**South African National Essential Medicine List**
**Primary Healthcare/ Adult Hospital Level of Care Medication Review Process**
**Component: Mental health conditions**

## MEDICINE REVIEW

**TITLE:** Methadone for opioid substitution therapy compared to placebo or no methadone substitution treatment

**Date**: 19 August 2021

### Key findings

- Methadone is currently included in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicine List for acute management of **opioid detoxification/ withdrawal.**
- We conducted a review of available evidence to determine the efficacy and safety of **methadone maintenance therapy** (MMT) in people dependent on heroin.
- A literature search conducted on **5 July 2021** identified one relevant systematic review of 7 randomised controlled trials (RCTs) with a total of 1287 participants. The review was of low quality as assessed using AMSTAR2 tool.
- MMT was shown to have a superior **retention rate** compared to placebo or no treatment (i.e., detoxification, wait-listing or non-pharmacological management). The absolute risk reduction (ARR) was 57.04%; 95% confidence interval (CI) 52.21% to 62.86%; 4 RCTs, n=750, $I^2$=23%; with a number needed to treat (NNT) of 2 to retain one heroin-dependent patient in a MMT program (95% CI 1.5 to 2.0); *low certainty evidence*
- Suppression of heroin use (measured by **urine/hair analysis**) was shown to be more effective with MMT than no MMT. Morphine is a metabolite of heroin that is detected in urine and hair. Dichotomous data pooled from 6 RCTs (n=1129) showed that MMT had less morphine positive urine/hair measurements amongst patients at follow up compared to the controlled conditions RR=0.66, 95% CI 3.26 to 2.04; $I^2$=53.67%; *certainty evidence*. A NNT of 6 indicates that about one in six patients will benefit from MMT compared to no MMT
- The analysis of 4 RCTs (n=576) found no mortality benefit as studies. This study was likely underpowered (RR=0.48, 95% CI 0.10 to 2.39; $I^2$=24.57%); *low certainty evidence.*
- **Safety data** were not evaluated in the review. Adverse events and risk of diversion were not reported as outcomes in any of the included RCTs.
- Operationalising MMT in South Africa would require an adequate service delivery platform to prevent accidental or intentional overdose-related deaths and to prevent diversion.

### PHC/ADULT HOSPITAL LEVEL EXPERT REVIEW COMMITEE RECOMMENDATION:

| Type of recommendation | We recommend against the option and for the alternative (strong) | We suggest not to use the option (conditional) | We suggest using either the option or the alternative (conditional) | We suggest using the option (conditional) | We recommend the option (strong) |
|---|---|---|---|---|---|
| | | X | | | |

**Recommendation:** The PHC/Adult Hospital Level Committee recommends that the service delivery platform be strengthened to allow for the safe inclusion of methadone in the essential medicine list as MMT for opioid dependence.

*Rationale:* Moderate quality evidence indicates that MMT is effective in achieving retention in care and reduction of illicit opioid use among people with opioid dependence. However, the length of follow-up was short and ancillary services (psychosocial, medical, and psychiatric) were often provided in addition to methadone, which may have contributed to retention in care. The meta-analysis did not show a mortality benefit, which may be due to a lack of power. There were concerns that the current service delivery platform is not adequate to deliver MMT safely, considering the risk of respiratory depression in toxicity and the risk of diversion to illicit drug markets.

**Level of Evidence: Systematic review of low methodological quality; low certainty of evidence**

**Review indicator:** Adequate health service delivery platform

**NEMLC RECOMMENDATION (9 DECEMBER 2021):**

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| Methadone may be made available for pilot sites selected and monitored by the NDoH Mental Health and Substance Use Programme. Data from such sites should inform further decisions regarding inclusion on the national essential medicine list for universal access. |
| **Monitoring and evaluation considerations:** Retention in care; mortality; diversion; accidental or intentional misuse by patient contacts |
| **Research priorities**: Feasibility study of district level decentralised services in the South African setting. |

## 1. Executive Summary

**Date:** July 2021
**Medicine (INN):** Methadone
**Medicine (ATC):** N07BC02
**Indication (ICD10 code):** Opioid substitution therapy (F11.2)
**Patient population:** Adults and adolescents with opioid dependence
**Prevalence of condition:** 0.47% of total population; 0.84% of 15-39 year age group (GBD data 2019 http://ghdx.healthdata.org/gbd-results-tool )
**Level of Care:** Primary Healthcare and Adult Hospital Level of care
**Prescriber Level:** Doctor prescribed
**Current standard of Care:** Nil (new indication)
**Efficacy estimates: (preferably NNT)**
**Reviewer name(s):** Trudy Leong, Lesley Robertson
**PTC affiliation: Gauteng Provincial PTC (LR)**

## 2. Name of author(s)/motivator(s): Trudy Leong, Lesley Robertson

## 3. Author affiliation and conflict of interest details

- Trudy Leong, Essential Drugs Programme, Affordable Medicines Directorate, National Department of Health: no conflicts of interest related to methadone.
- Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no conflicts of interest related to methadone.

## 4. BACKGROUND

Global Burden of Disease data for 2019 reveal opioid use disorders to have a prevalence of 0.47% in South Africa, accounting for 0.4% of all DALYs.[1] The burden is highest in the 15–39 year age group, with a prevalence of 0.84% and causing 0.87% of DALYs. However, these figures do not address the indirect burden, which includes an increased risk of HIV and Hepatitis C infection (particularly among those who inject heroin) and increased criminal behaviour.

A motivation for maintenance treatment (MMT) as opioid substitution therapy (OST) was received for inclusion on the national Essential Medicines List in December 2018. The WHO 2009 *Guidelines for the psychosocially assisted pharmacological treatment of opioid dependence,*[2] a systematic review by Mattick et al. (2009),[3] and an economic evaluation by Murphy et al. (2016),[4] was cited, noting the following benefits:

- reduced mortality
- increased retention in care and reduced illicit opioid use
- reduced risk of HIV infection and reduced viral hepatitis C (HCV) infection
- lower emergency and hospital care costs
- reduced criminal behaviour

Specifically, a low-threshold, decentralised service using a task-shifting approach in the primary healthcare setting was advocated for. This is to ensure best outcomes, which are seen when care is accessible and non-punitive, and when there are adequate doses of methadone and support for take-home dosing. While the optimal duration of treatment is unknown, it is likely that continued or long-term treatment will be needed.

*Retention in care and mortality benefits*

Retention in care appears to be key to reducing mortality among people dependent on opioids.[5] In a recent meta-analysis of 23 cohort studies (total study population 483 524), Santo et al. (2021)[5] found time receiving MMT to be associated with a reduction in all-cause mortality by over half (RR 0.47; 95%CI, 0.41-0.54) when compared to time not receiving any OST. This association was consistent regardless of patient sex, age, geographic location, HIV or HCV infection, and whether opioids were injected. In terms of cause-specific mortality, for any OST (methadone or buprenorphine maintenance treatment), Santo et al. found time on OST associated with reduced suicide, cancer, drug-related, alcohol-related, and cardiovascular related mortality. However, compared to the remaining time on MMT, the first four weeks after stopping treatment were associated with more than 6-fold increase in all-cause mortality (RR 6.58; 95%CI 4.93-8.79) and the remaining time off OST with almost double (RR, 1.81; 95%CI, 1.50-2.18) all-cause mortality compared with the time on OST. The authors conclude that retention with sufficient OST coverage is key. Hence, improving access to care is pivotal.

*Criminal activity*

While Mattick et al.[3] found the effect of MMT on criminal activity to be non-significant, an economic evaluation by Murphy et al. (2016) [4] suggests that MMT may be associated with reduced criminal-justice related costs, based on the findings of one retrospective cohort analysis. However, a systematic review of RCTs, quasi-experimental, and cohort studies conducted by Moore et al. (2019)[6] did not find consistent evidence for reduced recidivism with MMT initiation in prison, although community-based treatment and reduced illicit opioid use post-incarceration were more likely. A 2015 Cochrane review[7] which combined methadone and buprenorphine RCTs, found no reduction of drug use or criminal activity among opiate using offenders (low quality evidence). A more thorough evaluation of the literature is needed to be certain of an association between MMT and reduced criminal activity.

*HIV infection*

In the economic evaluation by Murphy et al.,[4] MMT was found to be economically advantageous in averting HIV infection and increasing access to ART. A 2011 Cochrane review[8] of prospective observational studies found OST with methadone or buprenorphine may avert HIV infection through reduced high-risk drug-related behaviour (injecting opioids and sharing of needles). An association with reduced sex-related risk behaviour was less evident. While a lower proportion of injecting drug users reported multiple sex partners or exchanges of sex for drugs or money, OST had little effect on condom use.

Among people who inject drugs with HIV infection, a systematic review of observational studies[9] found being on OST (with methadone or buprenorphine) was associated with increased recruitment onto ART, a 2-fold increase in ART adherence, reduced attrition, and increased viral suppression compared to those not on OST. It is however possible that inherent differences in the populations could account for at least some of the differences in ART outcomes.

*Access to health and social care*

Observational studies reveal a wide variation in retention rates, with reduced retention over time. Analysing data from 24 cohort studies, O'Connor et al. (2020)[10] found 12-month retention rates for MMT ranged from 20.3% to 94.0%, with a median of 60.7%. At three years (from 6 of the 24 studies), the median rate dropped to 54.0% (range 20.0%–82.0%). They found younger age, ongoing illicit substance use (particularly cocaine and heroin use), lower methadone doses, criminal activity/incarceration, and negative attitudes to MMT were associated with reduced retention in care.

In South Africa, Marks et al.,(2020)[11]argue that social cohesion, with strong peer support, contributed to a 12-month retention rate of 74% in a cohort of 53 people on MMT. However, this cohort excluded people who had no accommodation or social support system as well as those with a history of criminal behaviour, traumatic brain injury, or a psychotic disorder.

There is little evidence regarding optimal healthcare systems and how best to train healthcare providers in OST delivery. Writing on OST services in the USA, Blanco and Volkow (2019)[12] note that even when trained in OST

healthcare professionals tend to not offer treatment and coverage remains poor. They suggest destigmatisation, enhanced institutional support, and improved reimbursement rates are needed to improve service provision, together with increasing decentralised services in the primary care setting.

*NDOH implementation plan for South Africa*

After receiving the motivation for MMT in December 2018, the PHC/Adult Hospital Hospital Level Committee raised concerns related to institutional capacity for prevention of diversion (in particular high-level diversion within the supply chain system) and effective service delivery. However, a detailed implementation plan has been drafted by the NDOH,Directorate for Mental Health and Substance Use with input from multiple stakeholders. Costing of a decentralised service, including personnel costs, was conducted by the University of Witwatersrand Health Economics and Epidemiology Research Office ($HE^2RO$). The NEMLC also recommended the development of an Opioid Substitution Therapy (OST) Provincial checklist to assist implementation. Currently, service capacity in the primary care setting is still unclear and a demonstration study would assist.

The NDOH implementation plan envisages an annual scale up in numbers of people on MMT over five years from 1000 to 6600. However, demand may be considerably higher than that envisaged. According to SACENDU,[13] almost 4800 people accessed abstinence-based rehabilitation services for heroin/opiate use during 2019. Smoking was the most common route of administration; 10–20% injected heroin. However, between July and December 2019, just over 9000 people who inject drugs accessed community-based harm reduction services for needles and syringes. While just over 1200 people were on OST at the end of December 2019 (excluding OST users at Durban community-based harm reduction services), this number was limited by interrupted methadone availability, difficulties transitioning to buprenorphine, and unaffordability of both medicines.

The aim of this review is to evaluate the RCT evidence for efficacy and safety of methadone in OST, with the goal of facilitating universal health coverage for people with opioid dependence.

## 5. PURPOSE/OBJECTIVE

**Question:** What is the efficacy and safety of methadone for OST for opioid dependent people?

**Eligibility criteria for the review:**

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|---|---|
| **Population:** | People with opioid dependence. |
| **Intervention:** | Methadone as opioid substitution therapy |
| **Comparison:** | No pharmacological treatment or non-pharmacological/ psychosocial interventions |
| **Outcomes:** | All-cause mortality; overdose-specific mortality; overdoses; reduction in illicit opioid use; retention in treatment; adverse events |
| **Study designs:** | Systematic reviews of randomised controlled trial, randomised controlled trials* |

**Systematic reviews of randomised controlled trials (RCTs) were the preferred studies as these studies offer the highest level of evidence in the hierarchy of evidence, followed by RCTs.[14]*

## 6. METHODS

A review of the evidence was conducted by searching selected electronic databases (Epistemonikos and the Cochrane Library) on 5 July 2021. The search strategy is shown in Appendix 1. Screening of records and selection of studies was done by one reviewer (TL) and checked by a second reviewer (LR) with conflicts resolved on consensus. Data extraction from the included studies was done independently. Table 1 reports the main characteristics and outcomes of the included studies and table 2 lists the excluded studies. The reviewers independently assessed the quality of the included systematic reviews and randomised controlled trials (RCTs) using the AMSTAR2[15] and Risk of Bias 2.0[16] (RoB 2) tool for all outcomes.

## 7. RESULTS

### Results of the search

The search produced 649 records. Two additional records were sourced by reviewing bibliographies and references of guidelines, and one additional record was shared by an expert. After the removal of duplicates, 664 records were screened using title and abstract. RCT records prior to 2008 were also excluded as most systematic reviews included records up to December 2008. Twenty-eight full text articles were assessed for eligibility. After excluding records that did not meet the PICO criteria, one systematic review[3] was identified for inclusion in the qualitative synthesis as shown in the PRISMA diagram (Figure 1). Table 1 describes the main characteristics and outcomes of the included study and table 2 lists the excluded studies.

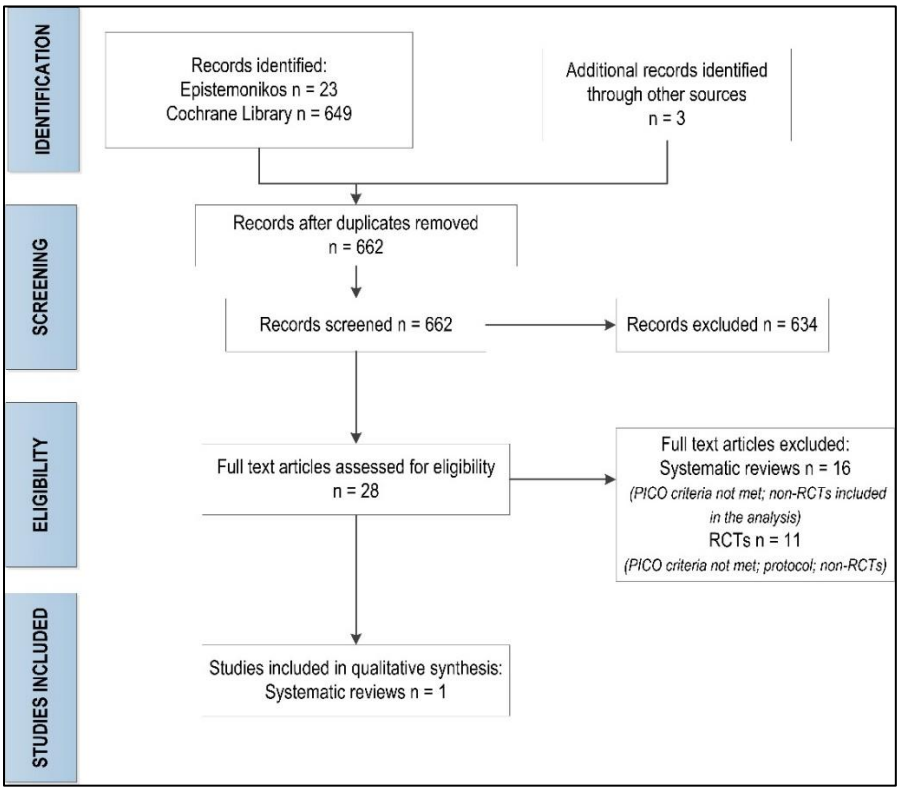


**Figure 1: PRISMA flow diagram**

### Description of the systematic review:

Outcomes of the study by Mattick et al., [3]comparing MMT to no OST for opioid dependence by is described below:

**Primary outcomes:**

- ***Retention in treatment programmes***

  Data on retention in treatment were available from 7 RCTs[19,21-26] (n=1287). While all studies showed a positive significant effect, they were too heterogeneous to conduct a pooled analysis. However, a sub-analysis was conducted of the newer RCTs[19, 21, 23, 24] with low heterogeneity (Figure 1). These RCTs evaluated retention in treatment over follow up periods of one month (which took place in prison, Kinlock 2007[217]), four months (Schwartz, 2006[23]) and six months (Gruber, 2008[19]; Sees, 2000[24]). The sub-analysis showed that MMT has a superior retention rate over control (75.2% vs 16.0%) with an absolute risk reduction (ARR) of 58.8% (95%CI 53.0% to 64.6%). The NNT is 2 to retain one heroin-dependent patient in a methadone maintenance treatment program (95% CI 1.5 to 1.9); high certainty evidence

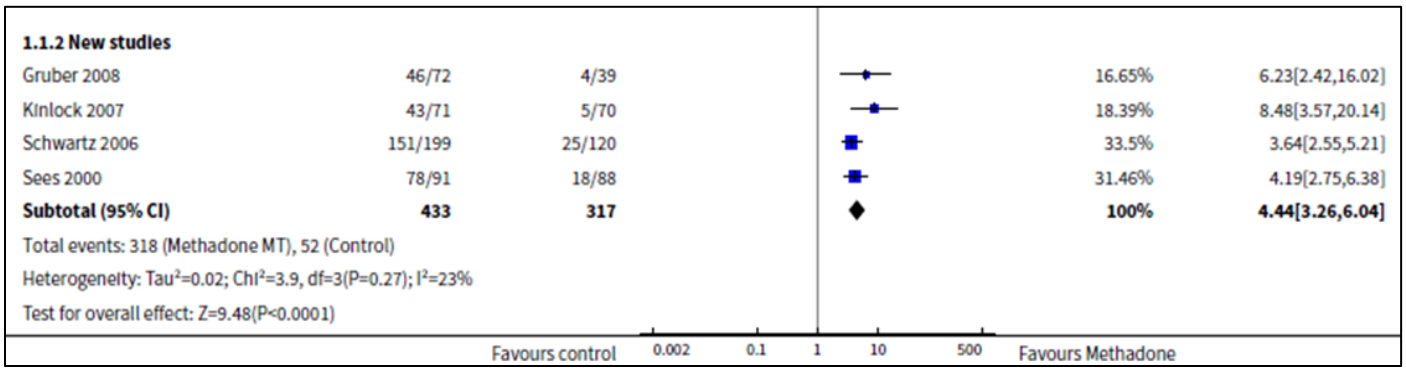


**Figure 1: Forest plot of newer RCTs – retention in treatment of MMT compared to no MMT**

- ***Morphine positive urine/hair analysis***

Suppression of heroin use measured by urine/hair analysis was more effective with MMT than non-pharmacological measures. Morphine is a metabolite of heroin that is detected in urine and hair, and this is an objective measure for reduction in illicit heroin use. Dichotomous data were pooled from 6 RCTs (n=1129),[17,19,21,23,26,27] two of which were conducted in prison (Dolan, 2003[17] and Kinlock, 2007[21]). Participants on MMT had less morphine positive urine/hair measurements at follow up compared to the control RR=0.66, 95% CI 3.26 to 2.04; $I^2$=53.67% (Figure 2); high certainty evidence. A NNT of 6 indicates that about one in six patients will benefit from MMT compared to detoxification, a waitlist, or control (non-pharmacological management).

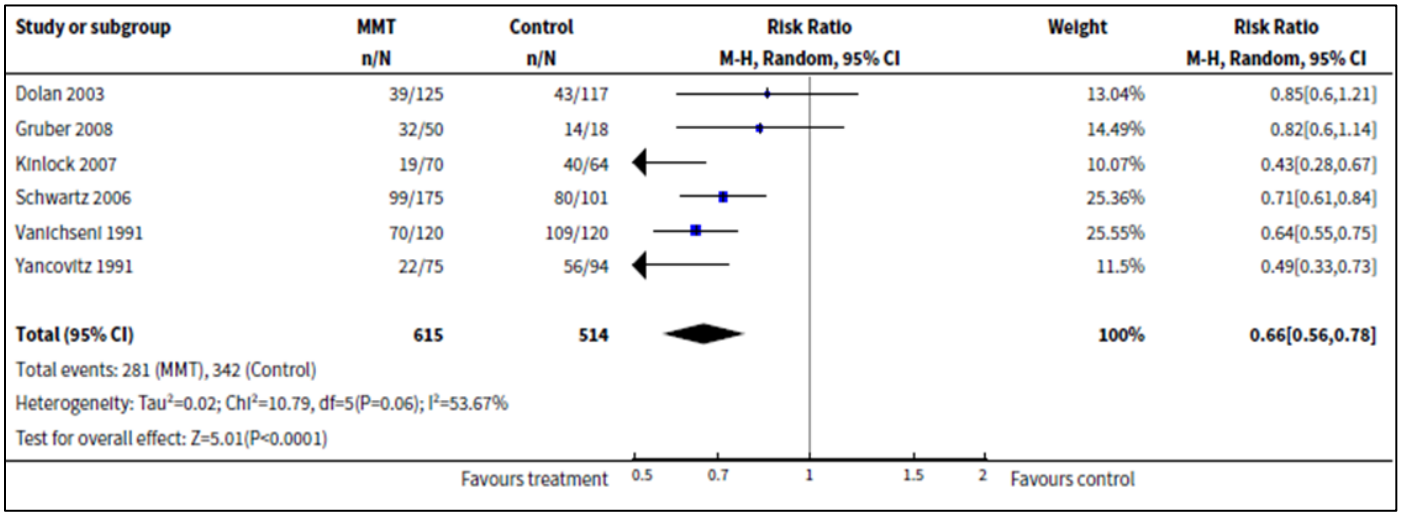


**Figure 2: Forest plot comparing MMT to no MMT for morphine positive urine/hair analysis**

- ***Mortality***

The analysis was likely underpowered to detect a mortality benefit. (RR=0.48, 95% CI 0.10 to 2.39; $I^2$=24.57%); moderate certainty evidence.

**<u>Quality assessment of the systematic review</u>**

- ***Quality assessment of the systematic review***

Confidence in the quality of the systematic review using the AMSTAR2 tool was assessed independently by TL and LR to be of low quality (see table 3). The protocol was developed in 2000, whilst the Cochrane risk of bias tool has subsequently been updated to be more robust.

- ***Risk of bias of RCTs included in the meta-analysis***

Risk of bias assessment of the RCTs in the review focussed on assessment of the randomisation procedure, as the Cochrane reviewers considered blinding was challenging to apply in the RCTs given the comparisons that were analysed (i.e., MMT versus no MMT/detoxification or waiting list).

Risk of bias was assessed as:

a. Low risk of bias (allocation clearly independent of clinical staff)
b. Moderate risk of bias (some doubt about the independence of the allocation procedure)
c. High risk of bias (inadequate separation of randomisation from clinical staff)

Risk of bias was assessed on four domains: sequence generation, allocation concealment, incomplete outcome data, and being free of other bias. Overall risk of bias of the RCTs was assessed as moderate, with randomisation assessed as moderate to high risk of bias.

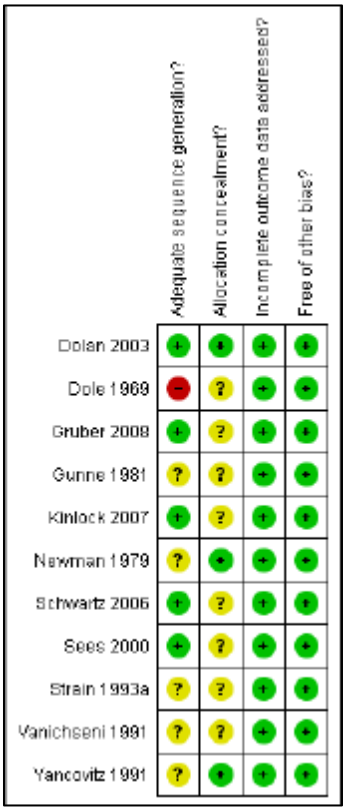


**Figure 3. Methodological quality summary: review authors' judgements about each methodological quality item for each included study (Mattick et al, 2009[3])**

- ***Other data***

There is very limited RCT evidence comparing methadone to placebo/ no methadone treatment. A 2019 PEER umbrella systematic review by Korownyk et al., 2019,[28] which included systematic reviews and RCTs published before June 2018, also only identified the review by Mattick et al (2009) for evaluation of MMT. Korownyk et al. conducted additional sub-analyses of the same RCTs (removing studies involving prison inmates but combining older and newer studies) with similar results to those of Mattick et al.'s analyses.

**DISCUSSION**

The RCT evidence reviewed by Mattick et al. (2009)[6] indicates that MMT is effective in retaining people in care for up to 6 months and in reducing heroin use. However, no significant effect on mortality was demonstrated, possibly related to small study populations and short follow up periods in RCTs.

*Adverse effects and adverse reactions*
Adverse events were not reported on by Mattick et al.[6] In general, safety of methadone prescribing is poorly researched,[29] making it difficult to decide upon risk mitigation strategies in clinical practice.

According to the WHO,[30] commonly reported adverse drug reactions reported in the product label includes disturbed sleep, nausea and vomiting, constipation, dry mouth, increased perspiration, sexual dysfunction, menstrual irregularities in women and weight gain.

Observational studies suggest that the period during which MMT is initiated carries a high-risk for mortality. Pooling results from 11 observational studies, Santo et al.[5] found the first 4 weeks of MMT were associated with a nearly 3-fold risk of all-cause mortality compared to the remainder of time on OST (RR, 2.81; 95%CI, 1.55-5.09). They did not make a comparison between the first four weeks and time not on OST. Further research is needed regarding risk and mitigating factors for mortality during the first four weeks of treatment.

**CONCLUSION**
Low quality evidence[3] indicates that methadone is an effective maintenance intervention for the treatment of heroin dependence as it retains patients in treatment and decreases heroin use when compared to placebo or treatments other than OST (e.g., opioid detoxification). Methadone maintenance was not superior to placebo or no methadone maintenance treatment with regards to mortality.

Observational data indicate MMT is associated with reduced all-cause and selected cause specific mortality,[5] for as long as there is retention in care. However, retention rates are highly variable between studies and tend to reduce over time.[10] While adequate methadone dosing is a factor in improving treatment retention, psychosocial and service-related factors also play a role. As stated by Mattick et al.,[3] "*The quality of the therapeutic relationship with staff in methadone clinics plus the intensity of these ancillary services, combined with the dose of methadone prescribed will all act to enhance the outcome for methadone treatment. The extent that clinical programs move away from such an approach might be expected to impact on the effectiveness of methadone."*

Greater understanding is also needed regarding the feasibility of implementing a decentralised OST programme in South Africa. The availability of a sufficient service delivery platform is required to optimise treatment outcomes in an affordable manner. Adverse events such as diversion or accidental poisoning by others (e.g., children) were not explored in this review.

**8. Alternative agents:**

- Buprenorphine, oral – review underway
- Buprenorphine and naltrexone, oral – review underway
- Levo alpha acetyl methadol (LAAM) – not currently registered in South Africa
- Morphine slow release, oral - provides a feeling of euphoria that is not ideal in this patient setting
- Dihydrocodeine, oral - provides a feeling of euphoria that is not ideal in this patient setting

## Table 1. Characteristics of included studies

| Citation | Study design | Population | Intervention vs Comparator | Outcomes | Effect sizes | Comments |
|---|---|---|---|---|---|---|
| Mattick RP et al. Cochrane Database Syst Rev. 2009;(2):CD002209[3] | Systematic review of 11 RCTs conducted in USA, Sweden, Australia, Hong Kong and Thailand.<br><br>Study duration varied from 1 month to 2 years. | n = 1969<br><br>Heroin-dependent Individuals. Mostly males of ± 30-40 years of age, often unemployed, unmarried, with previous treatment histories and prevalence of use of other drugs. | Methadone maintenance treatment<br>*vs.*<br>no methadone maintenance treatment (includes detoxification, wait-listed or control/non-pharmacological management)<br><br>RCTs noted the provision of substantial ancillary services, including counselling, psycho-social services, medical services and often psychiatric care. | **Primary outcomes:**<br>• Retention in treatment programmes<br>• proportion of urine or hair analysis results positive for heroin (or morphine)<br>• self-reported heroin use<br>• criminal activity<br>• mortality | **Primary outcomes:**<br>MMT vs no MMT treatment<br>• *Retention in treatment programmes (7 RCTs)*<br>  • Data too heterogenous for a pooled analysis<br>  • Sub-analysis of newer RCTs (n=750, 4 RCTs) showed MMT was superior to no treatment: 318/423 (75.2%) vs 52/317 (16.4%); ARR 58.8% (95%CI 53.0% to 64.6%); NNT 2 (1.5 to 1.9); RR=4.44, 3.26 to 2.04; $I^2$=23%.<br>• *Proportion of urine or hair analysis results positive for heroin (or morphine) (n=1129, 6 RCTs)*<br>  • 281/615 (45.7%) vs 342/514 (66.5%); ARR 19.6% (95% CI 13.9 to 25.4%); NNT 6 (95% CI 3.9 to 7.2); RR=0.66; 0.56 to 0.78; I2=53.7%<br>• *Self-reported heroin use (6 RCTs)*<br>  • Data too heterogeneous for a pooled estimate.<br>• *Criminal activity (n=363, 3 RCTs)*<br>  • RR 0.39; 0.12 to 1.25; $I^2$=21.13%<br>• *Mortality (n=576, 4 RCTs)*<br>  • RR=0.48; 0.10 to 2.39; $I^2$=24.57% | • Cochrane review of old RCTs, is the basis for many guidelines that recommends methadone as the gold standard for opioid maintenance treatment. Subsequent RCTs compares methadone maintenance treatment (MMT) to newer interventions.<br>• Systematic review of low to moderate quality as per AMSTAR assessment (see table 3).<br>• Risk of bias of RCTs included in the systematic review were assessed overall, by authors as of moderate risk.<br>• There is very limited RCT evidence comparing methadone to placebo/ no methadone treatment. The authors' concluded that observational data confirmed the analysis on retention in treatment, but showed criminality and mortality benefits (the latter was not statistically significant in the systematic review).<br>• RCTs showed that ancillary treatment enhances MMT.<br>• Response to methadone is dose-dependent and most of the included RCTs used doses higher than what is generally used in clinical practice.<br>• MMT was compared to placebo, opioid detoxification or waiting list. Of note is that there is no "waiting list" programme in South Africa, currently.<br>• MMT is part of the OST programme which also aims to facilitate reintegration into the workforce and education system and to improve social functioning – equity considerations as well as strong collaborative partnership with Social Development Services is required. |

## Table 2. List of excluded publications

| No | Citation | Reason for Exclusion |
|---|---|---|
| 1 | Sordo L, Barrio G, Bravo MJ, et al. Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies. BMJ. 2017 Apr 26;357:j1550. https://pubmed.ncbi.nlm.nih.gov/28446428/ | Subsequent systematic review done by Ma et al, 2019 |
| 2 | Praveen KT, Law F, O'Shea J, Melichar J. Opioid dependence. BMJ Clin Evid. 2011 Sep 20;2011:1015. https://pubmed.ncbi.nlm.nih.gov/21929827/ | 2011 evidence review - later Systematic reviews |
| 3 | Dennis BB, Sanger N, Bawor M, et al. A call for consensus in defining efficacy in clinical trials for opioid addiction: combined results from a systematic review and qualitative study in patients receiving pharmacological assisted therapy for opioid use disorder. Trials. 2020 Jan 6;21(1):30. https://pubmed.ncbi.nlm.nih.gov/31907000/ | QoL, patient acceptability outcomes - PICO criteria not met |
| 4 | Nguemo Djiometio JB, Buzuayew A, Mohamud H,et al. Effectiveness of opiate substitution treatment in reducing HIV risk behaviors among African Caribbean and Black people: a systematic review. JBI Evid Synth. 2021 Apr 12. https://pubmed.ncbi.nlm.nih.gov/33851941/ | Prevention of HIV – PICO criteria not met |
| 5 | Pujol CN, Paasche C, Laprevote V, et al. Cognitive effects of labeled addictolytic medications. Prog Neuropsychopharmacol Biol Psychiatry. 2018 Feb 2;81:306-332. https://pubmed.ncbi.nlm.nih.gov/28919445/ | Systematic review of observational studies |
| 6 | McQueen K, Taylor C, Murphy-Oikonen J. Systematic Review of Newborn Feeding Method and Outcomes Related to Neonatal Abstinence Syndrome. J Obstet Gynecol Neonatal Nurs. 2019 Jul;48(4):398-407. https://pubmed.ncbi.nlm.nih.gov/31034790/ | Neonatal Abstinence Syndrome associated with breastfeeding – PICO criteria not met |
| 7 | 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://pubmed.ncbi.nlm.nih.gov/23787716/ | QtC screening with methadone maintenance therapy – PICO criteria not met |

| No | Citation | Reason for Exclusion |
|---|---|---|
| 8 | Amato L, Minozzi S, Davoli M, Vecchi S. Psychosocial combined with agonist maintenance treatments versus agonist maintenance treatments alone for treatment of opioid dependence. Cochrane Database Syst Rev. 2011 Oct 5;(10):CD004147. https://pubmed.ncbi.nlm.nih.gov/21975742/ | Evaluating adjunctive psychosocial intervention, not the pharmacological agonist therapy – PICO criteria not met |
| 9 | Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. Cochrane Database Syst Rev. 2003;(3):CD002208. https://pubmed.ncbi.nlm.nih.gov/12917925/ | Methadone dosing for maintenance therapy - more recent systematic review by Bao et al, 2009 |
| 10 | Roux P, Lions C, Michel L, et al. ANRS Methaville Study Group. Predictors of non-adherence to methadone maintenance treatment in opioid-dependent individuals: implications for clinicians. Curr Pharm Des. 2014;20(25):4097-105. https://pubmed.ncbi.nlm.nih.gov/24001291/ | Pretreatment predictors for MMT to achieve good retention and adherence - PICO criteria not met |
| 11 | Gibson A, Degenhardt L, Mattick RP, Ali R, White J, O'Brien S. Exposure to opioid maintenance treatment reduces long-term mortality. Addiction. 2008 Mar;103(3):462-8. https://pubmed.ncbi.nlm.nih.gov/18190664/ | Comparator is buprenorphine - PICO criteria not met |
| 12 | Green A, Kaul A, O'Shea J, Sharma E, Bennett L, Mullings EL, Munafò MR, Nutt DJ, Melichar JK, Donaldson LF. Opiate agonists and antagonists modulate taste perception in opiate-maintained and recently detoxified subjects. J Psychopharmacol. 2013 Mar;27(3):265-75. https://pubmed.ncbi.nlm.nih.gov/23364815/ | Non-RCT, effect of opiate antagonists & agonists on taste perceptions - PICO criteria not met |
| 13 | Roux P, Michel L, Cohen J, Mora M, Morel A, Aubertin JF, Desenclos JC, Spire B, Carrieri PM; ANRS Methaville Study Group. Methadone induction in primary care (ANRS-Methaville): a phase III randomized intervention trial. BMC Public Health. 2012 Jun 28;12:488. https://pubmed.ncbi.nlm.nih.gov/22741944/ | Study protocol |
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| 23 | Ramli FF, Syed Hashim SA, Mohd Effendy N. Factors Associated with Low Bone Density in Opioid Substitution Therapy Patients: A Systematic Review. Int J Med Sci. 2021 Jan 1;18(2):575-581. https://pubmed.ncbi.nlm.nih.gov/33390827/ | observational studies only, exploring factors associated with low bone density among people on OST - PICO criteria not met |
| 24 | O'Connor AM, Cousins G, Durand L, et al. Retention of patients in opioid substitution treatment: A systematic review. PLoS One. 2020 May 14;15(5):e0232086. https://pubmed.ncbi.nlm.nih.gov/32407321/ | Mostly observational data, but 4 RCTs, but investigates the effect of non-pharmaceutical adjunctive interventions, not of methadone alone - PICO criteria not met |
| 25 | Feelemyer JP, Jarlais DCD, Arasteh K, et al. Changes in quality of life (WHOQOL-BREF) and addiction severity index (ASI) among participants in opioid substitution treatment (OST) in low and middle income countries: an international systematic review. Drug Alcohol Depend. 2014 Jan 1;134:251-258. https://pubmed.ncbi.nlm.nih.gov/24200104/ | No distinction between methadone and buprenorphine and no comparative placebo/no treatment studies - PICO criteria not met |
| 26 | Minozzi S, Amato L, Jahanfar S, et al. Maintenance agonist treatments for opiate-dependent pregnant women. Cochrane Database Syst Rev. 2020 Nov 9;11(11):CD006318. https://pubmed.ncbi.nlm.nih.gov/33165953/ | Compares methadone to buprenorphine or morphine, not placebo - PICO criteria not met |

| No | Citation | Reason for Exclusion |
|---|---|---|
| 27 | Schwartz RP, Jaffe JH, O'Grady KE, et al. Interim methadone treatment: impact on arrests. Drug Alcohol Depend 2009;103:148–154. https://pubmed.ncbi.nlm.nih.gov/19443133/ | Investigates interim methadone treatment, not methadone maintenance treatment - PICO criteria not met |

## Table 3: Evaluating the methodological quality of the Mattick et al (2009)[6] systematic review and meta-analysis – AMSTAR 2 tool (Shea 2017[2])

| No. | Criteria | Yes/ Partial Yes/ No | Comment |
|---|---|---|---|
| **1** | Research questions and inclusion criteria for the review included the components of PICO | Yes | - |
| **2*** | Report of the review contained an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol | Yes | This is an update of the initial review. Study protocol was first published in 2000, Issue 3. Initial review first published in 2002, Issue 4. |
| **3** | Review authors explained selection of the study designs for inclusion in the review | No | - |
| **4*** | Review authors used a comprehensive literature search strategy | Yes | - |
| **5** | Review authors perform study selection in duplicate | Yes | - |
| **6** | Review authors perform data extraction in duplicate | Yes | - |
| **7*** | Review authors provided a list of excluded studies and justify the exclusions | Yes | - |
| **8** | Review authors described the included studies in adequate detail | Yes | - |
| **9*** | Review authors used a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review | Yes | - |
| **10** | Review authors reported on the sources of funding for the studies included in the review. | No | - |
| **11*** | For meta-analyses, review authors used appropriate methods for statistical combination of results | Yes | - |
| **12** | For meta-analyses, review authors assessed the potential impact of RoB in individual RCTs on the results of the meta-analysis or other evidence synthesis | Yes | - |
| **13*** | Review authors accounted for RoB in individual RCTs when interpreting/ discussing the results of the review | Yes | - |
| **14** | Review authors provided a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review | No | Review authors performed a statistical investigation of heterogeneity in the results but did not discuss the impact of this on the results of the review. |
| **15*** | For quantitative synthesis, review authors carried out an adequate investigation of publication bias (small study bias) and discussed its likely impact on the results of the review | No | Despite a RoB assessment of individual studies, there was no explicit intention or report of publication bias assessment. |
| **16** | Review authors reported any potential sources of conflict of interest, including any funding they received for conducting the review | Yes | - |

** Critical domains = 2, 4, 7, 9, 11, 13, 15*

**Rating overall confidence in the results of the review**

- *High:* No or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest
- *Moderate:* More than one non-critical weakness*: the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that were included in the review
- *Low:* One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest
- *Critically low*: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies

(*Multiple non-critical weaknesses may diminish confidence in the review and it may be appropriate to move the overall appraisal down from moderate to low confidence).

**OVERALL ASSESMENT: Low quality**

*Rationale:* One critical flaw (#15) and more than one non-critical weakness (# 3, 10, 14)

*Conclusion:* The AMSTAR assessment suggests that if the review has one critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest

## Appendix I: Search strategy

**Date of the search**: 5 July 2021

| |
|---|
| **Database:** Epistemonikos<br><br>*Search strategy:* (title:((title:(opioid substitution) OR abstract:(opioid substitution))) OR abstract:((title:(opioid substitution) OR abstract:(opioid substitution)))) AND (title:(methadone) OR abstract:(methadone))<br>*- restricted to systematic reviews*<br><br>23 records retrieved, 13 records excluded, 10 records screened, 10 excluded, no records included for evidence synthesis |
| **Database**: Cochrane Library<br><br>*Search strategy:* "methadone" and "opioid maintenance"<br><br>*- restricted to systematic reviews*<br>16 records retrieved, 3 duplicates, 13 records screened, 12 excluded, 1 record included for evidence synthesis<br><br>*- restricted to RCTs*<br>649 records retrieved, 245 records excluded, 13 duplicates excluded, 391 records screened, 376 records excluded, 15 full-text screens, 185records excluded, no records included for evidence synthesis |

## Appendix 2: Evidence to decision framework

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| QUALITY OF EVIDENCE OF BENEFIT | **What is the certainty/quality of evidence?**<br>High [ ] Moderate [ ] Low [X] Very low [ ]<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | *Overall certainty:* Moderate certainty<br>• *Retention in treatment:* moderate certainty<br>• *Urine/hair analysis:* moderate certainty<br>• *Mortality benefit (not statistically significant):* moderate certainty<br>AMSTAR2 assessment of the Cochrane review (Mattick et al, 2009) was assessed to be of low quality; whilst Cochrane reviewers assessed the included RCTs to be of moderate certainty. |
| EVIDENCE OF BENEFIT | **What is the size of the effect for beneficial outcomes?**<br>Large [ ] Moderate [X] Small [ ] None [ ] | *Overall benefit:* Moderate effect<br>• Retention in treatment: NNT 2<br>• Urine/hair analysis: NNT 6<br>• Mortality benefit (not statistically significant ) - underpowered to show a mortality benefit |
| QUALITY OF EVIDENCE OF HARM | **What is the certainty/quality of evidence?**<br>High [ ] Moderate [ ] Low [ ] Very low [ ] Uncertain [X]<br>*High quality:* confident in the evidence<br>*Moderate quality:* mostly confident, but further research may change the effect<br>*Low quality:* some confidence, further research likely to change the effect<br>*Very low quality:* findings indicate uncertain effect | Very limited safety data reported in RCTs. |
| EVIDENCE OF HARMS | **What is the size of the effect for harmful outcomes?**<br>Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X] | Safety data not evaluated in the review and not reported on in the RCTs. |
| BENEFITS & HARMS | **Do the desirable effects outweigh the undesirable harms?**<br>Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ] | |
| THERAPEUTIC INTERCHANGE | Therapeutic alternatives available:<br>Yes [X] No [ ]<br>List the members of the group.<br>List specific exclusion from the group: | *Rationale for therapeutic alternatives included:*<br>• Buprenorphine/ buprenorphine and naltrexone – refer to respective medicine review<br>*Rationale for exclusion from the group:*<br>• Levo alpha acetyl methadol (LAAM) – not currently registered in South Africa and widely discontinued in early 2000s due to ventricular dysrhythmia (O'Conner 2020)<br>• Morphine slow release, oral – provides a feeling of euphoria that is not ideal in this patient setting<br>• Dihydrocodeine, oral – provides a feeling of euphoria that is not ideal in this patient setting |
| FEASABILITY | **Is implementation of this recommendation feasible?**<br>Yes [ ] No [ ] Uncertain [X] | Methadone 2mg/ml solution is currently SAHPRA registered. There are currently two more products under evaluation by SAHPRA.<br>However, the operational management of MMT as part of a psychosocially assisted OST programme is uncertain. Clinical governance principles need to be agreed upon between the various stakeholders. |
| RESOURCE USE | **How large are the resource requirements?**<br>More intensive [ ] Less intensive [ ] Uncertain [ ] | **Price of medicines:**<br>**Medicine** \| **Tender price (ZAR)** \| **SEP (ZAR)**<br>Methadone 2mg/ml, 60 ml solution \| 56.50* \| 105.16**<br>* Contract circular HP12-2020LQ [accessed 12 July 2021]<br>** SEP for Equity Methadone®, SEP database, 26 November 2021<br>**Other resources:** Staffing |

| | JUDGEMENT | EVIDENCE & ADDITIONAL CONSIDERATIONS |
|---|---|---|
| VALUES, PREFERENCES, ACCEPTABILITY | **Is there important uncertainty or variability about how much people value the options?**<br>Minor [ ] Major [ ] Uncertain [X]<br>**Is the option acceptable to key stakeholders?**<br>Yes [X] No [ ] Uncertain [ ] | Patients: Local survey data lacking, but methadone considered to be acceptable to heroin addicts.<br><br>Healthcare workers: Considered to be acceptable to healthcare workers managing care centres. However, outside of these centres healthcare workers voiced clinical governance and capacity concerns implying that general decentralization of OST programmes requires much health systems strengthening. |
| EQUITY | **Would there be an impact on health inequity?**<br>Yes [X] No [ ] Uncertain [ ] | |

| Version | Date | Reviewer(s) | Recommendation and Rationale |
|---|---|---|---|
| Initial | 19 August 2021 | TL, LR | Methadone not be recommended for decentralised OST (conditional recommendation) until such time as an adequate service delivery platform is in place to support the implementation of an OST programme nationally. |

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