South African National Essential Medicine List
Primary Healthcare Medication Review Process
Component: Pain

MEDICINE REVIEW:

1. Executive Summary

Date: 10 June 2018
Medicine (INN): Oxycodone
Medicine (ATC): N02AA05
Indication (ICD10 code): Chronic cancer pain (R52.0/R52.9)
Patient population: Adult patients requiring morphine tablets
Prevalence of condition: n/a
Level of Care: Primary level (clinics, community health centres and district hospital)
Prescriber Level: Primary care doctor
Current standard of Care: Either tramadol or morphine syrup (an add on therapy for chronic pain at primary level)
Efficacy estimates:
- Standard Mean Difference (SMD) for pain intensity between CR oxycodone and CR morphine: 0.14, 95% CI 0.01 to 0.27; I^2 =7% - low quality evidence;
- Sensitivity analysis did not corroborate this result (SMD 0.12, 95% CI -0.02 to 0.26); *Schmidt-Hansen et al 2017.*
Reviewer name(s): Dr M Namane; Ms P Lentsoane; Ms TD Leong
PTC affiliation: Western Cape PPTC

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

1. Dr M Namane
2. Ms P Lentsoane
3. Ms TD Leong

3. Author affiliation and conflict of interest details

a. University of Cape Town/Metro Health Services, Western Cape and Committee member of PHC Expert Review Committee; No conflicts of interest
b. National Department of Health (SAHPRA) and Committee member of PHC Expert Review Committee; No conflicts of interest
c. National Department of Health, Essential Drugs Programme and Secretariat to PHC Expert Review Committee; No conflicts of interest

4. Background

The review of oxycodone by PHC Review committee was requested by the NEMLC. The rationale for this request provided at the NEMLC meeting of 2 November 2017[1] was:
'As long acting morphine tablets were currently out of stock, it was recommended that the PHC Committee review other alternatives (e.g. oxycodone) for the pain chapter.'

[1] Minutes of the NEMLC meeting of 2 November 2017

5. **Purpose/Objective i.e. PICO question#1** [comparison to current standard of care for a specific indication]:
-P *(patient/population):* Patients managed at primary level with severe chronic pain
-I *(intervention): oral* oxycodone
-C *(comparator): oral* morphine
-O *(outcome):* 1. Efficacy (pain control) 2. Adverse effects

(P) Amongst adult patients with severe pain requiring opioids at primary level is **(I) oral** oxycodone compared to **(C)** oral morphine treatment **(O)** as effective in controlling pain and are adverse effects of oxycodone acceptable?

6. **Methods:**
   1. **Data sources**
   Pubmed & Cochrane library
   Searches conducted on 10, 11, 26 and 30 June 2018

   2. **Search strategy**

   Study inclusion criteria:
   Type of studies: RCTs and SRs

   Pubmed:filter: systematic
   MeSH Terms: ("oxycodone"[MeSH Terms] OR "oxycodone"[All Fields]) AND chronic[All Fields] AND ("cancer pain"[MeSH Terms] OR
   ("cancer"[All Fields] AND "pain"[All Fields]) OR "cancer pain"[All Fields])
   This search strategy retrieved 163 articles, three of which were relevant to the clinical question. One Cochrane review and 2 RCTs (note that the RCTs by Mucci-LoRusso (1998); and Corli et al (2016) are included in the Cochrane review).

   Evidence from additional RCTs was synthesised to review indications other than cancer pain as well as an overview of adverse events (see Appendix I). Seven studies were found to be relevant for PHC, 5 for Cochrane SRs and 2RCTs. Six studies are of adults and 1 for children & adolescents)

   A further search on use of oxycodone for in Emergency Units yielded no articles. The relevance of this search is that patients with distressing pain often present to Emergency units (and most of the EUs in SA are located within primary healthcare facilities). The research done in US in EUs was mainly to assess the trends for opioid use. Interestingly the findings were that use was increasing and this was deemed to be problematic.

   3. **Excluded studies:**

Type of study	***Reason for exclusion***
1.*All studies which SRs & RCTs whose outcomes were for pain control post-surgical procedures done at higher levels of care and conditions not managed at primary levels.*	*Not relevant for primary level setting*

4. Evidence synthesis

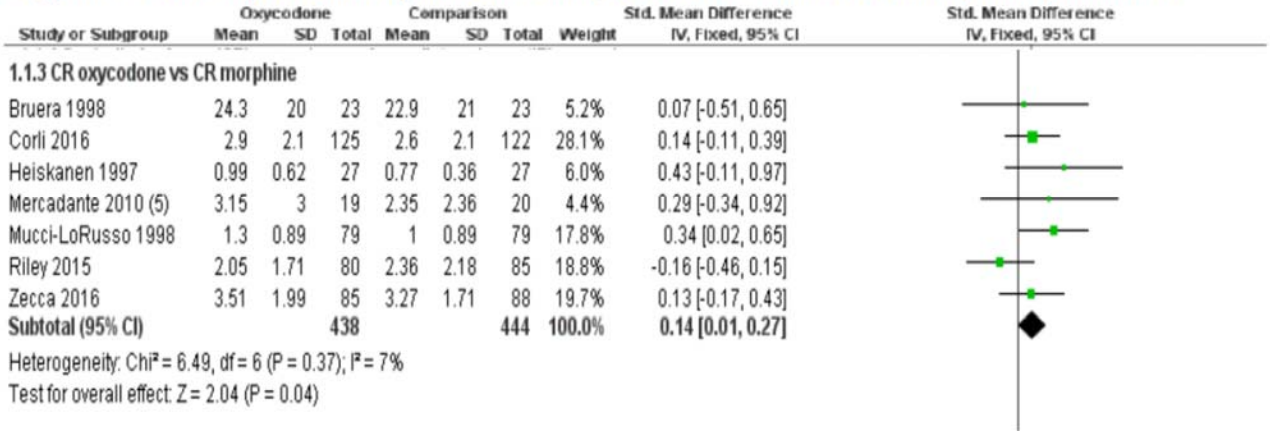
Table 1: Systematic review for indication – adult chronic cancer pain

Author, date	*Type of study*	*n*	*Population*	*Intervention*	*Comparators*	*Primary outcome*	*Effect sizes*	*Comments*
Schmidt-Hansen et al, 2017	Systematic review and meta-analysis	Pooled analysis of 7 of 9 RCTs	Cancer pain in adults	CR oxycodone	CR morphine	Pain relief	CR oxycodone vs CR morphine: pain relief significantly better after treatment with CR morphine (SMD 0.14, 95% CI 0.01 to 0.27; I^2=7%; low quality evidence). However, sensitivity analysis did not corroborate this result (SMD 0.12, 95% CI -0.02 to 0.26). Adverse events (constipation; drowsiness/ somnolence;/nausea; vomiting) similar. No data available to compare quality of life; whilst data from 1 study showed lower patient acceptability for CR oxycodone vs CR morphine (8/23 vs 11/23 patients)	RCTs of low methodological quality. RCTs were underpowered with low precision and various pain scales were used across studies.

5. Evidence quality:

There are limited trials comparing oxycodone vs morphine for outcomes that are relevant for use at primary level besides for cancer pain control (For an overview of other pain indications – see Appendix I). The Cochrane review indicated low quality evidence. Despite the Cochrane review showing that adverse events were similar with both morphine and oxycodone; the reported adverse events for oxycodone and other opioids are concerning (see Appendix I).

Figure 4. Forest plot of comparison: 1 Pain, outcome: 1.1 Pain intensity and pain relief.



7. Alternative agents: N/A

EVIDENCE TO DECISION FRAMEWORK

<table>
<tr><th></th><th>JUDGEMENT</th><th>SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS</th></tr>
<tr><td>QUALITY OF EVIDENCE</td><td>What is the overall confidence in the evidence of effectiveness?

Confident [ ] Not confident [X] Uncertain [ ]</td><td></td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?

Benefits outweigh harms [ ] Harms outweigh benefits [ ] Benefits = harms or Uncertain [X]</td><td></td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [ ] No [ ]

List the members of the group.

List specific exclusion from the group:</td><td>Rationale for therapeutic alternatives included:

References:

Rationale for exclusion from the group:

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

Is the option acceptable to key stakeholders?
Yes [ ] 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 10 mg SR (60)</td><td>104.11*</td></tr><tr><td>Morphine 30 mg SR (60)</td><td>163.77*</td></tr><tr><td>Morphine 60 mg SR (60)</td><td>324.39 to 648.79**</td></tr><tr><td>Oxycodone 5 mg SR (60)</td><td>208.18 to 416.37**</td></tr><tr><td>Oxycodone 10 mg SR (60)</td><td>312.79 to 625.58**</td></tr><tr><td>Oxycodone 20 mg SR (60)</td><td>426.76 to 853.52**</td></tr><tr><td>Oxycodone 40 mg SR (60)</td><td>533.73 to 1067.46**</td></tr><tr><td>Oxycodone 80 mg SR (60)</td><td>658.80 to 1317.59**</td></tr></table>* Contract circular HP09-2016SD (accessed 10 June2018)
**SEP database 5 June 2018 – 30% to 60% of SEP
(Note: Estimated equinalgesic dose ratio of oxycodone: morphine is 1.5; Mercadante et al, 2011)
Additional resources: n/a</td></tr>
</table>

EQUITY	**Would there be an impact on health inequity?** Yes: ☐ No: ☐ Uncertain: ☒ X	
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes: ☐ No: ☒ X Uncertain: ☐	

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 this evidence review, the PHC Committee was of the opinion that it was reasonable to recommend oral slow release oxycodone formulations as an alternative only when there are supply constraints with oral slow release morphine formulations. However, for purposes of the PHC STGs and EML, slow release oxycodone should not be recommended due to concerns of addiction.
Rationale: Limited evidence suggests that oxycodone offers similar levels of pain relief and overall adverse events to morphine. However, it is not justified to include oxycodone in the PHC EML due to concerns of addiction associated with oxycodone and given that supply challenges with morphine has historically not been of a consistent and long-term nature.
Level of Evidence: I Systematic review and meta-anaysis, Expert opinion

NEMLC accepted the PHC Committee's recommendation at the NEMLC meeting of 5 July 2018.[10]

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
☐	☒ X	☐

VEN status:

Vital	Essential	Necessary
☐	☒ X	☐

Monitoring and evaluation considerations

Research priorities

APPENDIX I

In addition to evidence reviewed to answer the PICO question, other placebo-controlled RCTs were reviewed to determine other indications for oxycodone and adverse effects associated with oxycodone.

Table 2: Other systematic reviews and RCTs

Author, date	*Type of study*	*n*	*Population*	*Intervention*	*Comparators*	*Primary outcome*	*Effect sizes*	*Comments*
Cooper, 2017	SR		Children & adolescents with chronic non-cancer pain			Pain control	No studies testing opioids were found for children from birth to 17 year olds	Very low quality of evidence
Da Costa, 2014	SR	8275 (22 trials)	Adults with hip and/ or knee OA	Opioids (including oxycodone in 10 trials)	placebo	Pain reduction & improvement in function	NNT (pain reduction) = 10 (95% CI 8 to 14 NNT (improvement of function) = 11 (95% CI 7 to 14)	The pooled risk ratio was 1.49 (95% CI 1.35 to 1.63) for any adverse event. ADRs resulting in hospitalisation, persistent disability, or death 1,3% (opioids) vs 0,4% (placebo)
Els, 2017	SR	>18,000 (16 Cochrane Reviews of These papers included 61 studies with more than 18,000 participants)	Adults with chronic non-cancer pain	Opioids (14 different opioid medicines, including codeine, morphine, and oxycodone)	placebo	Adverse events associate with medium and long-term use of opioids	1.opioids compared to placebo (risk ratio (RR) 1.42, 95% confidence interval (CI) 1.22 to 1.66) 2. opioids compared to a non-opioid active pharmacological comparator, with a similar risk ratio (RR 1.21, 95% CI 1.10 to 1.33). 3. serious adverse events with opioids compared to placebo (RR 2.75, 95% CI 2.06 to 3.67).	Examples of ADRs reported were: dizziness, drowsiness, fatigue, hot flushes, increased sweating, nausea, pruritus, and vomiting. There was however no ADRs reported on addiction, cognitive dysfunction, depressive symptoms or mood disturbances, hypogonadism or other endocrine

								dysfunction, respiratory depression, sexual dysfunction, and sleep apnoea or sleep-disordered breathing.
Gaskell, 2016	SR	687 (5 studies)	637 adult participants with painful diabetic neuropathy and 50 participants with postherpetic neuralgia.	Opioids (pregabalin, gabapentin, MR oxycodone, and FDC of MR oxycodone & naloxone)	placebo	Neuropathic pain relief	Overall, there was no 'substantial benefit' (at least 50% pain relief). Three studies n =537 with painful diabetic neuropathy) reported on outcomes equivalent to 'moderate benefit' from oxycodone compared to placebo , the NNT= 5.7	All studies had confounders and there was a lot of heterogeneity between the studies. There is very low quality evidence that oxycodone (as oxycodone MR) is of value in the treatment of painful diabetic neuropathy or postherpetic neuralgia
Gaskell, 2016	SR		Patients with fibromyalgia	oxycodone	placebo	FMS-related pain	No study satisfied the inclusion criteria	There is low quality evidence and therefore uncertainty about estimates of benefit and harm of oxycodone for FMS.

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10. Minutes of the NEMLC meeting of 5 July 2018.