

**South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Palliative Care**

MEDICINE REVIEW:

1. Executive Summary

Date: 15 July 2017
Medicine (INN): Hyoscine butylbromide (butylscopolamine)
Medicine (ATC): A03BB01
Indication (ICD10 code): The treatment of respiratory tract secretions in patients who are weak or close to death. R06.0 + (Z51.5)
Patient population: Patients with excessive respiratory secretions at end of life
Prevalence of condition: One third of dying patients (13)
Level of Care: Palliative care: doctor or professional nurse
Prescriber Level: Hospital level of care
Current standard of Care: n/a
Efficacy estimates: (preferably NNT): n/a
Motivator/reviewer name(s): A. Sherriff
PTC affiliation: Free State Provincial PTC

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

A. Sherriff

3. Author affiliation and conflict of interest details

Dept Oncology University of Free State; No conflict of interests declared.

4. Introduction/ Background

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. Management of this symptom is mainly for the benefit of the caregivers and patients are unlikely to be aware of it. Hyoscine butylbromide is a peripherally acting antimuscarinic, anticholinergic agent and reduces the production of saliva; and has some effect in reducing respiratory secretions. Early initiation at a dose of 20mg SC/IM, increasing to a maximum dose of 120mg, "death rattle" can be decreased. Supporting evidence is limited, because of the vulnerability of the population and recommendations are generally based on expert opinion(1).

5. Purpose/Objective i.e. PICO

- P: Patients who are weak or close to death with respiratory secretions
- I: Hyoscine butylbromide (butylscopolamine)
- C: Hyoscine hydrobromide (scopolamine), glycopyrronium, atropine, octreotide
- O: Reduce respiratory secretions

6. Methods:

i) Search described in the WHO EML review

- a. Data sources:** Medline (2000-2012), Embase (2000-2012) electronic databases; hand search of the references included in studies/papers retrieved in these databases; 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.

- b. **Search strategy:** Not described - "A Working Group (WG) of directors from the International Association for Hospice and Palliative Care (IAHPC) was formed to work on this project. 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 WHO – Essential Medicines in Palliative Care (January 2013) 4 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".

ii) **Second search strategy**

- a. **Data source:** Pubmed and Medline (2012 to 15 July 2017)
- b. **Search strategy: MeSH** search terms: (Respiratory secretions [death rattle]) AND hyoscine butylbromide[antimuscarine]

One additional systematic review (2013) was retrieved in the search, which included 11 studies that reported on the effectiveness of various interventions. (13)

7. Evidence synthesis

i) WHO EML: Pharmacological treatment of excessive respiratory tract secretions in palliative care: summary of evidence

Reference	Study type	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.	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.	Authors conclusion: <i>“there was no evidence to show that any intervention, be it pharmacological or non-pharmacological, was superior to placebo in the treatment of noisy breathing.....We acknowledge that in the face of heightened emotions when death is imminent, it is difficult for staff not to intervene patients need to be closely monitored for lack of therapeutic benefit and adverse effects while relatives need time, explanation and</i>

					<i>reassurance to relieve their fears and concern”.</i>
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 hydrobromide 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
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 IAHPD List for the treatment of respiratory tract secretions in palliative care.		D
CKS Guidelines (2007)	Clinical guidelines based on literature review and			Supports use of antimuscarinics	D

	expert opinion				
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

(2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12)

ii) Additional evidence reviewed

Reference	Study type	Subjects	Results	Comment	Level of Evidence (GRADE)
Martin et al, 2013	Systematic review of 39 studies: - 2RCTs, observational studies (cross-sectional surveys, cohort studies, qualitative interviews), medical records review	Studies described research about death rattle in the terminally ill. Included patients', relatives', or professional caregivers' experience with death rattle.	Scopolamine, glycopyrronium, hyoscine butylbromide, atropine, and/or octreotide have been studied, but only one study used a placebo group. No evidence that the use of any antimuscarinic agent is superior to no treatment	Research question and search was adequate. Despite appropriate steps taken to minimise risk of bias during selection, data extraction and quality assessment of studies, risk of bias cannot be ruled out as only 2 of 39 studies were RCTs; the rest were observational studies and reviews of medical records. However, the authors do conclude that antimuscarinics are no better than placebo.	C

Evidence quality:

WHO EML 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

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS				
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>There is no evidence that the use of an antimuscarinic agent is superior to no treatment. However, studies on the effect of pharmacologic interventions are limited by their lack of placebo group.</p>				
BENEFITS & HARMES	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>					
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/></p> <p>List the members of the group: n/a</p> <p>List specific exclusion from the group: n/a</p>	<p>Rationale for therapeutic alternatives included: n/a References: n/a</p> <p>Rationale for exclusion from the group: n/a References: n/a</p>				
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input checked="" type="checkbox"/> <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p>Please refer to EUnetHTA core model assessment (NEMLC report for the review of the Adult Hospital Level chapter 24: Medicines used in palliative care (2017-2019) http://www.health.gov.za/index.php/standard-treatment-guidelines-and-essential-medicines-list/category/286-hospital-level-adults</p> <p>The total weighted score for this assessment was 0.70, favouring hyoscine as ranked and measured by the Adult Hospital Level Committee (Refer to the excel spreadsheet for detailed information – noting that the domain for ethical analysis scored the highest).</p>				
RESOURCE USE	<p>How large are the resource requirements?</p> <p>More intensive Less intensive Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	<p>Cost of medicines/ month:</p> <table border="1"> <thead> <tr> <th>Medicine</th> <th>Cost (ZAR)</th> </tr> </thead> <tbody> <tr> <td>Hyoscine butylbromide 20mg/ml</td> <td>R 5.20*</td> </tr> </tbody> </table> <p>*Contract circular RT297-2019 Additional resources: n/a</p>	Medicine	Cost (ZAR)	Hyoscine butylbromide 20mg/ml	R 5.20*
Medicine	Cost (ZAR)					
Hyoscine butylbromide 20mg/ml	R 5.20*					
EQUITY	<p>Would there be an impact on health inequity?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>					
FEASIBILITY	<p>Is the implementation of this recommendation feasible?</p> <p>Yes No Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>					

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
	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

Recommendation: The Adult Hospital Level Committee recommends that consideration be made for the inclusion of hyoscine butylbromide injection in palliative care for “death rattle”.

Rationale: Despite the lack of evidence of benefit for hyoscine to reduce respiratory secretions in the terminally ill patient, parenteral hyoscine is standard of care in many international guidelines⁵ to reduce “death rattle”. The Adult Hospital Level Committee also considered ethics and other value judgements (as assessed by the HTA Core Model assessment), and proposes compassionate use of parenteral hyoscine for death rattle in terminally ill patients.

Level of Evidence: III Guidelines, Expert opinion

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

VEN status:

Vital	Essential	Necessary
<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>

NEMLC MEETING OF 5 DECEMBER 2019

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee, above.

Monitoring and evaluation considerations

Research priorities

References:

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13. Martine E. Lokker, RN, MSc, Lia van Zuylen , PhD, Carin C.D. van der Rijt, PhD, Agnes van der Heide, PhD. Prevalence, Impact, and Treatment of Death Rattle: A Systematic Review. *Journal of Pain and Symptoms Management*. June 19, 2013