South African National Essential Medicine List
Adult Hospital Level Medication Review Process
Component: Mental Health and Substance Use

MEDICINE REVIEW

1) Executive Summary

Date: 6 September 2018
Medicine (INN): Buprenorphine
Medicine (ATC): N07BC01
Indication (ICD10 code): Opiate withdrawal (F11.3/F11.4)
Patient population: Adults with opiate dependence
Prevalence of condition: Local epidemiological data lacking, but globally an estimated 0.2% of adults have reported unsanctioned opioid use (Gowig, 2017).
Level of Care: Secondary level (Hospital)
Prescriber Level: Medical officers
Current standard of Care: Methadone, oral
Efficacy estimates: (preferably NNT)
Buprenorphine vs methadone:

- *Average treatment duration:*
  Mean difference (MD) 1.30 days, 95% CI −8.11 to 10.72; n = 82; studies = 2; I2=57% low quality

- *Withdrawal treatment completion:*
  126/226 vs 122/231; RR 1.04, 95% CI 0.91 to 1.20; n = 457; studies = 5, I2=0%; moderate quality; NNT = 34

- *Adverse effects:* RCTs reported no significant AEs for either agent.

Motivator/reviewer name(s): Ms TD Leong, Ms L Mopelo, Dr L Robertson
PTC affiliation: Dr L Robertson – Gauteng Provincial PTC

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

Primary reviewers: Ms TD Leong, Ms L Mopelo
Secondary reviewers: Dr L Robertson

3) Author affiliation and conflict of interest details

Primary reviewers:

- Ms TD Leong: National Department of Health, Essential Drugs Programme, Secretariat to the Adult Hospital Level Committee (2017-2020); no conflicts declared
- Ms L Molepo: National Department of Health, Contract Management Unit; no conflicts declared

Secondary reviewer:

- Dr L Robertson: Department of Psychiatry, University of the Witwatersrand; the South African Society of Psychiatrists, Adult Hospital Level Committee member (2017-2020). Conflict of interests: Dr Reddys: Annual Congress attendance and accommodation, 2014-2019; AstraZeneca: Lunch 25 July 2017; Sanofi: Lunch 21 March 2018; Lundbeck: Lunch 29 January 2019.

4) Introduction/ Background

Dependence on opioids such as heroin or pharmaceutical opiates is a complex disorder that involves physiological, psychological, genetic, behavioural, and environmental factors[i]. Opioid use disorder is a major public health concern affecting the individual user (premature mortality and morbidity concerns such as disability, transmission of HIV, hepatitis C) and society (crime, healthcare and law enforcement costs, family and community disruption and lost productivity). An estimated 0.2% of adults worldwide have reported illicit opioid use[ii]. Opiate withdrawal or detoxification is not a stand-alone treatment, but rather the initial treatment step for relapse prevention and rehabilitation when the goal is to remain free of all opioid use[iii]. Detoxification process is highly unpleasant for patients with low completion rates.

Pharmaceutical formulations that are available on the South African market for opiate withdrawal include methadone syrup and buprenorphine sublingual tablets. Current recommendations in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicines List, 2015 for moderate to severe disorders includes methadone, oral and if methadone is unavailable, tramadol, oral[iv]. However, during the review of the 2015 version, an external comment was received for consideration of buprenorphine, oral. Methadone and buprenorphine are opioid agonists - methadone as a full agonist has safety concerns of reduced motor function and respiratory depression; whilst buprenorphine as a partial agonist may precipitate withdrawal; though there have been reports of fatal respiratory depression when used with other agents such as benzodiazepines[v]. Other safety concerns associated with methadone include QT prolongation[vi] and unintentional lethal overdose[vii].

This medicine review evaluates the evidence for buprenorphine compared to methadone for medically managed opiate withdrawal.

5) Purpose/Objective i.e. PICO question

-P: Adults with moderate to severe opiate addiction who are undergoing withdrawal (to be used as relief therapy for withdrawal symptoms).
-I: Buprenorphine, oral
-C: Methadone, oral
-O: *Primary outcomes:* Efficacy – management of opiate withdrawal and safety – Respiratory depression.
Secondary outcome: Decreased risk of neonatal abstinence syndrome.

Question: Is buprenorphine, oral as effective and safe as methadone, oral, for relief of withdrawal symptoms in adults (including pregnant women) with moderate to severe opiate addiction when used short-term in an inpatient setting?

6) Methods:

a) Data sources: Cochrane library, Pubmed, Trips database, Google scholar.
Search restricted to systematic reviews and randomised controlled trials directly comparing buprenorphine to methadone. (If these are unavailable in the published literature, cohort studies, clinical guidelines, and case series to be reviewed in accordance with grading as per SORT criteria).
Limited to published literature; grey literature not included.

Two reviewers (TDL and LM) conducted the literature search, data extraction and evidence analysis; and disagreements to be resolved through consensus (to ensure credibility and reliability of the data).
Secondary peer review done by LR.

b) Search strategies:

i) Cochrane library:

(1) Search strategy A:
Search terms: Opiate withdrawal AND adults AND methadone OR buprenorphine
Studies retrieved: 36 systematic reviews and excluded (as not relevant to PICO question)

(2) Search strategy B:
Search terms: Opiate withdrawal AND adults AND methadone AND buprenorphine
Studies retrieved: 14 systematic reviews; 13 excluded (as not relevant to PICO question)

(3) Search strategy C:
Search terms: Opiate withdrawal AND adults AND methadone OR buprenorphine
Studies retrieved: 80 RCTs; 80 excluded (as not relevant to PICO question)

ii) Pubmed:
Search terms: ((((("analgesics, opioid"[All Fields] OR "analgesics, opioid"[MeSH Terms] OR ("analgesics"[All Fields] AND "opioid"[All Fields]) OR "opioid analgesics"[All Fields] OR "opioid"[All Fields]) AND withdrawal[All Fields]) AND ("methadone"[MeSH Terms] OR "methadone"[All Fields])) AND ("buprenorphine"[MeSH Terms] OR "buprenorphine"[All Fields])) AND ("organization and administration"[MeSH Terms] OR ("organization"[All Fields] AND "administration"[All Fields]) OR "organization and administration"[All Fields] OR "management"[All Fields] OR "disease management"[MeSH Terms] OR ("disease"[All Fields] AND "management"[All Fields]) OR "disease management"[All Fields]) AND ("2017/11/13"[PDat] : "2018/11/12"[PDat])
Studies retrieved: 120 articles all of which were not relevant to the PICO question.
Note: Search was restricted to publications after 1 November 2017 to retrieve any additional RCTs or systematic reviews published after the Cochrane review by Gowig et al, 2017.

c) Excluded studies: See Appendix I

d) Evidence synthesis

Author, date	*Type of study*	N	Population	Comparators	Primary outcome(s)	Effect sizes	Comments
Gowing et al, 2017	Systematic review	6 RCTs compared methadone vs buprenorphine	Patients with opioid dependency who underwent opioid withdrawal	Buprenorphine vs methadone	•Mean days in treatment •Completion of withdrawal treatment •Adverse effects •Intensity of withdrawal	Buprenorphine vs methadone: •*Average treatment duration:* Mean difference (MD) 1.30 days, 95% CI −8.11 to 10.72; n = 82; studies = 2; I2=57% low quality •*Withdrawal treatment completion:* 126/226 vs 122/231; RR 1.04, 95% CI 0.91 to 1.20; n = 457; studies = 5, I2=0%; moderate quality •*Adverse effects:* RCTs reported no significant AEs for either agent.	Systematic review had an 'a priori' design and research questions clear and although only 3 were answered, there was insufficient and inadequate data for a meta-analysis to determine the intensity of withdrawal of buprenorphine vs methadone. Various database searched and minimal selection and publication bias as grey literature and publications in multiple languages searched. Steps taken to minimize risk of bias for study selection, data extraction; through consultation and discussion where there was uncertainty. Appropriate assessment of quality of RCTs adequately reported. Heterogeneity across RCTs assessed using relevant methodology and adverse events were defined. Buprenorphine and methadone appear to be equally effective, but data are limited and there is uncertainty regarding the rate of dose tapering (studies show conflicting results regarding the rapid vs slow tapering of buprenorphine to accomplish completion of withdrawal treatment). Studies heterogenous, and meta-analysis only possible for 2 RCTs (for outcome treatment duration) and 5 RCTs (completing withdrawal). Although study findings were reasonably consistent, study settings varied and studies were small.

							Treatment was administered either as inpatient or outpatient, and the effect of supervision on completion and duration of treatment is uncertain. Study subjects were mostly male, and further research is needed using male/female as a variable. No studies investigating use in pregnancy was included in this review. Despite RCTS showing no significant adverse effects in either buprenorphine or methadone groups; authors of the review acknowledged the difficulty in differentiating adverse effects of treatment from the signs and symptoms of opioid withdrawal.

e) Evidence quality: Limited RCT evidence that are small and of low to moderate methodological quality.

7) Alternative agents: As per the current Adult EML and STG, 2015 recommendations, tramadol may be considered if methadone is unavailable.

8) Discussion:

- *Dosage considerations*

Varying dosing regimens were used in the studies included by Gowing et al (2017) and the authors were unable to make dosage recommendations. While South African guidelines (Weich et al., 2017, ref iii) recommend that buprenorphine is commenced at a low dose and then gradually increased to ameliorate buprenorphine-induced withdrawal, the six studies of buprenorphine vs methadone did not follow this regimen, but gradually tapered the buprenorphine from an initial dose. Thus, dosing will most likely have to be individualized according to severity of the opiate dependence and withdrawal, as with methadone. Clinical observation and use of a structured instrument such as the objective opioid withdrawal scale (OOWS) rating scale and guidance from the South African Addiction Medicine Society (SAAMS) Guideline[viii] is advised.

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- *Non-pharmacological interventions*
  Pharmacotherapy should generally not be used exclusively for opioid use disorder. Medication-assisted withdrawal should include integrated, adjunctive psychosocial treatment. Possibly starting with addiction counselling and participating in a mutual help group. Successful pharmacotherapy is dependent on a multidisciplinary, coordinated approach to care including social worker services, individual and group counselling and individual case-management.
  Medically managed withdrawal must be accompanied by:
  - education regarding the dangers of opiate use following a period of abstinence as tolerance reduces rapidly – i.e. previously tolerated doses may be fatal due to respiratory depression.
  - continuity of care with a rehabilitation program and post-rehabilitation with treatment plans
  - attention to social stressors (domestic violence, housing, unemployment) to assist with prevention of relapse.

- *Pregnancy*
  No studies have been identified comparing buprenorphine to methadone for opioid withdrawal in pregnancy. Evidence for safety is extrapolated from evidence in OST, which suggests both may be used in pregnancy without teratogenic effects. Observational data[ix] suggests buprenorphine is safe for the management of withdrawal in pregnancy, among inpatient and outpatients. Buprenorphine monotherapy, and not in combination with naloxone should be used in pregnancy.

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 [x] Not confident [ ] Uncertain [ ]</td><td>Gowing et al, 2017 (see evidence synthesis table, above)</td></tr>
<tr><td>BENEFITS & HARMS</td><td>Do the desirable effects outweigh the undesirable effects?
Benefits outweigh harms [x] Harms outweigh benefits [ ] Benefits = harms or Uncertain [ ]</td><td>See evidence synthesis table, above.</td></tr>
<tr><td>THERAPEUTIC INTERCHANGE</td><td>Therapeutic alternatives available:
Yes [x] No [ ]

List the members of the group:
Buprenorphine
Buprenorphine-naloxone

List specific exclusion from the group: n/a</td><td>Rationale for therapeutic alternatives included:
The buprenorphine component of buprenorphine-naloxone is the same medicine as buprenorphine without naloxone. The addition of naloxone is to reduce diversion and does not increase adverse effects compared to buprenorphine alone. Included as a therapeutic alternative to increase choice regarding cost and availability.
References:
FDA approved package insert: Suboxone sublingual tablets, December 2011.

Rationale for exclusion from the group: n/a
References: n/a</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 [x]

Is the option acceptable to key stakeholders?
Yes [x] No [ ] Uncertain [ ]</td><td>Expert opinion</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:
<table><tr><th>Medicine</th><th>Cost (ZAR)</th></tr><tr><td>Methadone 2mg/ml, 500 ml</td><td>540.39*</td></tr><tr><td>Buprenorphine SL, 2 mg (7)</td><td>93.09 to 155.15**</td></tr><tr><td>Buprenorphine SL, 8mg (7)</td><td>372.52 to 620.86**</td></tr><tr><td>Buprenorphine/naloxone SL, 2/ 0.5 mg (7)</td><td>63.54 to 105.90**</td></tr><tr><td>Buprenorphine/naloxone SL, 8/2 mg (7)</td><td>254.92 to 424.87**</td></tr></table>*State Price – Quotation from Equity Pharmaceuticals, 2019
**SEP database (60% to 100% of SEP), accessed 6 November 2019 https://mpr.code4sa.org/

<u>Comparative costing analysis for various protocols:</u>
• Buprenorphine protocols: Stikland Hospital protocol
• Methadone protocol: Adult Hospital Level STGs and EML, 2015
<table><tr><th>Medicine</th><th>Max total dose /treatment (mg)</th><th>Cost</th></tr><tr><td>Methadone</td><td>150 mg</td><td>81.06*</td></tr><tr><td>Buprenorphine</td><td>28 mg</td><td>186.22 to 310.37 **</td></tr><tr><td>Buprenorphine/ naloxone</td><td>28 mg</td><td>127.30 to 212.16 **</td></tr></table>Additional resources: n/a</td></tr>
</table>

EQUITY	**Would there be an impact on health inequity?** Yes [x] No [ ] Uncertain [ ]	Reduces health inequity if methadone is unavailable, as public healthcare sector users would have no access to medication-assisted withdrawal, whereas those who can afford it, may access buprenorphine.
FEASIBILITY	**Is the implementation of this recommendation feasible?** Yes [x] No [ ] Uncertain [ ]	Buprenorphine is safe, easily administered, and use is short-term for detoxification only.

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 Adult Hospital Level Committee recommended that buprenorphine (in monotherapy or in combination with naloxone) be regarded a therapeutic equivalent of methadone and thus procured if methadone is unavailable.

Rationale:

There is no evidence of any significant difference between methadone and buprenorphine in efficacy or adverse effects in medication assisted opioid withdrawal. Because of current cost differences, methadone is still considered the preferred option.

Level of Evidence: II Meta-analysis of low-moderate quality studies

Review indicator:

Evidence of efficacy	Evidence of harm	Price reduction
[ ]	[ ]	[X]

VEN status:

Vital	Essential	Necessary
[ ]	[X]	[ ]

NEMLC MEETING OF 5 DECEMBER 2019:

NEMLC accepted the proposal as recommended by the Adult Hospital Level Committee (see above).

Monitoring and evaluation considerations

Audit of rational medicine use.

Survey of women who have limited access to rehabilitation.

Research priorities

Epimediological data for opioid-dependancy in pregnancy.

References:

[i] Mistry CJ, Bawor M, Desai D, Marsh DC, Samaan Z. Genetics of Opioid Dependence: A Review of the Genetic Contribution to Opioid Dependence. Curr Psychiatry Rev. 2014 May;10(2):156-167. https://www.ncbi.nlm.nih.gov/pubmed/25242908

[ii] Gowing L, Ali R, White JM, Mbewe D. Buprenorphine for managing opioid withdrawal. Cochrane Database Syst Rev. 2017 Feb 21;2:CD002025. https://www.ncbi.nlm.nih.gov/pubmed/28220474

[iii] Welch L et al. South African Guidelines for the management of Opioid use disorders (Part 1). Prof Nurs Today 2017;21(1). file:///C:/Users/user/Downloads/911-Article%20Text-5221-1-10-20170323%20(1).pdf

[iv] Adult Hospital Level STGs and EML, 2015.

[v] Kintz P. A new series of 13 buprenorphine-related deaths. Clin Biochem. 2002 Oct;35(7):513-6. https://www.ncbi.nlm.nih.gov/pubmed/12493578

[vi] Pani PP, Trogu E, Maremmani I, Pacini M. QTc interval screening for cardiac risk in methadone treatment of opioid dependence. Cochrane Database Syst Rev. 2013 Jun 20;(6):CD008939. https://www.ncbi.nlm.nih.gov/pubmed/23787716

[vii] South African Medicines Formulary. 12th Edition. Division of Clinical Pharmacology. University of Cape Town, 2016.

[viii] Hedegaard H, Bastian BA, Trinidad JP, Spencer M, Warner M. Drugs Most Frequently Involved in Drug Overdose Deaths: United States, 2011-2016. Natl Vital Stat Rep. 2018 Dec;67(9):1-14. https://www.ncbi.nlm.nih.gov/pubmed/30707673

[ix] Bell J, Towers CV, Hennessy MD, et al. Detoxification from opiate drugs during pregnancy. Am J Obstet Gynecol 2016;215:374.e1-6. http://dx.doi.org/10.1016/j.ajog.2016.03.015

APPENDIX I

Excluded studies for following Cochrane Library searches that were not relevant to the PICO question:

A: Cochrane library

i. Search strategy A:

Amato et al. Cochrane Database Syst Rev. 2013 Feb 28;(2):CD003409	Methadone tapering regimen
Minozzi et al. Cochrane Database Syst Rev. 2014 Apr 29;(4):CD006749.	Population: Only adolescents
Amato et al. Cochrane Database Syst Rev. 2011 Sep 7;(9):CD005031.	Psychosocial vs pharmacological approaches.
Matticke et al. Cochrane Database Syst Rev. 2014 Feb 6;(2):CD002207.	Opioid dependence
Schmist-Hansen et al. Cochrane Database Syst Rev. 2015 Mar 31;(3):CD009596.	Cancer pain
Wiffen et al. Cochrane Database Syst Rev. 2015 Sep 30;(9):CD011603	Neuropathic pain
Rahini-Movagher et al. Cochrane Database Syst Rev. 2013 Jan 31;(1):CD007775.	Maintenance treatment for opioid dependence
David et al. Cochrane Database Syst Rev. 2013 Jun 6;(6):CD003086.	Smoking cessation
Minozzi et al. Cochrane Database Syst Rev. 2011 Apr 13;(4):CD001333.	Naltrexone maintenance therapy
Perry et al. Cochrane Database Syst Rev. 2015 Jun 2;(6):CD010910.	Interventions for female drug-using offenders
Nielsen et al. Cochrane Database Syst Rev. 2016 May 9;(5):CD011117.	Maintenance agonist therapy
Perry et al. Cochrane Database Syst Rev. 2015 Jun 2;(6):CD010862.	Pharmacological interventions for drug-using offenders in reducing criminal activity and/or drug use
Gowig et al. Cochrane Database Syst Rev. 2011 Aug 10;(8):CD004145.	Oral substitution treatment for opioid dependent injecting drug users on risk behaviours and rates of HIV infections
Basurto et al. Cochrane Database Syst Rev. 2013 Jul 26;(7):CD009179.	Acute pancreatitis pain
Minozzi et al. Cochrane Database Syst Rev. 2013 Dec 23;(12):CD006318.	Maintenance treatment in opiate-dependant pregnant women
Rahimi-Movaghar et al. Cochrane Database Syst Rev. 2018 Jun 21;6:CD007522.	Opium withdrawl
Brown et al. Cochrane Database Syst Rev. 2015 May 14;(5):CD009705.	Opioids for agitation in dementia
Eccleston et al. Cochrane Database Syst Rev. 2017 Nov 13;11:CD010323.	Chronic non-cancer pain
Ferri et al. Cochrane Database Syst Rev. 2013 Jun 5;(6):CD009879.	Slow release morphine as maintenance therapy
Wiffen et al. Cochrane Database Syst Rev. 2017 Jul 6;7:CD012592.	Opioids for cancer pain
Ferri et al. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD003410.	Heroin maintenance therapy
Faggiano et al. Cochrane Database Syst Rev. 2003;(3):CD002208.	Methadone maintenance
Pani et al. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD002950.	Antidepressants for cocaine dependence and problematic cocaine use
Pani et al. Cochrane Database Syst Rev. 2010 Jan 20;(1):CD007024.	Disulfarim
Pani et al. Cochrane Database Syst Rev. 2010 Sep 8;(9):CD008373.	Pharmacological treatment for depression during opioid agonist treatment for opioid dependence.
Chaparro et al. Cochrane Database Syst Rev. 2013 Aug 27;(8):CD004959.	Chronic low back pain
Wiffen et al. Cochrane Database Syst Rev. 2017 May 16;5:CD012508	Cancer pain
Da Costa et al. Cochrane Database Syst Rev. 2014 Sep 17;(9):CD003115.	Osteoarthritis
Wiffen et al. Cochrane Database Syst Rev. 2017 Jul 19;7:CD012564.	Opioids for cancer-related pain in children and adolescents
Cooper et al. Cochrane Database Syst Rev. 2017 Jul 26;7:CD012538.	Opioids for chronic non-cancer pain in children and adolescents
Ahmad et al. Cochrane Database Syst Rev. 2010 Nov 10;(11):CD007710.	Pain relief for outpatient hysteroscopy
Els et al. Cochrane Database Syst Rev. 2017 Oct 30;10:CD012509.	Adverse effects of opioids used for chronic non-cancer pain

ii. Search Strategy B:

Gowing et al. . Cochrane Database Syst Rev. 2017 Feb 29. (5):CD002021	Opioid antagonists with minimal sedation for opioid withdrawal
Faggiano F et al. Cochrane Database Syst Rev. 2003 July 21; (3): CD002208	Methadone maintenance at different dosages for opioid dependence
Amato L et al. Cochrane Database Syst Rev.2013 Feb 28; (2): CD003409	Methadone at tapered doses for the management of opioid withdrawal
Wiffen PJ et al. Cochrane Database Syst Rev. 2017 July 6;(7): CD012592	Opioids for cancer pain - an overview of Cochrane reviews
Amato L et al. Cochrane Database Syst Rev.2011 Sep 7; (9) CD005031	Psychosocial and pharmacological treatments versus pharmacological treatments for opioid detoxification
Rahimi-Movaghar A et al. Cochrane Database Syst Rev. 2018 June 21; (6): CD007522	Pharmacological therapies for management of opium withdrawal
Els C et al. Cochrane Database Syst Rev. 2017 Oct 30; (10): CD012509	Adverse events associated with medium- and long-term use of opioids for chronic non-cancer pain: an overview of Cochrane Reviews
Rahimi-Movaghar A et al. Cochrane Database Syst Rev. 2013 Jan 31; (1): CD007775	Pharmacological therapies for maintenance treatments of opium dependence
Minozzi S et al. Cochrane Database Syst Rev.2014 Apr 29; (4): CD006749	Detoxification treatments for opiate dependent adolescents
Ferri M et al. Cochrane Database Syst Rev. 2013 Jun 5; (6): CD009879	Slow-release oral morphine as maintenance therapy for opioid dependence
Minozzi S et al. Cochrane Database Syst Rev. 2013 Dec 23; (12) CD006318	Maintenance agonist treatments for opiate-dependent pregnant women
Pani PP et al. Cochrane Database Syst Rev. 2010 Sep 8; (9): CD008373	Pharmacological treatment for depression during opioid agonist treatment for opioid dependence
Saulle et al. Cochrane Database Syst Rev. 2017 Apr 27;4:CD011983.	Supervised dosing with a long-acting opioid medication in the management of opioid dependence.