

**South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Palliative Care**

MEDICINE MOTIVATION:

1. Executive Summary

Date: 29 July 2017
Medicine (INN): Betamethasone/ dexamethasone
Medicine (ATC): H02AB01/H02AB02
Indication (ICD10 code): Fatigue, when treating the underlying cause is not possible or effective (Z51.5)
Patient population: Adult palliative care patients
Prevalence of condition: Unknown
Level of Care: Primary health care or hospital level
Prescriber Level: Trained palliative care doctor /palliative care teams
Current standard of Care: Nil on EDL – new STG
Efficacy estimates: (preferably NNT) n/a
Motivator/reviewer name(s): Motivator: Dr S.R. Krause/ Reviewer: Dr Renee de Waal
PTC affiliation: n/a

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

Dr Renee de Waal

3. Author affiliation and conflict of interest details

University of Cape Town; PHC Committee member (2016-2018)
No conflicts of interest

4. Introduction/ Background

Fatigue (defined as a subjective feeling of tiredness, weakness, or lack of energy) in palliative care patients has many disease- or treatment-related causes. Despite limited evidence, corticosteroids (dexamethasone in particular) are widely used to treat fatigue in palliative care patients. The EML PHC ERC received a motivation for betamethasone for this indication from the Palliative Care TWG. The rationale for betamethasone rather than dexamethasone is that oral dexamethasone is available only through section 21 motivation. In contrast, betamethasone, which is considered equivalent to dexamethasone for this indication by palliative care clinicians, is easier to access.

5. Purpose/Objective i.e. PICO question [comparison to current standard of care for a specific indication]:

- P (*patient/population*): Adult palliative care patients
- I (*intervention*): Betamethasone (or dexamethasone)
- C (*comparator*): Placebo, no treatment

-**O** (*outcome*): 1. Efficacy (improvement in symptoms of fatigue) 2. Adverse effects

(P) Amongst adult palliative care patients with symptoms of fatigue, in whom treatment of the underlying cause is not effective or possible, is **(I)** betamethasone compared to **(C)** placebo/no treatment **(O)** effective in terms of improvement in fatigue symptoms, with minimal/acceptable side effects?

6. Methods:

a. Data sources

Pubmed - searches conducted on 29 July 2017

b. Search strategy

Study inclusion criteria:

Type of studies: RCTs and systematic reviews

Search terms:

("palliative care"[MeSH Terms] OR ("palliative"[All Fields] AND "care"[All Fields]) OR "palliative care"[All Fields]) AND ("fatigue"[MeSH Terms] OR "fatigue"[All Fields]) AND ("adrenal cortex hormones"[Pharmacological Action] OR "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroids"[All Fields])

Search retrieved 41 articles.

Substituting the term 'betamethasone' for 'corticosteroids' retrieved 3 articles – all found in the first search. Substituting the term 'dexamethasone' for 'corticosteroids' retrieved 15 articles – 2 were additional to the first search: the updated Cochrane Review (described below), and another narrative review (excluded). Substituting the terms 'life threatening illness' or 'life limiting illness' for 'palliative care' retrieved no articles.

The search found:

- no RCTs that involved betamethasone, and 1 that involved dexamethasone(1);
- 3 systematic reviews (1 in German – could only retrieve English abstract; 1 full text not obtainable by committee)(2);
- 3 uncontrolled prospective or retrospective cohort studies(3-5); and
- 4 narrative reviews(6-9).

c. Evidence synthesis

<i>Author, date</i>	<i>Type of study</i>	<i>n</i>	<i>Population</i>	<i>Intervention</i>	<i>Comparators</i>	<i>Primary outcome</i>	<i>Effect sizes</i>	<i>Comments</i>
Mucke, 2015	Systematic review							The only relevant study included of dexamethasone was the clinical trial described below. No studies of betamethasone were included.
Yennurajalingam, 2013	RCT	84	Patients with advanced cancer	Dexamethasone 4 mg 12 hourly for 14 days	Placebo	Change in Functional Assessment of Chronic Illness – Fatigue (FACIT-F) scale at Day 15	Mean (\pm SD) FACIT-F change from baseline was 9.0 (\pm 10.3) in the dexamethasone group, and 3.1 (\pm 9.6) in the control group ($p=0.008$).	

Several narrative reviews have mentioned that corticosteroids (in general) may be effective in treating fatigue in palliative care patients but most studies quoted did not assess fatigue as a primary endpoint (7). Several observational studies have attempted to identify patients who would benefit most from corticosteroid treatment. However, no clear criteria for treatment have yet been identified.

d. Evidence quality:

Very limited evidence – use seems to be guided by expert opinion only.

No clear evidence for efficacy, or safety.

No clear evidence regarding dose or duration of treatment, or to list specific indications/contraindications.

7. Alternative agents: n/a

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 checked="" type="checkbox"/> <input type="checkbox"/></p>	
BENEFITS & HARMS	<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.</p> <p>List specific exclusion from the group:</p>	<p>Rationale for therapeutic alternatives included:</p> <p>References:</p> <p>Rationale for exclusion from the group:</p> <p>References:</p>
VALUES & PREFERENCES /	<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 type="checkbox"/> <input checked="" type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input checked="" type="checkbox"/></p>	

RESOURCE USE	How large are the resource requirements? More intensive <input type="checkbox"/> Less intensive <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/>	Cost of medicines/ month: <table border="1"> <tr> <th>Medicine</th> <th>Cost (ZAR)</th> </tr> <tr> <td>n/a</td> <td></td> </tr> <tr> <td></td> <td></td> </tr> </table> Additional resources:	Medicine	Cost (ZAR)	n/a			
	Medicine	Cost (ZAR)						
n/a								
EQUITY	Would there be an impact on health inequity? Yes <input type="checkbox"/> No <input type="checkbox"/> Uncertain <input checked="" type="checkbox"/>							
FEASIBILITY	Is the implementation of this recommendation feasible? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/>	Not feasible for general PHC use. Requires palliative care training.						

	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
Type of recommendation	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Recommendation:

Betamethasone is not considered appropriate for prescription at Primary Health Care level at this stage. It could be considered at hospital level, or for prescription by specially trained district palliative care teams (with access at certain PHC facilities via down-referral mechanisms if necessary).

Rationale: Evidence for efficacy is limited, and there are potential risks of adverse effects. Current use is largely based on expert opinion, and is recommended for specific patients only, generally for short-term use, as the benefits appear to be short-lived. Selecting patients for treatment of fatigue, and prescribing betamethasone in this setting, requires palliative care training and experience, which is not currently the norm for PHC facility staff.

Level of Evidence: III 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 type="checkbox"/>	<input type="checkbox"/>

Monitoring and evaluation considerations

Research priorities

References:

1. Yennurajalingam S, Frisbee-Hume S, Palmer JL, Delgado-Guay MO, Bull J, Phan AT, et al. Reduction of cancer-related fatigue with dexamethasone: a double-blind, randomized, placebo-controlled trial in patients with advanced cancer. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2013;31(25):3076-82.
2. Mucke M, Mochamat, Cuhls H, Peuckmann-Post V, Minton O, Stone P, et al. Pharmacological treatments for fatigue associated with palliative care. *Cochrane Database Syst Rev*. 2015(5):CD006788.
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5. Matsuo N, Morita T, Matsuda Y, Okamoto K, Matsumoto Y, Kaneishi K, et al. Predictors of Responses to Corticosteroids for Cancer-Related Fatigue in Advanced Cancer Patients: A Multicenter, Prospective, Observational Study. *Journal of pain and symptom management*. 2016;52(1):64-72.
6. Barnes EA, Bruera E. Fatigue in patients with advanced cancer: a review. *International journal of gynecological cancer : official journal of the International Gynecological Cancer Society*. 2002;12(5):424-8.
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9. Franco OH, Steyerberg EW, Peeters A, Bonneux L. Effectiveness calculation in economic analysis: the case of statins for cardiovascular disease prevention. *J Epidemiol Community Health*. 2006;60(10):839-45.