

World Health Organization

Essential Medicines in Palliative Care

EXECUTIVE SUMMARY

Prepared by:

International Association for Hospice and Palliative Care (IAHPC)

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BACKGROUND

The World Health Organization (WHO) defines essential medicines as those which satisfy the primary health care needs of the population. To advance application of the concept, the WHO also developed a Model List of Essential Medicines (EML) which is updated every two years, and is based on the criteria of safety, efficacy and cost effectiveness of each medicine listed. The concept and the EML are presented to countries as expert guidelines which they can use to develop their own essential medicines policies and lists.

The current EML includes specific recommendations for palliative care in children, but none for adults.

In 2007, in response to a request from the World Health Organization (WHO), the International Association for Hospice and Palliative Care (IAHPC) developed a List of Essential Medicines for Palliative Care based on the consensus of palliative care workers from around the world. IAHPC designed a process of five steps, which included developing a set of ethical guidelines; identifying the most common symptoms in palliative care; identifying a list of medicines to treat those symptoms; carrying out a survey using a modified Delphi process with more than 300 participants from 56 countries; and convening a meeting of representatives from 26 regional, international, and scientific pain and palliative care organizations to develop the final list. Twenty-one symptoms were identified as the most common in palliative care, and 33 medicines were included in the IAHPC List of Essential Medicines for Palliative Care (De Lima, 2007). This list was presented to the 16th WHO Expert Committee on the selection and use of essential medicines in 2007 to be considered for inclusion in the palliative care section. However, this list was not based on scientific evidence but on expert opinion. Therefore the expert committee decided to include the following statement in the palliative care section of the EML which still appears:

The WHO Expert Committee recognizes the importance of listing specific medicines in the Palliative Care Section. Some medicines currently used in palliative care are included in the relevant sections of the Model List, according to their therapeutic use, e.g. analgesics. The Guidelines for Palliative Care that were referenced in the previous list are in need of update. The Committee expects applications for medicines needed for palliative care to be submitted for the next meeting (WHO 2011).

Other palliative care organizations and institutions have identified or developed lists of essential medicines for palliative care but with the exception of one recently developed in Germany, all have been based on expert opinion (Lindqvist et al 2013; Merriman et al 2012; Good et al. 2005; Nauck et al, 2004).

In 2008, a group of paediatric palliative care specialists submitted an application for a list of essential medicines for the WHO EML (children) (Aindow and Brooke 2008). This application included a list of the most distressing symptoms in paediatric palliative care and recommended 17 medicines to be included in the EML (children).

In the fall of 2012, the Department on the Selection and use of Essential Medicines requested the IAHPC to prepare a summary of available evidence in support of the development of a List of Essential Medicines for palliative care to ensure access to appropriate medicines for the pharmacological management of the most prevalent and distressing symptoms in adult patients with life threatening and life-limiting conditions worldwide. This document summarizes the methodology followed, the main findings and results of the process and the recommended medicines and formulations needed for the treatment of each symptom. This application does not offer recommendations for the treatment of underlying diseases or conditions, only the symptoms associated with the disease and/or its treatment.

DEFINITION OF PALLIATIVE CARE (WHO, 2002)

Palliative care is an approach that improves the quality of life of patients and their families facing the

problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems physical, psychosocial and spiritual. Palliative care:

- provides relief from pain and other distressing symptoms;
- affirms life and regards dying as a normal process;
- intends neither to hasten or postpone death;
- integrates the psychological and spiritual aspects of patient care;
- offers a support system to help patients live as actively as possible until death;
- offers a support system to help the family cope during the patients illness and in their own bereavement;
- uses a team approach to address the needs of patients and their families, including bereavement counselling, if indicated;
- will enhance quality of life, and may also positively influence the course of illness;
- is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.

Life threatening illness is used to describe illnesses where it is expected that death will be a direct consequence of the specified illness. (Australian Government Department of Health and Ageing, 2012).

OBJECTIVES

- To identify the most important symptoms in palliative care, taking into account prevalence and associated distress
- To identify appropriate pharmacological approaches for management of individual symptoms
- To determine effectiveness and safety of identified pharmacological approaches

METHODS

A Working Group (WG) of directors from the IAHPHC was formed to work on this project. Members of the WG include Michael I. Bennett (UK), James Cleary (USA), David Currow (Australia), Liliana De Lima (USA), Arthur Lipman (USA), and Scott Murray (UK). Tania Pastrana (Germany) was invited as research consultant. The group was chaired by Lukas Radbruch (Germany) and coordinated by LDL.

Step 1: Identification of the most common causes of death:

The WHO Global mortality data was used to identify the main causes of mortality.

Step 2: Identification of the most common and distressing symptoms in palliative care:

Based on these results, an electronic search strategy was utilized to identify the most common symptoms occurring in the identified causes of mortality:

- MEDLINE (2000 - 2012)
- EMBASE (2000 - 2012)
- Hand search of the references included in studies/papers identified from above
- Hand search of specialist palliative care journals: American Journal of Hospice and Palliative Care, European Journal of Palliative Care, Journal of Hospice and Palliative Nursing, Journal of Pain and Symptom Management, Journal of Pain and Palliative Care Pharmacotherapy, Journal of Palliative Care, Palliative Medicine, Palliative Nursing, and Supportive Care in Cancer.
- Hand searches of white papers and government reports.

Step 3: Identification of the medicines recommended for the treatment of the symptoms:

The WG identified the evidence for the pharmacological treatment of the symptoms identified in Step 1 and using data provided by a study commissioned to the Palliative Care Group in Bonn by the German Drug Commission, supplemented by evidence based reviews and evidence based

guidelines provided by members of the WG, a process was undertaken to identify evidence to support the pharmacological management of these symptoms. Only meta- analyses and systematic reviews specific to the pharmacological management of the identified symptom palliative care were sought. Additional literature based on expert opinion was sought on the MEDLINE and EMBASE databases mentioned above. Hand searches were also performed. Analyses were based on efficacy and safety. Due to resource and time limitations, the WG decided to recommend not more than two medications. For the same limitations stated above, cost analyses were not carried out.

Each symptom is presented in a separate section with supporting references and GRADE levels of evidence.

MAIN RESULTS

Step 1: The most common causes of death globally for 2008 were heart disease, cancer, stroke, chronic respiratory disease, injury, and diabetes (WHO 2011). Trends in mortality over the last 50 years indicate that Non Communicable Diseases (NCDs) are becoming the most common cause of death, with the exception of Sub Saharan Africa and a few nations in other regions, where communicable diseases are the main causes of death (United Nations Department of Economic and Social Affairs 2012).

Step 2: Due to the difficulty in implementing high quality prospective studies of symptoms and associated distress using validated tools in patients receiving palliative care, only a few studies were identified with high GRADE levels. Most of the available evidence of prevalent and distressing symptoms is comprised of retrospective case reviews, expert opinion and case reports. (Carr et al. 2012; De Lima 2007; Tuffrey-Wijne et al. 2007; Good et al. 2006; Homsy et al. 2006; Solano et al. 2006; Plan et al. 2005; Wilson 2004; Lynn et al. 2003; Walsh et al. 2000)

Analysis of available evidence suggested 11 symptoms occurring in the advanced stages and end of life stage for the mortality conditions identified in Step 1, which are priorities in palliative care:

- Anorexia
- Anxiety
- Constipation
- Delirium
- Depression
- Diarrhoea
- Dyspnea
- Fatigue
- Nausea and vomiting
- Pain
- Respiratory tract secretions

Step 3: Fifteen medications were identified as essential for the treatments of these symptoms. All the recommended medications are off patent and available in generic forms and the majority are already included in other sections of the WHO EML. Table 1 lists the symptoms and medicines.

Most of the systematic reviews of symptom management were with patients with cancer, and many of these reviews concluded that there was insufficient evidence to draw any firm conclusions. The medicines which were identified should be added to the EML in order to ensure access to appropriate pharmacological symptom control in palliative care and prevent and relieve suffering of patients with advanced, life threatening and life limiting conditions.

SUMMARY OF RECOMMENDATIONS

Note: The following statements are used in the sections under each suggested medicine:

- *Recommendation for inclusion* is used when the recommended medicine is already included in another section of the WHO EML.
- *Recommended formulation and/or dosage for inclusion* is used when the recommended formulation is already included in another section of the EML.

- *New recommended medicine for addition* is used for medicines not listed in the WHO EML
- *New recommended formulation and/or dosage for addition to EML* is used when new formulations are recommended which are currently not listed in the EML.

Anorexia (appetite loss)

Recommended medicine for inclusion: DEXAMETHASONE

Recommended formulations for inclusion:

Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt)

Oral liquid: 2 mg/5 mL

New recommended formulation for addition:

Dexamethasone tablet 4mg

- A meta-analysis shows a benefit of dexamethasone in adult patients with a clinical diagnosis of anorexia-cachexia related to cancer although there is insufficient evidence to define the optimal dose.
- Dexamethasone is included in the EML in anti-allergy/anaphylaxis and in the hormones/anti-hormones sections, and as an appetite stimulant in the EML(c) palliative care section.

Anxiety

Recommended medicines for inclusion: DIAZEPAM and LORAZEPAM

Recommended formulations for inclusion:

Diazepam:

Injection: 5 mg/mL

Oral liquid: 2 mg/5 mL

Rectal solution: 2.5 mg; 5 mg; 10 mg.

Tablet: 5 mg; 10 mg.

Lorazepam:

Parenteral formulation: 2mg/mL in 1-mL ampoule

New recommended formulation for addition:

Lorazepam: tablets 1mg and 2.5mg

- Benzodiazepines are considered the mainstay of pharmacological therapy for acute anxiety, although evidence is based largely on expert opinion.
- Good quality evidence to support the role of benzodiazepines in the treatment of anxiety associated with terminal illness is limited.
- No studies comparing the safety and efficacy of one benzodiazepine over another were identified.
- The choice of benzodiazepines for inclusion in the EML for the management of acute anxiety in palliative care is therefore determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.
- Lorazepam is included in WHO EML as an anticonvulsant/antiepileptic.
- Lorazepam can be administered subcutaneously and can be administered as a continuous infusion with other medicine for symptom management when the enteral route is no longer available. Lorazepam can also be administered via the oral route with rapid onset and ease of administration.

Constipation

Recommended medicines for inclusion: DOCUSATE SODIUM and SENNA

Recommended formulations for inclusion:

Docusate sodium:

Capsule: 100 mg; Oral liquid: 50 mg/5 mL

Senna:

Oral liquid: 7.5 mg/5 mL

New recommended medicine for addition: SODIUM PICOSULFATE

New recommended formulation for addition:

Sodium Picosulfate oral liquid 7.5 mg/mL

- There is a lack of evidence to support the use of one laxative, or combination of laxatives over another. Expert opinion supports the use of a stimulant laxative as first line for the management of constipation in palliative care including opioid induced constipation. If a stimulant laxative alone is insufficient expert opinion supports the addition of a stool softener.
- Docusate sodium is a faecal softening agent already included in the EML(c) as a laxative in the palliative care section.
- Lactulose is faecal softening agent already included in the WHO EML(c) as a laxative in the palliative care section.
- Senna is a stimulant laxative already included in the WHO EML
- Sodium Picosulfate stimulates enteric movements.

Delirium (Confusion)

Recommended medicine for inclusion: HALOPERIDOL

Recommended formulations for inclusion:

Injection: 5 mg in 1-mL ampoule.

Oral liquid: 2 mg/mL

Solid oral dosage form: 0.5 mg; 2mg; 5 mg

- Haloperidol is widely used in the management of psychotic disorders in both the adult and child population. Haloperidol is considered the first choice therapy in the management of agitation associated with delirium in end of life care. There is randomized controlled trial evidence to support the use of haloperidol in management of delirium hospitalized adults with AIDs.
- Haloperidol is included in the EML as an antipsychotic both for children and adults.

Depression

Recommended medicines for inclusion: AMITRIPTYLINE and FLUOXETINE

Recommended formulations for inclusion:

Amitriptyline: Tablet: 10 mg; 25 mg

Fluoxetine: solid oral dosage form 20 mg (as hydrochloride)

New recommended dosage forms for addition:

Amitriptyline: tablet 75mg

- Amitriptyline can reduce the symptoms of depression in palliative care specifically when a rapid onset of action is required for short-term use.
- Amitriptyline is already included in the EML as antidepressant and in the EML(c) in palliative care.
- Fluoxetine is included in the EML for the treatment of depressive disorders and in the EML(c) in palliative care. The dosage form currently listed is 20mg capsules/tablets.
- Fluoxetine can be taken as a single daily dose.

Diarrhoea

New recommended medicine for addition: LOPERAMIDE

New recommended formulation for addition:

Loperamide 2mg tablet or capsule

- Loperamide works by decreasing the activity of the myenteric plexus and also decreases colonic mass movements and suppresses the gastro colic reflex.

- Loperamide a synthetic piperidine derivative is an opioid drug effective against diarrhoea resulting from gastroenteritis or inflammatory bowel disease.
- Loperamide reduces peristalsis in the gut, increases water re-absorption, and promotes faecal continence.
- In most countries of the world it is available generically. The oral application is easier than the subcutaneous injection required for octreotide therapy.
- A few studies indicate that Loperamide may be effective for the treatment of diarrhoea in palliative care patients. However the evidence is limited and the recommendation is based mostly on expert opinion.

Dyspnoea (breathlessness)

Recommended medicine for inclusion: MORPHINE

Recommended formulations for inclusion:

Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg.

Injection: 10 mg/mL

Oral liquid: 10 mg/5 mL

Tablet (immediate release): 10 mg.

Tablet (controlled release): 10 mg; 30 mg; 60 mg.

- There is good quality evidence to show that morphine (oral and parenteral) is effective in the treatment of dyspnoea in palliative care. Morphine is already included in the WHO EML as an analgesic and in palliative care (children). The use of morphine for the treatment of dyspnoea in adults in palliative care is recommended.

Fatigue

Recommended medicine for inclusion: DEXAMETHASONE

Recommended formulations for inclusion:

Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt)

Oral liquid: 2 mg/5 mL

New recommended formulations for addition:

Tablet 4mg

- Very few studies have been conducted to evaluate the effectiveness of corticosteroids in fatigue in adults. No trials were identified to compare effectiveness of one corticosteroid with another.
- Dexamethasone is included in the WHO EML as antiallergic, as a hormone (complementary), for palliative care (children) and as an antiemetic.
- Dexamethasone is widely available worldwide as oral tablets (0.5mg, 2mg).
- Improvements in pain and quality of life with corticosteroids had a resultant positive effect on fatigue with a reduction in severity of this symptom.
- Expert opinion strongly supports the short-term use of dexamethasone in adults.

Nausea and Vomiting

Recommended medicine for inclusion: METOCLOPRAMIDE

Recommended formulations for inclusion:

Injection: 5 mg (hydrochloride)/mL in 2-mL ampoule.

Oral liquid: 5 mg/5 mL

Tablet: 10 mg (hydrochloride)

- The evidence base for the pharmacological treatment of nausea and vomiting in palliative care is weak and based largely on clinical experience and proven efficacy of these agents in other situations. It is suggested that if the cause of emesis is known or suspected, the choice of first line agent(s) should correlate with this cause.
- Metoclopramide is a prokinetic antiemetic already included in EML. Metoclopramide is

recommended for the first line management of nausea and vomiting associated with delayed gastric emptying.

Pain

Recommended medicines for inclusion: IBUPROFEN and MORPHINE

Recommended formulations for inclusion:

Ibuprofen:

Oral liquid: 200 mg/5 mL

Tablet: 200 mg; 400 mg; 600 mg.

Morphine:

Granules (modified release) (to mix with water): 20 mg; 30 mg; 60 mg; 100 mg; 200 mg.

Injection: 10 mg/mL

Oral liquid: 10 mg/5 mL

Tablet (controlled release): 10 mg; 30 mg; 60 mg.

Tablet (immediate release): 10 mg.

- Morphine is the strong opioid of choice in moderate to severe pain and this is confirmed by a number of consensus guidelines. There is extensive clinical experience of its use and its use should be promoted to ensure adequate analgesia as necessary.
- The inclusion of both immediate release and sustained release oral preparations enables morphine to be successfully used in both acute and chronic pain.
- Non-steroidal anti-inflammatory agents are considered the co-analgesic of choice for bone pain. There is insufficient evidence to support the use of one NSAID over another for this indication. Given that ibuprofen is included in the WHO EML and there is ample evidence to demonstrate its safety and efficacy, it seems as an appropriate choice.

Respiratory Tract Secretions

New recommended medicine for addition: HYOSCINE BUTYLBROMIDE

New recommended formulation for addition:

10 mg/mL injectable

- Expert opinion and case series support the use of antimuscarinic agents in prevention of accumulation of respiratory tract secretions during the dying phase. There is no substantial evidence from systematic review that any intervention, be it pharmacological or non-pharmacological, is superior to placebo in the treatment of death rattle.
- Hyoscine butylbromide is commonly used as an antimuscarinic agent to control excessive secretions in palliative care.
- It is available in formulations for administration by oral and parenteral routes, and is generally the agent of first choice to control excessive secretions.
- Because it does not cross the blood-brain barrier, hyoscine butylbromide is preferred over hyoscine hydrobromide for patients at the end of life.

Table 1 - Grading of Recommendations Assessment, Development and Evaluation (GRADE 2007)

Code	Quality of Evidence	Definition
A	High	Further research is very unlikely to change our confidence in the estimate of effect. <ul style="list-style-type: none"> - Several high-quality studies with consistent results. - In special cases: one large, high-quality multi-centre trial
B	Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. <ul style="list-style-type: none"> - One high-quality study - Several studies with some limitations
C	Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. <ul style="list-style-type: none"> - One or more studies with severe limitations
D	Very Low	Any estimate of effect is very uncertain. <ul style="list-style-type: none"> - Expert opinion - No direct research evidence - One or more studies with very severe limitations

Table 2 – Summary of recommended medicines for palliative care in adults:

Medicine	Currently included in WHO EML	Recommended use in Palliative Care	Recommended formulations and/or dosage forms <i>(New formulations and dosage forms in italics)</i>
AMITRIPTYLINE	<p>Antidepressant: 25mg oral tablets</p> <p>Palliative care (children): Tablet: 10 mg; 25 mg.</p>	Depression	Tablet: 10 mg; 25 mg; <i>75 mg.</i>
DEXAMETHASONE	<p>Anti-allergy/anaphylaxis: Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt)</p> <p>Hormones and antihormones (compl - children): Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt). Oral liquid: 2 mg/5 mL</p> <p>Palliative Care (children): Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt). Tablet: 2 mg.</p>	Anorexia Fatigue	Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt) Oral liquid: 2 mg/5 mL <i>Tablet: 4 mg.</i>
DIAZEPAM	<p>Anticonvulsants/Antiepileptics Gel or rectal solution: 5 mg/mL in 0.5 mL; 2-mL; 4-mL tubes.</p> <p>Palliative Care (children): Injection: 5 mg/mL Oral liquid: 2 mg/5 mL Rectal solution: 2.5 mg; 5 mg; 10 mg. Tablet: 5 mg; 10 mg.</p>	Anxiety	Injection: 5 mg/mL. Oral liquid: 2 mg/5 mL. Rectal solution: 2.5 mg; 5 mg; 10 mg. Tablet: 5 mg; 10 mg.

DOCUSATE SODIUM	Palliative Care (children): Capsule: 100 mg. Oral liquid: 50 mg/5 mL	Constipation	Capsule: 100 mg. Oral liquid: 50 mg/5 mL
FLUOXETINE	Palliative Care (c) Solid oral dosage form: 20 mg (as hydrochloride) Medicines used in depressive disorders Solid oral dosage form: 20 mg (as hydrochloride)	Depression	Solid oral dosage form: 20 mg (as hydrochloride)
HALOPERIDOL	Anti-psychotic Injection: 5 mg in 1-mL ampoule. Tablet: 2 mg; 5 mg. Anti-psychotic (children): Injection: 5 mg in 1-mL ampoule. Oral liquid: 2 mg/mL Solid oral dosage form: 0.5 mg; 2 mg; 5 mg.	Delirium	Injection: 5 mg in 1-mL ampoule. Oral liquid: 2 mg/mL Solid oral dosage form: 0.5 mg; 2mg; 5 mg
HYOSCINE BUTYLBROMIDE	Not included	Respiratory Tract Secretions	<i>Injection: 10mg/mL</i>
IBUPROFEN	Analgesic: Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg. Palliative Care (children): Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg. Complementary list (neonatal care): Solution for injection: 5 mg/mL Antimigraine (children): Tablet: 200 mg; 400 mg.	Pain	Oral liquid: 200 mg/5 mL Tablet: 200 mg; 400 mg; 600 mg.
LOPERAMIDE	No	Diarrhoea	<i>Solid oral form: 2mg</i>

LORAZEPAM	Anticonvulsants/Antiepileptics Parenteral formulation: 2 mg/mL in 1-mL ampoule; 4mg/mL in 1-mL ampoule.	Anxiety	<i>Tablet: 1 mg; 2.5 mg</i> Parenteral formulation: 2mg/mL in 1-mL ampoule
METOCLOPRAMIDE	Anti-emetic Injection: 5 mg (hydrochloride)/mL in 2-mL ampoule. Oral liquid: 5 mg/5 mL Tablet: 10 mg (hydrochloride).	Nausea and vomiting	Injection: 5 mg (hydrochloride)/mL in 2-mL ampoule. Oral liquid: 5 mg/5 mL Tablet: 10 mg (hydrochloride)
MORPHINE	Analgesic: Injection: 10 mg (morphine hydrochloride or morphine sulphate) in 1-mL ampoule. Oral liquid: 10 mg (morphine hydrochloride or morphine sulphate)/5 mL Tablet: 10 mg (morphine sulphate). Tablet (prolonged release): 10 mg; 30 mg; 60 mg (morphine sulphate). Preoperative medicine: Injection: 10 mg (sulphate or hydrochloride) in 1-mL ampo Palliative Care (children): Granules (modified release) (to mix with water): 20mg; 30 mg; 60 mg; 100 mg; 200 mg. Injection: 10 mg/mL Oral liquid: 10 mg/5 mL Tablet (immediate release): 10 mg. Tablet (controlled release): 10 mg; 30 mg; 60 mg.	Pain Dyspnea	Injection: 10 mg/mL Oral liquid: 10 mg/5 mL Tablet (immediate release): 10 mg. Tablet (controlled release): 10 mg; 30 mg; 60 mg.
SENNA	Palliative Care (children): Oral liquid: 7.5 mg/5 mL Laxative Tablet: 7.5 mg (sennosides) (or traditional dosage forms).	Constipation	Oral liquid: 7.5 mg/5 mL
SODIUM PICOSULFATE	No	Constipation	<i>Oral liquid: 7.5 mg/mL</i>

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APPENDIX

Monographs and Summary of Evidence

ANOREXIA

Recommended medicine for inclusion: DEXAMETHASONE

Recommended formulations for inclusion:

Injection: 4 mg/mL in 1-mL ampoule (as disodium phosphate salt)

Oral liquid: 2 mg/5 mL

New recommended dosage forms for addition to EML:

Dexamethasone tablet 4mg

New medicines for addition to EML: none

Definition

Anorexia is the lack or loss of appetite for food, which may occur in patients with cancer, AIDS and other chronic diseases. Anorexia may lead to cachexia, a complex syndrome characterized by progressive tissue nutritional depletion and profound weight loss.

Scope

- Reduced food and fluid intake is normal at the end of life.
- Treatment of anorexia and weight loss may not be appropriate if these symptoms are not having a direct impact on quality of life.
- Management of anorexia and weight loss includes identification and, if appropriate, treatment of possible underlying cause(s) and should include the use of pharmacological and non pharmacological treatment approaches.
- This application considers only the pharmacological management of fatigue.
- If treatment of the underlying cause is not possible or is not effective, pharmacological management of anorexia and weight loss may be appropriate.

Corticosteroids in the management of anorexia and weight loss in palliative care

Recommendations

- Systematic reviews of small number of studies suggest oral or parenteral corticosteroids may be of use in the short term management of anorexia in palliative care.
- Dexamethasone is included in the WHO EML for the treatment of Allergy/anaphylaxis, for the treatment with hormones and antihormones (compl - children) and in the EML(children) for Palliative Care.
- Dexamethasone is included in the IAHPCL List of Essential Medicines (expert opinion) for the treatment of Anorexia, Nausea, Neuropathic pain and Vomiting.
- Optimal dose and duration of therapy with corticosteroids has not been established. Dexamethasone usually is initiated with a higher dosage (12-24 mg per day) and then tapered off during the next 2-3 weeks until a maintenance dosage of 2-8 mg per day is reached. The use of 4 mg tablets is recommended to facilitate initial titration and maintenance treatment.

Where this alone is insufficient: evidence for management of this symptom

- Anorexia may be linked with low cortisol levels which may be improved with corticosteroid therapy.

Additional supporting information for this drug:

Corticosteroids have a number of potential roles in palliative care in the treatment of:

- Fatigue
- Pain relief
- Nerve compression, dyspnea, raised intracranial pressure
- Anticancer hormone therapy

DEXAMETHASONE IN THE TREATMENT OF ANOREXIA IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Lesniak et al. (2008)	Systematic review and metanalysis of studies on the effect of megestrol acetate (MA) in patients with cancer anorexia-cachexia syndrome. RCT with patients with non-hormone-sensitive cancer and ACS and assessed the effects of MA compared with placebo, other drugs or different doses of MA.	30 studies of randomized trials were included.	Comparing MA with α glucocorticosteroids (prednisolone 30 mg/d11, dexamethasone 3 mg/d29) a comparable rate of patients with an appetite improvement and a comparable rate of patients with weight gain.	Randomization process was not described in most cases Only one study (from 1999) compared MA with dexamethasone.	B
Yavuzsen et al. (2005)	SR of studies comparing methylprednisolone, prednisone or dexamethasone with placebo	6 studies of (647 patients) were included: 3 studies comparing IV or oral methylprednisolone with placebo (402 adult patients). 2 multicentre studies used IV methylprednisolone and measured QOL in preterminal cancer. 1 study compared oral prednisolone with placebo (61 adult patients). 2 studies compared dexamethasone with placebo (184 patients).	The multicentre studies found IV methylprednisolone improved appetite, pain, QOL, vomiting and well-being. Weight was not statistically changed. In a 14 day randomized double-blind cross-over trial that compared oral methylprednisolone 16mg/dose BD with placebo, appetite and performance status improved. Results showed a significant improvement in appetite and well-being in those taking prednisolone. One study found a significant improvement after 2 weeks but this disappeared by 4 weeks. Dexamethasone was beneficial in reducing post chemotherapy side-effects including anorexia.	Most patients enrolled in the studies were also receiving chemotherapy. Dosage and type of corticosteroid differed between studies such that the optimal dose and duration of therapy are unknown. Short courses (e.g. 2 weeks) are recommended because benefits diminish after 4 weeks	B
Shragge et al. (2006)	Critical review of literature on anorexia in patients with advanced cancer.	52 articles met the inclusion criteria	The appetite stimulating effects of corticosteroids tend to dissipate after four weeks, whilst progestins, such as megestrol acetate, provide meaningful relief to only a minority of patients.	Due to the paucity of studies specifically investigating the management of anorexia by patients with advanced malignant disease, the conclusions drawn from this review must be regarded with caution.	C
De Lima et al (2007)	Consensus list based on expert opinion (2007)	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Dexamethasone (0.5-4 mg tablets and 4 mg/mL injectable) included in the IAHPIC List for the treatment of anorexia in palliative care.		D

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Good et al. (2006)	Survey among palliative care practitioners, commissioned by the Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia to compile a list of drugs they considered essential.	100 physicians in Australia and New Zealand	Dexamethasone e was identified as essential for the management of anorexia by 69% of the participants.		D
Nauck et al (2004)	Prospective survey (expert opinion)	57 palliative care units in Germany (1304 patients) in a 3 month census period	Dexamethasone was one of the most commonly prescribed drugs during inpatient treatment.		D

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ANXIETY

Recommended medicines for inclusion: DIAZEPAM and LORAZEPAM

Recommended formulations for inclusion to EML:

Diazepam:

Injection: 5 mg/mL

Oral liquid: 2 mg/5 mL

Rectal solution: 2.5 mg; 5 mg; 10 mg.

Tablet: 5 mg; 10 mg.

Lorazepam:

Parenteral formulation: 2mg/mL in 1-mL ampoule

New recommended formulations for addition to EML:

Lorazepam: tablets 1mg and 2.5mg

Definition

- Anxiety is defined as the apprehensive anticipation of future danger or misfortune accompanied by a feeling of dysphoria or somatic symptoms of tension. The focus of anticipated danger may be internal or external.
- Anxiety is characterized by excessive feelings of fear apprehension and worry. Anxiety may be associated with symptoms of depression, poor concentration, insomnia, irritability, panic attacks, sweating, tremor and nausea.
- Anxiety is frequent in palliative care.
- A combination of psychotherapeutic and pharmacological approaches has proven to be more effective than administering these treatments separately. This application only covers the pharmacological approach to treatment.

Overview of Pharmacological Management Options

Benzodiazepines are considered the mainstay of therapy in the management of anxiety in palliative care. However, there are no good quality studies on the role of benzodiazepines (or other drugs) in the treatment of anxiety in palliative care to draw a conclusion about their efficacy. Evidence of use in palliative care is based on expert opinion

DIAZEPAM

- Diazepam has a wide therapeutic index (wide margin of safety against toxicity) and high oral bioavailability (~100%).
- The onset of action following oral administration is around 15 minutes
- Duration of effect 3-30 hours (slow / fast metabolisers). The plasma half-life is 20-100 hours; active metabolite nordiazepam 30-200 hours.
- The injection not suitable for subcutaneous administration.
- Diazepam is currently included in three sections in the WHO EML: for the treatment of anxiety disorders, for anticonvulsant/antiepileptic treatment and for palliative care.
- Diazepam is included in the IAHPCL List of Essential Medicines in Palliative Care for the treatment of anxiety (expert opinion).

LORAZEPAM

- Lorazepam has an oral bioavailability of 93%
- The onset of action following sublingual administration is 5 min and following oral administration is 10-15 min.
- Injection can be administered by the sublingual route but is not recommended for subcutaneous administration.
- Plasma half-life much shorter than diazepam (12-15 hours) which makes it useful as a prn medication. However, the duration of effect does not correlate with plasma concentrations and can be longer (up to 72 hours).

Additional supporting information for benzodiazepines

- A recent systematic review published in November 2012 (Nübling et al. 2012) with

a comprehensive search strategy (Radbruch et al. 2012) on treatment of anxiety in palliative care patients included 12 studies. However, only two small controlled trials investigated alprazolam. Five surveys with 3469 patients reported on treatment of anxiety, but no detailed information on specific medications or regimens was provided.

- No evidence of improved efficacy of one benzodiazepine over another was identified. Considering the lack of evidence from clinical trials, the recommendation for benzodiazepines has to be based on clinical expertise. The choice(s) of benzodiazepine for inclusion in the EML is therefore likely to be determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference. Expert opinion strongly supports the use of lorazepam and diazepam for treatment of anxiety.
- Lorazepam may be preferred to diazepam for treating acute attacks because of the rapid onset of effect when administered sublingually and it also tends to cause less sedation.
- Lorazepam is the preferred agent for the prolonged treatment of anxiety in the critically ill adult as recommended by the Society of Critical Care Medicine (Shapiro et al. 1995).
- Diazepam may be more appropriate for chronic anxiety symptoms because of its medium to long half-life.
- Lorazepam is available as an expidet tablet with 1 mg or 2.5 mg. This application form can be used sublingually, providing a quick onset of effect, and it also makes it suitable for patients who are unable to swallow, either because of impairment of the gastrointestinal passage or because of reduced consciousness level.
- Lorazepam is currently included in the WHO EML for anticonvulsant/antiepileptic treatment.
- Lorazepam and diazepam are both included in the IAHPC List of Essential Medicines in Palliative Care (expert opinion) for the treatment of anxiety and insomnia.

Where this alone is insufficient evidence for management of this symptom

- There are no studies comparing the safety or efficacy of one benzodiazepine over another. The choice(s) of agent for inclusion in the EML is therefore likely to be determined by availability of suitable formulations, route of administration, pharmacokinetics and clinical preference.

BENZODIAZEPINES IN THE TREATMENT OF ANXIETY IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Nübling et al. (2012)	Systematic review	12 studies included: 1 systematic review, 4 RCTs, 3 prospective and 2 retrospective surveys, 2 case reports, 1 review HIV/AIDS and cancer patients	Alprazolam was effective, but not superior to the control group. In 2 controlled trials no analysis of specific benzodiazepines was possible from the other trials	Anxiety was not always the primary endpoint Controlled trials with small study sizes only Assessment scales as well as drug regimens were not comparable	B
Jackson, Lipman (2004)	Systematic review	Prospective randomized trials with or without blinding involving the use of pharmacological agents for the treatment of anxiety at the end of life	No study met the inclusion criteria No data available to enable any assessment to be made	Insufficient evidence to draw a conclusion about the effectiveness of pharmacotherapy for anxiety in terminally ill patients Majority of literature on drug therapy for anxiety in palliative care is anecdotal	C
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Lorazepam and Diazepam are included in the IAHPCL for the treatment of anxiety in palliative care.		D
Good et al (2006)	Expert opinion	Survey			D

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CONSTIPATION

Recommended medicines for inclusion: DOCUSATE SODIUM and SENNA

Recommended formulations for inclusion:

Docusate sodium:

Capsule: 100 mg; Oral liquid: 50 mg/5 mL

Senna:

Oral liquid: 7.5 mg/5 mL

New recommended medicines for addition: SODIUM PICOSULFATE

New formulations for addition:

Sodium Picosulfate oral liquid 7.5 mg/mL

Definition

Constipation is defined as a condition in which there is difficulty in emptying the bowels, usually associated with hardened faeces. There is a wide range in normal bowel habit and constipation cannot simply be defined in terms of stool frequency. Severe constipation includes obstipation and faecal impaction, which can progress to bowel obstruction.

Scope

- Management of constipation comprises identification and, if appropriate, treatment of possible underlying cause(s)
- Non pharmacological management of constipation with attention to fluid intake, nutrition and mobility is important but may be limited by anorexia and general debilitation in palliative care.
- This application only covers the pharmacological management of constipation.

Overview of management options: Laxatives

- Stimulant laxatives
- Osmotic laxatives (stool softeners)

Recommendations

- Constipation is one of the most troublesome and persistent symptoms in palliative care patients and should be treated with laxatives.
- An extensive literature search confirmed there is limited good quality evidence to confirm the effectiveness of laxatives in constipation associated with palliative care in adults and children.
- There is a lack of evidence to support the use of one laxative, or combination of laxatives, over another and choice can be related to cost effectiveness and availability as much as to efficacy.
- Constipation is an almost inevitable consequence of opioid use. Laxatives must be prescribed for any patient receiving strong opioids, which is very common in palliative care.

Evidence for management of this symptom:

- A recent systematic review (Baeder et al, 2012) with a comprehensive search strategy (Radbruch et al. 2012) on the laxative treatment for constipation in palliative care patients, identified 10 controlled trials. Four trials evaluated opioid antagonists (methylnaltrexone subcutaneously, oxycodone / naloxone orally), the others tested a broad range of different laxatives.
- This evidence supports the efficacy of laxatives in the management of functional constipation. However there is insufficient evidence to recommend one laxative over another.
- Considering the low level of evidence from clinical trials, the recommendation for docusate sodium, senna and sodium picosulfate is based on expert opinion.

Additional supporting information for these medications:

DOCUSATE SODIUM

- Docusate sodium is a faecal softener and passively acts as an adjunct drug. It is commonly

listed as a laxative, but it does not directly stimulate bowel emptying.

- It is widely available with an established safety profile.
- Docusate sodium is available as both capsules and a liquid formulation
- Docusate sodium appears to be better tolerated, particularly at high doses than lactulose which is associated with bloating and colic.
- Approximate costs indicate a unit dose of docusate sodium (oral solution) is cheaper than lactulose.
- Docusate sodium is currently included in the WHO EML for palliative care (children).

SENNA

- Senna is the name given to the sennosides, which are hydroxyanthracene glycosides derived from Senna leaves.
- Causes local irritation in colon, which promotes peristalsis and bowel evacuation. Softens faeces by increasing water and electrolytes in large intestine.
- Senna is available in both oral liquid and oral tablet formulations. It is inexpensive and widely used as a stimulant laxative.
- Senna is included in the WHO EML for Palliative Care (children) and as a Laxative.
- Senna is included in the IAHPCL List of Essential Medicines in Palliative Care for constipation (expert opinion).

SODIUM PICOSULFATE

- Sodium picosulfate is hydrolyzed by colonic bacteria to the active form, which causes local irritation in colon, which promotes peristalsis and bowel evacuation. The pharmacology is similar to Senna.
- Sodium picosulfate is available in oral tablet formulations. It is inexpensive and widely used as a stimulant laxative.
- Sodium picosulfate is not included in the WHO EML.

Where this alone is insufficient evidence for the management of this symptom:

- Constipation, due to increase in gastrointestinal transit time is an inevitable consequence of opioid use. Therefore use of a stimulant laxative is the most appropriate choice in opioid induced constipation.
- Laxatives and stool softeners may be needed at high doses, particularly in opioid induced constipation in palliative care.
- Where high dose stimulant laxative is insufficient to manage constipation expert opinion supports the use of a combination of stimulant laxative and osmotic agent.
- Bulk forming laxatives are unlikely to be appropriate in palliative care.
- There is little good quality trial evidence to confirm the effectiveness of laxatives in constipation associated with palliative care.
- In addition, there is a lack of evidence to recommend the use of one laxative, or combination of laxatives, over another.
- In the absence of any data showing greater efficacy of one agent over another, the choice of laxative is likely to be determined by factors such as availability of suitable formulations, route of administration, pharmacokinetics and cost-effectiveness.

PHARMACOLOGICAL TREATMENT OF CONSTIPATION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Bader et al (2012)	Systematic review	10 controlled trials included. 7 studies with cancer patients, 3 studies with mixed study populations including patients with cancer or HIV/AIDS, nursing home residents.	4 trials on opioid antagonists (methylnaltrexone subcutaneously, oxycodone / naloxone orally), the others tested a broad range of different laxatives. Methylnaltrexone is effective compared to placebo. Little information available on the comparison of different laxatives	7 studies with small trial size. Only two of the studies with methylnaltrexone and a recent study with polyethylenglycol, sodium picosulfate and lactulose recruited a higher number of patients. Mostly patients with opioid treatment.	B
Miles et al. (2006)	Systematic review of randomized controlled trials	4 controlled trials (280 patients) fulfilled the inclusion criteria were identified.	Laxatives evaluated were lactulose, senna, co-danthramer, Misrakasneham (traditional Indian herbal medicine) and magnesium hydroxide/liquid paraffin. All the laxatives demonstrated a limited level of efficacy although a significant number of patients required rescue medication. Only significantly different treatments were in a trial in which lactulose plus senna were more effective than co- danthramer.	The treatment of constipation in palliative care is based on inadequate experimental evidence, such that there are insufficient randomized controlled trial data. Recommendations for laxative use can be related to costs at much as to efficacy	B
McNicol et al. (2003)	Systematic review to assess the management of opioid side effects in the context of cancer pain management	17 studies on opioid-induced constipation. Can be broadly divided into articles describing trials of various laxatives and articles comparing/exploring the degree of constipation in relation to a specific opioid or its route of administration. 4 studies on use of laxatives 4 studies of opioid antagonist naloxone	No evidence of improved efficacy of one agent over another. Overall naloxone was found effective.	Optimal dose and frequency not established and some patients reported a reduction in analgesia.	B
CKS (2007)	Consensus guideline		Docusate, Senna and Sodium Picosulfate included for the pharmacological treatment of constipation.		D
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Senna (3mg tablet), included in the IAHPCL List for the treatment of constipation in palliative care.		D

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<p>Good et al (2006)</p>	<p>Survey among palliative care practitioners, commissioned by the Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia to compile a list of drugs they considered essential.</p>	<p>100 physicians in Australia and New Zealand</p>	<p>Docusate and Senna were identified as essential for the management of constipation by 58% of the participants.</p>		<p>D</p>
<p>Nauck et al (2004)</p>	<p>Prospective survey (expert opinion)</p>	<p>57 palliative care units in Germany (1304 patients) in a 3 month census period</p>	<p>Sodium picosulfate was among the most commonly prescribed drugs during inpatient treatment.</p>		<p>D</p>

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DELIRIUM

Recommended medicines for inclusion: HALOPERIDOL

Recommended formulations for inclusion:

Injection: 5 mg in 1-ml ampoule.

Oral liquid: 2 mg/ml.

Solid oral dosage form: 0.5 mg; 2mg; 5 mg

Definition

- Delirium (confusion) is very common in the terminal stages of advanced disease and is associated with a short prognosis. Features suggested being highly specific to acute delirium states are acute onset, fluctuating course, disorganized thinking, inattention, memory impairment and disorientation.
- Delirium may be hyperactive (presenting with agitation, hyper arousal, and restlessness), or hypoactive (presenting with drowsiness, lethargy and reduced levels of arousal), or a mixed pattern in which the symptoms fluctuate between hyperactive and hypoactive.

Scope

- Management of delirium comprises identification and wherever possible treatment of possible underlying cause(s):
 - Medicines
 - Organ failure
 - Hypoxia
 - Infection
 - Hypercalcaemia
 - Fluid or electrolyte disturbance
- Delirium is commonly caused by medicines and the patient's current medicines should be reviewed before pharmacological management is initiated.
- When treatment of the underlying cause(s) of delirium is not possible or unsuccessful, pharmacological management is necessary. Causal treatment may not be indicated in patients with limited prognosis and pharmacological symptomatic therapy has to be initiated without delay.

HALOPERIDOL

- Haloperidol is considered as first choice therapy in the management of delirium during the terminal phases of disease.
- Haloperidol has been shown to be effective in the management of both hyperactive and hypoactive delirium in adult patients during the terminal phases of disease. However, the amount of evidence is limited.
- A recent systematic review (Perrar et al. 2013) with a comprehensive search strategy (Radbruch et al. 2012) identified two controlled studies and a survey on the use of neuroleptics for treatment of delirium in palliative care patients. In both controlled studies haloperidol was as effective as chlorpromazine or aripiprazol, but significantly more effective than lorazepam.
- Considering the lack of evidence from clinical trials, the recommendation for haloperidol is based on clinical expertise. Expert opinion strongly supports the use of haloperidol for treatment of delirium in adults.

Additional supporting information for this drug:

- Haloperidol has an oral bioavailability of 60-70%
- Onset of action 10-15 minutes if given SC; >1hour if given orally.
- The time to peak plasma concentration is 10-20 minutes subcutaneously and 30-40 minutes if given orally.
- Duration of action up to 24 hours, sometimes longer.
- The use of haloperidol carries the risk of extrapyramidal side-effects. When compared with chlorpromazine, haloperidol has less effect on the cardiovascular system.

- Haloperidol does not have any antimuscarinic properties
- Haloperidol is widely available and at low cost
- Available in UK, USA and Australia as both oral (enteral) and parenteral formulations
- Haloperidol is included in the WHO EML for management of psychotic disorders in adults and children (complementary).
- Haloperidol is included in the IAHPC List of Essential Medicines in Palliative Care for the management of delirium, nausea, vomiting and terminal restlessness (expert opinion)

Where this alone is insufficient: evidence for management of this symptom:

Despite the absence of good quality clinical trials, haloperidol is widely used in the management of delirium in palliative care.

HALOPERIDOL IN THE TREATMENT OF DELIRIUM IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Perrar et al (2013)	Systematic review	Two controlled trials (1 RCT, 1 cohort study) and a survey on neuroleptics for treatment of acute delirium in palliative care patients. AIDS and cancer patients included.	Haloperidol was as effective as clopromazine or aripiprazol. Extrapyramidal side effects were frequent with haloperidol.	Benzodiazepines were burdened with side effects, including deterioration of the delirium. Treatment arm with lorazepam was discontinued in the RCT. Sample sizes were small.	B
Jackson and Lipman (2004)	Systematic review Primary objective was to identify and evaluate studies examining medications used to treat patients suffering from delirium during the terminal phases of disease. Prospective studies with or without randomization and/or blinding.	Only 1 study met the criteria.	Compared chlorpromazine, haloperidol and lorazepam in 30 hospitalized adult AIDS patients. Data from this single study suggests that haloperidol is the most suitable drug therapy; chlorpromazine may be an acceptable alternative.	Further research needed but authors comment on the considerable ethical problems in undertaking a clinical trial of effective treatment of such a symptom in this group of patients. The lorazepam arm of this study was stopped due to excess sedation.	C
Kehl (2004)	Systematic review of the evidence on the pharmacological treatment for terminal restlessness or delirium.	14 studies met the criteria.	The majority of authors favour use of neuroleptics, usually haloperidol for treating terminal restlessness or delirium.	Insufficient evidence to suggest that a single medication or class of medications is appropriate for terminal restlessness.	C
De Lima L. (2007)	Consensus list based on expert opinion (2007)	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Haloperidol (0.5 - 5 mg tablets, 0.5 - 5 mg drops, and 0.5 - 5 mg/mL injectable) is included in the IAHPC List for the treatment of delirium in palliative care.		D
Good et al (2006)	Survey among experts commissioned by the Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia surveyed palliative care practitioners in Australia to compile a list of drugs they considered essential.	100 physicians in Australia and New Zealand	Haloperidol was identified as essential for the treatment of delirium by 84% of the respondents.		D
Nauck et al (2004)	Prospective survey (expert opinion)	57 palliative care units in Germany (1304 patients) in a 3 month census period.	Haloperidol was among the most commonly prescribed drugs during inpatient treatment.		D

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Radbruch L, Alt-Epping B, Rolke R, Ujeyl M, Nauck F. [Methods and development of therapy recommendations for symptom control in palliative medicine]. *Schmerz* 2012; 26: 475-80.

DEPRESSION

Recommended medication for inclusion: AMITRIPTYLINE and FLUOXETINE

Recommended formulations for inclusion:

Amitriptyline: Tablet: 10 mg; 25 mg

Fluoxetine: solid oral dosage form 20 mg (as hydrochloride)

New recommended dosage forms for addition to EML:

Amitriptyline: tablet 75mg

New medicines for addition to EML: none

Definition

- Depression is characterized by persistent feelings of extreme sadness and low mood associated with loss of interest in activities and inability to experience pleasure. There are often associated biological features of significant changes in appetite and weight, disturbed sleep, fatigue and poor concentration.
- Diagnosing and providing treatment for a major depressive episode in patients with a terminal illness can improve quality of life.
- Diagnosis of major depression in a terminally ill patient often relies more on the psychological or cognitive symptoms (worthlessness, hopelessness, excessive guilt, and suicidal ideation) than the physical/somatic signs (weight loss, sleep disturbance) described in depression in patients who are not terminally ill.
- The key indicators of depression in the terminally ill are persistent feelings of hopelessness and worthless and/or suicidal ideation.
- Depression in palliative care is likely to be significantly under-recognized and under-treated as the symptoms overlap with symptoms of the underlying condition.

Scope

- Treatment of pain and other reversible physical symptoms should be instituted before or concurrently with initiation of specific depressive treatment.
- Psychological approaches to depression in palliative care, particularly cognitive behavioural therapy are important.
- Management of depression includes the use of pharmacological and non pharmacological treatment approaches.
- This application considers only the pharmacological management of depression.
- Anxiety commonly exists as co-morbidity with depression in palliative care. Management of anxiety is considered in a separate section in this application.

Pharmacological Management Options: Tricyclic Antidepressants (TCAs) and Selective Serotonin Reuptake Inhibitors (SSRIs)

AMITRIPTYLINE

- Amitriptyline is the most widely used tricyclic antidepressant and has been proven to be safe and effective in the treatment of depression.
- Amitriptyline acts primarily as a serotonin-norepinephrine reuptake inhibitor, with strong actions on the serotonin transporter and moderate effects on the norepinephrine transporter. It has negligible influence on the dopamine transporter and therefore does not affect dopamine reuptake, being nearly 1,000 times weaker on it than on serotonin.
- Amitriptyline is included in the EML for the treatment of depression and in the EML(c) for palliative care. The dosage form listed is 20mg capsules/tablets.
- Amitriptyline is included in the IAHPC List of Essential Medicines in Palliative Care for the treatment of depression and as a coadjuvant in the treatment of neuropathic pain (expert opinion).

FLUOXETINE

- Fluoxetine is a selective inhibitor of serotonin reuptake. Fluoxetine has practically no

affinity to other receptors such as α 1-, α 2-, and β -adrenergic; serotonergic; dopaminergic; histaminergic; muscarinic; and GABA receptors.

- Fluoxetine is available as an oral solution 20mg/5ml and 10mg, 20mg and 40mg oral capsules/tablets.
- Fluoxetine is included in the EML for the treatment of depressive disorders and in for palliative care for children. The dosage form currently listed is 20mg capsules/tablets.
- Fluoxetine can be taken as a single daily dose.
- Fluoxetine does however have a prolonged time before a therapeutic effect is established and this may be a limiting factor to its use in patients in the terminal stages.

Recommendations

- A systematic review and a meta-analysis (Rayner et al. 2010, Rayner et al. 2011) evaluated 25 studies, and reported that both tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs), were shown to be more effective than a placebo. Improvement of depressive symptoms took several weeks of therapy. The therapeutic benefit persisted after 18 weeks, though side effects such as dry mouth or sexual dysfunction caused patients to stop their medication with prolonged treatment duration. However, patients taking an antidepressant were more likely to experience sexual dysfunction. They concluded that there was insufficient evidence to support the use of one antidepressant in preference to another.
- A recent systematic review identified (Ujeyl and Müller-Oerlinghausen 2012) with a comprehensive search strategy (Radbruch et al. 2012) published in November 2012 on the treatment of depression in chronic illness identified 40 trials (16 studies in neurological patients, 24 in general medical conditions, 9 in patients at the end of life or in advanced disease stages) and found moderate evidence of efficacy of antidepressants (SSRI: selective serotonin reuptake inhibitors and NSMRI: non-selective monoamine reuptake inhibitors), though the evidence was not conclusive for some diseases and medication classes. Some studies showed superior efficacy of NSMRI compared to SSRI.
- There is less evidence on antidepressive therapy in palliative care patients, but moderate evidence of efficacy is supported by expert opinion.
- Although derived from fewer studies, RCTs consistently support tricyclic antidepressants and selective serotonin reuptake inhibitors for treating depression in cancer when treatment lasts 6 weeks or longer. Critical gaps include that the evidence base does not address late-stage cancer (for example, terminal care) or delivery system changes.
- 3 trials (62 participants) demonstrated that oral psychostimulants, as monotherapy, significantly reduced short term depressive symptoms in comparison with placebo with non-significant heterogeneity.
- There is some randomized clinical trial evidence to suggest that in the short-term, psychostimulants reduce the symptoms of depression and may have a role in when rapid onset therapy is required for short-term use, such as in end of life care.
- No evidence addressed depression management in advanced heart failure or dementia.
- Use of selective serotonin re-uptake inhibitors depression has been associated with an increased risk of suicidal ideation and behaviour.
- Antidepressive therapy often requires higher dosages of antidepressants. Amitriptyline may be titrated up to 225 mg per day for treatment of depression. The 75 mg tablet facilitates treatment with higher dosages in palliative care patients.

PHARMACOLOGICAL TREATMENT OF DEPRESSION IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Ujeyl, Muller-Oerlinghausen (2012)	Systematic review of randomized controlled trials assessing the effectiveness of antidepressants in chronic illness	40 controlled trials included, with 16 studies in neurological, 24 in general medical conditions and 9 studies in patients at the end of life or in advanced disease stages. 28 studies using SSRI, 18 studies with NSMRI and 3 studies with other antidepressants were included.	Results show moderate evidence of efficacy of antidepressants for general medical conditions. However, in most of the reviewed general medical conditions study results were heterogeneous. In neurological conditions SSRI were not effective	Heterogeneous study designs Most studies had too small sample sizes. Lack of efficacy was predominantly shown in larger trials, which might indicate publication bias.	A
Bech et al (2000)	Meta analysis of randomized controlled trials to provide an estimate of the effect of fluoxetine compared with placebo and tricyclic antidepressants (TCAs), and to investigate reasons for early discontinuation from acute treatment.	16 randomized double blind controlled trials involving 3447 patients in the USA centres. 13 randomized double blind controlled trials involving 643 patients in non USA centres.	Fluoxetine was superior to placebo but effect size was low. In trials comparing fluoxetine vs. TCA, the results for all trials and for the USA trials showed a trend in favour of fluoxetine. Those for the non-USA trials showed a trend in favour of TCA.	When combined, the results showed that significantly fewer patients on fluoxetine discontinued treatment because of adverse events.	A
Mottram et al. (2006)	Systematic review of RCTs to examine the efficacy of antidepressant classes, to compare the withdrawal rates associated with each class and describe the side effect profile of antidepressant drugs for treating depression in patients described as elderly, geriatric, senile or older adults, aged 55 or over. Trials had to at least compare 2 active antidepressants.	32 trials provided data for inclusion in the review in terms of efficacy, withdrawal and side effect analysis.	No difference in efficacy when comparing classes of antidepressants. TCAs compared less favourably with SSRIs in terms of numbers of patients withdrawn irrespective of reason and number withdrawn due to side effects. Further analyses demonstrated that TCA related antidepressants had similar withdrawal rates to SSRIs irrespective of reason of withdrawal or withdrawal due to side effects. The qualitative analysis of side effects showed a small increased profile of gastro-intestinal and neuropsychiatric side effects associated with classical TCAs.	Results must be interpreted with caution due to the heterogeneity of the drugs and patient populations.	A

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Rayner et al. (2011)	Systematic review of randomized controlled trials assessing the effectiveness of antidepressants in physical illness	25 studies included in the review 7 trials in HIV/AIDS, 6 in Parkinson's disease, 4 in cancer, 3 in COPD, 2 in multiple sclerosis, 2 in end stage renal and one in chronic heart failure. 13 studies compared an SSRI with placebo, 4 compared a TCA with placebo, and 4 three-armed trials compared a SSRI and a TCA with placebo.	Antidepressants are effective in treating depression in palliative care. Both classes of antidepressant were more efficacious than placebo, but before nine weeks the effect was statistically significant for only TCAs Superiority over placebo is apparent within 4–5 weeks and increases with continued use with the largest effect occurring at 9-18 weeks.	Effect sizes may be overestimated due to biases such as selective reporting and publication. Increase of efficacy over time may indicate a delayed onset of action in this population. However, with increasing treatment duration more patients discontinued treatment because of side effects such as dry mouth (mostly with TCA) or nausea (SSRI).	A
Rayner et al. (2010)	Systematic review of clinical trials of antidepressants in physically ill people to determine whether antidepressants help.	51 studies included in the review.	Antidepressants (TCAs and SSRIs) are better than placebo in treating depression in physically ill people. Antidepressants improved depressive symptoms within 4-5 weeks of treatment, and this benefit persisted after 18 weeks. Patients taking an antidepressant were more likely to experience sexual dysfunction and dry mouth, and were more likely to stop taking their medication after 6-8 weeks of treatment.	There are no grounds to recommend one antidepressant over another on the basis of this review. The decision to prescribe antidepressants should take account of patients' preferences, symptoms, and possible interactions with other medicines they are taking.	A
Candy et al. (2008)	Systematic review of randomized controlled trials assessing the effectiveness of psychostimulants in the treatment of depression and to assess adverse events associated with psychostimulants Adults of either sex with a diagnosis of depression (patients with serious concomitant medical illness were included in this review but not specifically palliative care)	24 RCTs identified 5 drugs evaluated: dexamphetamine, methylamphetamine, methylphenidate, modafinil and pemoline. Psychostimulants were administered as a monotherapy, adjunct therapy, as oral or IV and in comparison with a placebo or an active therapy 13 trials included data suitable for meta-analysis	Most effects were measured in the short term (up to 4 weeks). 3 trials (62 participants) demonstrated that oral psychostimulants, as monotherapy, significantly reduced short term depressive symptoms in comparison with placebo with non-significant heterogeneity. A similar effect was found for fatigue. In the short term, psychostimulants were acceptable and well tolerated. Modafinil was evaluated separately (due to difference in pharmacology) and no statistically significant difference in depression symptoms was found between modafinil and placebo Some evidence that in the short-term, psychostimulant reduce the symptoms of depression and may have a role in certain circumstances e.g. when established treatments for depression have failed or is rapid onset therapy is required for short-term use. This reduction reaches statistical significance but clinical significance is less clear.	Overall quality of trials poor. Insufficient evidence for this review to recommend the use of psychostimulants above other more established treatments of depression. However, as a result of heterogeneity in psychostimulant intervention and comparative treatments, and the paucity of RCTs with sufficient data for qualitative analysis, few clinically relevant conclusions can be drawn.	B

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Lorenz et al (2008)	Systematic review of randomized and non randomized studies that addressed "end of life," including terminal illness and chronic, eventually fatal illness with ambiguous prognosis and intervention treatments that addressed pain, dyspnea, depression, advanced care planning, continuity and caregiving.	33 high-quality systematic reviews and 89 relevant intervention studies	Evidence synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification	Strong evidence supports treating cancer associated depression with psychotherapy, tricyclics, and selective serotonin reuptake inhibitors.	B
Rodin et al. (2007)	Systematic review conducted by the Supportive Care Guidelines Group of Cancer Care Ontario's Program in Evidence-based Care (PEBC)	7 trials of pharmacological agents and 4 of non-pharmacological interventions.	2 trials detected significant reduction in depressive symptoms for mianserin vs. placebo 1 trial found alprazolam to be superior to progressive muscle relaxation. 4 drug trials found no significant difference between groups on depression measures although post treatment reduction of symptoms was observed for all groups in 2 trials comparing active treatments (fluoxetine vs. desipramine and paroxetine vs. amitriptyline). Of the 4 trials involving nonpharmacological therapies for the management of depression, two detected a benefit for treatment (a multicomponent nurse delivered intervention and an orientation program) over usual care.	Not specific to palliative care Limited evidence for the effectiveness of pharmacological and psychosocial interventions. No evidence for the superiority of one treatment modality over another. Based on evidence, combined approaches to the treatment of depression may be the most effective.	B
Carr et al (2002)	Systematic review	Patients with any cancer diagnosis The prevalence rates for major depressive disorder and clinically significant depressive symptoms are about 10 to 25 percent	Tricyclic antidepressants and selective serotonin reuptake inhibitors were uniformly effective, given sufficient treatment duration (more than 6 weeks).		B
Lan et al. (2002)	Systematic review	Randomized controlled trials that assessed treatments for depression in palliative care patients. Adults only. 3 RCTs on the treatment of depression met inclusion criteria	Of 73 women with advanced cancer, those treated with the TCA mianserin had a significant improvement in depression with no differences between the groups in terms of side effects In 40 patients with advanced cancer the SSRI fluoxetine and the TCA desipramine were equally effective in improving depression with no statistically significant difference in adverse effects In 50 terminal patients with mixed anxiety and depressive symptoms, both thioridazine and placebo showed an improvement in depression with a statistically significant difference favouring thioridazine	Paucity of good data on effective treatments for depression in the palliative care population	B

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Anderson (2001)	Meta analysis of randomized controlled trials	A systematic search found 108 meta-analyses of the use of antidepressants in depressive disorders. Defining newer antidepressants as those introduced since the early 1980s, 18 meta-analyses were selected as being informative about their relative efficacy and tolerability in comparative randomized controlled studies (RCTs).	Little difference in efficacy between most new and old antidepressants Superior efficacy of serotonin and noradrenaline re-uptake inhibitors (SNRIs) over selective serotonin re-uptake inhibitors (SSRIs) Slower onset of therapeutic action of fluoxetine over other SSRIs Different side effect profile of SSRIs to TCAs with superior general tolerability of SSRIs over TCAs Poorer tolerability of fluvoxamine than other SSRIs in a within group comparison; no increased the risk of suicidal acts or ideation in fluoxetine compared with TCAs (or placebo) in low-risk patients.	In general, the meta-analyses were of uneven quality, as were the studies included, which limits the confidence in many of the results. Generalizing from mostly short-term randomized controlled studies to clinical practice requires caution.	B
Trindadae et al. (1998)	Meta-analysis of double-blind randomized controlled trials involving at least one SSRI and one TCA For the study of adverse effects only trials that had at least 20 patients in each arm and that reported rates of adverse effects in both arms were included	84 trials reporting on 18 adverse effects were included.	7 adverse effects occurred statistically significantly more often with SSRIs (nausea, anorexia, diarrhoea, insomnia, nervousness, agitation and anxiety) and 5 that occurred statistically significantly more often with TCAs (dry mouth, constipation, dizziness, sweating and blurred vision) No statistically significant differences between drug classes in terms of drop-outs due to adverse effects.	SSRIs and TCAs are both associated with adverse effects although the key effects differ between the drug classes	B
De Lima (2007)	Consensus list based on expert opinion.	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Amitriptyline (tablets 50-150mg) included in the IAHPC List for the treatment of depression in palliative care.		D
Nauck et al (2004)	Prospective survey (expert opinion)	57 palliative care units in Germany (1304 patients) in a 3 month census period.	Amitriptyline was among the most commonly prescribed drugs during inpatient treatment.		D

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DIARRHOEA

New recommended medication for addition to EML: LOPERAMIDE

New recommended formulation for addition to EML:

Loperamide 2mg tablet or capsule

Definition

- Diarrhoea is defined by WHO as having three or more loose or liquid stools per day, or as having more stools than is normal for that person.
- It is usually a symptom of gastrointestinal infection, which can be caused by a variety of bacterial, viral and parasitic organisms. Infection is spread through contaminated food or drinking-water, or from person to person as a result of poor hygiene.
- Severe diarrhoea leads to fluid loss, and may be life-threatening, particularly in young children and people who are malnourished or have impaired immunity.
- Diarrhoea can usually be divided into different types and treatment will vary depending on cause: secretory, osmotic, mechanical, or disordered motility.
- In palliative care, the overuse of laxatives, typically seen when the management of constipation is suddenly "stepped-up", is a common cause. Other causes include partial intestinal obstruction, pancreatic insufficiency, Clostridium difficile infection, chemotherapeutics, and radiation enteritis.
- Severe constipation and faecal impaction can also cause diarrhoea as backed-up, liquefied stool may be all that the patient can pass ("overflow diarrhoea").

Scope

- Management of diarrhoea comprises identification and, if appropriate, treatment of possible underlying cause(s)
- Adequate hydration needs to be part of the treatment for diarrhoea, including the use of rehydration salts. This application only covers pharmacological treatment.

Loperamide in the treatment of Diarrhoea

- Loperamide a synthetic piperidine derivative is an opioid drug effective against diarrhoea resulting from gastroenteritis or inflammatory bowel disease.
- Loperamide reduces peristalsis in the gut, increases water reabsorption, and promotes faecal continence.
- Loperamide is an opioid-receptor agonist and acts on the μ -opioid receptors in the myenteric plexus of the large intestine; by itself it does not affect the central nervous system.
- It works by decreasing the activity of the myenteric plexus, which, like morphine, decreases the tone of the longitudinal smooth muscles but increases the tone of circular smooth muscles of the intestinal wall. This increases the amount of time substances stay in the intestine, allowing for more water to be absorbed out of the faecal matter. Loperamide also decreases colonic mass movements and suppresses the gastrocolic reflex.
- Loperamide may be less effective in patients with extensive colorectal resections. In these patients octreotide may be more effective.

Additional supporting information for this drug:

- In most countries of the world loperamide is available generically. The oral application is easier than the subcutaneous injection required for octreotide therapy.
- AIDS-related diarrhoea is a common cause of morbidity and mortality in HIV positive individuals, especially in the sub-Saharan Africa. Loperamide is readily available and has been found to be useful in this condition.
- Fluid leakage around a faecal impaction is sometimes mistaken as diarrhoea. Loperamide is contraindicated in such scenario.

- Loperamide (2mg tablet) is recommended for the treatment of diarrhoea in the WHO Guidelines for the clinical management of HIV infections in adults.
- Loperamide is included in the IAHPC List of Essential Medicines in Palliative Care (expert opinion) for the treatment of diarrhoea.

Evidence for management of this symptom

- A recent systematic review (Pastrana and Meißner, 2013) with a comprehensive search strategy (Radbruch et al. 2012) on loperamide for treatment of diarrhoea in palliative care patients identified 7 controlled trials in patients with HIV/AIDS or cancer. Loperamide was superior compared to placebo and to acetorphan, though the comparison with octreotide was less conclusive
- In a separate (unpublished) systematic review with a similar search strategy on opioid treatment for diarrhoea found only one additional study comparing diphenoxylate with octreotide, with more responder in the octreotide group (Yavuz et al. 2002).
- Considering the low level of evidence from clinical trials, the recommendation for loperamide is based on expert opinion.

PHARMACOLOGICAL TREATMENT OF DIARRHOEA IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Author (year)	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Pastrana and Meißner (2012)	Systematic review	7 controlled trials included 6 RCTs and one cohort study 6 studies with cancer patients (5 radiation- or chemotherapy-induced diarrhoea, one study in leukaemia) One study in patients with HIV	Loperamide was superior compared to placebo and to acetorphan. Comparison with octreotide was less conclusive (3 studies octreotide superior, one study loperamide superior)	All studies with small trial sizes Most patients had undergone abdominal surgery. Following extensive colorectal resection, less effect from loperamide is to be expected.	B
Bhattacharya et al. (2009)	Systematic review	Octreotide in chemotherapy induced diarrhoea in colorectal cancer Two randomized trials, four non-randomized studies and two case-series.	Octreotide had much better outcome as compared to loperamide	All studies with small trial sizes	B
Yavuz et al. (2002)	Randomized controlled trial	61 patients with radiation-induced diarrhoea treated with octreotide or diphenoxylate	More responder in the group with octreotide than with diphenoxylate		B
Nwachukwu et al. (2008)	Randomised controlled trials comparing an antimotility agent or an adsorbent with another antimotility agent, placebo, an adsorbent or no treatment in children and adults diagnosed with HIV and presenting with diarrhoea of 3 or more weeks duration.	One CT was identified	Not enough evidence to support or refute their use in controlling this condition.	Antimotility agents (Loperamide, Diphenoxylate, Codeine) and adsorbents (Bismuth Subsalicylate, Kaolin/Pectin, Attapulgite) are readily available, and have been found to be useful in this condition and so, are often used.	C
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Loperamide (tablets 2mg) included in the IAHPC List for the treatment of diarrhoea in palliative care.		D

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DYSPNOEA**Recommended medicine for inclusion: MORPHINE****Recommended formulations for inclusion:**

Injection: 10 mg/mL

Oral liquid: 10 mg/5 mL

Tablet (immediate release): 10 mg.

Tablet (controlled release): 10 mg; 30 mg; 60 mg.

Definition

Dyspnoea is the unpleasant sensation of being unable to breathe adequately (breathlessness). Three main components contribute to dyspnoea: afferent signals, efferent signals, and central information processing. Dyspnoea results when a "mismatch" occurs when the need for ventilation (afferent signalling) is not met by the physical breathing (efferent signaling). It is a common symptom in palliative care and increases in prevalence and severity as the underlying disease or condition progresses.

Anxiety is often a major component of breathlessness.

Scope

- Dyspnoea is a complex multidimensional symptom with physical psychological and emotional dimensions.
- Pharmacological palliation of breathlessness is not only appropriate when any potentially reversible underlying cause of this symptom has been identified and treated, but may also be effective in parallel with causal therapies.
- In many palliative care cases the treatment of the underlying cause is deemed inappropriate because of the patient's poor clinical state.
- Pharmacological management should be accompanied by appropriate non pharmacological measures, including anxiety management and adaptation of the environment.
- This application only covers pharmacological management of dyspnoea.

Morphine in the Management of dyspnoea

- In systematic reviews and meta-analysis, enteral or subcutaneous strong opioids have shown to significantly improve the sensation of dyspnoea in adults with advanced disease.
- A recent systematic review (Simon et al. 2012) with a comprehensive search strategy (Radbruch et al. 2012) on four different treatment options (opioids, benzodiazepines, corticosteroids and oxygen) for the relief of breathlessness in palliative care patients, included five systematic reviews and 10 randomized controlled trials and found that opioids (oral and parenteral) were the only drug group with evidence for relief of breathlessness.
- When administered at appropriate doses, opioids reduce rate of breathing and sensation of dyspnoea, without measurable changes in oxygen saturation or pCO₂.
- Doses of enteral or subcutaneous morphine used for the management of dyspnoea are generally 25 – 50% of analgesic doses.

Additional supporting information for this medication:

- Morphine is included in the WHO EML as an analgesic and for palliative care (children).
- Morphine is widely regarded as first line opioid of choice in acute and chronic severe pain.
- Morphine is available in many countries in the world in oral, rectal and parenteral formulations at a low cost.
- Morphine is included in the IAHPCL List of Essential Medicines in Palliative Care (expert opinion) for the treatment of moderate to severe pain and for the treatment of dyspnoea.

Where this alone is insufficient: evidence for management of this symptom

- There is no evidence to support the use of nebulised opioids in the management of dyspnoea.

PHARMACOLOGICAL TREATMENT OF DYSPNOEA IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Ben-Aharon et al (2008)	Systematic review of RCT. Pharmacologic and non-pharmacologic interventions for dyspnoea palliation in cancer patients	18 trials identified: 14 evaluated pharmacologic interventions: seven assessing opioids (a total of 256 patients), five assessing oxygen (137 patients), one assessing helium-enriched air, and one assessing furosemide. 4 evaluated non pharmacologic interventions (403 patients).	SC morphine resulted in a significant reduction in dyspnoea Visual Analogue Scale (VAS) compared with placebo. No difference was observed in Dyspnoea VAS score when nebulized morphine was compared with SC morphine, although patients preferred the nebulized route. Addition of benzodiazepines to morphine was significantly more effective than morphine alone, without additional adverse effects. Oxygen was not superior to air for alleviating dyspnoea, except for patients with hypoxemia. Acupuncture was not beneficial.	Nursing-led interventions improved dyspnoea.	A
Lorenz et al (2008)	Systematic review of randomized and non randomized studies that addressed "end of life," including terminal illness and chronic, eventually fatal illness with ambiguous prognosis and intervention treatments that addressed pain, dyspnoea, depression, advanced care planning, continuity and caregiving.	33 high-quality systematic reviews and 89 relevant intervention studies. Evidence synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification	Strong evidence supports treating dyspnoea from chronic lung disease with short-term opioids.		A
Jennings et al. (2012)	Systematic review and meta analysis of studies which were double blind, randomised, placebo controlled trials of opioids for the treatment of dyspnoea secondary to any cause. Random effects meta-analyses were performed on all included studies and on various subgroups (studies involving nebulised opioids or patients with chronic obstructive pulmonary disease (COPD). Subgroups were compared using meta-regression.	18 studies were included: 9 involved the non-nebulised route 9 involved the nebulised route.	The meta-analysis showed a statistically significant positive effect of opioids on the sensation of breathlessness. Meta-regression indicated a greater effect for studies using oral or parenteral opioids than for studies using nebulised opioids. The results of the subgroup analysis of the COPD studies were essentially similar to the results of the main analysis. There is evidence to support the use of oral or parenteral opioids to palliate breathlessness although numbers of patients involved in the studies were small. No evidence was found to support the use of nebulised opioids. Multiple dosing studies in opioid naïve patients had most problems with adverse effects.	Further research with larger numbers of patients, using standardized protocols and with quality of life measures is needed.	A

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Simon et al. (2012)	Systematic review and other controlled studies included patients with COPD, carcinoma chronic heart failure and interstitial pulmonary disease	1 systematic review (Jennings et al 2001) and 8 RCTs identified	The systematic review reported significant efficacy for oral/parenteral morphine; however, no efficacy was reported for nebulized morphine One RCT was adequately powered and reported significant effect.	Most trials had a small number of subjects Further RCT on various application forms are currently in preparation or are in the recruiting phase Further RCT showed partially contradictory results, but were for the most part pilot studies with a lack of power	B
Brown et al. (2005)	Systematic review In-depth review of the nebulised studies included in the Cochrane review (Jennings et al 2001).	9 trials identified	3 had positive results, rest failed to show any improvement	Small number of subjects, variety of disease states and doses of nebulised morphine and different outcome measures limit interpretation of the studies.	B
Jennings et al. (2001)	Systematic review (Cochrane Database of Systematic Reviews) Double blind placebo controlled or crossover RCTs of opioid drugs in relieving breathlessness in patients receiving palliative care for malignancy or other advanced disease.	18 trials identified: oral/parenteral (n=9) and nebulised (n=9) All 9 nebulised trials were of morphine and 3 of the oral/parenteral trials were morphine.	Statistically strong evidence for a small and probably clinically significant effect of oral and parenteral opioids. No evidence that nebulised opioids as more effective than placebo.	All but one of the studies identified were small (8 and 18 subjects).	B
Viola et al. (2008)	Systematic review done by the Supportive Care Guidelines Group of the Cancer Care Ontario Program in Evidence-Based Care.	3 systematic reviews (1 with meta-analysis), 2 practice guidelines and 28 controlled trials identified. Adult patients with advanced cancer or other chronic condition and Dyspnoea treated with opioids, benzodiazepines, phenothiazines or corticosteroids. 3 studies evaluated morphine and 4 dihydrocodeine	Results of individual trials mixed but SR with meta-analysis showed a significant benefit for Dyspnoea with systemic opioids. Nebulised morphine was not effective in controlling Dyspnoea. In ten trials of systemic opioids in other patient populations, there were mixed results.		B
CKS (2007)	Consensus guideline	Based on literature review and expert opinion.		Supports use of systemic opioids	D
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Morphine (IR: 10-60 mg tablets, IR: 10mg/5mL oral solution, IR 10 mg/mL injectable, SR 10 mg tablets and SR 30 mg tablets) included in the IAHPCL for the treatment of dyspnoea in palliative care.		D
Good et al. (2006)	Survey among experts commissioned by the Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia surveyed palliative care practitioners in Australia to compile a list of drugs they considered essential.	100 physicians in Australia and New Zealand	Morphine was identified as essential for the treatment of Dyspnoea by 94% of the respondents.		D

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Nauck (2004)	Expert opinion	Prospective survey in 57 palliative care units in Germany, including 1304 patients in a 3 month census period	Morphine was the second most frequently used drug in German palliative care units, used in 42% of patients	Supports the use of morphine for the treatment of dyspnoea in palliative care, though it was not clear how much morphine was used for pain and how much for dyspnoea.	D
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FATIGUE**Recommended medicine for inclusion: DEXAMETHASONE****Recommended formulations for inclusion:**

Injection: 4 mg/ml in 1-ml ampoule (as disodium phosphate salt)

Oral liquid: 2 mg/5 mL

New formulations for addition:

Tablet 4mg

Definition

Fatigue is defined as a subjective feeling of tiredness, weakness or lack of energy. The pathophysiology is not fully understood but in most palliative care patients will be multifactorial, including disease- and treatment-related causes. Physical fatigue is the transient inability of a muscle to maintain optimal physical performance, and is made more severe by intense physical exercise. Mental fatigue is a transient decrease in maximal cognitive performance resulting from prolonged periods of cognitive activity. It can manifest as somnolence, lethargy, or directed attention fatigue.

Cancer-related fatigue (CRF) is defined as a common, persistent, and subjective sense of tiredness related to cancer and/or its treatments that interferes with usual functioning. This is distinguishable from normal fatigue in that symptoms in CRF are severe, distressing and persist, regardless of adequate amounts of sleep and rest.

CRF is usually multi factorial; it may be caused by tumour-related and/or treatment-related factors such as decreases in the availability of metabolic substrates, hormonal changes, increase in pro-inflammatory cytokines, cachexia, neurophysiological changes in skeletal muscle, muscle wasting, decreased ventilatory ability, anaemia, and altered sleep patterns.

However, fatigue is a common symptom in palliative care, not only in cancer patients, but also in patients with diseases that are not associated with cancer, but who require palliative care (e.g. cardiac, pulmonary or renal failure, amyotrophic lateral sclerosis or multiple sclerosis).

Scope

- Fatigue is a complex multidimensional symptom comprising physical, cognitive and emotional aspects.
- Fatigue at the end of life may have a protective role. Treatment of fatigue may not be appropriate if this symptom is not having a direct impact on quality of life.
- Management of fatigue comprises identification and, if appropriate, treatment of possible underlying cause(s) and the use of pharmacological and non pharmacological management of the fatigue itself.
- This application considers only the pharmacological management of fatigue.
- An application for the inclusion of palliative care medications in the WHO EML(c) in 2008, did not recommend any medications for the treatment of fatigue.

DEXAMETHASONE

- Dexamethasone is a potent synthetic member of the glucocorticoid class of steroid drugs.
- Dexamethasone acts as an anti-inflammatory and immunosuppressant.
- When taken orally, it is more potent than the naturally occurring hormone cortisol and than prednisone.
- The plasma half life of dexamethasone is 3.5-4.5 hours but as the effects outlast the significant plasma concentrations of steroids, the plasma half-life is of little relevance and the use of biological half life is more applicable.
- The biological half life of dexamethasone is 36-54 hours, therefore dexamethasone is especially suitable in conditions where continuous glucocorticoid action is desirable.
- The approximate equivalent anti-inflammatory doses 750microgram dexamethasone ~5mg prednisolone.
- Dexamethasone has high glucocorticoid activity but insignificant mineralocorticoid effect and is particularly suitable for high dose therapy.

Additional supporting information for this medication:

- Dexamethasone is included in the WHO EML as antiallergic, as a hormone (complementary), for palliative care (children) and as an antiemetic.
- Dexamethasone is widely available worldwide as oral tablets (0.5mg, 2mg).

Recommendations

- Very few studies have been conducted to evaluate the effectiveness of corticosteroids in fatigue in adults.
- Improvements in pain and quality of life with corticosteroids had a resultant positive effect on fatigue with a reduction in severity of this symptom. However, clinical trials with corticosteroids do not use improvement in fatigue as a primary outcome.
- No trials were identified to compare effectiveness of one corticosteroid with another.
- A recent systematic review published in November 2012 (Thiem et al. 2012) with a comprehensive search strategy (Radbruch et al. 2012) on treatment with corticosteroids and androgens for the relief of fatigue in palliative care patients included 11 controlled studies as well as four uncontrolled studies, two case series and two surveys with glucocorticoids (all in cancer patients). Glucocorticoids improved quality of life but results for changes of fatigue and weakness were inconsistent. Tiredness and energy were not improved.
- Considering the lack of evidence from clinical trials, the recommendation for dexamethasone has to be based on clinical expertise. Expert opinion strongly supports the short-term use of dexamethasone in adults (Radbruch et al. 2008).
- There are a number of known potential adverse effects of corticosteroids and these must always be considered before dexamethasone is used. This includes muscular weakness with prolonged use of corticosteroids.
- Given the toxicity associated with long term use, consideration of steroids in palliative care should be restricted to use in the terminally ill with fatigue and a specific short-term treatment goal
- There is no difference in effectiveness between oral and parenteral application. The oral route is easier and is preferred by most patients.

Where this alone is insufficient: evidence for management of this symptom in adults

- Although expert opinion supports the use of corticosteroids for the management of a variety of symptoms, including fatigue in palliative care, the evidence is weak.
- Other options for treatment of fatigue include megestrol acetate, methylphenidate and modafinil. However, evidence for these medications is weak as well, and clinical expertise disfavours their use except for selected patients.
- Non-pharmacological support includes light aerobic training as well as energy-conserving therapies.

DEXAMETHASONE IN THE TREATMENT OF FATIGUE IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Thiem et al (2012)	Systematic review to identify clinical trials with corticosteroids or androgens in palliative care patients with weakness and/or tiredness	39 trials included: 11 controlled studies, 4 uncontrolled studies, 2 case series and 2 surveys with glucocorticoids, all in cancer patients. Seven of the controlled studies were double-blind RCTs	3 of 6 controlled studies measuring strength or weakness as an endpoint found significant improvement with corticosteroids. Another one was nearly significant. 4 RCTs evaluated the intensity of fatigue, but only one showed significant improvement	Glucocorticoids improved quality of life but results for changes of fatigue and weakness were inconsistent. Tiredness and energy were not improved. Trial sizes were small	B
Peuckmann-Post et al. (2010)	Systematic review of randomized controlled trials (RCTs) concerning adult palliative care with focus on pharmacological treatment of fatigue. The primary outcome had to be non-specific fatigue (or related terms such as asthenia).	22 studies met the inclusion criteria (1,632 patients and 11 medications)	Recent fatigue research seems to focus on modafinil, which may be beneficial although the evidence is insufficient.	Based on limited evidence, no specific drug for treatment of fatigue in palliative care patients was recommended. Surprisingly, corticosteroids have not been a research focus for fatigue treatment, although these drugs are frequently used. Amantadine and methylphenidate should be further examined. Consensus regarding fatigue assessment in advanced disease is needed.	B
Minton et al. (2008)	Meta analysis of RCT - Studies had to be designed to test a drug against placebo or usual care, had to have stated aims that included improvement in the level of quality of life, and had to use a multi-item measure of fatigue. -The trials had to use a robust measure of fatigue.	27 trials met the criteria (6,746 patients)	Meta-analysis of 2 studies (n = 264) indicated that methylphenidate was superior to placebo. Meta-analysis of 10 studies (n = 2226) in anaemic cancer patients undergoing chemotherapy indicated that erythropoietin was superior to placebo. 4 studies among anaemic patients (n= 964), improvement in fatigue was associated with darbepoetin, compared with placebo. Progestational steroids and paroxetine were no better than placebo in the treatment of CRF.	The overall effect size for all drug classes was small. There was a high rate of adverse effects in all of the trials not related to the type of study medication. Most withdrawals occurred because of disease progression and/or protocol violations.	B

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Carroll JK et al. (2007)	Systematic review to identify and analyze clinical trials in the US, Canada and Europe that assessed pharmacological interventions for cancer-related fatigue.	32 clinical trials: 19 prospective open trials and 13 RCTs. 2 clinical trials of corticosteroids and 1 trial of anabolic steroids. 2 studies were randomized, double-blind crossover studies	Studies reported improvements in symptoms, especially pain and showed improved quality of life and reduced fatigue. Single agent used in each trial, 1 each of prednisolone, methyl prednisolone and megestrol acetate)	None of the 3 reported clinical trials of corticosteroids had improvement in fatigue as a primary outcome measure Sample sizes small (37-84/study) Studies were of short duration.	B
Lawrence et al (2004)	Evidence report on the topic of Symptom Management in Cancer: Pain, Depression, and Fatigue. Commissioned by the Office of Medical Applications of Research at the National Institutes of Health (USA) to the Agency for Healthcare Research and Quality, through its Evidence-Based Practice Centre program. The purpose of the report was to search for and summarize evidence on several key questions related to these symptoms. SR of studies designed to determine the occurrence of cancer-related fatigue (CRF), the methods used to assess it, and the efficacy of the available treatments.	Studies which met the criteria: - 27 on the occurrence of CRF - 56 on the assessment - 10 RCT of treatments.	The occurrence of CRF was found to range from 4% to 91%. The methods of fatigue assessment were highly variable. Exercise programs may prevent or treat fatigue in some subsets of cancer patients, and the use of epoetin alfa for correction of anaemia has been shown to ameliorate fatigue.	Few population-based studies and no longitudinal studies of cancer-related fatigue have been performed. - The number of subjects in the treatment trials was small and their methodological quality was inconsistent.	B
Mock et al. (2004)	Cancer Related Fatigue (CRF) assessment and treatment guidelines based on evidence for the National Comprehensive Cancer Network (NCCN)	Based on 195 peer reviewed publications.	A few clinical reports of the use of corticosteroids and psychostimulants suggest the need for further research.	Supports the use of corticosteroids for the treatment of CRF.	B
Radbruch et al (2008)	Report from an expert group of the European Association of Palliative Care based on available evidence.		Screening for fatigue should include questions on weakness as a paraphrase for the physical dimension and on tiredness as a paraphrase for the cognitive dimension. Treatment of fatigue should include causal interventions for secondary fatigue and symptomatic treatment with pharmacological and nonpharmacological interventions. Strong evidence has been accumulated that aerobic exercise will reduce fatigue levels in cancer survivors and patients receiving cancer treatment.	Expert opinion supports the use of corticosteroids for short-term treatment of fatigue.	D

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Nauck et al (2004)	Prospective survey (expert opinion)	57 palliative care units in Germany (1304 patients) in a 3 month census period	Dexamethasone was among the most commonly prescribed drugs during inpatient treatment.		D
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NAUSEA AND VOMITING

Recommended medicine for inclusion: METOCLOPRAMIDE

Recommended formulations for inclusion:

Injection: 5 mg (hydrochloride)/mL in 2-mL ampoule.

Oral liquid: 5 mg/5 mL

Tablet: 10 mg (hydrochloride)

Definition

- Nausea is an unpleasant sensation often accompanied by the urge to vomit.
- Vomiting is the forceful expulsion of gastric contents through the mouth.
- Although nausea and vomiting often occur together they are in fact separate symptoms.

Scope

- Management of nausea and vomiting comprises identification and wherever possible treatment of possible underlying cause(s)
- Most cancer chemotherapy is highly emetogenic. Appropriate management of chemotherapy-induced nausea and vomiting depends on the chemotherapy regime.
- Mechanisms of post-operative nausea and vomiting are likely to be different to nausea and vomiting in palliative care
- Symptomatic management of nausea and vomiting should not be deferred until the underlying cause of the nausea and vomiting has been identified and if appropriate treated, but should be initiated without delay. Pharmacological management is the mainstay of treatment of nausea and vomiting, however non pharmacological measures including avoidance of precipitants and the use of acupuncture may have a role.
- This application only covers the pharmacological treatment of nausea and vomiting.

Overview of management options

- Pharmacological management based on knowledge of the most important pathophysiological mechanisms for emetogenesis and the relevant neurotransmitters is suggested for optimum management of nausea and vomiting but the evidence to support this approach has been questioned.
- Unfortunately it is not always possible to identify the precise mechanism(s) underlying the presence of nausea and vomiting. A pragmatic approach addressing the most likely mechanism is indicated, differentiating for example between toxic or metabolic nausea and retention vomiting.
- Antiemetics should be prescribed regularly and as required.
- If a single first line antiemetic does not relieve nausea and vomiting the antiemetic regime should be reviewed to ensure that:
 - The likely pathophysiological mechanisms underlying nausea and vomiting are being targeted
 - The patient is receiving the medication and that it is being absorbed
 - The dose is appropriate
- If necessary a second antiemetic with a complementary mechanism of action may be added. Combinations of antiemetics with antagonistic actions should be avoided.
- Alternatively the first line antiemetic can be changed to a single second line antiemetic with a more appropriate or broader spectrum of action.
- Where the enteral route is unavailable or absorption is not reliable an alternative route of administration, either rectal or subcutaneous (or intravenous if long term central venous access is available) is required
- Antiemetic administration via subcutaneous bolus injections or continuous subcutaneous (or intravenous if long term central venous access is available) infusion is the route of choice where the enteral and rectal routes are unavailable and regular dosing is required

Classes of drugs appropriate for pharmacological management of nausea and vomit

- Neuroleptics: Haloperidol, levomepromazine, chlorpromazine, prochlorperazine
- Antiemetic antihistamines: Cyclizine, promethazine

- 5HT3 antagonists: Ondansetron
- Corticosteroids: Dexamethasone
- Prokinetic antiemetics: Metoclopramide, domperidone

ANTIEMETICS IN PALLIATIVE CARE

METOCLOPRAMIDE

- Metoclopramide is a D2-receptor antagonist with mixed 5-HT3 receptor antagonist/ 5-HT4 receptor agonist and prokinetic properties
- Its action is antagonized by antimuscarinics.
- Metoclopramide can cause extrapyramidal side effects.
- Oral bioavailability: 50-80%
- Duration of action following single dose: 1-2 hours
- Metoclopramide is recommended for the first line management of nausea and vomiting associated with delayed gastric emptying.
- Regurgitation suggests gut hypomotility which responds to a gastrokinetic antiemetic such as metoclopramide.
- Metoclopramide is included in the WHO EML as an antiemetic.
- Metoclopramide is included in the IAHPCL List of Essential Medicines in Palliative Care (expert opinion) for the treatment of nausea and vomit.
- Metoclopramide is included as the preferred antiemetic in the IAHPCL Essential Opioid Prescription Package (expert opinion).

Recommendations

- If cause of emesis established, choice of first line agent should correlate with this cause. For effective control, a combination of antiemetics with complementary actions may be necessary
- In palliative care, the most common cause for vomit is gastric stasis which responds well to metoclopramide.
- Most of the evidence base for pharmacological treatment of nausea and vomiting in palliative and terminal care is weak. Two recent reviews (Benze et al. 2012a, 2012b) with a comprehensive search strategy (Radbruch et al. 2012) on antiemetic therapy in palliative care patients indicate a moderate evidence of the effectiveness of metoclopramide for the treatment of nausea and vomiting.

Where this alone is inadequate evidence for management of this symptom

- The moderate to weak evidence from clinical trials is supported by clinical expertise. Expert opinion strongly supports the use of metoclopramide in palliative care patients with nausea or vomiting.
- Availability of a combination of antiemetics with different mechanisms of action is recommended to ensure appropriate first and second line management for each underlying pathophysiological mechanism. For patients with chemotherapy- or radiation therapy-related nausea 5HT3 antagonists might be preferable. Neuroleptics were more effective than metoclopramide in some trials, but side effects have to be considered
- In the absence of any data showing greater efficacy of one agent over another, the choice of antiemetics within a class for inclusion in the EML likely to be determined by other factors such as availability of suitable formulations, route of administration, pharmacokinetics, cost effectiveness and potential for other roles in palliative care.

PHARMACOLOGICAL TREATMENT OF NAUSEA AND VOMIT IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Type of Study	Subjects	Results	Comment	Level of Evidence (GRADE)
Benze et al. (2012a)	Systematic review	30 studies included. All studies focused on cancer patients. 13 studies with metoclopramide.	Metoclopramide is seen as an effective drug in many studies and was superior in both trials that tested it against placebo. The slow release form was superior to the immediate release form in one trial. Studies comparing metoclopramide with active control found higher efficacy with levosulpirid and tropisetron. In patients with advanced cancer not being treated with chemotherapy or radiation therapy, metoclopramide can be used to reduce nausea and vomiting. Within the group of neuroleptics, levosulpirid and levomepromazine seem to have good antiemetic potential but the evidence level is low. All in all the evidence is moderate at best.	Studies in patients with AIDS, COPD, heart failure, ALS or MS were not detected. Neuroleptics, such as levosulpirid or levomepromazine are alternatives to metoclopramide but their adverse effects have to be considered carefully. Most studies had small study sizes. More well designed studies in palliative care patients are needed in order to provide evidence based antiemetic therapy.	B
Benze et al (2012b)	Systematic review	75 studies included: 36 addressed 5HT3 receptor antagonists, steroids, antihistamines, anticholinergics, somatostatin analogs, benzodiazepines and cannabinoides, 13 considered 5HT3 receptor antagonists, 10 somatostatin antagonists 9 steroids 5 cannabinoides 4 anticholinergics 1 antihistamines None considered benzodiazepines	Evidence for any drug used as an antiemetic is low. For patients with cancer contradictory results were published: the larger studies showed a positive effect of 5HT3 receptor antagonists and better efficacy, as compared to metoclopramide, dexamethasone and neuroleptics. Heterogeneous results were found for steroids, with a positive trend for patients with cancer. In palliative care patients with nausea and vomiting 5HT3 receptor antagonists can be used if treatment with other antiemetics, such as metoclopramide and neuroleptics is not sufficient.	Recommendations in the literature are mainly based on studies in patients with cancer. Regarding symptom control of nausea and vomiting in patients with COPD, progressive heart failure and ALS no studies were undertaken in patients receiving palliative care. Data insufficient for recommendations on the treatment of patients with AIDS and MS due to the small size of included patient groups. The overall strength of evidence is low. More well designed studies in palliative care patients are needed in order to provide evidence-based therapy	B

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<p>Glare et al. (2004)</p>	<p>Systematic review of studies of antiemetics used in the treatment of advanced cancer</p>	<p>21 studies included: 2 systematic reviews 7 RCTs 12 uncontrolled studies or case series. Only adult studies identified</p>	<p>Two possible approaches were identified: (a) mechanistic approach which attempts to correlate choice of antiemetic with suspected underlying cause (b) empirical approach in which various antiemetics are trialed without regard to the underlying cause of the nausea. Response rates to antiemetic treatment were lower in controlled studies than in the uncontrolled studies. Metoclopramide appears to be more effective than placebo Little evidence from well designed studies for other widely used antiemetics such as haloperidol, cyclizine and methotrimeprazine Used empirically, steroids have been used as adjuvants in patients with nausea not responding to other therapy although results are conflicting Good evidence for the effectiveness of steroids in symptomatic bowel obstruction Two RCTs indicate the effectiveness of 5HT3 antagonists in palliative care</p>	<p>Evidence base for the pharmacological treatment of nausea and vomiting in advanced cancer is weak and contradictory.</p>	<p>B</p>
<p>Davis & Hallerberg (2010)</p>	<p>Systematic review of antiemetics for emesis in cancer unrelated to chemotherapy and radiation.</p>	<p>93 articles included: 14 were RCTs Eligible studies included randomized controlled trials (RCTs), prospective single-drug studies, studies that used guidelines based on the aetiology of emesis, cohort, retrospective and case series or single-patient reports. Studies that involved treatment of chemotherapy, radiation, or post operation related emesis were excluded. Studies that involved the treatment of emesis related to bowel obstruction were included</p>	<p>Metoclopramide had modest evidence (B) based on RCTs and prospective cohort studies. Ocreotide, dexamethasone, and hyoscine butylbromide are effective in reducing symptoms of bowel obstruction, based on prospective studies and/or one RCT. There was no evidence that either multiple antiemetics or antiemetic choices based on the aetiology of emesis were any better than a single antiemetic. There is poor evidence for dose response, intraclass or interclass drug switch, or antiemetic combinations in those individuals failing to respond to the initial antiemetic.</p>	<p>Most studies were of low quality, based either on lack of blinding, lack of description of the method of randomization, concealment, and/or attrition.</p>	<p>C</p>
<p>Basch et al. (2011)</p>	<p>Systematic review to update the American Society of Clinical Oncology (ASCO) guideline for antiemetics in oncology.</p>	<p>37 trials met the inclusion and exclusion criteria. 2 systematic reviews from the Cochrane Collaboration were identified; one surveyed the paediatric literature.</p>	<p>Combined anthracycline and cyclophosphamide regimens were reclassified as highly emetic. Patients who receive this combination or any highly emetic agents should receive a 5-HT(3) receptor antagonist, dexamethasone, and a neurokinin 1 (NK(1)) receptor antagonist. A large trial validated the equivalency of fosaprepitant, a single-day intravenous formulation, with aprepitant; either therapy is appropriate. Preferential use of palonosetron is recommended for moderate emetic risk regimens, combined with dexamethasone. For low-risk agents, patients can be offered dexamethasone before the first dose of chemotherapy. Patients undergoing high emetic risk radiation therapy should receive a 5-HT(3) receptor antagonist before each fraction and for 24 hours after treatment and may receive a 5-day course of dexamethasone during fractions 1 to 5.</p>		<p>C</p>

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Vignaroli et al (2012)	Consensus list of essential prescription package for pain treatment, using a Delphi process	57 palliative care experts from 39 countries.	Metoclopramide was recommended as a first-line therapy in the management of opioid-induced nausea, but there was no consensus on dosing schedule.	No studies to indicate if antiemetics should be used for the prevention of opioid-induced nausea.	D
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Metoclopramide (10mg tablets and 5mg/mL injectable), included in the IAHPC List for the treatment of nausea and vomiting in palliative care.	Also included for the treatment of nausea and vomiting in the list: Dexamethasone (0.5-4mg tablets and 4mg/mL injectable) and haloperidol (0.5 - 5 mg tablets; 0.5 - 5 mg drops; 0.5 - 5 mg/mL injectable).	D
CKS (2007)	Consensus guideline	Based on literature review and expert opinion.	Supports use of metoclopramide as an antiemetic		D
Cancer Care Alliance, UK. Network Supportive and Palliative Care Guidelines, (2006)	Consensus guideline based on literature review and expert opinion	Assessment and management of nausea and vomiting in patients of 16 years and over in palliative care	Metabolic – haloperidol, levomepromazine Gastric stasis – metoclopramide, domperidone; consider trial of steroids GI disturbance and/or organ damage – cyclizine Bowel obstruction – Consider trial of steroids; consider metoclopramide if no colic. High bowel obstruction – cyclizine and haloperidol. Low bowel obstruction – levomepromazine; consider hyoscine butylbromide or octreotide for anti-secretory effects Raised ICP – cyclizine (consider steroids if raised ICP) Psychological factors – levomepromazine, benzodiazepine Cause unknown/terminal - levomepromazine		D
Good et al (2006)	Survey among palliative care practitioners, commissioned by the Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia to compile a list of drugs they considered essential.	100 physicians in Australia and New Zealand	Metoclopramide was identified as essential for the management of nausea by 86% of the participants.		D
Nauck et al (2004)	Prospective survey (expert opinion)	57 palliative care units in Germany (1304 patients) in a 3 month census period.	Amitriptyline was among the most commonly prescribed drugs during inpatient treatment.		D

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PAIN

Recommendations for inclusion: IBUPROFEN and MORPHINE

Recommended formulations for inclusion to EML:

Ibuprofen:

Oral liquid: 200 mg/5 mL

Tablet: 200 mg; 400 mg; 600 mg.

Morphine:

Injection: 10 mg/mL

Oral liquid: 10 mg/5 mL

Tablet (controlled release): 10 mg; 30 mg; 60 mg.

Tablet (immediate release): 10 mg.

Definition

- Pain is an unpleasant sensor and emotional experience associated with actual or potential tissue damage or described in terms of such damage (IASP 2011)

Scope

- Pain is multidimensional having physical, psychological, social and spiritual aspects that all have to be addressed.
- This application only covers the pharmacological management of pain.
- The pharmacological management of pain is appropriate at all times including when active treatment aimed at cure or prolongation of life is being considered.
- Management of pain should not be deferred until the underlying cause of the pain has been identified, but identification and if appropriate, treatment of the underlying cause should be undertaken simultaneously.

Classes of drug that are used for the management of pain:

- Paracetamol
- Non steroidal anti-inflammatory drugs (this application recommends ibuprofen)
- Weak opioids
- Strong opioids

Analgesics in the management of pain in palliative care

IBUPROFEN

- Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used for pain relief, fever reduction, and swelling.
- Ibuprofen has an antiplatelet effect, though relatively mild and somewhat short-lived compared with aspirin or prescription antiplatelet drugs. Ibuprofen also acts as a vasoconstrictor.
- Ibuprofen is included in the EML as an analgesic and anti-migraine agent. Ibuprofen has proven efficacy as an analgesic and has minimal adverse effects when administered at the recommended dosages. The formulations currently included in the EML are oral tablets 200mg and 400mg and 600mg and oral liquid 200 mg/5 mL.
- Ibuprofen is included in the IAHPCL List of Essential Medicines in Palliative Care (expert opinion) for the treatment of mild to moderate pain.

MORPHINE

Morphine is widely accepted as the strong opioid of choice in moderate to severe pain. This is confirmed by a number of consensus guidelines (see table below).

- Morphine is the most abundant alkaloid found in opium, the dried latex extracted by shallowly slicing the unripe seedpods of the *Papaver somniferum* poppy.
- Morphine is the prototype narcotic drug and is the standard against which all other opioids are tested. Morphine has proven efficacy as an analgesic and has an important role in the management of moderate to severe pain in palliative care.
- Morphine is a phenanthrene opioid receptor agonist – its main effect is binding to and activating the μ -opioid receptors in the central nervous system. In clinical settings, morphine exerts its principal pharmacological effect on the central nervous system and gastrointestinal tract.
- Activation of the μ -opioid receptors is associated with analgesia, sedation, euphoria, physical dependence, and respiratory depression.
- The effects of morphine can be countered with opioid antagonists such as naloxone and naltrexone.
- Morphine is included in the EML as an analgesic, as pre-operative medication and sedation for short-term procedures and as analgesic for palliative care (c).
- Morphine is included in the IAHPC List of Essential Medicines in Palliative Care (expert opinion) for the treatment of moderate to severe pain and for the treatment of dyspnea.
- Other opioids such as hydromorphone or oxycodone can be used as alternatives for treatment of pain in palliative care. No advantage of any opioid has been described in the systematic reviews (Caraceni et al. 2012). Morphine is the most widely available strong opioid and given its proven efficacy, its use is recommended in moderate to severe pain in palliative care.
- Morphine is available in wide range of application forms. Costs are low for oral application forms such as tablets or solution

Recommendations

- Non-steroidal anti-inflammatory drugs (NSAIDs) have theoretical advantage in bone or soft tissue pain due to their peripheral anti-inflammatory effect. Their efficacy in reducing pain and opioid doses has been demonstrated although not specifically in patients with bony metastases or mucositis.
- Inclusion of ibuprofen as an analgesic for management of mild pain in palliative care
- Inclusion of morphine as a strong analgesic for management of moderate to severe pain in palliative care
- Opioids in many countries of the world are underutilized often due to lack of knowledge and skills needed to properly evaluate, assess and treat pain and the fear of physicians, patients and their families of opioid addiction and tolerance. Additionally, strict regulations and control of these agents in many countries create difficulties in the prescription and dispensing processes.

IBUPROFEN IN THE MANAGEMENT OF MILD TO MODERATE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
McNicol et al. (2005)	Systematic review Randomized controlled trials (RCTs) and controlled clinical trials that compared NSAID vs. placebo; NSAID vs. NSAID; NSAID vs. NSAID plus opioid; opioid vs. opioid plus NSAID; or NSAID vs. opioid.	42 trials involving 3,084 patients with cancer pain receiving NSAIDs or paracetamol alone or in combination with opioids	Clinical heterogeneity of study methods and outcomes precluded meta-analysis 7 out of 8 papers that compared NSAID with placebo demonstrated superior efficacy of NSAID with no difference in adverse effects. Four papers demonstrated increased efficacy with increased dose, but no dose-dependent increase in side effects within the dose ranges studied. There was no clear evidence to suggest superiority of one NSAID over another. 9/14 papers suggested a slight but statistically significant advantage of between NSAID in combination with an opioid versus either single entity Based upon limited data, NSAIDs appear to be more effective than placebo for cancer pain; clear evidence to support superior safety or efficacy of one NSAID over another is lacking; and trials of combinations of an NSAID with an opioid have disclosed either no difference (4 out of 14 papers), a statistically insignificant trend towards superiority (1 out of 14 papers), or at most a slight but statistically significant advantage (9 out of 14 papers), compared with either single entity.	The short duration of studies and the heterogeneity limits the generalization of their findings on efficacy and safety of NSAIDs for cancer pain.	A
Lorenz et al (2008)	Systematic reviews of randomized and non randomized studies that addressed "end of life," including terminal illness and chronic, eventually fatal illness with ambiguous prognosis and intervention treatments that addressed pain, dyspnea, depression, advanced care planning, continuity and caregiving	33 high-quality SR and 89 relevant intervention studies included. 9 SR focused on pain of which 4 addressed cancer pain. 24 reports of interventions Evidence synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification	Strong evidence supports treating mild to moderate cancer pain with NSAIDs, including ibuprofen		A
CKS (2007)	Consensus guidelines		NSAIDs including ibuprofen for the management of to moderate pain.		D
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Ibuprofen (200 and 400mg tablets) included in the IAHPC List for the treatment of mild to moderate to pain in palliative care.		D

MORPHINE IN THE MANAGEMENT OF MODERATE TO SEVERE PAIN IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Caraceni et al. (2012)	Consensus guidelines based on evidence from 24 systematic literature reviews on different aspects of opioid management of pain in advanced cancer.	9 RCT included (654 patients) 8 were designed as superiority trials RCT compared oral administration of morphine, oxycodone, and hydromorphone. 2 SR support the use of oral morphine for cancer pain 1 SR of oxycodone updates an earlier review and meta-analysis. 1 review supports the use of hydromorphone.	7 of the superiority trials showed no significant differences in efficacy among the medications. No significant differences in efficacy reported in the meta-analysis of oxycodone compared with morphine or hydromorphone in four studies. 1 unpublished trial showed a difference with slight significance in favour of morphine compared with hydromorphone. 1 trial demonstrated equivalence for morphine and hydromorphone. The comparison of the tolerability profiles of the three opioids was similar.	Morphine has remained the first choice for reasons of familiarity, availability, and cost, rather than proven superiority. The data show no important differences between morphine, oxycodone, and hydromorphone given by the oral route and permit a weak recommendation that any one of these three drugs can be used as the first choice strong opioid for moderate to severe cancer pain.	A
Wiffen PJ et al. (2007) (updated version of a previous Cochrane review published in 2003)	Systematic review Published RCTs reporting on the analgesic effect of oral morphine in adults and children with cancer pain. Any comparator trials were considered. Trials with fewer than ten participants were excluded.	54 studies (3749 participants) met the inclusion criteria: 15 compared oral modified release morphine (Mm/r) preparations with immediate release morphine (MIR). 12 compared Mm/r in different strengths, five of these included 24-hour modified release products. 13 compared Mm/r with other opioids. 6 compared MIR with other opioids. 2 compared oral Mm/r with rectal Mm/r. 2 compared MIR with MIR by a different route of administration. 1 was found comparing each of the following: Mm/r tablet with Mm/r suspension; Mm/r with non-opioids; MIR with non-opioids; and oral morphine with epidural morphine.	Morphine shown to be an effective analgesic. Pain relief did not differ between Mm/r and MIR. Modified release versions of morphine were effective for 12 or 24-hour dosing depending on the formulation. Daily doses in studies ranged 25- 2000 mg with an average of between 100 - 250 mg. Dose titration were undertaken with both instant release and modified release products.	Adverse effects were common but only 4% of patients discontinued treatment because of intolerable adverse effects. The randomized trial literature for morphine is small given the importance of this medicine. Most trials recruited fewer than 100 participants and did not provide appropriate data for meta-analysis. Trial design was frequently based on titration of morphine or comparator to achieve adequate analgesia, then crossing participants over in crossover design studies. It was not clear if these trials are sufficiently powered to detect any clinical differences between formulations or comparator drugs. Studies added to the review reinforce the view that it is possible to use modified release morphine to titrate to analgesic effect. Qualitative evidence for effectiveness of oral morphine which compares well to other available opioids. Limited evidence to suggest that transmucosal fentanyl provides more rapid pain relief for breakthrough pain compared to morphine.	A
WHO (2012)	Pediatric pain treatment guidelines based on evidence and expert opinion.		Morphine recommended as the first-line strong opioid for the treatment of persisting moderate to severe pain in children with medical illnesses. Insufficient evidence to recommend any alternative opioid in preference to morphine as the opioid of first choice.	Selection of alternative opioid analgesics to morphine should be guided by considerations of safety, availability, cost and suitability including patient-related factors. Only for children.	A

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Lorenz et al (2008)	Systematic reviews of randomized and non randomized studies that addressed “end of life,” including terminal illness and chronic, eventually fatal illness with ambiguous prognosis and intervention treatments that addressed pain, dyspnea, depression, advanced care planning, continuity and caregiving	33 high-quality SR and 89 relevant intervention studies included. 9 SR focused on pain of which 4 addressed cancer pain. 24 reports of interventions Evidence synthesized using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) classification	Strong evidence supports treating cancer pain with opioids, including oral morphine.		A
Caraceni et al. (2010)	Systematic review to evaluate the evidence that oral morphine can be recommended as the first choice opioid in the treatment of moderate to severe cancer pain.	17 studies (2,053 patients) and 1 meta-analysis were included.	Studies do not add significant information to the previous Cochrane review confirming the limitation of efficacy and tolerability data on opioid-naive and non-selected populations of cancer patients treated with morphine and suggesting that oral morphine, oxycodone and hydromorphone have similar efficacy and toxicity in this patient population.	The choice among these drugs can be influenced by several factors, including availability, cost and other local considerations.	A
McNicol et al. (2003)	Systematic review to assess the management of opioid side effects in the context of cancer pain management or, in the event that no evidence was available for cancer pain, for chronic non cancer pain.	67 studies met inclusion criteria for analysis	The type, strength, and consistency of evidence for available interventions to manage opioid side effects vary from strong (eg, on the use of naloxone to reverse respiratory depression or constipation) to weak (eg, changing from the oral to epidural route of morphine administration to manage sedation).	The lack of well-designed, randomized controlled trials and the heterogeneity of populations and study designs made the drawing of firm conclusions difficult and precluded performance of meta-analysis. Well-designed trials in the specified populations are required to furnish clinicians with secure evidence on managing opioid side effects successfully.	C
Vignaroli et al (2012)	Consensus list of essential prescription package for pain treatment, using a Delphi process	57 palliative care experts from 39 countries.	Morphine selected by more than 84% of the participants as first-line opioid for the treatment of moderate to severe pain (5mg orally every 4 hrs).	33% of the participants reported having difficulties accessing morphine in their countries.	D
CKS (2007)	Consensus guidelines		Morphine regarded as opioid of first choice in the management of moderate and severe acute and chronic pain including that of palliative care.		D
De Lima (2007)	Consensus list based on expert opinion	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Morphine (IR: 10-60 mg tablets, IR: 10mg/5mL oral solution, IR 10 mg/mL injectable, SR 10 mg tablets and SR 30 mg tablets) included in the IAHPCL for the treatment of moderate to severe pain in palliative care.		D

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Good et al. (2006)	Survey among experts commissioned by the Joint Therapeutics Committee of the Australian and New Zealand Society of Palliative Medicine, Palliative Care Australia and the Clinical Oncological Society of Australia surveyed palliative care practitioners in Australia to compile a list of drugs they considered essential.	100 physicians in Australia and New Zealand	Morphine was identified as essential for the treatment of severe pain by 98% of the respondents.		D
Nauck et al. (2004)	Prospective survey (expert opinion)	57 palliative care units in Germany (1304 patients) in a 3 month census period.	Morphine was the second most frequently used drug in German palliative care units, used in 42% of patients Supports the use of morphine for the treatment of moderate to severe pain in palliative care.	Not clear how much morphine was used for pain and how much for dyspnea.	D
Hanks et al. (2001)	Consensus Guidelines (Updated and revised by Caraceni et al in 2012) (see above)			Morphine regarded as opioid of first choice in the management of moderate and severe acute and chronic pain including that of palliative care.	D
WHO (1996)	Consensus guideline			Morphine regarded as opioid of first choice in the management of moderate and severe acute and chronic pain including that of palliative care.	D

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RESPIRATORY TRACT SECRETIONS

Recommended medicine for addition: HYOSCINE BUTYLBROMIDE

New recommended formulations for addition:

10 mg/mL injectable

Definition

Excessive respiratory tract secretions (also referred to as death rattle), is used to describe a rattling noise produced by accumulated secretions in the airway which oscillate in time with inspiration and expiration. Generally occurs in patients who are extremely weak and close to death.

Scope

- Excessive respiratory tract secretions are associated with decreased consciousness and associated depression of reflexes (cough and swallow) at end of life. The patient is unlikely to be aware of, or distressed by accumulated respiratory secretions.
- Management of this symptom is therefore primarily for the benefit of those present in the last hours and days.
- Non pharmacological management includes positioning (and in some cases oropharyngeal suction) to reduce accumulation of secretions.
- This application only covers the pharmacological management of excessive respiratory tract secretions.

Antimuscarinic Drugs in the Management of Excessive Respiratory Tract Secretions

Antimuscarinic drugs (hyoscine hydrobromide, hyoscine butylbromide and glycopyrronium) can be effective in drying of respiratory secretions but there is no substantial evidence from systematic review, that any intervention is superior to placebo in the treatment of this symptom.

Evidence for management of this symptom with antimuscarinic agents

- A recent systematic review published in November 2012 (Pastrana et al. 2012) with a comprehensive search strategy (Radbruch et al. 2012) identified 6 controlled trials on antimuscarinic drugs and found no difference between hyoscine hydrobromide, hyoscine butylbromide and glycopyrronium. Only one methodologically weak trial compared hyoscine hydrobromide to placebo.
- Antimuscarinic drugs reduce the production of saliva and have some effect on reducing respiratory secretions.
- Considering the lack of evidence from clinical trials, the recommendation for the use of antimuscarinic drugs in the management of excessive respiratory tract secretions has to be based on clinical expertise. Expert opinion strongly supports the use of these medications in palliative care patients in the terminal stage with respiratory secretions.
- There is considerable experience in the use of antimuscarinic drugs in the management of excess salivation and drooling in patients with neurological disabilities.
- Antimuscarinic drugs are less likely to be effective when secretions are the result of lung abnormalities (e.g. bronchial secretions) or reflux of gastric contents.

HYOSCINE BUTYLBROMIDE

- Hyoscine butylbromide is a peripherally acting antimuscarinic, anticholinergic agent used as an abdominal-specific antispasmodic. It is a quaternary ammonium compound which blocks the action of acetylcholine at parasympathetic sites (both muscarinic and nicotinic receptors) in smooth muscle, and in secretory glands. It causes decreased motility of the gastrointestinal tract and the urogenital tracts, and is useful in the treatment of spasms in these regions.
- Several pharmacokinetic studies in humans have consistently demonstrated the low systemic availability of hyoscine butylbromide after oral administration, with plasma concentrations of the drug generally being below the limit of quantitation. The bioavailability of hyoscine butylbromide, estimated from renal excretion, was generally <1%. However, because of its high tissue affinity for muscarinic receptors, hyoscine butylbromide remains available at the site of action in the intestine and exerts a local spasmolytic effect (Tygat, 2007)
- Relatively short duration of action (<1 hour) following single subcutaneous dose, but effect

prolonged with repeated doses.

- It is available in formulations for administration by oral and parenteral routes, and is generally the agent of first choice to control excessive secretions.
- Because it does not cross the blood-brain barrier, hyoscine butylbromide may be the preferred over hyoscine hydrobromide for patients at the end of life.
- Hyoscine butylbromide is included in the IAHPC List of Essential Medicines for the treatment of respiratory secretions in palliative care (expert opinion).

PHARMACOLOGICAL TREATMENT OF EXCESSIVE RESPIRATORY TRACT SECRETIONS IN PALLIATIVE CARE: SUMMARY OF EVIDENCE					
Reference	Study	Subjects	Results	Comment	Level of Evidence (GRADE)
Bennett et al. (2002)	Systematic review	Literature search to 2001 from which evidence was summarized and graded. Clinical guidelines were constructed based on evidence from volunteer and clinical studies.	Low doses of antimuscarinics will readily inhibit salivary secretion but have a much lesser effect on bronchial secretions. Clinical studies demonstrate that subcutaneous hyoscine hydrobromide 400 mg is more effective at improving symptoms at 30 min than glycopyrronium 200 mg by the same route. Clinically, around ¾ patients with death rattle receive antimuscarinic drugs and beneficial response seen in ~80%. Higher response rates seen in studies in which drug therapy combined with conservative interventions. Hyoscine butylbromide results in tachycardia in a dose-dependent fashion. Doses of 200microgram hyoscine hydrobromide can cause bradycardia.	Optimal drug regimen has not been determined In general IV route results in faster onset but shorter duration of action than IM route. Author suggests an initial SC bolus of 1 of the 3 agents; if effective at review after 30 minutes, give SC infusion. All agents cause mouth dryness and can result in urine retention	A
Wee, Hillier (2008)	Systematic review	Adults and children with noisy breathing at the end of life. Identified studies were RCTs, controlled before and after studies or interrupted time series and of 10 or more subjects. Studies were included if there was a pharmacological and or non- pharmacological intervention.	30 studies identified but only 1 met the inclusion criteria Included study was a randomized placebo-controlled trial of the use of hyoscine hydrobromide HH tended to reduce death rattle compared with placebo but this was not significant. No evidence to show that any intervention, pharmacological or non- pharmacological, is superior to placebo in the treatment of death rattle.	A larger randomized study comparing atropine, hyoscine butylbromide and hyoscine hydrobromide is in progress.	B
Pastrana et al. (2012)	Systematic review	4 randomized controlled trials and 2 cohort studies included, only very few patients with non-cancer diseases	In one cohort trial with 170 patients hyoscine was superior to glycopyrronium. Glycopyrronium was superior in 2 small trials In the largest trial with 333 patients no difference was reported between hyoscine hydro bromide and hyoscine butylbromide.	4 studies with small trial sizes (10-36 patients), placebo control in only one trial	C
Douglas et al. (2009)	Evidence-based prescribing guidelines to allow safe and effective symptom control for patients dying with renal failure. Based on literature review and consensus of experts.	60 articles included in the literature review.	Anticholinergic drugs can reduce respiratory tract secretions in the dying phase. Glycopyrronium or hyoscine butylbromide are recommended for renal patients. There is evidence that glycopyrronium accumulates in renal impairment and that dose reduction is required.	Half of the normal dose of glycopyrronium should be used in renal patients. Hyoscine hydrobromide crosses the bbb and may lead to excessive drowsiness or paradoxical agitation in elderly patients with comorbidity. Patients with uraemia are more sensitive to the effects of drugs which cross the bbb therefore hyoscine hydrobromide not recommended for patients with advanced CKD.	C

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Lindqvist et al. (2013)	List of 4 essential medicines for palliative care (expert opinion)		For RTS, there was consensus (n=90) on the use of an antimuscarinic drug, but no consensus on a single one among 4 different drugs.	Expert opinion – all participants from European countries.	D
De Lima (2007)	Consensus list based on expert opinion.	Delphi survey with more than 100 physicians and pharmacists from 22 countries.	Hyoscine butylbromide (20 mg/1mL oral solution, 10 mg tablets, 10 mg/mL injectable) included in the IAHPCL List for the treatment of respiratory tract secretions in palliative care.		D
CKS Guidelines (2007)	Clinical guidelines based on literature review and expert opinion			Supports use of antimuscarinics	D
Good, et al (2006)	Expert opinion	Survey		Supports use of hyoscine hydrobromide	D
Nauck et al (2004)	Expert opinion	Survey		Supports use of hyoscine hydrobromide	D

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