South African National Essential Medicine List
Primary and Adult Hospital Level of Care Medication Review Process
Component: Mental Health Conditions

MEDICINE REVIEW

TITLE: Buprenorphine or buprenorphine-naloxone for opioid substitution therapy compared to placebo, no opioid substitution treatment, or methadone

Date: 30 November 2021

Key findings

- Buprenorphine and buprenorphine-naloxone are not currently included in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicine List for the management of opioid use disorders. However, they may be considered as alternatives to methadone in opioid substitution therapy (OST).[1-3] Buprenorphine is a partial agonist at μ opioid receptors and is safer than methadone (a full agonist) in overdose as it causes less respiratory depression. Naloxone is an opioid antagonist effective when injected but not when taken orally. The addition of naloxone to buprenorphine sublingual tablets blocks the opioid effect of buprenorphine if there is misuse of the medication with injection of the tablets.

- We conducted a review of the available evidence to determine the comparative effectiveness and safety of buprenorphine and buprenorphine-naloxone in OST for people with opioid dependence.

- A literature search conducted on 26 February 2021 yielded 31 relevant systematic reviews, of which six[4-9] were included in the evidence synthesis after quality appraisal. A further review,[10] published after the search date, was provided by an expert in the field. Thus, evidence from seven systematic reviews published between 2011 and 2021 was appraised.

- For **all-cause mortality**,[10] buprenorphine was associated with:
  - reduced mortality in cohort studies comparing time on buprenorphine compared to time off OST (log-transformed rate ratio (RR) 0.34 (95% CI 0.26 to 0.45), I^2=52.3%; approximately 10 deaths per 1000 person-years), *low certainty evidence.* This is similar to methadone, which was associated with a reduction of approximately 7 deaths /1000 person-years (RR 0.47 (0.41 to 0.54), I^2=90.0%).
  - no difference in mortality during the first four weeks of treatment compared to the remaining time on treatment (RR 0.58 (0.18 to 1.85), I^2=81.5%). Conversely, methadone was associated with increased mortality during the first four weeks of treatment (RR 2.81 (1.55 to 5.09), I^2=96.1%), *low certainty evidence.*
  - increased mortality in the first four weeks after stopping OST (RR 4.58 (2.37 to 9.94), I^2=83.2%), as was methadone (RR 6.58 (4.93 to 8.79), I^2=89.6%), *low certainty evidence.*

- For **retention in care**, compared to placebo, detoxification, or non-pharmacological interventions, buprenorphine:
  - showed superiority among **adults with any opioid dependence**,[5] at low doses of 2–6mg, risk ratio (RR) 1.50 (1.19 to 1.88) I^2=71.52%, NNT=5 (2.8-13.2) *moderate certainty evidence*; medium doses of 7–15mg, RR 1.74 (1.06 to 2.87) I^2=91.34% NNT=3 (1.3-41.6), moderate certainty evidence; and high doses of ≥16mg, RR 1.82 (1.15 to 2.90) I^2=85.84%, NNT=3 (CI 1.3-16.6); *moderate certainty evidence.*
  - showed superiority for among **people with pharmaceutical opioid dependence**,[8] RR 0.33 (0.23 to 0.47) I^2=7.75%, NNT=6 (5.2 to 7.5), *moderate certainty evidence*
  - showed superiority among **adolescents**,[6] RR 0.37 (0.26 to 0.54), NNT=2 (1.7 to 2.7), *low certainty evidence.*

- For **retention in care**, compared to methadone:
  - Buprenorphine showed no difference among **adults with any opioid dependence**[5] at medium and high doses (*high and low certainty evidence*, respectively) but was less effective at flexible doses, risk ratio (RR) 0.83 (0.73 to 0.95) I^2=56.13%; NNT=10 (6.1 to 33.3) and low doses, RR= 0.67 (0.52 to 0.87) I^2=0%; NNT=6 (3.8 to 13.9), *high and moderate certainty evidence*, respectively.
  - Buprenorphine showed no difference among **people with pharmaceutical opioid dependence,**[8] RR 0.81 (0.56 to 1.18), low certainty evidence) or among **pregnant women,**[7] RR 0.66 (0.37 to 1.20), *moderate certainty evidence*.

- For **reduction of illicit opioid use**, compared to placebo, detoxification, or non-pharmacological treatment:

- Buprenorphine showed superiority among **adults with any opioid dependence**[5] at high doses, standardised mean difference (SMD)= -1.7 (-1.85 to -0.49), *moderate certainty evidence*, but not at medium or low doses (*moderate certainty evidence*).
- Buprenorphine showed superiority among **people with pharmaceutical opioid dependence**,[8] risk ratio (RR) 0.63 (0.43 to 0.91), NNT=4 (2.8 – 18.2), *low certainty evidence*.
- Buprenorphine was not effective among **adolescents**,[6] RR=0.97 (0.78 – 1.22), *low certainty evidence*.
- was not effective among **offenders**,[9] RR= 0.57 (0.27 to 1.2), *very low certainty evidence.*

➡ For **reduction of illicit opioid use**, compared to methadone, buprenorphine showed no difference among **adults with any opioid dependence** [5]at flexible, medium, or low doses (*moderate, low, and very low certainty evidence*, respectively), **people with pharmaceutical opioid dependence**[8] (moderate certainty evidence), or among **pregnant women**[7] (*low certainty evidence*).

➡ For **maternal and fetal outcomes of pregnancy**,[7] compared to methadone,
- Buprenorphine was associated with a greater **birth weight** (mean difference (MD) ranged from 530.00 gr (662.78 gr to 397.22 gr) to 215.00 gr (238.93 gr to 191.07 gr, *very low quality evidence*).
- Buprenorphine showed no difference in number of babies with **neonatal abstinence syndrome** (*very low certainty evidence*) but showed superiority in severity of neonatal abstinence syndrome in the strongest study (MOTHER study, n=131) as evidenced by a shorter duration of neonatal hospital stay (MD 6.70 (6.24 to 7.16)) and lower doses of morphine (MD 9.30 (8.68 to 9.92), *very low certainty evidence*.

➡ Evidence for **HIV risk reduction**[4] was insufficient to assess effectiveness of buprenorphine. While *low certainty* evidence suggests that OST (buprenorphine and methadone) reduces drug-related HIV risk behaviour and may be associated with a reduction in number of sexual partners, the evidence may not be generalisable to South Africa.

➡ Evidence for **reduction of criminal activity**[5, 9] was insufficient to assess effectiveness of buprenorphine. *Low certainty* evidence suggesting that OST is not effective in reducing criminal activity may not be generalisable to South Africa.

➡ Evidence for **reduction of other substance use**[5] was only available for cocaine and benzodiazepines and was insufficient to assess effectiveness.

➡ **Adverse events** were poorly documented.
- Compared to detoxification and non-pharmacological treatment among **people with pharmaceutical opioid dependence**,[8] buprenorphine was associated with fewer adverse effects, RR 0.19 (0.06 to 0.57) I^2=0%, NNH=6.2 (5.3 to 11.6)), *low certainty evidence*.
- Compared to methadone, buprenorphine was associated with less sedation in two RCTs among **adults with any opioid dependence.**[5]
- Compared to methadone among **pregnant women,** *low certainty evidence* showed no difference in serious adverse events for mother or child. Buprenorphine was associated with fewer non-serious adverse events for the mother, RR 1.22 (1.07 to 1.38), NNH=10 (5.5 to 33.3) with no difference for the child, *very low certainty evidence*.

➡ We found no evidence in the systematic reviews to distinguish between buprenorphine, sublingual tablets, and buprenorphine-naloxone, sublingual tablets, in terms of effectiveness or safety. Of note, a Canadian health technology assessment[3] which reviewed evidence evaluating buprenorphine formulations published between 2014 and March 2019 found no studies examining the comparative effectiveness of buprenorphine/naloxone on diversion or misuse.

➡ Compared to not receiving OST, buprenorphine is associated with an approximately 60% reduction in all-cause mortality for as long as the person is receiving treatment, *moderate certainty evidence*. Compared to placebo or non-pharmacological treatment, buprenorphine is effective for retention in care.

➡ Unlike methadone, buprenorphine is not associated with increased mortality during initiation of OST. It may therefore be easier to initiate treatment with buprenorphine rather than methadone in low-resourced, non-specialist settings. Buprenorphine is as effective at medium or high doses. While buprenorphine is less effective than methadone for retention in care at flexible and low doses, experts were of the opinion that this may not be applicable to South Africa as dose requirements may differ to high-income countries.

➡ No difference was found between buprenorphine and methadone regarding illicit opioid use.

➡ In pregnancy, buprenorphine may be associated with greater birth weight and a shorter hospital stay for neonatal abstinence syndrome compared to methadone. However, the quality of evidence is insufficient to make a firm recommendation for preferential use in pregnancy.

- We did not review evidence evaluating diversion as an outcome. As an opioid agonist, buprenorphine is vulnerable to misuse and diversion.[1, 2]
- *Low certainty evidence* indicates that the main advantage of buprenorphine over methadone is that it is not associated with increased mortality during treatment induction, allowing for less intensive dosing supervision. While this may reduce the demand on direct clinical services, vigilant stock control and prevention of diversion to illicit drug markets is still advised.

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 Committee recommends that the NEMLC guides on the final decision.
Rationale: Buprenorphine is effective as OST in retention in care and reduction of illicit opioid use. Observational evidence suggests that buprenorphine is not associated with increased mortality during the first four weeks of treatment (as opposed to methadone). Clinical experience suggests less toxicity with overdosing of buprenorphine compared to methadone. Low certainty evidence also suggests reduced hospital stay for babies with neonatal abstinence syndrome compared to methadone when taken during pregnancy. There may be concerns that the current service delivery platform is not sufficient and diversion of buprenorphine to the illicit drug markets is a risk requiring vigilant processes. However, buprenorphine may be easier to administer at point of care.
Level of Evidence: III RCTs of low methodological quality
Review indicator: Service delivery platform, price reduction

NEMLC RECOMMENDATION (9 DECEMBER 2021):
NEMLC recommends that buprenorphine is not included on the national essential medicine list. The service delivery platform is currently insufficient for national implementation of OST with buprenorphine, considering the risk of diversion to illicit drug markets. There is insufficient local data to inform a cost-benefit decision vs methadone.
Review indicator: Service delivery platform, price reduction of buprenorphine, safety concerns with methadone use

Monitoring and evaluation considerations

Research priorities
Stakeholder views and total healthcare costing

1. Executive Summary

Date: 18 November 2021
Medicine (INN): Buprenorphine
Medicine (ATC): N07BC01
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; methadone also under consideration)
Efficacy estimates: (preferably NNT)
Motivator/reviewer name(s): L. Robertson and H. Temmingh
PTC affiliation: L. Robertson affiliated to Sedibeng District Health PTC in Gauteng province

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

Lesley Robertson
Henk Temmingh

Secondary reviewer:
Trudy Leong

3. Author affiliation and conflict of interest details

- Lesley Robertson, Department of Psychiatry, University of the Witwatersrand: no conflicts of interest related to buprenorphine
- Henk Temmingh, Department of Psychiatry and Mental Health, University of Cape Town: no conflicts of interest related to buprenorphine
- Trudy Leong, Essential Drugs Programme, National Department of Health: no conflicts of interest related to buprenorphine

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.[11] 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.[2]

As well as reducing cravings and withdrawal symptoms, opioid substitution treatment (OST) is associated with reduced overdose-related mortality, HIV and hepatitis C infection, and criminal behaviour.[2] Retention in care is necessary to achieve the goals of OST, and requires accessibility. Therefore, to have a public health impact, it is recommended that OST be delivered in a range of settings, including primary healthcare and correctional services. During 2021, the PHC-Adult Hospital Expert Review Committee requested stakeholder input regarding implementation of OST using methadone. Some reluctance at primary care level was expressed; areas of concern included the workload in supervising methadone dosing and logistics in stock management.

Buprenorphine is an alternative agonist substitution treatment to methadone. Buprenorphine is a partial agonist at μ opioid receptors and is considered safer than methadone (a full agonist) in overdose as it causes less respiratory depression.[3] Thus, it may be easier to use during initiation of treatment and allow for more frequent take-home doses, important considerations in low-resourced settings where daily supervised dosing may not be practical. Naloxone is an opioid antagonist effective when injected but not when taken orally. In buprenorphine/naloxone sublingual tablets, the naloxone is added to the buprenorphine in an attempt to prevent diversion with intravenous injection of the tablets.

5. PURPOSE/OBJECTIVE

Buprenorphine and buprenorphine/naloxone sublingual tablets are not currently included in the Adult Hospital Level Standard Treatment Guidelines and Essential Medicine List for the management of opioid dependence. The purpose of this review was to determine the comparative effectiveness and safety of buprenorphine and buprenorphine/naloxone sublingual tablets in younger people and adults for the maintenance treatment of opioid dependence (15 to 60 year old).

Questions:

What is the effectiveness and safety of buprenorphine compared to placebo, detoxification, or non-pharmacological treatment?

What is the effectiveness and safety of buprenorphine compared to methadone?

PICO Eligibility criteria:

- **Population:** People with opioid-related disorders (including special populations: adolescents, pregnant women, prison populations).
- **Interventions:** buprenorphine OR buprenorphine/naloxone, oral formulations.
- **Comparators:** No treatment, placebo, psychosocial interventions, or active comparators limited to either methadone, buprenorphine/naloxone oral formulations.
- **Outcomes:**

  Primary:

  1) Retention in care
  2) Reduction of illicit opioid use
  3) Safety:
     a. Mortality-all cause
     b. Mortality from overdose
     c. Morbidity: QTc prolongation
     d. Morbidity: hepatotoxicity
     e. Maternal and fetal outcomes of pregnancy

  Secondary:

  5) Reduction of HIV associated risk and other risk behaviour.
  6) Reduction of criminal involvement
  7) Improvement of anxiety, depression, and sleep
  8) Reduction of other substance use
  9) Improvement in quality of life (employment, socialization)

6. METHODS

a. Data sources

Pubmed, CINAHL, PsycINFO, Web of Science, Scopus, and the Cochrane Database of Systematic Reviews (CDSR).

b. Search strategy

Databases (Pubmed, CINAHL, PsycINFO, Cochrane Library Database of Systematic Reviews, Web of Science, Scopus) were searched for systematic reviews containing efficacy and safety data on buprenorphine and buprenorphine/naloxone oral formulations. Searches were conducted to include citations from 1990 (1st Jan 1990) till present day (26 Feb 2021) and confined the search to systematic reviews of randomized trials and observational research, or a combination of both, in the English language literature, using filters. We used a combination medical subject heading terms (MESH terms) and keywords in the search. We searched terms "buprenorphine" and MESH terms "opioid-related disorders" as well as related keywords in the title and abstract of citations. All English language articles were included. The search strings are available in **Appendix I - Search strategy**.

c. Selection of studies:

We included systematic reviews of primary studies (randomised trials, cohort, case-control, and cross-sectional research), as defined by the presence of a clear research question regarding maintenance treatment with buprenorphine as the intervention, with a defined population, comparators and outcomes consistent with our PICO question, systematic reporting of literature search, stipulation of study inclusion and exclusion criteria, quality appraisal, and reproducible data synthesis.

We excluded the following studies:

1. Clinical guidelines and manuscripts containing selected secondary research (i.e., systematic reviews, meta-analyses) such as umbrella reviews.
2. We excluded narrative reviews, unless these were systematic in nature, and where nature of data precluded re-analysis of data in the form of a meta-analysis.
3. In case the same research group had a more recent up-to-date review with the same methodology and the same research aims, we excluded the older versions.

d. Evidence quality

Selected systematic reviews underwent duplicate (conducted by LR and HT independently) quality appraisal. Quality was determined using criteria set out by the AMSTAR 2 appraisal tool and based on the scoring of seven critical domain items as recommended by Shea et al., 2017.[12] Studies that were rated as "critically low" in quality according to AMSTAR-2 criteria were excluded from the evidence synthesis.

The GRADE evidence to decision (GRADE-EtD) framework was used to derive certainty of evidence (classified into high, moderate, low, or very low certainty). We inspected systematic reviews for quality appraisal methodology used. Where the authors had assessed quality of evidence using GRADE, we adopted their assessment. Where outcomes were not assessed by the authors, we applied GRADE to make our own assessment of quality.

Review findings were combined according to our pre-defined outcomes with subgrouping in terms of population type (adult, adolescent, criminal justice, pregnant women). Where pooled risk ratios were reported we transformed them into number needed to treat (NNT) using formulas from the Cochrane Handbook of Systematic Reviews.

7. RESULTS

Results of the search

The search yielded a total of 549 citations (Pubmed: n=95; CINAHL: n=7; PsycINFO: n=9; Web of Science: n=176; Scopus: n=171; CDSR: n=91). Citations were combined using Covidence software and duplicates were removed. A total of 403 citations remaining after removal of duplicates (n=146). Two authors LR and HT independently screened abstracts and full-text articles and selected studies. Disagreements were discussed and a decision was made on the inclusion of studies. One additional review was added after contact with public health expert in the field. The selection process is outlined in **Figure 1. PRISMA diagram**. After removal of irrelevant articles (see Error! Reference source not found.), a total of 32 systematic reviews were selected for quality appraisal.

On quality appraisal, 22 reviews were rated as being of critically low quality (**d overall ratings**) and were therefore not used in the evidence synthesis. One low quality and two high quality reviews were also not used in the evidence synthesis as the included primary research was duplicated with other more recent or more extensive reviews.

Finally, seven systematic reviews were included in the evidence synthesis. These studies are described in **Table 2. Studies included in evidence synthesis**. Results of the primary outcomes, according to our PICO question, reported on by the seven reviews are found in:

Table 3. MortalityTable 3. Mortality

Table 4. Retention in care

Table 5. Illicit opioid use on urine testing
Table 6. Maternal and fetal outcomes of pregnancy

Results of secondary outcomes are available in:

Table 7. Reduction of HIV risk
Table 8. Reduction of criminal activity
Table 9. Reduction of other substance use
Table 10. Adverse events

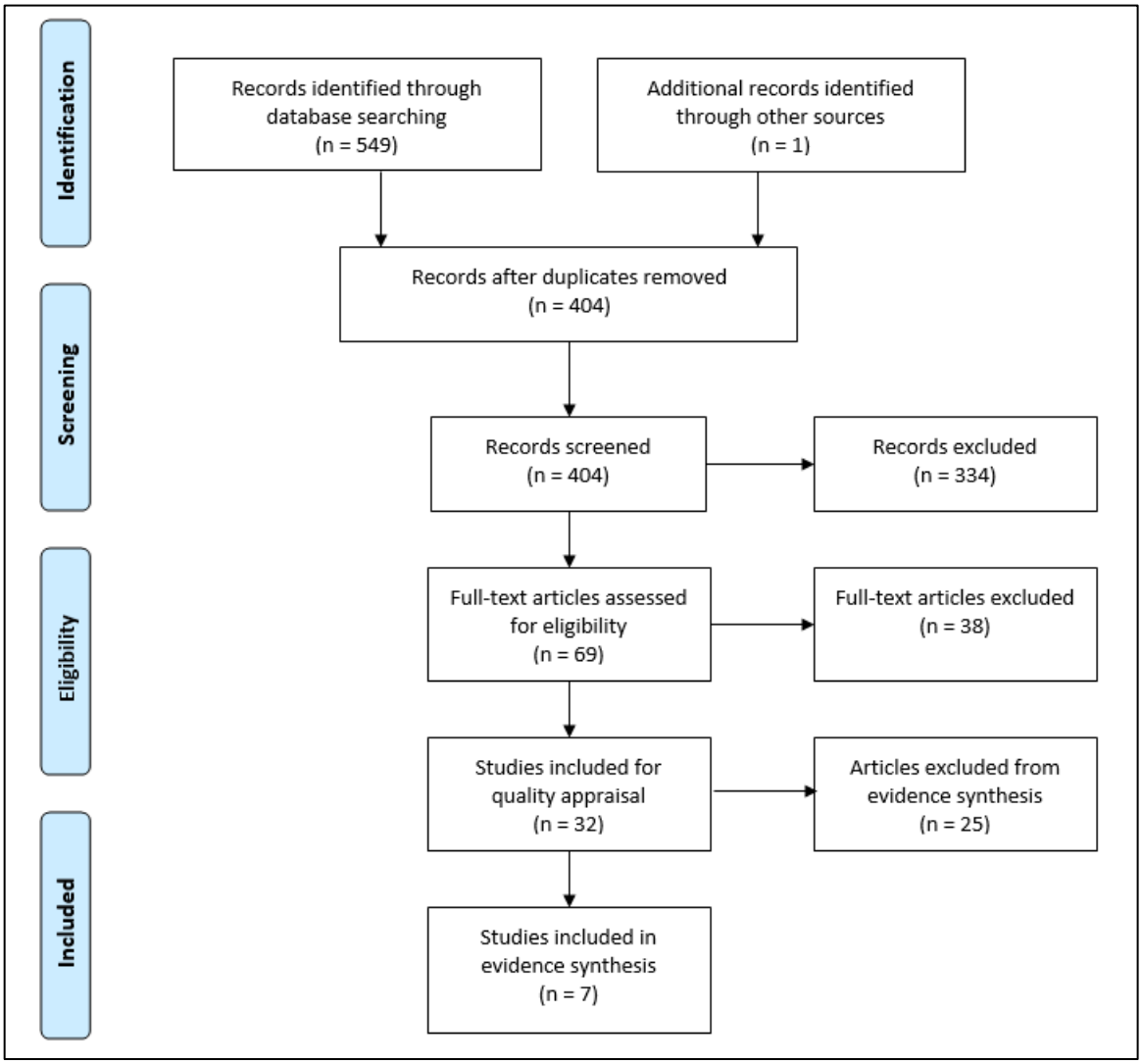


Table 1. Studies included in quality appraisal and overall ratings

Study/year/title (N=32)	AMSTAR-2 Items 1-16[12]															
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**
Barnett et al., 2001[13] A meta-analysis comparing buprenorphine to methadone for treatment of opiate dependence	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Overall rating: Critically low															
Bhaji et al., 2019[14] Reduction in mortality risk with opioid agonist therapy: a systematic review and meta-analysis	Y	pY	N	pY	Y	Y	N	Y	Y	N	Y	Y	N	Y	N	Y
	Overall rating: Critically low															
Brogly et al., 2014[15] Prenatal buprenorphine versus methadone exposure and neonatal outcomes: systematic review and meta-analysis	Y	N	Y	N	Y	Y	N	pY	N	N	Y	N	Y	Y	Y	Y
	Overall rating: Critically low															
Castells et al., 2009[16] Efficacy of opiate maintenance therapy and adjunctive interventions for opioid dependence with comorbid cocaine use disorders: A systematic review and meta-analysis of controlled clinical trials	Y	N	N	pY	N	N	N	Y	N	Y	Y	Y	Y	Y	Y	Y
	Overall rating: Critically low															
Crowley & Hout, 2017[17] Effectiveness of pharmacotherapies in increasing treatment retention and reducing opioid overdose death in individuals recently released from prison: A systematic review	N	N	Y	Y	N	N	N	pY	Y	N	NA	NA	Y	N	NA	Y
	Overall rating: Critically low															
Dalton & Butt, 2019[18] Does the Addition of Naloxone in Buprenorphine/Naloxone Affect Retention in Treatment in Opioid Replacement Therapy? A Systematic Review and Meta-Analysis	Y	N	Y	pY	Y	N	N	N	N	N	Y	N	N	Y	Y	Y
	Overall rating: Critically low															
Faggiano et al., 2003[19] Methadone maintenance at different dosages for opioid dependence	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
	Overall rating: Low Relevant studies all included by Mattick et al. 2014, therefore not included in evidence synthesis.															
Fareed et al., 2010[20] Heroin anticraving medications: a systematic review	N	N	N	N	N	N	N	N	N	N	NA	NA	N	N	NA	Y
	Overall rating: Critically low															
Farré et al., 2010[21] Retention rate and illicit opioid use during methadone maintenance interventions: a meta-analysis	Y	N	N	N	N	Y	N	N	N	N	N	N	N	N	N	N
	Overall rating: Critically low															
Gowing et al., 2011[4] Oral substitution treatment of injecting opioid users for prevention of HIV infection	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	Y	Y
	Overall rating: High Include in evidence synthesis															
Hedrich et al., 2011[22] The effectiveness of opioid maintenance treatment in prison settings: a systematic review	Y	N	Y	Y	Y	Y	N	pY	N	N	NA	NA	Y	NA	NA	Y
	Overall rating: Critically low															
Jones et al., 2012[23] Buprenorphine treatment of opioid-dependent pregnant women: A comprehensive review	Y	N	Y	pY	N	N	N	pY	N	N	NA	NA	N	N	NA	Y
	Overall rating: Critically low															
Korownyk et al., 2019[24] Opioid use disorder in primary care: PEER umbrella systematic review of systematic reviews	Y	pY	Y	pY	Y	Y	N	Y	N	N	Y	Y	Y	Y	N	Y
	Overall rating: Critically low (ppraised on the review of included RCTs)															
Ma et al., 2019[25] Effects of medication-assisted treatment on mortality among opioids users: a systematic review and meta-analysis	Y	N	N	pY	N	Y	N	pY	N	N	Y	N	N	Y	Y	Y
	Overall rating: Critically low															
Mattick et al., 2014[5] Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y
	Overall rating: Low Include in evidence synthesis															
Minozzi et al., 2014[6] Maintenance treatments for opiate -dependent adolescents	Y	Y	N	Y	Y	Y	Y	Y	Y	N	NA	NA	Y	Y	NA	Y
	Overall rating: Moderate Include in evidence synthesis															
Minozzi et al., 2020[7] Maintenance agonist treatments for opiate-dependent pregnant women	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Overall rating: High Include in evidence synthesis															

Moore et al., 2019[26] Effectiveness of medication assisted treatment for opioid use in prison and jail settings: A meta-analysis and systematic review	Y	N	Y	N	N	N	N	pY	Y	N	NA	NA	N	Y	NA	Y
	Overall rating: Critically low															
Nielsen et al., 2016[8] Opioid agonist treatment for pharmaceutical opioid dependent people	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Overall rating: High Include in evidence synthesis															
Noormohammadi et al., 2016[27] Buprenorphine Versus Methadone for Opioid Dependence in Pregnancy	Y	N	Y	pY	N	N	N	Y	N	N	NA	NA	N	N	NA	Y
	Overall rating: Critically low															
Perry et al., 2015[9] Pharmacological interventions for drug-using offenders	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
	Overall rating: High Include in evidence synthesis															
Perry et al., 2019[28] Interventions for female drug-using offenders	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	Y
	Overall rating: High Exclude as the only relevant study is included in Perry et al. 2015 – no new information.															
Rahimi-Movaghar et al., 2013[29] Pharmacological therapies for maintenance treatments of opium dependence	Y	pY	N	Y	Y	Y	Y	Y	Y	Y	NA	NA	Y	Y	NA	Y
	Overall rating: High Exclude as both relevant studies also included in Mattick et al., 2014.															
Santo et al., 2021[10] Association of Opioid Agonist Treatment With All-Cause Mortality and Specific Causes of Death Among People With Opioid Dependence: A Systematic Review and Meta-analysis	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	N	Y
	Overall rating: Low Include in evidence synthesis															
Sharma et al., 2016[30] Pharmacotherapy for opioid dependence in jails and prisons: research review update and future directions	N	N	Y	N	N	N	N	pY	N	N	NA	NA	N	N	NA	Y
	Overall rating: Critically low															
Simoens et al., 2005[31] The effectiveness of community maintenance with methadone or buprenorphine for treating opiate dependence	Y	N	N	pY	Y	Y	N	N	N	N	NA	NA	N	Y	NA	Y
	Overall rating: Critically low															
Sordo et al., 2017[32] Mortality risk during and after opioid substitution treatment: systematic review and meta-analysis of cohort studies	Y	N	N	pY	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y
	Overall rating: Critically low															
Timko et al., 2016[33] Retention in medication-assisted treatment for opiate dependence: A systematic review	N	N	N	pY	Y	Y	N	pY	N	N	NA	NA	N	N	NA	Y
	Overall rating: Critically low															
Underhill et al., 2014[34] HIV prevention for adults with criminal justice involvement: A systematic review of HIV risk-reduction interventions in incarceration and community settings	Y	Y	Y	Y	Y	Y	N	Y	Y	N	NA	NA	N	N	NA	Y
	Overall rating: Critically low															
West et al., 2000[35] A meta-analysis comparing the effectiveness of buprenorphine and methadone	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
	Overall rating: Critically low															
Yee et al., 2014[36] The prevalence of sexual dysfunction among male patients on methadone and buprenorphine treatments: a meta-analysis study	Y	N	N	pY	N	Y	N	N	N	N	Y	N	Y	N	Y	Y
	Overall rating: Critically low															
Zedler et al., 2016[37] Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: a systematic review and meta-analysis of safety in the mother, fetus and child	Y	N	Y	pY	Y	Y	N	Y	Y	N	Y	Y	Y	Y	Y	Y
	Overall rating: Critically low															

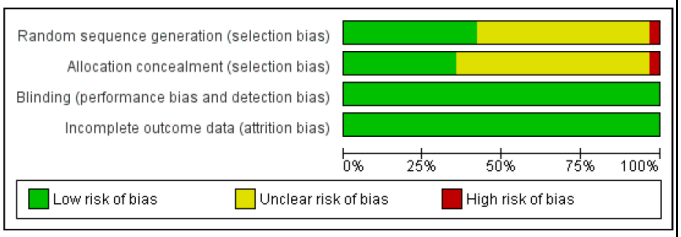
Grey columns= critical domains (2, 4, 7, 9, 11, 13, 15) as recommended by Shea et al. (2017).[12] N=no; pY=partial yes; Y=yes

Rating of overall confidence in the results of the reviews:

- 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).

Table 2. Studies included in evidence synthesis

Author, year, population	Study details	Outcomes	AMSTAR 2
Gowing et al., 2011[4] Injecting opioid users Cochrane review of RCTs and observational studies N=38 studies (n≈12,400)	N=3 RCTs (n=295) relevant to PICO. For outcome of interest, the RCT data were only usable as prospective cohort studies as within group comparison between baseline and follow-up. Follow up period ranged from 3 months to 24 weeks. All three at high ROB for random sequence generation and for allocation concealment. One study (Marsch 2005, n=134) also at high ROB due to performance and detection bias.	• Reduction of HIV risk	High quality • No weaknesses
Mattick et al., 2014[5] Adults with opioid dependence Cochrane review of RCTs N=31 RCTs (n=5430)	N=29 RCTs included in statistical comparisons *Vs Placebo* N=9 RCTs (n=5 fixed low dose (2-6mg/ day) of buprenorphine, n=4 fixed medium dose (7-15mg/ day), n=5 fixed high dose (≥16mg/day) *Vs Methadone* N=20 RCTs (n=11 flexible dose of buprenorphine and methadone, n=3 fixed low doses (buprenorphine 2–6mg vs methadone <40mg), n=6 fixed medium doses (buprenorphine 7-15mg vs methadone 60mg, n=1 fixed high dose (buprenorphine ≥16mg vs methadone 90mg) Sample sizes ranged from 50 to 514 participants. Maintenance period ranged from 2 weeks to 12 months. ROB – only one RCT at high risk for random sequence generation and allocation concealment. All other studies at unclear or low risk on each domain. **Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.**  	• Retention in care • Reduction of illicit opioid use • Reduction of other substance use • Reduction in criminal activity	Low quality • One critical flaw Item 15: inadequate assessment of publication bias • One non-critical weakness Item 3: inadequate explanation for not including observational studies Note: No assessment of selective reporting bias or other bias. Blinding in open label studies was assessed as low risk because outcomes deemed to be objective
Minozzi et al., 2014[6] Adolescents with opioid dependence Cochrane review of RCTs N=2 RCTs (n=189)	N=1 RCT (n=154) relevant to PICO. 12 weeks maintenance duration Buprenorphine-naloxone flexible dose up to 24 mg/0.5mgday per day for 9 weeks and then tapered and stopped at week 12 vs detoxification with buprenorphine High ROB • allocation concealment • blinding (performance bias and detection bias) for subjective outcome measures. Low ROB • random sequence generation, blinding for objective outcomes, incomplete data, selective reporting	• Retention in care • Reduction of illicit opioid use	Moderate quality • Two non-critical weaknesses Item 3: inadequate explanation for not including observational studies Item 10: funding sources of included studies not reported

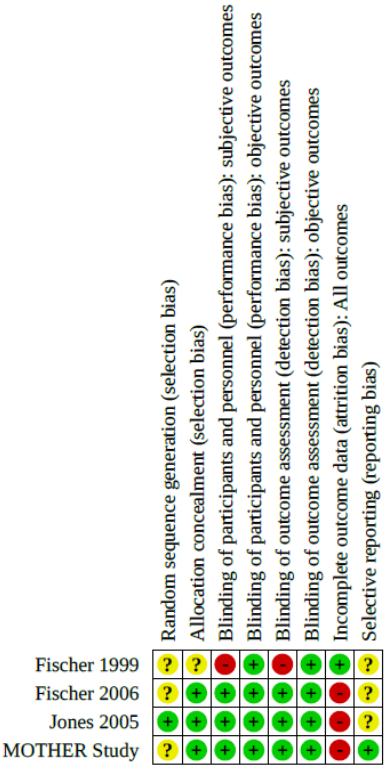
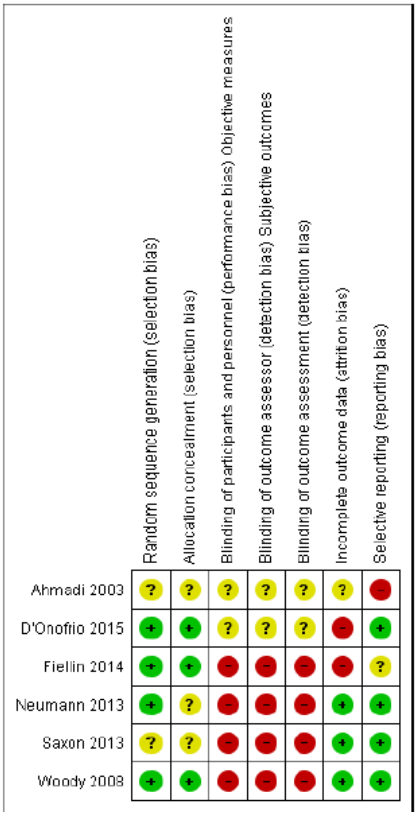
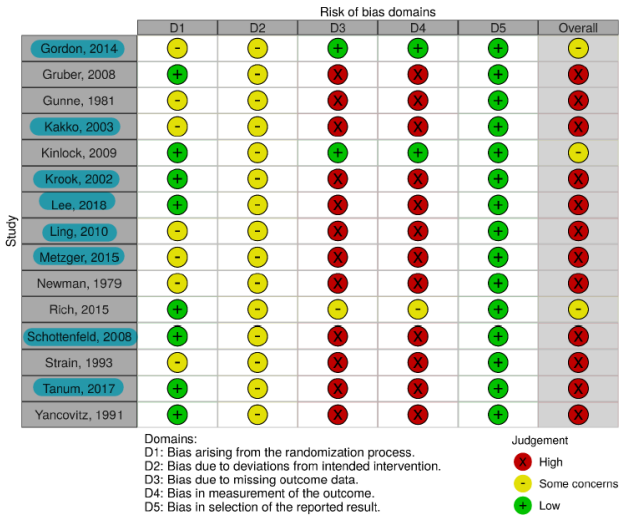
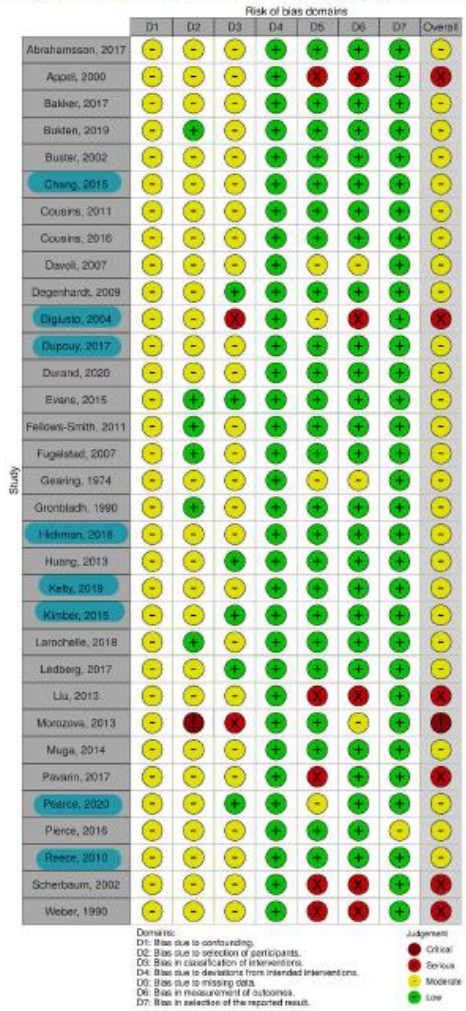
Minozzi et al., 2020[7] Pregnant women with opioid dependence Cochrane review of RCTs N=4 RCTs (n=271)	N=3 RCTs (n=223) in quantitative synthesis. All vs methadone Two small studies and one larger multicentre study (MOTHER study, n=175).  	• Retention in care • Reduction of illicit opioid use • Birth weight • Neonatal abstinence syndrome • Serious maternal adverse events • Serious neonatal adverse events	High quality • One non-critical weakness Item 3: inadequate explanation for not including observational studies
Nielsen et al., 2016[8] People with pharmaceutical opioid dependence Cochrane review of RCTs N=6 RCTs (n=607)	N=6 RCTs (n=607) relevant to PICO *Vs detoxification and non-pharmacological interventions* N=3 RCTs (n=248). Sample sizes ranged from 53 to 113. Maintenance period ranged from one month to 14 weeks. One study was a subsample of a larger study (Woody et al., 2008) which was also included in Minozzi et al., 2014. Nielsen et al. used data for 53 youth who reported pharmaceutical opioids as their primary substance dependence. *Vs methadone* N=3 RCTs (n=360). Sample sizes ranged from 54 to 136. Maintenance period unclear in one study (n=54), 12 weeks and 24 weeks in the other two. One study (Ahmadi 2003 (n=136), using data up to 12 weeks, is also included by Mattick et al., 2014, using data up to 24 weeks of maintenance. All open-label studies were assessed at high ROB on blinding for both objective and subjective outcome measures.	• Retention in care • Reduction of illicit opioid use	High quality • One non-critical weakness Item 3: inadequate explanation for not including observational studies

	Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.  		
Perry et al., 2015[9] Heroin using offenders Cochrane review of RCTs N=14 RCTs (n= 2647)	N=2 RCTs (n=169) relevant to PICO *Vs placebo* N=1 RCT (n=36 female offenders). Maintenance period 12 weeks. Assessed as: High ROB on random sequence generation and selective reporting Low ROB on allocation concealment and other bias Unclear risk on blinding (performance and detection bias for objective and subjective measures) and attrition. *Vs methadone* N=1 RCT (n=133 male offenders with jail terms ≤90 days), which was also included by Mattick et al., 2014.	• Reduction in illicit opioid use • Reduction in criminal activity	High quality • One non-critical weakness Item 3: inadequate explanation for not including observational studies
Santo et al., 2021[10] People with opioid dependence Systematic review and meta-analysis of RCTs and observational studies N=15 RCTS (n=3852) N=36 cohort studies (n=749 634)	***Comparison:*** *Time receiving buprenorphine vs time not on OST* N=8 RCTs (n=713), follow-up duration range 3 months – 2 years in qualitative synthesis. Seven of the eight RCTs assessed as overall high ROB (see figure below, buprenorphine studies highlighted in blue) N=8 cohort studies (n=127 168 person years) Five were registry studies from Australia, Canada, France, and the UK. Three were clinic-based studies from Taiwan (national data) and Australia (state and a single clinic). Seven of the eight cohort studies assessed as moderate ROB (see figure below, buprenorphine studies highlighted in blue)	• Mortality	Low quality • One critical flaw Item 15: inadequate assessment of publication bias • One non-critical weakness Item 10: funding sources of included studies not reported

eFigure 44: ROB-2 for RCTs

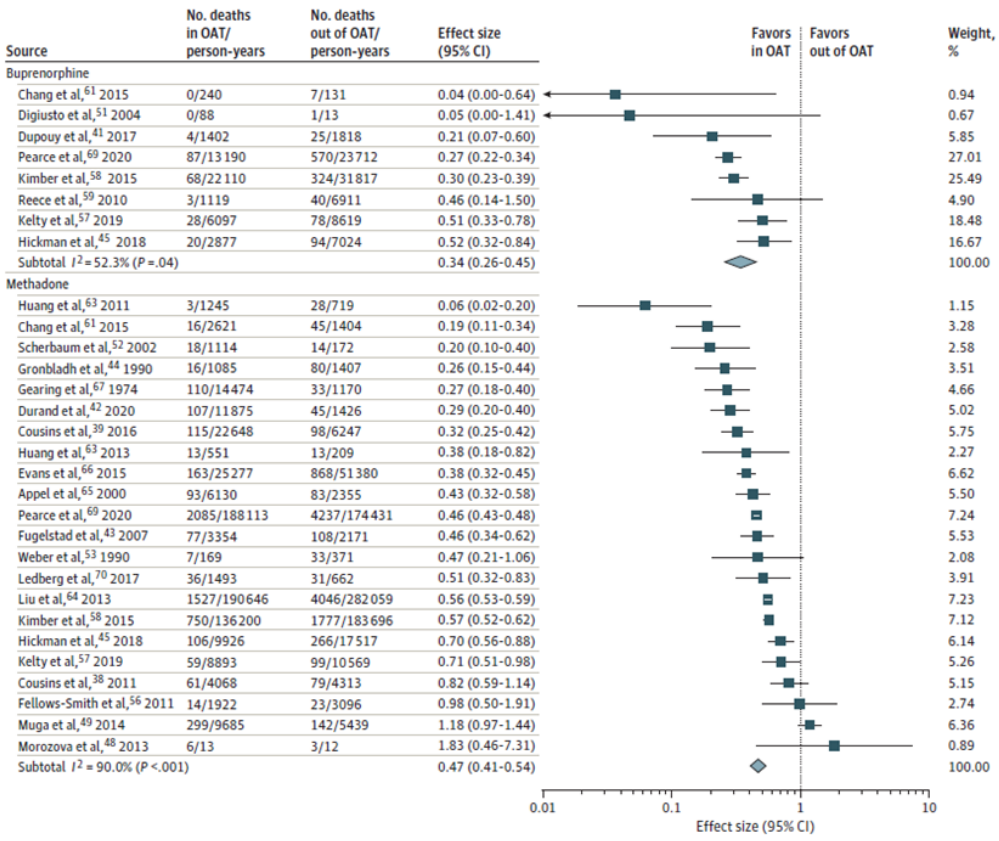


eFigure 37: ROBINS-I for community-based observational studies used in analyses



<table>
<tr><th colspan="5">Table 3. Mortality</th></tr>
<tr><th>Author, date</th><th>Trials with outcome (N)/ participants (n)</th><th>Comparison</th><th>Effect sizes (95% CI)</th><th>Quality of evidence (GRADE)</th></tr>
<tr><td>Mattick et al., 2014</td><td>N=5 RCTs
n=1171</td><td>No comparison</td><td>One death reported in control group of one RCT</td><td>Insufficient power to assess mortality</td></tr>
<tr><td rowspan="3">Santo et al., 2021

People with opioid dependence receiving OST
N=15 RCTS (n=3852)
N=36 cohort studies
(n=749 634)</td><td>N=3 RCTs
n=1860 in statistical analysis</td><td>Time on vs time off buprenorphine</td><td>Not significant</td><td>Insufficient power to assess mortality</td></tr>
<tr><td>N=8 cohort studies
n=127 168 person years</td><td>Number of deaths during time on vs time off buprenorphine</td><td>Log-transformed rate ratio (RR) 0.34 (0.26 to 0.45)</td><td>Low**
(rated by LR – observational studies of moderate ROB)

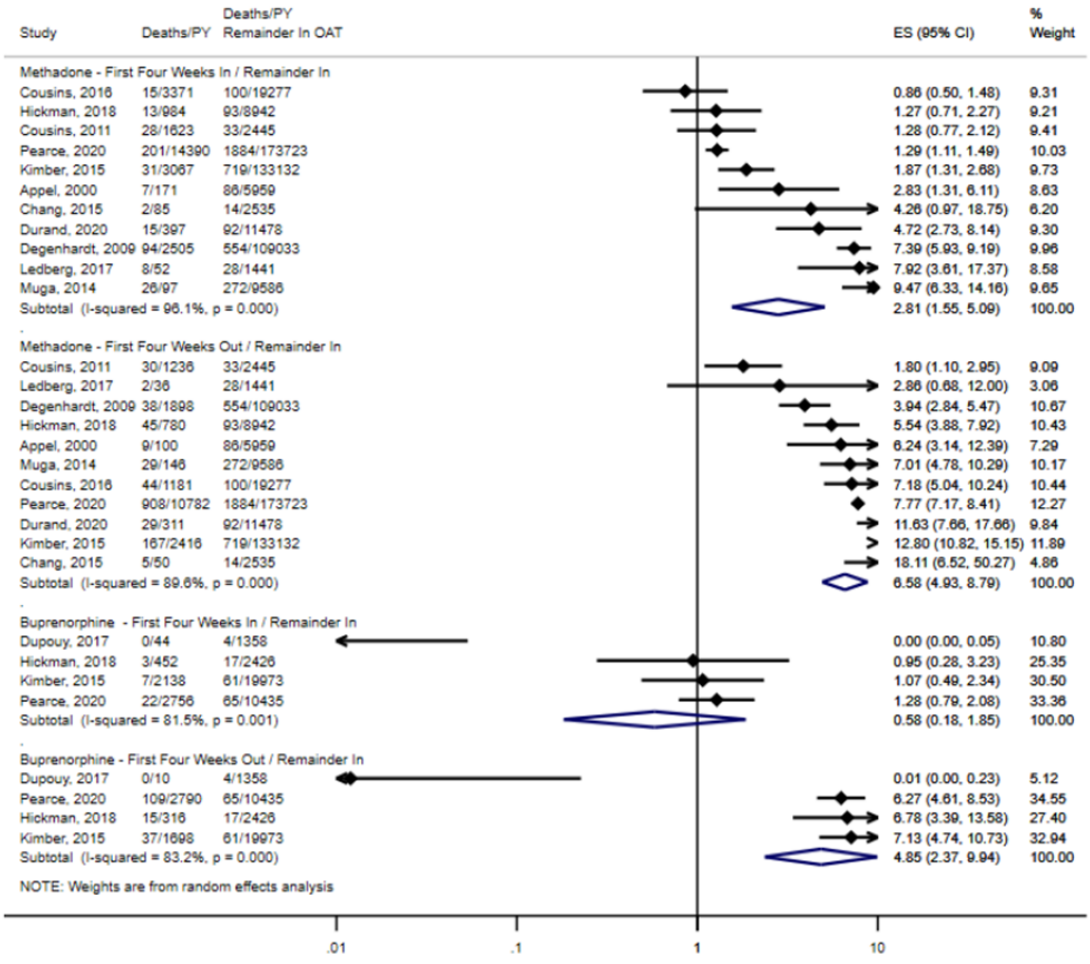
<u>Note</u>: effect size similar to that of methadone RR 0.47 (0.41 to 0.54)</td></tr>
<tr><td colspan="4">Figure. Studies on the Association of Opioid Agonist Treatment (OAT) With All-Cause Mortality From Randomized Clinical Trials and Cohort Studies by Administration of Buprenorphine or Methadone
 

Weights are from random-effects analysis.</td></tr>
<tr><td>N=4 cohort studies
n=39 582 person years</td><td>Number of deaths during first 4 weeks on buprenorphine vs remainder of time on buprenorphine</td><td>Log-transformed rate ratio (RR) 0.58 (0.18 to 1.85)</td><td>Low**
(rated by LR)

<u>Note:</u> First 4 weeks on methadone associated with increased mortality compared with remainder of time on methadone, RR 2.81 (1.55 to 5.00).</td></tr>
</table>

	N=4 cohort studies n=39 006 person years	Number of deaths during the first 4 weeks off buprenorphine vs time on buprenorphine	RR 4.58 (2.37 to 9.94)	Low** (rated by LR) <u>Note:</u> First 4 weeks off methadone also associated with increased mortality compared to time on methadone, RR 6.58 (4.93 to 8.79)

C. All cause mortality by time period on or off methadone or buprenorphine



<u>Results re OST in general (buprenorphine and methadone studies combined)</u>

Association with reduced all-cause mortality while receiving OST compared to time off OST consistent regardless of sex, age, geographic location, HIV status, and hepatitis C virus status and whether drugs were taken through injection. There was lower risk of suicide (RR, 0.48; 95%CI, 0.37-0.61), cancer (RR, 0.72; 95%CI, 0.52-0.98), drug-related (RR, 0.41; 95%CI, 0.33-0.52), alcohol-related (RR, 0.59; 95%CI, 0.49-0.72), and cardiovascular-related (RR, 0.69; 95%CI, 0.60-0.79) mortality during OST.

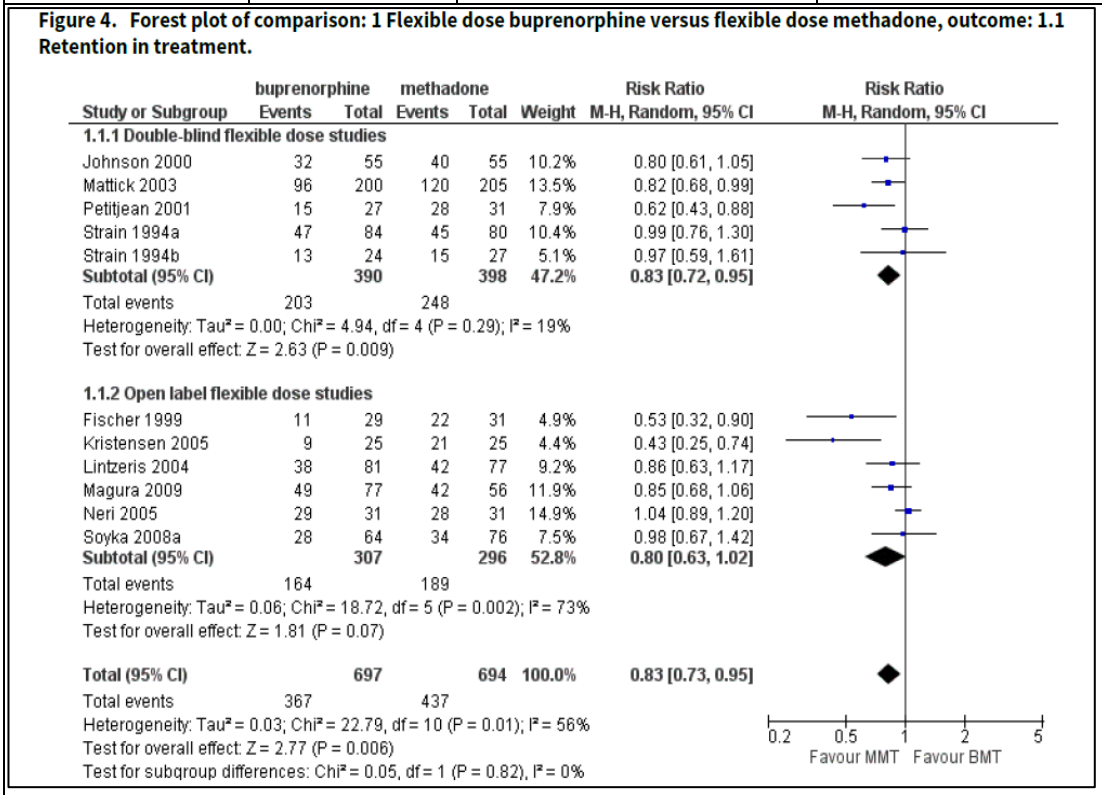
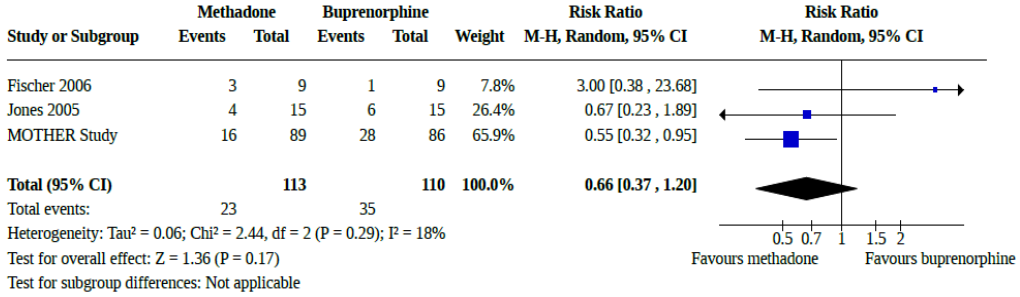
Table 4. Retention in care				
Study	**Trials with outcome (N)/ participants (n)**	**Comparators**	**Effect sizes (95% CI)**	**Quality of evidence (GRADE)**
Mattick et.al., 2014 Adults with opioid dependence N= 31 trials N=5430	N= 5 RCTs n=1001	*Vs Placebo* High dose buprenorphine	RR= 1.82 (1.15 to 2.90) I^2=85.84% NNT=3 (1.3-16.6) (ACR=0.4)	High **** (Rated by Mattick et.al)
	N=4 RCTs, n=887	*Vs Placebo* Medium dose buprenorphine	RR=1.74 (1.06 to 2.87) I^2=91.34% NNT=3 (1.3-41.6) (ACR=0.4)	Moderate*** (HT-down 1 level for inconsistency)
	N=5 RCTs N=1131	*Vs Placebo* Low dose buprenorphine	RR= 1.50 (1.19 to 1.88) I^2=71.52% NNT=5 (2.8-13.2) (ACR=0.4)	Moderate*** (HT-downgrade 1 level for inconsistency)
	n= 11 RCTs n=1391	*Vs Methadone* Flexible dosing	RR=0.83 (0.73 to 0.95) I^2=56.13% NNT=10 (6.1-33.3) (ACR=0.6)	High **** (Rated by Mattick et.al) <u>Note:</u> Possibly should be downgraded 1 level for indirectness
	Figure 4. Forest plot of comparison: 1 Flexible dose buprenorphine versus flexible dose methadone, outcome: 1.1 Retention in treatment.  			
	N=1 RCT (n=142)	*Vs Methadone* High doses	RR= 0.79 (0.2 to 3.16)	Low** (rated by HT- down for imprecision 2 levels)
	N=7 RCTs (n=780)	*Vs Methadone* Medium doses	RR=0.87 (0.69 to 1.1) I^2=53.12%	High**** (rated by HT)
	N=3 RCTs (n= 253)	*Vs Methadone* Low doses	RR= 0.67[0.52 to 0.87] I^2=0% NNT=6 (3.8-13.9) (ACR=0.55)	Moderate**** (Rated by HT, falls short of optimum information size downgrade by 1)
Nielsen et al., 2016	N=3 RCTs (n=247)	*Vs placebo/ detoxification/*	RR=0.33 (0.23 to 0.47) NNT=6 (5.2-7.5)	Moderate quality*** (Rated by Nielsen et. Al.)

Table 4. Retention in care				
People with pharmaceutical opioid dependence (N=6 trials		*psychological treatment*	(ACR=0.25)	
	N=3 RCTs (n=360) One RCT (Ahmadi 2003, n=136) also included in Mattick 2014	*Vs Methadone*	RR 0.69 (0.39 to 1.22)	Low** (Rated by Neilsen et. Al.)
Minozzi et al., 2014 Adolescents (15-18yrs)	N= 1 RCT (n=152)	*Vs Detoxification*	RR=0.37 (0.26 to 0.54) NNT=2 (1.7 to 2.7)	Low ** (Rated by Minozzi et. al.)
Minozzi et al., 2020 Pregnant women	N=3 trials (n=223)	*Vs Methadone*	RR 0.66 (0.37 to 1.20) [strongest trial favours methadone]	Moderate *** (Rated by Minozzi et. al.)

Analysis 1.1. Comparison 1: Methadone versus buprenorphine, Outcome 1: Dropout rate



ACR=assumed control risk (calculated from control event rate)

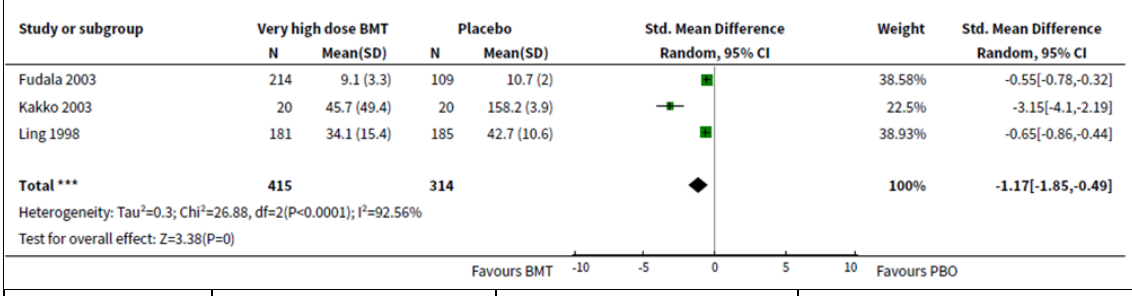
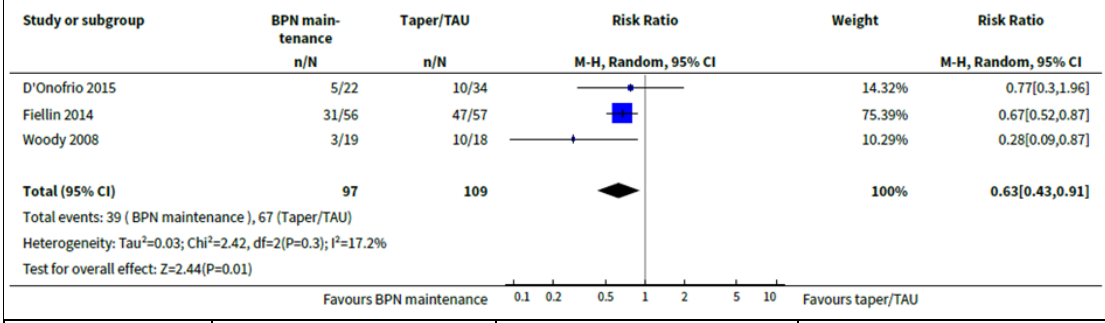
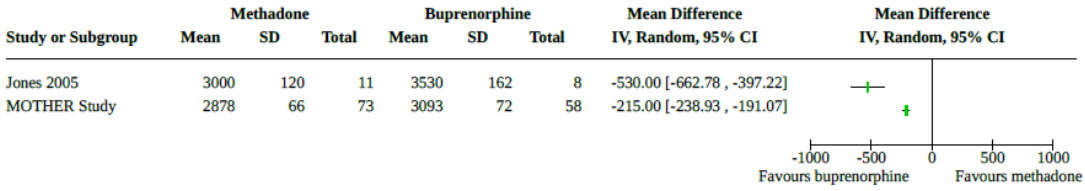
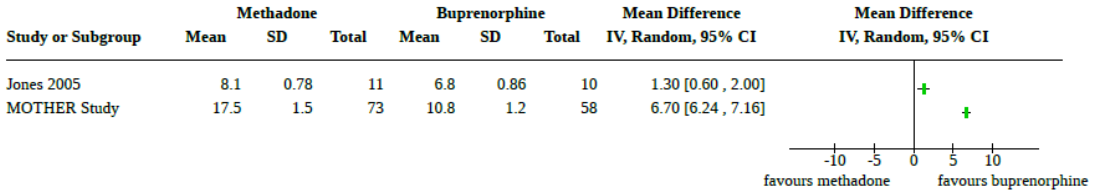
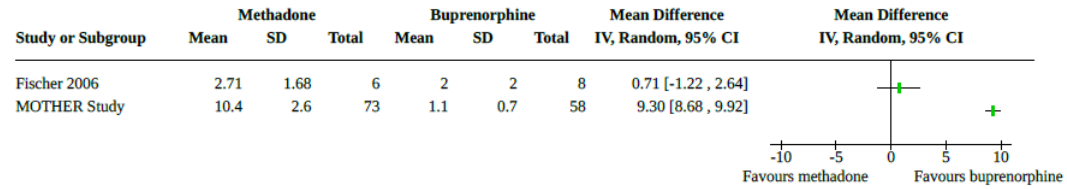
Table 5. Illicit opioid use on urine testing				
Author, date	**Trials with outcome (N)/ participants (n)**	**Comparators**	**Effect sizes (95% CI)**	**Quality of evidence (GRADE)**
Mattick et.al., 2014 Adults with opioid dependence N=31 trials	N=3 RCTs n=729	*Vs Placebo* (high dose ≥16mg)	SMD= - 1.7 (-1.85 to -0.49)	Moderate*** (Rated by Mattick et al.)
	Analysis 7.2. Comparison 7 High-dose buprenorphine versus placebo, Outcome 2 Morphine-positive urines.  			
	N=2 RCTs n=463	*Vs Placebo* (medium dose)	SMD= -0.08 (-0.78 to 0.62) I^2=88.09%	Low (downgraded by LR for inconsistency, indirectness)
	N=2 RCTs N=487	*Vs Placebo* (low dose)	SMD= 0.1 (-0.8 to 1.01) I^2=94.63%	Low (downgraded by LR for inconsistency, indirectness)
	N= 8 RCTs n=1027	*Vs Methadone* (flexible doses)	SMD= -0.11 (-0.23 to 0.02) I^2=0%	Moderate*** (Rated by Mattick et al.)
	N=4 RCTS N=476	*Vs Methadone* (medium doses)	SMD= 0.25 (-0.08 to 0.58) I^2=67.92%	Low (downgraded by LR for inconsistency and indirectness)
	N=1 RCT N=59	*Vs Methadone* (low doses)	SMD= -0.35 (-0.87 to 0.16)	Very low (downgraded by LR for indirectness, imprecision)
Nielsen et al., 2016 People with pharmaceutical use N=6 trials	N= 3 RCTs n=206	*Vs Detoxification or psychological Rx*	RR 0.63 (0.43 to 0.91) NNT=4 (2.8 – 18.2) ACR=0.61	Low** (Rated by Nielsen et al.)
	Analysis 2.2. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 2 Opioid positive (per urine drug screen, last week of treatment maintenance).  			
	N= 2 RCTs n=196	*Vs Methadone*	RR 0.81 (0.56 to 1.18)	Moderate*** (Rated by Nielsen et al.)
Minozzi, et. Al., 2014 Adolescents N=2 trials	N=1 RCT n= 152	*Vs Detoxification and no treatment*	RR=0.97 (0.78 – 1.22)	Low ** (Rated by Minozzi et al.)
Minozzi et al., 2020 Pregnant women N=3 trials	N=2 RCTs n=151	*Vs Methadone*	RR 1.81 (0.70 to 4.68)	Low ** (Rated by Minozzi et al.)
Perry et. al., 2015 Offenders N=14 RCTs 2647 participants	N= 1RCT n=36 females	*Vs Placebo*	RR= 0.57 (0.27 to 1.2)	Very low* (rated by HT, downgraded for imprecision 2 levels and risk of bias 1 level)

Table 6. Maternal and fetal outcomes of pregnancy

~~*Author, date*~~ ~~Trials/ participants (n)~~	**Outcome** ~~Meta-analysis (n)~~	~~**Effect sizes (95% CI)**~~	**Quality of evidence (GRADE)**
	~~Low quality evidence that agonist treatments are not effective in reducing drug use among offenders~~		
~~**Minozzi et al., 2020**~~	~~**Birth weight**~~ 2 RCTs (n=150)	~~Results not pooled.~~ Both studies favour buprenorphine	~~Very low*~~ (Rated by Minozzi et al.)
3 RCTs (n=223) *Vs Methadone*	**Analysis 1.3. Comparison 1: Methadone versus buprenorphine, Outcome 3: Birth weight**  Methadone / Buprenorphine / Mean Difference / Mean Difference Study or Subgroup: Mean SD Total — Mean SD Total — IV, Random, 95% CI — IV, Random, 95% CI Jones 2005: 3000 120 11 — 3530 162 8 — -530.00 [-662.78 , -397.22] MOTHER Study: 2878 66 73 — 3093 72 58 — -215.00 [-238.93 , -191.07] -1000 -500 0 500 1000 Favours buprenorphine / Favours methadone		
	Apgar Score 2 RCTs (n=163)	MD 0 (0.03 lower to 0.03 higher)	Low** (Rated by Minozzi et al.)
	Number treated for neonatal abstinence syndrome 3 RCTs (n=166)	RR 1.19 (0.87 to 1.63)	Low** (Rated by Minozzi et al.)
	Length of neonatal hospital stay 2 RCTS (n=152)	Results not pooled. Both RCTs favour buprenorphine	Very low* (rated by LR, downgraded for attrition bias, heterogeneity, imprecision)
	Analysis 1.7. Comparison 1: Methadone versus buprenorphine, Outcome 7: Length of hospital stay  Methadone / Buprenorphine / Mean Difference / Mean Difference Study or Subgroup: Mean SD Total — Mean SD Total — IV, Random, 95% CI — IV, Random, 95% CI Jones 2005: 8.1 0.78 11 — 6.8 0.86 10 — 1.30 [0.60 , 2.00] MOTHER Study: 17.5 1.5 73 — 10.8 1.2 58 — 6.70 [6.24 , 7.16] -10 -5 0 5 10 favours methadone / favours buprenorphine		
	Total amount of morphine for neonatal abstinence syndrome 2 RCTs (n=145)	Results not pooled. Stronger study favours buprenorphine	Very low* (rated by LR, downgraded for attrition bias, heterogeneity, imprecision)
	Analysis 1.8. Comparison 1: Methadone versus buprenorphine, Outcome 8: Total amount of morphine for NAS  Methadone / Buprenorphine / Mean Difference / Mean Difference Study or Subgroup: Mean SD Total — Mean SD Total — IV, Random, 95% CI — IV, Random, 95% CI Fischer 2006: 2.71 1.68 6 — 2 2 8 — 0.71 [-1.22 , 2.64] MOTHER Study: 10.4 2.6 73 — 1.1 0.7 58 — 9.30 [8.68 , 9.92] -10 -5 0 5 10 Favours methadone / Favours buprenorphine		

ACR=assumed control risk (calculated from control event rate)

Table 7. Reduction of HIV risk

Author, date	Outcome Trials)/ participants (n)	Effect sizes (95% CI)	Quality of evidence (GRADE)
Gowing et al., 2011 3 prospective cohort studies	**Frequency in injecting** 1 study (n=88) Follow up period 18 weeks	Reduction in number of injections/30days from 30.1±2.7 to 2.2±3.3 (40% attrition)	
	Lott 2006 (1) methadone (2) buprenorphine (3) LAAM — Injections of any drug per week in prior 30 days, mean±SEM — (1) 38.4±2.5, N=35; (2) 30.1±2.7, N=30; (3) 34.1±3.1, N=23 — (1) 2.5±2.9, N=24; (2) 2.2±3.3, N=18; (3) 2.2±4.2, N=11 — P<0.01 fo all med-ications		
	Drug risk assessed by HIV risk behaviour score 1 study (n=134) Follow up period 24 weeks	Improvement in score from 6.3±6.1 to 1.4±3.0 (31% attrition)	
	Marsch 2005 — HIV Risk Behavior Score (mean±SD) for prior month — 6.3±6.1, N=134 — 1.4±3.0, N=92 — P<0.001		
	Sex-related risk assessed by HIV risk behaviour score 1 study (n=134) Follow up period 24 weeks	Some improvement – significance unclear	
	Marsch 2005 — HIV Risk Behavior Score (mean±SD) for prior month — 3.7±4.4 — 3.1±3.3 — P=0.01		
	Overall HIV risk scores 1 study (n=24) Follow up period 3 months	Some improvement irrespective of intensity of non-pharmacological intervention. Possibly not significant.	
	Chawarski 2008 (1) Standard (2) enhanced services — ARI Score — (1) 62.73±31.74, N=12; (2) 65.17±32.16, N=12 — (1) 52.36±20.24, N=11; (2) 48.33±16.93, N=12 — P<0.05 for both groups		
	Main results re OST in general: OST associated with statistically significant reductions in illicit opioid use, injecting use and sharing of injecting equipment. It is also associated with reductions in the proportion of injecting drug users reporting multiple sex partners or exchanges of sex for drugs or money but has little effect on condom use.		

Table 8. Reduction of criminal activity

Author, date	Trials with outcome (N)/ participants (n)	Comparators	Effect sizes (95% CI)	Quality of evidence (GRADE)
Mattick et al., 2014	Self-reported criminal activity N=2RCTs (n=328)	*Vs methadone*	SMD=-0.1 (-0.31 to 0.12), I^2=0%	Very low (downgraded by LR for ROB, indirectness, imprecision)
Perry et al., 2015	Dichotomous outcomes (e.g., arrest) N=1RCT (n=116) Also included by Mattick et al.	*Vs methadone*	RR=1.25 (0.83 to 1.88)	Very low (downgraded by LR for ROB, indirectness, imprecision)
	Main results re OST in general reported by Perry et al, 2015: Low quality evidence that agonist treatments are not effective in reducing criminal activity among offenders			

Table 9. Reduction of other substance use

Author, date	Trials with outcome (N)/ participants (n)	Comparators	Effect sizes (95% CI)	Quality of evidence (GRADE)
Mattick et al., 2014	Cocaine positive urine N=2 RCTs (n=446)	*Vs placebo*	Low dose (n=120) SMD=0.26 (-0.1 to 0.62) Medium dose (n=90) SMD=0.5 (0.05 to 0.94) High dose (n=296) SMD= 0.08 (-0.16 to 0.32]	
	Cocaine positive urine	*Vs methadone*	Flexible dosing SMD=0.1[(0.05 to 0.25)	

	N=6RCTs (n=919)			
	Benzodiazepine positive urine N=4 RCTs (n=486)	*Vs placebo*	Low dose (n=120) SMD= 0.03[-0.33,0.38] Medium dose (n=90) SMD -0.81(-1.27 to -0.36) High dose (n=336) SMD= -1.65 (-4.94 to 1.65)	
	Benzodiazepine positive urine N=6RCTs (n=859)	*Vs methadone*	Flexible dosing (n=859) SMD=0.05 (-0.12,0.22)	
Table 10. Adverse events				
Mattick et al., 2014	1RCT (n=58	*Vs methadone*	Less sedation among those on buprenorphine (26% vs 58%)	
Nielsen et al., 2016 People with pharmaceutical use	N=2RCTs (n=166)	*Vs placebo/ detoxification*	Fewer adverse events in buprenorphine group, RR=0.19 (0.06 to 0.57), I^2=0% NNH=6.2 (5.3 to 11.6) ACR=0.2	Low (downgraded for indirectness, imprecision)
	Analysis 2.7. Comparison 2 Full or partial opioid agonist maintenance versus placebo, detoxification only, or psychological treatment, Outcome 7 Adverse events. Study or subgroup: BPN maintenance n/N; Taper/TAU n/N; Risk Ratio M-H, Random, 95% CI; Weight; Risk Ratio M-H, Random, 95% CI Fiellin 2014 3/56 16/57 86.59% 0.19[0.06,0.62] Woody 2008 0/27 2/26 13.41% 0.19[0.01,3.84] **Total (95% CI) 83 83 100% 0.19[0.06,0.57]** Total events: 3 (BPN maintenance), 18 (Taper/TAU) Heterogeneity: Tau²=0; Chi²=0, df=1(P=0.99); I²=0% Test for overall effect: Z=2.96(P=0) Favours BPN maintenance 0.002 0.1 1 10 500 Favours taper/TAU			
Minozzi et al., 2020 Pregnant women	**Serious adverse events for the mother,** 1 RCT (n=175)	*Vs methadone*	RR 1.69 (0.75 to 3.83)	Low** (Rated by Minozzi et al.)
	Serious adverse events for the child, 1 RCT (n=131)	*Vs methadone*	RR 4.77 (0.59 to 38.49)	Low** (Rated by Minozzi et al.)
	Non-serious adverse events for the mother, 1 RCT (n=175)	*Vs methadone*	RR 1.22 (1.07 to 1.38) favours buprenorphine. NNH =10 (5.5 to 33.3) ACR=0.47	Low (Rated by LR, imprecision with small sample size)
	Non-serious adverse events for the child, 1 RCT (n=131)	*Vs methadone*	RR 1.08 (0.74 to 1.59)	Low (Rated by LR, imprecision with small sample size)

ACR=assumed control risk

8. DISCUSSION

In this review, we evaluated evidence from seven systematic reviews in order to make a recommendation regarding the use of buprenorphine for OST in South Africa. Compared to not receiving OST, buprenorphine is effective in reducing mortality (observational evidence) and retaining people in care (moderate certainty, RCT evidence). Compared to methadone, buprenorphine is as effective for retention in care at medium and high doses but not with low or flexible dosing. However, it is not known if the variation in effect of different doses is applicable to South Africa, where patient population may differ to the RCT study populations (for example, in the proportion who smoke rather than inject heroin). Buprenorphine is comparable to methadone in reducing illicit opioid use among the general adult population, those dependent on pharmaceutical opioids, and pregnant women.

Mortality

One review of observational studies[10] found buprenorphine differs from methadone in that it is not associated with increased mortality during the first four weeks of treatment compared to the remaining time on OST. This is consistent with clinical expectation as, being a partial agonist, buprenorphine causes less respiratory depression than methadone and is therefore safer in overdose.[2, 3] This finding has important service delivery implications for South Africa, as it reduces the need for daily supervised doses during treatment induction and allows for more frequent take-home

doses. With respect to take-home doses, safety in overdose also protects children and other household members upon accidental or intentional ingestion of the medication.

Maternal and fetal outcomes of pregnancy
One systematic review of three RCTs[7] found greater birth weight among babies born to mothers treated with buprenorphine versus methadone. While frequency of neonatal abstinence syndrome was similar in both groups, severity in the buprenorphine exposed group may be less, requiring shorter hospital stays. However, the certainty of evidence is low and, as the burden of care in South Africa is not known, potential cost-saving impact is unclear.

Overall, the evidence of benefit of buprenorphine compared to methadone in pregnancy, is insufficient to make a clear recommendation. High quality observational studies are needed to confirm RCT findings. Two systematic reviews[15, 37] (both of critically low quality) did include prospective cohort studies in their analyses, also examining for preterm birth and head circumference. However, only data unadjusted for confounding were available, and a true effect cannot be ascertained from the findings.

Reduction of HIV risk
We found no RCT evidence to support buprenorphine in reducing the risk of acquiring HIV infection. The one systematic review[4] was only able to use observational before/after data from three small RCTs using buprenorphine. While drug-related risk behaviour appeared to be improved, attrition rates were high in two studies and not reported in the third. Results for sex-related risk behaviour were only reported in one stud, with no reporting of attrition and are not interpretable.

Available evidence on HIV risk for OST in general (i.e., reduction of drug-related risk in terms of injecting and of multiple partners) may possibly be extrapolated to buprenorphine. However, most studies were conducted in high income countries and the generalisability to South Africa is unclear.

Reduction of criminal activity
Limited, low certainty RCT evidence[5, 9] from high-income countries suggests buprenorphine, similar to methadone, may not be effective in reducing criminal activity. Whether this is generalisable to South Africa is uncertain.

Buprenorphine/naloxone vs buprenorphine
We did not find any evidence comparing buprenorphine/naloxone to buprenorphine in terms of reduced misuse with injection of buprenorphine tablets. This may be related to our search strategy, as we did not specifically search for articles on diversion or misuse. However, a recent health technology assessment conducted by the Canadian Agency for Drugs and Technologies in Health (which reviewed evidence evaluating buprenorphine formulations published between 2014 and March 2019) found no studies examining the comparative effectiveness of buprenorphine/naloxone on diversion.

Limitations of this review
We did not review feasibility and acceptability studies or research specific to diversion, as was not included in the PICO eligibility criteria.

9. CONCLUSION AND RECOMMENDATIONS

Buprenorphine is effective as OST in retention in care and reduction of illicit opioid use. The main advantage over methadone is that it is not associated with increased mortality during the first four weeks of treatment (induction and up-titration phases). While this is low certainty (observational) evidence, it is consistent with clinical experience of greater safety with buprenorphine. Low certainty evidence also suggests reduced hospital stay for babies with neonatal abstinence syndrome compared to methadone during pregnancy.

Safety during treatment induction (and safety in overdose) may outweigh costs. Stakeholder views and total healthcare costing is recommended.

Appendix I - Search strategy

Utilising Pubmed MESH function and keywords with automatic term mapping

Pubmed				
Treatment effectiveness				
Concept 1	**Concept 2**	**Concept 3**	**Concept 4**	**Concept 5**
Population	**Intervention**	**Comparator**	**Outcome**	**Time/study type**
MeSH terms	**MeSH terms**			
"Opioid-related disorders" [MeSH]	"Buprenorphine" [MeSH]			
"Morphine Derivatives" [MeSH]				
Keywords	**Keywords**			
"Heroin" [tw] OR "Heroin use"[tw] OR "Heroin abuse" [tw] OR "Heroin misuse" [tw] OR "heroin dependence"[tw] OR "oxycodone"[tw] OR "Codeine" [tw] OR "opioid*"[tw] OR "opioid abuse" [tw] OR "opioid misuse" [tw] OR "opioid dependence"[tw] OR "morphine dependence"[tw] OR "morphine dependency"[tw] OR "opiate addiction"[tw] OR "opioid analgesics" OR "tramadol"[tw]	("buprenorphine"[All Fields] AND "naloxone"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "naloxone drug combination buprenorphine"[All Fields] OR ("buprenorphine"[All Fields] AND "naloxone"[All Fields]) OR "buprenorphine naloxone"[All Fields]			"review"[ptyp] "systematic review"[ptyp] "methadonea-analysis"[ptyp] "1970/01/01"[Pdat]: "2021/02/05"[Pdat])
	"buprenorphine/nx" [tw]			
	"buprenorphine/nal" [tw]			

Pubmed search components
Population
"Opioid-related disorders" [MeSH] OR "Morphine Derivatives" [MeSH] OR "Heroin" [tiab] OR "Heroin use"[tiab] OR "Heroin abuse" [tiab] OR "Heroin misuse" [tiab] OR "heroin dependence"[tiab] OR "oxycodone"[tiab] OR "Codeine" [tiab] OR "opioid*"[tiab] OR "opioid abuse" [tiab] OR "opioid misuse" [tiab] OR "opioid dependence"[tiab] OR "morphine dependence"[tiab] OR "morphine dependency"[tiab] OR "opiate addiction"[tiab] OR "opioid analgesics"[tiab] OR "tramadol"[tiab]
Intervention
"Buprenorphine" [MeSH] OR "buprenorphine/nx" [tiab] OR "buprenorphine/nal" [tiab]
("buprenorphine"[Title/Abstract] AND "naloxone"[Title/Abstract] AND "drug"[Title/Abstract] AND "combination"[Title/Abstract]) OR "naloxone drug combination buprenorphine"[All Fields] OR ("buprenorphine"[Title/Abstract] AND "naloxone"[Title/Abstract]) OR "buprenorphine naloxone"[Title/Abstract]
Limitations
("review"[ptyp] OR "systematic review"[ptyp]) OR "meta-analysis"[ptyp]
"1990/01/01"[Pdat]: "2021/02/18"[Pdat]
"English"[Language]
PubMed: Final search in title and abstract (Using MeSH and keywords)
("Opioid-related disorders"[MeSH Terms] OR "Morphine Derivatives"[MeSH Terms] OR "Heroin"[Title/Abstract] OR "Heroin use"[Title/Abstract] OR "Heroin abuse"[Title/Abstract] OR "Heroin misuse"[Title/Abstract] OR "heroin dependence"[Title/Abstract] OR "oxycodone"[Title/Abstract] OR "Codeine"[Title/Abstract] OR "opioid*"[Title/Abstract] OR "opioid abuse"[Title/Abstract] OR "opioid misuse"[Title/Abstract] OR "opioid dependence"[Title/Abstract] OR "morphine dependence"[Title/Abstract] OR "morphine dependency"[Title/Abstract] OR "opiate addiction"[Title/Abstract] OR "opioid analgesics"[Title/Abstract] OR "tramadol"[Title/Abstract]) AND ("Buprenorphine"[MeSH Terms] OR "buprenorphine/nx"[Title/Abstract] OR "buprenorphine/nal"[Title/Abstract]) AND (("review"[Publication Type] AND "systematic review"[Publication Type]) OR "meta-analysis"[Publication Type]) AND 1990/01/01:2021/02/26[Date - Publication] AND "English"[Language]

Cochrane Database of Systematic Reviews
Treatment effectiveness

Concept 1	Concept 2	Concept 3	Concept 4	Concept 5
Population	**Intervention**	**Comparator**	**Outcome**	**Time/study type**
MeSH terms	**MeSH terms**			
"Opioid-related disorders" [MeSH]	"Buprenorphine" [MeSH]			
"Morphine Derivatives" [MeSH]				
Keywords	**Keywords**			
"Heroin" [tw] OR "Heroin use"[tw] OR "Heroin abuse" [tw] OR "Heroin misuse" [tw] OR "heroin dependence"[tw] OR "oxycodone"[tw] OR "Codeine" [tw] OR "opioid*"[tw] OR "opioid abuse" [tw] OR "opioid misuse" [tw] OR "opioid dependence"[tw] OR "morphine dependence"[tw] OR "morphine dependency"[tw] OR "opiate addiction"[tw] OR "opioid analgesics" OR "tramadol"[tw]	("buprenorphine"[All Fields] AND "naloxone"[All Fields] AND "drug"[All Fields] AND "combination"[All Fields]) OR "naloxone drug combination buprenorphine"[All Fields] OR ("buprenorphine"[All Fields] AND "naloxone"[All Fields]) OR "buprenorphine naloxone"[All Fields]			Cochrane review "1970/01/01"[Pdat]: "2021/02/05"[Pdat])
	"buprenorphine/nx" [tw]			
	"buprenorphine/nal" [tw]			

Cochrane Database of Systematic reviews
Population
#1 MeSH descriptor: [Opioid-Related Disorders] explode all trees #2 MeSH descriptor: [Morphine Derivatives] explode all trees #3 "opioid-related disorders" OR "morphine derivatives" OR "heroin" OR "Heroin use" OR "Heroin use" OR "Heroin abuse" OR "Heroin abuse" OR "Heroin misuse" OR "Heroin misuse" OR "heroin dependence" OR "heroin dependence" OR "oxycodone" OR "oxycodone" OR "Codeine" OR "Codeine" OR "opioid*" OR "opioid*" OR "opioid abuse" OR "opioid abuse" OR "opioid misuse" OR "opioid misuse" OR "opioid dependence" OR "opioid dependence" OR "morphine dependence" OR "morphine dependence" OR "morphine dependency" OR "morphine dependency" OR "opiate addiction" OR "opiate addiction" OR "opioid analgesics" OR "opioid analgesics" OR "tramadol" OR "tramadol"
Intervention
#4 MeSH descriptor: [Buprenorphine] explode all trees #5 "Buprenorphine" OR "buprenorphine/nx" OR "buprenorphine/nal" OR "buprenorphine/naloxone" OR "opioid maintenance treatment" OR "opioid maintenance therapy" OR "medication assisted treatment" OR "opioid substitution treatment" OR "opioid substitution therapy" OR "opioid replacement therapy"
#6 #1 OR #2 OR #3 #7 #4 OR #5 #8 #6 AND #7 in Cochrane Reviews
Limitations
Cochrane Reviews
"1990/01/01"[Pdat]: "2021/02/xx"[Pdat]
"English"[Language]

CINAHL and PsycINFO				
Treatment effectiveness				
Concept 1	**Concept 2**	**Concept 3**	**Concept 4**	**Concept 5**
Population	**Intervention**	**Comparator**	**Outcome**	**Time/study type**
Major topics in Title or Abstract (TI OR AB)	**Major topics** in Title or Abstract (TI OR AB)			

“Opioid-related disorders”	“Buprenorphine”			
“Morphine Derivatives”				
Keywords/synonyms	Keywords/synonyms			
“Heroin” OR “Heroin use” OR “Heroin abuse” OR “Heroin misuse” OR “heroin dependence” OR “oxycodone” OR “Codeine” OR “opioid*” OR “opioid abuse” OR “opioid misuse” OR “opioid dependence” OR “morphine dependence” OR “morphine dependency” OR “opiate addiction” OR “opioid analgesics” OR “tramadol” OR	("buprenorphine" AND "naloxone" AND "drug" AND "combination") OR "naloxone drug combination buprenorphine" OR "buprenorphine" "naloxone" Buprenorphine/naloxone			review OR meta-analysis English language "1970/01/01" to"2021/02/05"
	“buprenorphine/nx” [tw]			
	"buprenorphine/nal" [tw]			
CINAHL and PsycINFO search components				
Population (S1)				
TI opioid-related disorders OR AB opioid-related disorders OR TI "morphine derivatives" OR AB "morphine derivatives" OR TI “heroin” OR AB “heroin’ OR TI “Heroin use” OR AB “Heroin use” OR TI “Heroin abuse” OR AB “Heroin abuse” OR TI “Heroin misuse” OR AB “Heroin misuse” OR TI “heroin dependence” OR AB “heroin dependence” OR TI “oxycodone” OR AB “oxycodone” OR TI “Codeine” OR AB “Codeine” OR TI “opioid*” OR AB “opioid*” OR TI “opioid abuse” OR AB “opioid abuse” OR TI “opioid misuse” OR AB “opioid misuse” OR TI “opioid dependence” OR AB “opioid dependence” OR TI “morphine dependence” OR AB “morphine dependence” OR TI “morphine dependency” OR AB “morphine dependency” OR TI “opiate addiction” OR AB “opiate addiction” OR TI “opioid analgesics” OR AB “opioid analgesics” OR TI “tramadol” OR AB “tramadol”				
Intervention (S2)				
TI “Buprenorphine” OR AB “Buprenorphine” OR TI “buprenorphine/nx” OR AB “buprenorphine/nx” OR TI "buprenorphine/nal" OR AB “buprenorphine/nal” OR TI “buprenorphine/naloxone” OR AB “buprenorphine/naloxone” OR TI “opioid maintenance treatment” OR AB “opioid maintenance treatment” OR TI “opioid maintenance therapy” OR AB “opioid maintenance therapy” OR TI “medication assisted treatment” OR AB “medication assisted treatment” OR TI “opioid substitution treatment” OR AB “opioid substitution treatment” OR TI “opioid substitution therapy” OR AB “opioid substitution therapy” OR TI “opioid replacement therapy” OR AB “opioid replacement therapy”				
CINAHL and PsycINFO Final search in title and abstract: S1 and S2				
Limiters				
“literature review”				
"1990/01/01" to "2021/02/26"				
“English”[Language]				

Scopus				
Treatment effectiveness				
Concept 1	**Concept 2**	**Concept 3**	**Concept 4**	**Concept 5**
Population	**Intervention**	**Comparator**	**Outcome**	**Time/study type**
Major topics in Title or Abstract (TI OR AB)	**Major topics in** Title or Abstract (TI OR AB)			
“Opioid-related disorders”	“Buprenorphine”			

“Morphine Derivatives”				
Keywords/synonyms	**Keywords/synonyms**			
“Heroin” OR “Heroin use” OR “Heroin abuse” OR “Heroin misuse” OR “heroin dependence” OR “oxycodone” OR “Codeine” OR “opioid*” OR “opioid abuse” OR “opioid misuse” OR “opioid dependence” OR “morphine dependence” OR “morphine dependency” OR “opiate addiction” OR “opioid analgesics” OR “tramadol” OR “adult*” OR “adolescent*” OR “pregnan*”	("buprenorphine"AND "naloxone" AND "drug" AND "combination") OR "naloxone drug combination buprenorphine" OR "buprenorphine" "naloxone" Buprenorphine/naloxone			review OR meta- analysis English language "1970/01/01" to"2021/02/05"
	“buprenorphine/nx” [tw]			
	"buprenorphine/nal" [tw]			
TITLE-ABS("opioid-related disorders" OR "morphine derivatives" OR "heroin" OR "Heroin use" OR "Heroin use" OR "Heroin abuse" OR "Heroin abuse" OR "Heroin misuse" OR "Heroin misuse" OR "heroin dependence" OR "heroin dependence" OR "oxycodone" OR "oxycodone" OR "Codeine" OR "Codeine" OR "opioid*" OR "opioid*" OR "opioid abuse" OR "opioid abuse" OR "opioid misuse" OR "opioid misuse" OR "opioid dependence" OR "opioid dependence" OR "morphine dependence" OR "morphine dependence" OR "morphine dependency" OR "morphine dependency" OR "opiate addiction" OR "opiate addiction" OR "opioid analgesics" OR "opioid analgesics" OR "tramadol" OR "tramadol") AND TITLE-ABS ("Buprenorphinerenorphine" OR "buprenorphine/nx" OR "buprenorphine/nal" OR "buprenorphinerenorphine/naloxone" OR "opioid maintenance treatment" OR "opioid maintenance therapy" OR "medication assisted treatment" OR "opioid substitution treatment" OR "opioid substitution therapy" OR "opioid replacement therapy") AND TITLE-ABS (“adult*” OR "adolescent*" OR "pregnan*" OR “prison*” OR “forensic” OR “criminal justice”) AND (LIMIT-TO (DOCTYPE , "re")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))				
Limiters				
“literature review”				
"1990/01/01" to "2021/02/26"				
“English”[Language]				

Web of Science				
Treatment effectiveness				
Concept 1	Concept 2	Concept 3	Concept 4	Concept 5
Population	Intervention	Comparator	Outcome	Time/study type
Major topics in Title or Abstract (TI OR AB)	Major topics in Title or Abstract (TI OR AB)			
“Opioid-related disorders”	“Buprenorphine”			
“Morphine Derivatives”				
Keywords/synonyms	Keywords/synonyms			
“Heroin” OR “Heroin use” OR “Heroin abuse” OR “Heroin misuse” OR “heroin dependence” OR “oxycodone” OR “Codeine” OR	("buprenorphine"AND "naloxone" AND "drug" AND "combination") OR "naloxone drug combination buprenorphine" OR "buprenorphine" "naloxone" Buprenorphine/naloxone			review OR meta-analysis English language "1970/01/01" to"2021/02/05"

“opioid*” OR “opioid abuse” OR “opioid misuse” OR “opioid dependence” OR “morphine dependence” OR “morphine dependency” OR “opiate addiction” OR “opioid analgesics” OR “tramadol” OR “adult*” OR “adolescent*” OR “pregnan*”				
	“buprenorphine/nx” [tw]			
	"buprenorphine/nal" [tw]			
TI=("opioid- related disorders" OR "morphine derivatives" OR "heroin" OR "Heroin use" OR "Heroin use" OR "Heroin abuse" OR "Heroin abuse" OR "Her oin misuse" OR "Heroin misuse" OR "heroin dependence" OR "heroin dependence" OR "oxycodone" OR "oxycodone" OR "Codeine" OR "Co deine" OR "opioid*" OR "opioid*" OR "opioid abuse" OR "opioid abuse" OR "opioid misuse" OR "opioid misuse" OR "opioid dependence" O R "opioid dependence" OR "morphine dependence" OR "morphine dependence" OR "morphine dependency" OR "morphine dependency" OR "opiate addiction" OR "opiate addiction" OR "opioid analgesics" OR "opioid analgesics" OR "tramadol" OR "tramadol") OR AB=("opioid-related disorders" OR "morphine derivatives" OR "heroin" OR "Heroin use" OR "Heroin use" OR "Heroin abuse" OR "Heroin abuse" OR "Her oin misuse" OR "Heroin misuse" OR "heroin dependence" OR "heroin dependence" OR "oxycodone" OR "oxycodone" OR "Codeine" OR "Co deine" OR "opioid*" OR "opioid*" OR "opioid abuse" OR "opioid abuse" OR "opioid misuse" OR "opioid misuse" OR "opioid dependence" O R "opioid dependence" OR "morphine dependence" OR "morphine dependence" OR "morphine dependency" OR "morphine dependency" OR "opiate addiction" OR "opiate addiction" OR "opioid analgesics" OR "opioid analgesics" OR "tramadol" OR "tramadol")				
TI=("Buprenorphinerenorphine" OR "buprenorphine/nx" OR "buprenorphine/nal" OR "buprenorphinerenorphine/naloxone" OR "opioid ma intenance treatment" OR "opioid maintenance therapy" OR "medication assisted treatment" OR "opioid substitution treatment" OR "opioid substitution therapy" OR "opioid replacement therapy") OR AB=("Buprenorphinerenorphine" OR "buprenorphine/nx" OR "buprenorphine /nal" OR "buprenorphinerenorphine/naloxone" OR "opioid maintenance treatment" OR "opioid maintenance therapy" OR "medication assi sted treatment" OR "opioid substitution treatment" OR "opioid substitution therapy" OR "opioid replacement therapy")				
TI=("adult*" OR "adolescent*" OR "pregnan*" OR "prison*" OR "forensic" OR "criminal justice") OR AB=("adult*" OR "adolescent*" OR "pr egnan*" OR "prison*" OR "forensic" OR "criminal justice")				
#3 AND #2 AND #1 **Refined by: DOCUMENT TYPES:** (REVIEW) AND **LANGUAGES:** (ENGLISH) AND [excluding] **RESEARCH AREAS:** (NUTRITION DIETETICS OR CELL BIOLOGY OR MEDICAL ETHICS OR BIOPHYSICS OR EDUCATION EDUCATIONAL RESEARCH OR HISTORY OR ENVIRONMENTAL SCIENCES ECOLOGY OR INFORMATION SCIENCE LIBRARY SCIENCE OR INSTRUMENTS INSTRUMENTATION OR REPRODUCTIVE BIOLOGY OR COMMUNICATION OR SPECTROSCOPY OR WOMEN APOS S STUDIES OR AGRICULTURE OR BUSINESS ECONOMICS OR ANATOMY MORPHOLOGY OR GENETICS HEREDITY OR INTERNATIONAL RELATIONS OR PHILOSOPHY OR ALLERGY OR BIOTECHNOLOGY APPLIED MICROBIOLOGY OR RADIOLOGY NUCLEAR MEDICINE MEDICAL IMAGING OR COMPUTER SCIENCE OR FOOD SCIENCE TECHNOLOGY OR ENGINEERING OR MICROBIOLOGY OR EVOLUTIONARY BIOLOGY OR DENTISTRY ORAL SURGERY MEDICINE OR IMAGING SCIENCE PHOTOGRAPHIC TECHNOLOGY OR PHYSICS OR PUBLIC ADMINISTRATION OR MATHEMATICAL COMPUTATIONAL BIOLOGY OR TRANSPORTATION OR CHEMISTRY OR PLANT SCIENCES OR VETERINARY SCIENCES OR GOVERNMENT LAW OR VIROLOGY OR ZOOLOGY OR MATHEMATICS) AND [excluding] **RESEARCH AREAS:** (MEDICAL INFORMATICS OR MEDICAL LABORATORY TECHNOLOGY OR BIOCHEMISTRY MOLECULAR BIOLOGY OR SPORT SCIENCES OR GERIATRICS GERONTOLOGY) *Databases= WOS Timespan=1990-2021* *Search language=Auto*				
Limiters				
“literature review”				
"1990/01/01" to "2021/02/26"				
“English”[Language]				

Database	**Filters**	**Fields**	**Returns**
PubMed	1970/01/01-2021/02/11 Review + Meta-Analysis + Systematic reviews English	Title and Abstract, MeSH	95
Cochrane Library	1970/01/01-2021/02/11 In Cochrane Reviews	Title, Abstract, keywords, MeSH	91
PsycINFO and CINAHL	1970/01/01-2021/02/11 Literature review English	Title, Abstract,	16

SCOPUS	2006-2016 Review; English	Title, Abstract,	171
Web of Science	1970/01/01-2021/02/11 Review; English (*see above)	Title, Abstract	176
Total			549

Appendix 2 Excluded studies

Study	Rationale for exclusion
Alinejad, S et al. 2015. A systematic review of the cardiotoxicity of methadone. Excli journal, 14**,** 577-600.	Wrong intervention
Andersen,HM et al. 2020. prenatal exposure to methadone or buprenorphine and long-term outcomes: a meta-analysis. early human development, 143, 13. 10.1016/j.earlhumdev.2020.104997.	Wrong intervention
Bi-Mohammed, Z et al. Prescription opioid abuse in prison settings: A systematic review of prevalence, practice and treatment responses. Drug Alcohol Depend, 171**,** 122-131. 10.1016/j.drugalcdep.2016.11.032.	Wrong comparator (explores abuse of buprenorphine or methadone in various formulations in prison settings); thematic analysis.
Borodovsky JT et al. 2018. Buprenorphine Treatment for Adolescents and Young Adults with Opioid Use Disorders: A Narrative Review. Journal of Addiction Medicine, 12**,** 170-183. 10.1097/ADM.0000000000000388.	Wrong study design – narrative review
Camenga, DR et al.. 2019. Medications for Maintenance Treatment of Opioid Use Disorder in Adolescents: A Narrative Review and Assessment of Clinical Benefits and Potential Risks. *Journal of Studies on Alcohol and Drugs,* 80**,** 393-402. 10.15288/jsad.2019.80.393.	Wrong study design – narrative review
Cramton, REM et al. 2013. Babies breaking bad: Neonatal and iatrogenic withdrawal syndromes. Current Opinion in Pediatrics, 25**,** 532-542. 10.1097/MOP.0b013e328362cd0d.	Wrong study design – narrative review
Davids E at al. 2004. Buprenorphine in the treatment of opioid dependence. Eur Neuropsychopharmacol, 14**,** 209-16. 10.1016/s0924-977x(03)00146-9.	Wrong study design – narrative review
Ducharme, S et al.. 2012. Update on the clinical use of buprenorphine: in opioid-related disorders. Canadian Family Physician, 58**,** 37-41.	Wrong study design – narrative review
Feelemyer, J et al. 2014. Retention of participants in medication-assisted programs in low- and middle-income countries: an international systematic review. Addiction, 109, 20-32. 10.1111/add.12303.	Wrong comparator – evaluates average retention rates for buprenorphine and methadone independently, no direct comparison
Fernandez, S et al. 2019. Differences in hospital length of stay between neonates exposed to buprenorphine versus methadone in utero: A retrospective chart review. Paediatrics and Child Health (Canada), 24**,** E104-E110. 10.1093/pch/pxy091.	Wrong study design – retrospective review
Heo, YA et al. 2018. Buprenorphine/Naloxone (Zubsolv ®): A Review in Opioid Dependence. CNS Drugs, 32**,** 875-882. 10.1007/s40263-018-0560-2.	Wrong study design – narrative review
Kelty, E et al. 2017. A Retrospective Cohort Study of Obstetric Outcomes in Opioid-Dependent Women Treated with Implant Naltrexone, Oral Methadone or Sublingual Buprenorphine, and Non-Dependent Controls. Drugs, 77, 1199-1210. 10.1007/s40265-017-0762-9.	Wrong study design – retrospective review
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Poon S et al. 2014. Safety of the newer class of opioid antagonists in pregnancy. Canadian Family Physician, 60, 631-632+E348.	Wrong study design – narrative review
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Yee, A et al. 2014. Clinical factors associated with sexual dysfunction among men in methadone maintenance treatment and buprenorphine maintenance treatment: a meta-analysis study. Int J Impot Res, 26, 161-6. 10.1038/ijir.2014.18.	Wrong outcomes – non-medicine related factors

Appendix3 Evidence to decision framework

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
QUALITY OF EVIDENCE OF BENEFIT	**What is the quality evidence/quality of evidence?** High [ ] Moderate [ ] Low [X] Very low [ ] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	RCT evidence downgraded in general because of indirectness in terms of generalisability to South Africa. In addition, there were no large, high quality RCTs. Observational evidence considered low quality despite being of large cohorts with a large magnitude of effect, as comprised before/ after comparisons rather than matched controls comparison.
EVIDENCE OF BENEFIT	**What is the size of the effect for beneficial outcomes?** ***Buprenorphine vs no OST*** Reduction in all-cause mortality Large [X] Moderate [ ] Small [ ] None [ ] Uncertain [ ] Retention in care Large [ ] Moderate [X] Small [ ] None [ ] Uncertain [ ] Reduction in illicit opioid use Large [ ] Moderate [ ] Small [X] None [ ] Uncertain [ ] ***Buprenorphine vs methadone*** Retention in care Large [ ] Moderate [ ] Small [ ] None [ ] Uncertain [X] Reduction in illicit opioid use Large [ ] Moderate [ ] Small [ ] None [X] Uncertain [ ] Improved neonatal outcomes Large [ ] Moderate [ ] Small [X] None [ ] Uncertain [ ]	***Buprenorphine vs no OST (placebo/ detoxification)*** • Reduction in all-cause mortality by 66% considered proportionately large (approximately 10 deaths per 1000 person-years). • NNT for retention in care ranged from 2 in adolescents to 5 at low doses in general adult population. • Only associated with reduced illicit opioid use at high doses. ***Buprenorphine vs methadone*** • Considered uncertain because of the variation in effect with dosing (no difference at medium or high doses, less effective at low or flexible doses) and uncertain generalisability to South Africa, where lower doses may be effective than in high-income countries. • No difference in effect on illicit opioid use • Very low certainty of a small, positive effect on birth weight and severity of neonatal abstinence syndrome
QUALITY OF EVIDENCE OF HARM	**What is the quality evidence/quality of evidence?** High [ ] Moderate [ ] Low [ ] Very low [X] *High quality:* confident in the evidence *Moderate quality:* mostly confident, but further research may change the effect *Low quality:* some confidence, further research likely to change the effect *Very low quality:* findings indicate uncertain effect	
EVIDENCE OF HARMS	**What is the size of the effect for harmful outcomes?** **L**arge [ ] Moderate [ ] Small [ ] None [X] Uncertain [ ]	No harmful adverse events were reported ***Buprenorphine vs no OST (placebo/detoxification)*** • Fewer adverse events in buprenorphine group (NNH 6) ***Buprenorphine vs methadone*** • Less sedation reported in 2 RCTs (quantified in 1) Fewer non-serious adverse events in pregnant women
BENEFITS & HARMS	**Do the desirable effects outweigh the undesirable harms?** Favours intervention [X] Favours control [ ] Intervention = Control *or* Uncertain [ ]	

	JUDGEMENT	EVIDENCE & ADDITIONAL CONSIDERATIONS
THERAPEUTIC INTERCHANGE	Therapeutic alternatives available: Yes [X] No [ ]	Naltrexone, an opioid antagonist may be considered an alternative for treatment of opioid dependence.[1, 2] Rationale for exclusion from the group: Requires full opioid withdrawal prior to treatment induction, with no opioid use for 10-14 days before starting naltrexone.[2] Relapse, with overdose of illicit opioids, and drop-out during induction may occur. May be more suitable for people who prefer an abstinence-based program.
FEASABILITY	**Is implementation of this recommendation feasible?** Yes [ ] No [ ] Uncertain [X]	Safety in overdose/ toxicity and safety during treatment induction mean that implementation of OST with buprenorphine is more feasible than with methadone. Take-home doses present less of a risk to other household members, including children. Buprenorphine is still vulnerable to misuse and to diversion to illicit drug markets. Therefore, feasibility limited by the need for strict stock-control, similar to methadone.
RESOURCE USE	**How large are the resource requirements?** More intensive [ ] Less intensive [ ] Uncertain [X]	**Price of oral medicines/ DDD** *(RCTs in Mattick et SR, 2014[5])* **Medicine** / **Tender price (ZAR)*** / **SEP (ZAR)#** / **60% of SEP** *Comparison 1:* Methadone 40 mg: 18.83 / - / - Buprenorphine 6 mg: n/a / 49.19 / 29.51 *Comparison 2:* Methadone 65 mg: 30.60 / - / - Buprenorphine 10 mg: n/a / 82.17 / 49.30 *Comparison 3:* Methadone 90 mg: 42.38 / - / - Buprenorphine 16 mg: n/a / 131.56 / 78.93 *Contract circular HP12-2020LQ, Methadone 2mg/ml, 60mL = R56.50 #SEP Database 26 November 2021, Buprenorphine 2 mg SLT = R16.40; 8mg SLT=R65.78 Resources are less intensive for labour (buprenorphine) related to doses administered under direct supervision (methadone), but buprenorphine is more expensive.
VALUES, PREFERENCES, ACCEPTABILITY	**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 [ ] No [ ] Uncertain [X]	There is no local survey data. Engagement with stakeholders around methadone had varied responses, with concerns raised by City of Cape Town PHC staff regarding the workload in PHC settings. Whether buprenorphine would be more acceptable to healthcare providers would need to be evaluated.
EQUITY	**Would there be an impact on health inequity?** Yes [X] No [ ] Uncertain [ ]	• OST with buprenorphine is only available at present to those who can afford it privately. • Safety during treatment induction would allow greater use in poorly resourced and rural settings than methadone would.

Version	Date	Reviewer(s)	Recommendation and Rationale
Initial	30 November 2021	LR, HT, TL	

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