminal restlessness. Lawlor et al found that the median number of causes per episode was 3 (range 1-6).[4 [Level III-2]] Delirium may be reversible in 49% patients with advanced cancer,[4 [Level III-2]] although this percentage may be lower in the last few days of life.

Medications are a common precipitating factor of delirium, with medications commonly prescribed in palliative care such as opioids, anticholinergics, selective serotonin reuptake inhibitors, tricyclics antidepressants, corticosteroids, anticonvulsants and benzodiazepines, are all possible causes. It is therefore recommended that a medication review is undertaken, and consideration given to dose reduction, substitution with less toxic medications, and discontinuation of unnecessary medications.

In the presence of deteriorating renal impairment morphine should be used with caution.[11 [Level V]] Morphine and its neurotoxic metabolites may accumulate increasing the risk of terminal restlessness. It may be necessary to substitute another opioid to manage pain. (see Management of Pain: Clinical Guideline).

Other common causes of terminal restlessness are metabolic disturbances, dehydration, hypercalcaemia, drug withdrawal, infection, hypoxia, renal or hepatic failure or cerebral causes. Most of these will not be easily reversed in the terminal phase and initiating treatment (eg. intravenous bisphosphonates for hypercalcaemia) may not be appropriate.

Non-pharmacological management

Simple non-pharmacological measures can be helpful in managing delirium.[11 [Level V]]

It is recommended to ensure a quiet environment with familiar people and objects, and to avoid bright lights or complete darkness.[11 [Level V]] Playing favourite music may also be useful and relaxing.[11 [Level V]]

Dehydration may contribute to terminal restlessness. However, there is insufficient evidence to determine if the use of subcutaneous rehydration improves symptoms and quality of life.[13 [Level I]] Increased fluid may worsen some symptoms in the terminal phase due to fluid retention.[13 [Level I]] The decision to rehydrate subcutaneously should be done on an individual basis. It will require knowledge of the individual patient situation, symptoms and wishes, and the advantages and disadvantages of rehydration.

Pharmacological management

Evidence from clinical trials is limited on the role of drug therapy for the treatment of delirium in terminally ill patients.[14 [Level I]]

Haloperidol

The data from the only randomised controlled study, would suggest that haloperidol is the most suitable medication for the treatment of patients with delirium near the end of life.[15 [Level II]] This conclusion is supported by the Cochrane review.[14 [Level I]]

Low dose haloperidol (< 3 mg per day) is effective in treating generalised delirium with few adverse effects.[2 [Level I]] In terminally ill AIDs patients, Breitbart et al found that during the first 24 hours the mean dose required to manage symptoms was 2.8 mg per day.[15 [Level II]] These doses are also supported by evidence that adequate occupancy of dopamine D_2 receptors to exert an antipsychotic effect is achieved with doses of 2 mg/day.[16 [Level II]]

After symptoms are controlled it is suggested that halving the dose may be possible. This is consistent with Breitbart et al's findings that the average maintenance dose after the first 24 hours was 1.4 mg per day, with a range of 0.4 - 3.6 mg.[15 [Level II]]

The adverse effects of haloperidol are dose related and therefore the lowest effective dose should be prescribed. Parkinson adverse effects were found to be common with higher dose haloperidol (>4.5 mg daily).[2 [Level I]]

Benzodiazepines

It may be necessary to complement the effect of haloperidol with anxiolytic and/or sedative medication, and benzodiazepines are effective in this role.[11 [Level V]] It has been reported that between 2-27% patients will need sedative medication to adequately control terminal restlessness.[17 [Level III-3] ,18,19 [Level IV]] Benzodiazepines should not be used alone for management of terminal restlessness as they may worsen delirium.[15 [Level II] ,11 [Level V]] There is limited evidence for the use of benzodiazepines in this setting. [11 [Level V]] The choice of benzodiazepine is based on availability, cost, setting (eg. community or inpatient facility), clinical situation and clinician experience with the various benzodiazepines for providing sedation.

Midazolam is commonly recommended because of its short duration of effect which facilitates rapid titration of dose.[12 [Level V]] It is given in doses of 2.5-5 mg subcutaneously no more frequently than hourly.[11 [Level V]] If repeated doses are required and have good effect then a subcutaneous infusion of midazolam may be appropriate. After consultation with a Palliative Care Specialist, midazolam could be initiated at low dose and titrated upwards until the necessary level of sedation is achieved to manage the terminal restlessness. Midazolam may not always be a practical choice because of lack of availability and cost.

Clonazepam is an alternative benzodiazepine that may be used for its anxiolytic and sedative properties. It has a duration of effect of 12 hours and the recommended dose is 500 micrograms when required.[20 [Level V]] It should not be given more frequently than every hour. When the oral solution is administered sublingually the onset of effect is within 5-10 minutes.[21 [Level III-2]]

Lorazepam may be given orally or sublingually in doses of 0.5-1 mg not more frequently than every hour. [11 [Level V]] When given sublingually the expected onset of action is 5 minutes.[20 [Level V]] Sublingual administration may not be effective if the patient has a dry mouth, as the tablet will not disperse adequately. Although lorazepam has a variable duration of effect of between 6-72 hours, it is most frequently prescribed every 12 hours when a continuous effect is required.[20 [Level V]]

Conclusion

When pharmacological action is required for managing terminal restlessness haloperidol is the medication of choice. It can be administered subcutaneously with small doses usually sufficient to manage delirium and improve cognitive function. In situation where terminal restlessness is not adequately managed a benzodiazepine may be added. The choice of benzodiazepine will be decided based on availability, setting, clinical situation and experience of the health care providers.

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