National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Palliative care

1. Executive Summary

Date:03 September 2017
Medicine (INN): Morphine syrup
Medicine (ATC): N02AA01
Indication (ICD10 code):R06.0 + (Z51.5)
Patient population: Patients receiving palliative care
Prevalence of condition: Breathlessness is a source of distress for 50-70% ofpatients requiring palliative care.
Level of Care: Primary Health Care
Prescriber Level: Doctor/ palliative care practitioner
Current standard of Care: n/a
Efficacy estimates: (preferably NNT):n/a
Motivator/reviewer name(s): Ms Pearl Lentsoane, with support from Secretariat Ms Trudy Leong.
PTC affiliation: n/a

2. Name of author(s)/motivator(s)

Ms Pearl Lentsoane, with support from the Secretariat Ms Trudy Leong.

3. Author affiliation and conflict of interest details

Ms Pearl Lentsoane: Mankweng hospital, AMS subcommittee Limpopo province; Member of the Primary Health Care Technical Sub-Committee of NEMLC; No conflicts of interest.
Ms Trudy Leong: National Department of Health, Essential Drugs Programme; Secretariat to the Primary Health Care Technical Sub-Committee of NEMLC; No conflicts of interest.

4. Introduction/ Background

Breathlessness is a source of distress for 50-70% of patients requiring palliative care. A complex physiological and psychological sensation, its causes are often multifactorial, including the underlying disease, cachexia, and deconditioning. As disease progresses dyspnoea occurs more frequently and at rest (Abernethy*et al*, 2003).

5. Search 1: PICO #1

Purpose/Objective i.e. PICO question 1
-P *(patient/population):* all palliative care patients experiencing dyspnoea
-I *(intervention):*oral morphine
-C *(comparator):* placebo
-O *(outcome):*Efficacy (relief of breathlessness).

(P) Amongst palliative care patients experiencing dyspnea or breathlessness, is**(I)** oral morphine compared to **(C)**placebo **, (O)** safe and effective to relieve dyspnea/breathlessness.

6. **Methods:**
   a. **Data sources:** Pubmed, Cochrane library

   b. **Search strategy**
      i. **Search strategy 1:**

*(((MeSH Terms: dyspnea; morphine))***filter: systematic**

The search strategy retrieved 20 articles, of which 5 were relevant to the PICO clinical question. Four studies were excluded for reasons outlined in the table below. The remaining studies were not relevant to the PICO.

Excluded studies

	Author, date	***Type of study***	***Reason for exclusion***
1	Jennings et al, 2013	Cochrane review	Review was withdrawn, (out of date)
2	Simon et al 2010	Cochrane review	Investigated the use of benzodiazepines for dyspnoea
3	Büche DJ,2006	Review article	Article only available in German
4	Bausewein C, 2014	Review article	The review included inhaled nebulised and intranasal opioids

      ii. **Search strategy 2:**

MeSH Terms*: palliative care; dyspnea; child*
Search strategy 2 retrieved 71 articles of which 3 were related to the PICO clinical question. The remaining articles where not relevant. Of the 3 relevant articles only 1 has dosing recommendations and the other 2 articles only make reference to the use of opioids for dyspnea in the pediatric population.

      iii. **Search strategy 3:**

MeSH Terms: *dyspnea; palliative care; child; morphine*
Search strategy3 retrieved 10 articles which were not related to the PICO clinical question.

      iv. **Search strategy 4:**

MeSH Terms: dyspnea; morphine; child
Search strategy4 retrieved 15 articles which were not related to the PICO clinical question.

c. Evidence synthesis:

i) Search strategy 1 (Adults)

Author, date	***Type of study***	***n***	***Population***	***Intervention***	***Comparators***	***Primary outcome***	***Effect sizes***	***Comments***
Barnes et al 2016,	Systematic review	n=117 for changes from baseline (7 RCTs); n=159 for post-treatment scores (11 RCTs)	Adults with advanced disease and terminal illness	Oral morphine	Placebo	Improvement in breath-lessness (measured by VAS or Borg scale), changes from baseline as well as post-treatmentassessed. (Post-treatment breathlessness assessed at variable time points:1 hour to 6 weeks).	The meta-analysis demonstrates a small treatment effect for breathlessness (change from baseline), seven studies, n=107; standardised mean difference−0.09, 95%CI −0.36 to 0.19; p = 0.54; I^2-74%. Post-treatment score, 11 studies, n=159, standardised mean difference−0.28, 95% CI −0.50 to −0.05; p = 0.02; I^2=8.4%	Evidence was considered very low quality (GRADE) for changes from baseline; and low quality for post-treatment scores. Constipation, nausea and vomiting, and drowsiness occurred significantly more frequently with opioids than placebo.
Jansen et al , 2017	Systematic literature review	Includes studies already stated above (2)						
Lanken et al,2008	American Thoracic Society Clinical Policy Statement: Palliative Care for Patients with Respiratory Diseases and Critical Illnesses	The following doses where recommended for the use of morphine in adults and children Adults : 5–10 mg, 4 hourly Children :0.2–0.5 mg/kg, 3–4 hourly						

ii) Search strategy 2 (Paediatrics)

Author, date	*Type of study*	*n*	*Population*	*Intervention*	*Comparators*	*Primary outcome*	*Effect sizes*	*Comments*
Johnston et al , 2005	Narrative Review.		Pediatric palliative care patients	Oral morphine		Improvement in symptoms of dyspnoea.	No trial data was described in the review	Guidelines following dose of oral morphine is recommended in children: Morphine 0.2-0.5 mg/kg every2-4 hourly (no maximum dose recommended).

There is a paucity of RCT evidence for opioids in the management of dyspnoea of children in palliative care. However, practice guidelines recommend opioids for dyspnoea.

7. **Evidence quality:** The RCTs included in the Cochrane Review were considered to be of low to very low quality. The trials were of small sizes and some studies did not give enough information to assess quality.

8. **Alternative agents:** Authors of a recent 2016 Cochrane review (8) concluded that "*There is no evidence for or against benzodiazepines for the relief of breathlessness in people with advanced cancer and COPD. Benzodiazepines caused more drowsiness as an adverse effect compared to placebo, but less compared to morphine. Benzodiazepines may be considered as a second- or third-line treatment, when opioids and non-pharmacological measures have failed to control breathlessness. There is a need for well-conducted and adequately powered studies".*

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	**SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS**
QUALITY OF EVIDENCE	**What is the overall confidence in the evidence of effectiveness?** Confident [X] Not confident [ ] Uncertain [ ]	
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable effects?** Benefits outweigh harms [X] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]	
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [ ] No [X] List the members of the group. List specific exclusion from the group:	Rationale for therapeutic alternatives included: References: Rationale for exclusion from the group: References:

<table>
<tr><td>VALUES & PREFERENCES / ACCEPTABILITY</td><td>Is there important uncertainty or variability about how much people value the options?
Minor [X] Major [ ] Uncertain [ ]

Is the option acceptable to key stakeholders?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
<tr><td>RESOURCE USE</td><td>How large are the resource requirements?
More intensive [ ] Less intensive [ ] Uncertain [X]</td><td>Cost of medicines/ month:<table><tr><th>Medicine</th><th>Cost (ZAR)*</th></tr><tr><td>Morphine syrup (Mist Morph) 10 mg/ 5 mL</td><td>R259.38</td></tr></table>* Refer to updated Morphine costing analysis done for the Adult Hospital Level review,19 September2017.
NDoH_EDP_Morphine costing_Adults_19Sep
Additional resources:</td></tr>
<tr><td>EQUITY</td><td>Would there be animpact on health inequity?
Yes [ ] No [X] Uncertain [ ]</td><td></td></tr>
<tr><td>FEASIBILITY</td><td>Is the implementation of this recommendation feasible?
Yes [X] No [ ] Uncertain [ ]</td><td></td></tr>
</table>

Type of recommendation	We recommend against the option and for the alternative	We suggest not to use the option or to use the alternative	We suggest using either the option or the alternative	We suggest using the option	We recommend the option
	☐	☐	☐	☐	**X**

Recommendation:

Based on the evidence review above, the Primary Health Care Committee recommends the addition of oral morphine for the management of palliative dyspnea in paediatric and adult patients receiving palliative care.

*Rationale:*Systematic review and meta-analysis of limited low quality RCTs suggests that oral opioids may be of benefit to palliate breathlessness in adults. There is a paucity of RCT data for the management of palliative dyspnoea in children; however morphine, oral is standard of care as recommmended in a number of guidelines.

Level of Evidence:II Systematic review of low to very low RCTs, III Guidelines

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
X	X	

VEN status:

Vital	Essential	Necessary
	X	

Monitoring and evaluation considerations

Research priorities

Johnston *et al,* 2005: " There are limited data surrounding the management of dyspnea in children at the end-of-life, suggesting tha this symptom is one that would benefit from further study".

References

1. Abernethy AP, Currow DC, Frith P, Fazekas BS, McHugh A, Bui C. Randomised,double blind, placebo controlled crossover trial of sustained release morphinefor the management of refractory dyspnoea. BMJ. 2003 Sep 6;327(7414):523-8.https://www.ncbi.nlm.nih.gov/pubmed/12958109
2. **Barnes H, McDonald J, Smallwood N, Manser R. Opioids for the palliation of refractory breathlessness in adults with advanced disease and terminal illness. Cochrane Database Syst Rev. 2016 Mar 31;3:CD011008.https://www.ncbi.nlm.nih.gov/pubmed/27030166**
3. Jansen K, Haugen DF, Pont L, Ruths S. 2017. Safety and effectiveness of palliativedrug treatment in the last days of life - a systematic literature review:J Pain Symptom Manage. 2017 Aug 9. pii: S0885-3924(17)30381-0.https://www.ncbi.nlm.nih.gov/pubmed/28803078
4. Lanken PN, Terry PB, Delisser HM, Fahy BF, Hansen-Flaschen J, Heffner JE, LevyM, Mularski RA, Osborne ML, Prendergast TJ, Rocker G, Sibbald WJ, Wilfond B,Yankaskas JR; ATS End-of-Life Care Task Force. An official American ThoracicSociety clinical policy statement: palliative care for patients with respiratory diseases and critical illnesses. Am J RespirCrit Care Med. 2008 Apr15;177(8):912-27.https://www.ncbi.nlm.nih.gov/pubmed/18390964
5. **Johnston DL, Hentz TA, Friedman DL. Pediatric palliative care. J PediatrPharmacolTher. 2005 Oct;10(4):200-14. https://www.ncbi.nlm.nih.gov/pubmed/23118638**

6. Robinson WM. Palliation of dyspnea in pediatrics. ChronRespir Dis.2012;9(4):251-6.https://www.ncbi.nlm.nih.gov/pubmed/22872362
7. NCCN Practice Guidelines in Oncology, Palliative Care. http://www.nccn.org/professionals/physician_gls/PDF/palliative.pdf
8. The Association of Paediatric Palliative Medicine Master Formulary, 4th edition. http://www.appm.org.uk/resources/APPM+Master+Formulary+2017+-+4th+edition.pdf