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Effectiveness of pharmacotherapies in increasing treatment retention and reducing opioid overdose death in individuals recently released from prison: a systematic review

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Summary

Background: Opioid dependence is common amongst the prison population, with increased risk of fatal overdose in the immediate post-release period. **Aim:** The study aimed to review the effectiveness of pharmacotherapies (Methadone (METH), Buprenorphine (BUP), levo-alpha acetyl methadol (LAAM), Naltrexone (NLT) and Naloxone (NLX)) in reducing overdose deaths and increasing treatment retention in opioid dependent prisoners on release. **Methods:** A systematic review of studies on recently discharged opioid dependent prisoners receiving METH, BUP, LAAM, NLT and/or NLX was conducted. Factors of interest regarded post-release treatment retention, non-fatal overdoses (NFODs), overdose mortality, and continued heroin and/or other illicit drug use. Searches were conducted using MESH terms; opioid related disorder, prisoner, NLT, NLX, METH, BUP, LAAM, overdose. Exclusion criteria were applied as per PRISMA guidelines. Quality, outcome and risk of bias assessments were applied across studies. **Results:** Eight randomised control trials (RCT), one non-randomised trial and five observational studies formed the data set. Agonist Opioid Treatment (AOT) (METH, BUP, LAAM) initiated pre-release was associated with significant post-release treatment retention on discharge into the community, and post-release reduction in heroin use. Prisoners on BUP or METH on discharge had significantly reduced mortality risks in the immediate four weeks post-release. There was insufficient evidence supporting a reduction in NFODs and continued other illicit drug use. **Conclusions:** The review underscores the need for prisoners on AOT to be supported with continued treatment on release into the community. Further research is warranted to investigate potential utility of long-acting NLT formulations and take-home NLX (THN) in pre –release opioid dependant prisoners.

Key Words: Prisoner; opioid replacement; overdose; methadone; buprenorphine; levo-alpha acetyl methadol; LAAM; naltrexone; naloxone; retention

1. Introduction

Opioid dependence has the greatest disease burden of all illicit drugs [15] with drug overdose deaths a significant contributor to this burden [14]. Problem drug use – and in particular opioid use, dependence and drug injecting behaviours – is significantly more prevalent amongst the prison population compared to the general population [25, 33, 63, 68]. People who inject drugs (PWID) have a lifetime incarceration prevalence of 56% to 90% [33], with continued and new injecting occurring when incarcerated [1, 23, 33]. The two week period following prison release is a particularly vulnerable period for overdose deaths [5, 57, 64, 69], mainly due to reduced tolerance to opioids, presence of relapse triggers, drug availability and on-going complex medical, psychological and social issues among this cohort [4, 24, 57]. Risk of post-release overdose is increased among prisoners aged between 25-35 years, with a history of injecting drug use (IDU), male gender and a diagnosis of mental illness [11, 24, 35, 69]. The tendency for prisoners to "celebrate" post-release may also be a contributing factor [57].

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Non-fatal overdoses (NFODs) occur more frequently than fatal overdoses and are associated with history of recent incarceration and increased mortality and morbidity rates [13, 36]. In terms of the prison population, exposure to hepatitis C, ever attempting suicide and a history of injecting heroin and/or other opiates increase risk of NFOD [59]. Risk factors for NFODs in the community include homelessness, a history of multiple arrests and/or imprisonments, longer time in prison, binge drug use and/or an increased frequency of injecting, street injecting, longer history of opiate use and poly-substance use [59; 74]. Marked variations in overdose deaths globally may reflect local differences in prison and community drug treatment policies, differences in drug use patterns, particularly injecting and polysubstance misuse and the availability and purity of heroin and other drugs [57].

Structured community based drug treatment programmes (particularly the range of treatments for heroin dependence using pharmacotherapies, methadone (METH), buprenorphine (BUP), levo-alpha acetyl methadol (LAAM), naltrexone (NLT) and naloxone (NLX)), spirituality/religion and family are identified as being protective for preventing relapse and drug overdose on release [4, 12]. The provision of community Agonist Opioid Treatment (AOT) using METH, BUP or LAAM is shown to increase treatment retention and reduce overdose deaths in the community [7, 9, 36, 47, 55]. Opioid dependent patients retained in METH maintenance treatment (MMT) have reduced mortality, reduced criminality and improved health compared to those who are not in MMT [8, 29]. BUP as a combined product with NLX has reduced potential for diversion [3], and similar benefits to METH, being: increased treatment retention, reduced illicit drug use and criminal activity in the community when compared to placebo [47, 53]. Other treatment options include LAAM which is a longer acting opioid agonist, with similar or better outcomes than METH [9]. Concerns regarding its potential to cause cardiac arrhythmias (QTc prolongation effect) have contributed to its discontinuation as an AOT [49]. Sustained release NLT is a full opioid antagonist; by blocking the effects of heroin and other opioids it has shown in improving treatment retention, reducing heroin use and cravings [32, 41, 42, 49]. Lastly, take-home NLX (THN) has been proposed as a novel preventative measure to reduce the likelihood of a fatal outcome from heroin overdose amongst drug users [49, 69] with anecdotal reports of small-scale interventions showing some possible benefits in the community setting [22, 62].

AOT, when provided in prison, reduces the in-prison use of heroin, injecting and syringe sharing and increases retention in post-release treatment when continued in the community [30]. However, its impact on post-release overdose rates is unclear [30]. In the prison setting, MMT is shown to reduce drug use, drug injecting, risk taking behaviour and HIV and hepatitis C virus (HCV) infection rates [18]. Whilst BUP is increasingly used in opioid dependence treatment [3, 49], it has poor bioavailability and must be taken sublingually, a factor that impacts on ingestion supervision and diversion potential in a prison setting [53]. BUP may have relevance for the choice of AOT for prisoners since most post-release overdoses for males are heroin related and for females involve benzodiazepines, cocaine and tricyclic antidepressants [24]. LAAM's prolonged duration of effect may also have some benefits in recently released prisoners allowing a greater time frame for the released prisoner to engage with community services before the onset of opioid withdrawals. NLT reduces heroin use and re-incarceration when compared with placebo alone but has no effect on reducing relapse or treatment retention [58]. There is evidence to support the use of NLT in highly motivated patients [72] and in prisoners on parole [11]. Outcomes are compromised by poor patient interest, high dropout rates and increased risk of overdose when the patient stops treatment, particularly in the first two weeks of discontinuation [10, 17, 60]. However, as its antagonist effect can last for up to six months, it affords post-release overdose protection during the high risk two to four week period, allowing patients to link with community treatment services [49]. Lastly, THN has potential utility to reduce post-release overdose if widely distributed among prisoners on release, their drug-taking peers, friends and family.

Despite the central role of AOT in community based services, its availability and utilisation in prisons is limited [66, 67]. The medical management of addiction, and in particular its management among prisoners, is often influenced by negative societal attitudes to drug users, including a failure to understand its chronic relapsing nature; that detoxification should be the most desired outcome for opioid dependent prisoners, and that prisons should be drug free [33, 66]. AOT is often perceived as simply replacing one drug for another and encouraging illicit drug use [33]. Discontinuation of AOT is a common occurrence for those entering prison [43, 52, 66]. Developments are slow and hampered by ambivalence among prison of-

ficials, doctors and staff, variation in health policies, difficulty in recruiting adequate numbers of suitably trained staff and restrictive criteria for eligibility [43, 65]. Extant research is unclear with regard to which pharmacotherapies are particularly suited to the prison population. Given the lack of evidence with regard to impact of pharmacotherapies in reducing preventable overdose deaths post-prison release, and with the expansion of prison drug treatment services, particularly in Europe, the increasing availability and use of long acting NLT and the rapid expansion of THN as a potential overdose prevention strategy, it is important that continued efforts to evaluate prison based pharmacotherapies be undertaken. The aim of the systematic review was to review existing scientific evidence and evaluate if prison based pharmacotherapies when provided pre-release improve post-release treatment retention and reduce post-release overdose.

2. Methods

A systematic review of studies on recently discharged opioid dependent prisoners receiving METH, BUP, LAAM, NLT and/or NLX was conducted. Factors of interest regarded post-release treatment retention, NFODs, overdose mortality rates, and continued heroin and/or other illicit drug use. Electronic searches using MESH terms and conducted on the following research databases: Cochrane Central Register of Controlled Trials, Medline, Embase, CINAHL and PsycINF0. MESH terms are presented in Table 1. Human studies (experimental randomised control and clinical trials, and observational cohort, case-control, and cross-sectional studies) were included with no restrictions placed on publication date or language.

Retrieved records included peer reviewed publications, other scientific publications (i.e. Scientific Monographs) and non-peer reviewed journals and grey literature (technical reports, conference papers, unpublished thesis). Additional hand searches were conducted on the reference lists of all selected articles, and by contacting experts (lead authors of all the included studies and lead authors of the previously completed systematic reviews of prison drug treatment and post-release overdose) (n=15) to enquire about their knowledge of other studies, published or unpublished relevant to this review. Inclusion criteria centred on studies reporting on prisoners with a history of opioid dependence or those deemed at risk of overdose on release from prison who were receiving AOT (METH, BUP, LAAM), NLT or a supply NLX at release; NLT and THN on release from prison, and measures relating to primary outcomes; treatment retention, NFODs, and overdose mortality, and secondary outcomes; continued use of heroin and other illicit drugs (self-reported and/or confirmed by biological markers).

For all studies that satisfied inclusion criteria data was extracted in a standardized format. Data was extracted by author, year, location, study design, intervention, study group, outcomes (primary and secondary), sample size, and follow up. A total of 357 articles were identified in the initial search phase. Of these, 286 were from Medline, 58 were from PsycINFO, eight from Embase and five from the Cochrane Central register for control trials and two additional articles were included from grey literature search. Of these 357 articles, 75 were found to be duplicates and were eliminated leaving 284 articles to be screened by title. Of these 284 articles screened, 120 were eliminated by title. The remaining 164 articles were reviewed by abstract and 140 were eliminated because they did not focus on the included pharmacotherapies and/or the primary outcomes of the systematic review. The final 24 articles were read in full text and two were excluded because the pharmacotherapies under review were not included, three were previous systematic reviews, one dealt with an offender residential unit and one dealt only with prisoner mortality while incarcerated. The PRISMA flowchart is presented in Figure 1.

The final 17 studies were cross-referenced against studies included in the previous systematic reviews to ensure potential studies had not been ex-

Table 1. MESH terms

Population - prison, inmate, parolee, opioid dependant, custodial, drug users, heroin users.
Intervention - overdose prevention, opioid agonist, antagonist, NLX, take home NLX, NLT, METH, BUP, opioid maintenance, agonist opioid treatment, LAAM.
Comparison - no treatment, other pharmacotherapy, psychosocial intervention only.
Outcome - overdose, death, mortality, treatment retention, effectiveness, drug related deaths.

METH=methadone, BUP=buprenorphine, NLX=naloxone, NLT=naltrexone,
LAAM= levo-alpha acetyl methadol

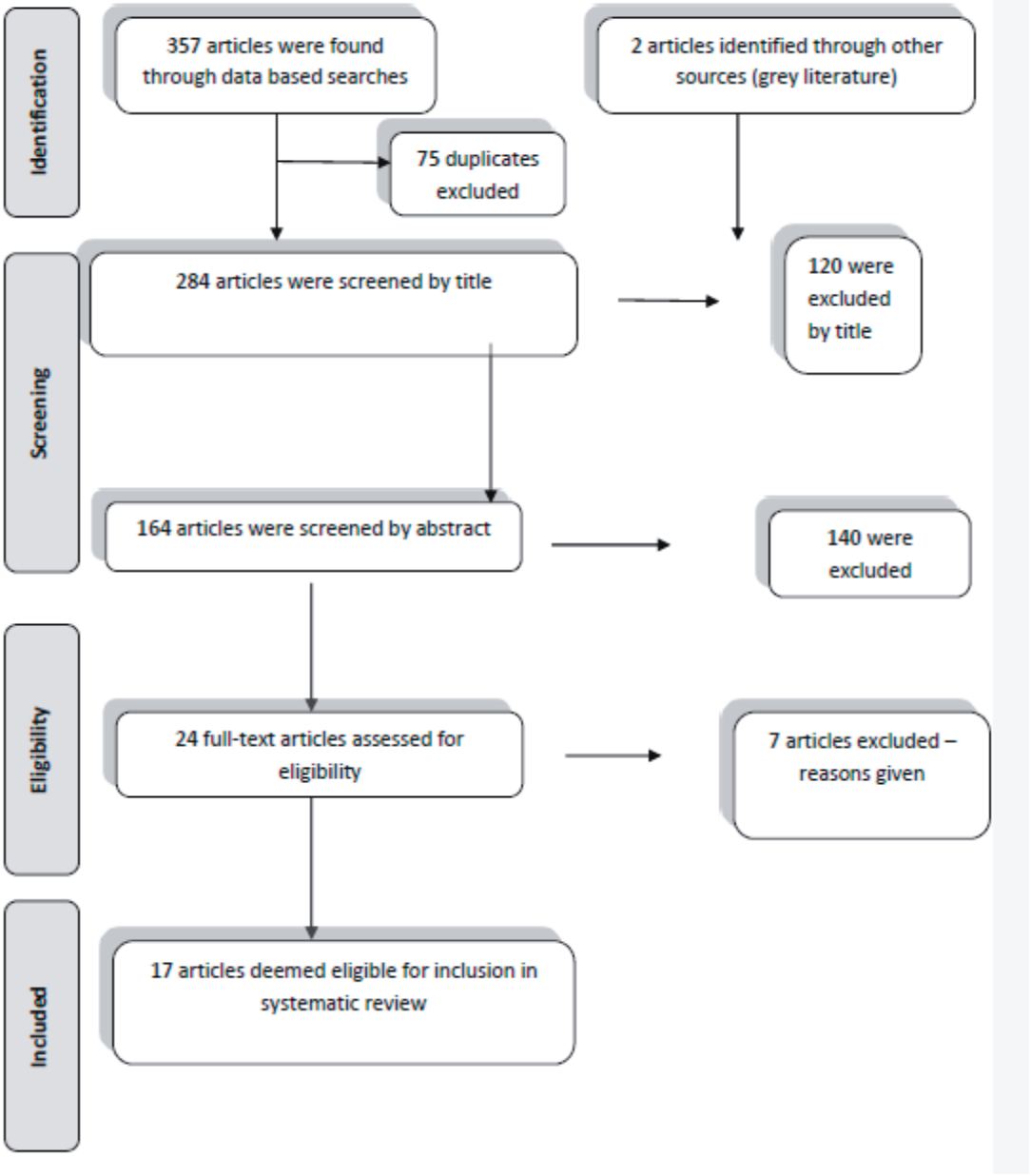

Figure 1. PRISMA flowchart

cluded. 11 of the 17 studies were randomised control trials (RCT)s. Of these four [27, 38-40] followed up the same sample of 211 patients at one, three, six and twelve months post-release; and were considered as one trial (one study entry). The remainder were one non randomised trial that arose from a feasibility study [75] and five observational studies. Eligible studies are presented in Table 2.

Quality, outcome and risk of bias assessments were applied across studies. Primary and secondary outcomes were compared in terms of no treatment versus other treatment (pharmacological or psychosocial), and synthesised per outcome in terms of number of studies reporting on each outcome with p values and effect sizes included (where available). Values of $p<0.05$ were considered a statistically significant outcome. Where appropriate, risk of bias was conducted across studies and at specific outcome level including whether the biases were considered likely to exaggerate or under-estimate any reported treatment effect. The risks of bias assessment pertained to selection, performance, detection, attrition, reporting and other sources of bias [31].

Table 2. Eligible Studies

Ref. No.	Author, Country	Date	Number	Intervention
	RCTs/ Clinical Trials			
1.	Dole et al., USA	1969	Male = 32	METH
2.	Kinloch et al., USA	2005	Male = 145	LAAM
3.	Kinloch et al., USA Gordon et al., USA	2007,2008,2009, 2008	Male = 211	METH
4.	Magura et al., USA	2009	Male = 113	BUP
5.	Lobmaier et al., Norway	2010	Male and female = 46	NLT
6.	McKenzie et al., USA	2012	Male = 90	METH
7.	Zaller et al., USA	2013	Male and female = 44	BUP
8.	Gordon et al.,USA	2014	Male and female= 213	BUP
9.	Lee et al., USA	2014	Male and female = 44	NLT
	Observational Studies			
10.	Magura et al., USA	1993	Male = 446	METH
11.	Dolan et al., Australia	2005	Male = 382	METH
12.	Garcia et al., Puerto Rico	2007	Male= 45	BUP
13.	Wicherrsham et al., Malaysia	2013	Male = 30	METH dose
14.	Degenhardt et al., Australia	2014	Male and Female = 16,453	METH and BUP (AOT)

METH=methadone, BUP=buprenorphine, NLX=naloxone, NLT=naltrexone, LAAM= levo-alpha acetyl methadol

3. Results

3.1. Characteristics of included studies

Overall, 14 studies (nine from the US; two from Australia, one from Malaysia, one from Norway, and one from Puerto Rico) involving a total of 18,277 individuals, 14,681 male and 3,596 females are presented in Table 3. Eight RCTs were included involving 877 individuals, 808 males and 69 females. Seven were from the USA and one was from Norway. One non-randomised trial was from the USA, involving 44 individuals, 37 males and seven females. Five observational studies involved 17,356 individuals, 13,836 males and 3,520 females. Two observational studies were from the United States (US), one from Australia, one from Puerto Rico and one from Malaysia. Pharmacotherapy interventions and comparisons were as follows. See Table 3;

- METH (experimental) vs. no pharmacotherapy +/- community referral (n=6)
- LAAM vs. no pharmacotherapy+ referral information (n=1).
- BUP vs. no pharmacotherapy +/- community referral (n=2)
- AOT (METH and BUP) vs. no pharmacotherapy (n=1)
- NLT vs. no pharmacotherapy (n=1)
- BUP vs. METH (n= 1)
- NLT vs. METH (n=1)
- METH ≥ 80mg versus METH < 80mg (n=1).

3.2. Synthesis of primary outcomes

3.2.1. Treatment Retention

Syntheses of results indicate that initiation of OSTs (METH, BUP, or LAAM) in prison prior to release had a significant impact on post-release treatment retention. The range for METH was 69%- 86%, BUP was 48%- 92% and LAAM was 95%. All studies reporting on treatment retention as outcome showed a significant difference in the numbers attending community treatment immediately post-release between those on AOT compared with those not on AOT [20, 27, 37, 38, 51, 56, 75]. Six of the eight studies showed this difference to be statistically significant ($p<0.05$). See Table Four.

Treatment retention and days in treatment at three, six and twelve months follow-up were also better in the pre-release treatment groups [20, 27, 37, 39, 40, 51, 75]. In studies that divided the non-treatment control into those with a structured refer-

Table 3. Characteristics of Included Studies

Ref No.	Study Design	Medication	Study Group	Specific Outcomes	Sample n	Follow up
1.	RCT	METH	Heroin dependent pre-release prisoners (male)	Treatment retention (primary). Heroin use (secondary)	32	7-10 months
2.	RCT	LAAM	Heroin dependent prerelease prisoners (male)	Treatment entry and treatment retention (primary). Heroin use (self report)(secondary)	145	9 months
3.	RCT	METH	Heroin dependent prerelease prisoners (male)	Treatment entry/retention (primary). Mortality (primary). Opioid urinalysis (secondary). Heroin use self report (secondary).	211	1, 3, 6, 12 months
4.	RCT	METH vs BUP	Opioid dependent short term prisoners (male)	Treatment entry (primary) Heroin use (self report) (secondary)	133	3 months
5.	RCT	NLT vs METH	Pre-release heroin dependent at least 2 months sentence time remaining (male and female)	Treatment retention (primary). Drug use/ self report at 6 months(secondary)	46	6 months
6.	RCT	METH	Pre-release opioid dependent prisoners (male)	Treatment retention (primary) Non fatal overdose (primary) Mortality (primary) Heroin and drug use (self report) (secondary)	90	2 weeks 6 months
7.	Feasibility-clinical trial	BUP	Opioid dependent prisoners (male and female)	Treatment retention (primary)	44	6 months
8.	RCT	BUP	Non opioid tolerant with heroin dependence histories (male and female)	Enter community treatment (primary)	213	10 days post-release
9.	RCT	NLT	Opioid depend patients not seeking AOT	Opiate relapse at week 4 self report and urine toxicology (secondary)	29	4 week
10.	Prospective cohort	METH	Daily heroin users -admitted for short sentences (male)	Treatment entry/treatment retention (primary) Drug use (self report) (secondary)	446	6.5 months
11.	Case control	METH	Opioid dependent prisoners in earlier trial in 2003 (male)	Mortality (primary).	382	48 months
12.	Prospective cohort	BUP	Opioid dependent pre-release prisoners (male)	Heroin use (self report) (secondary). Morphine drug screen (secondary).	45	1 month
13.	Prospective cohort	METH dose	Opioid dependent HIV positive patients (male)	Treatment retention (primary)	30	4 months
14.	Retrospective cohort	METH and BUP (0ST)	Opioid –dependent people entering AOT and released form prison at least once during 2000-2012 (male and female)	Post –prison release mortality (primary)	16, 453	1 week, 4 weeks, 12 months

METH=methadone, BUP=buprenorphine, NLX=naloxone, NLT=naltrexone,
LAAM= levo-alpha acetyl methadol

Table 4. Treatment Retention

Ref No.	Outcome	Intervention	Study type	Outcome	Positive outcome at p < 0.05	Comments	Possible impact of bias on treatment effect (from on Table 4)
1.	Treatment retention	METH versus referral or no treatment	RCT	Experimental (75%) vs. (0%) control retained in treatment at 6months		Statistical analysis not done on outcomes	None
3.				1 month experimental (68.6%) vs. control (8%) and (50%) 3 months (69%) vs. (8%) (50%) Number of days in treatment at 6 months (100) vs. (14) (58) 12 months (166) VS. (23) (91)	P= < .05 p < 0.0001 P< 0.0001 P<.002	Small sample	Relatively little
6.				Experimental group (86%) vs. control (41%) and (22%) Experimental group entered treatment within a shorter period of time (3)days vs. (9) and (5) days	P < 0.001 P=0.03	Small sample	None
10.			Observational	AOT in prison > entry into the community (85%) vs. (37%) Treatment retention at 6 months (27%) vs. (9%)	P< 0.01 P< 0.01	cohort	Underestimate
2.	Treatment retention	LAMM versus no treatment	RCT	Immediate post-release treatment retention (95%) vs. (10%) and (8%) 6 month retention treatment post (53 %) vs. (0%)	P< 0.01	No analysis at 6 months	Unclear
8.	Treatment retention	BUP versus no treatment	RCT	48/101(47.5%) entered community treatment in in-prison group compared to 43/101 (33.7%) of counseling only treatment.	P= 0.01	Small study, Included females	None
7.			Non-randomised trial	(92%) in prison treatment vs. (78%) of referral outside. Average days to entry were (3.2) vs. (9.2.) 6 month Treatment retention (83%) vs. (34 %.) Weeks retained in treatment (20) weeks vs. (13) weeks	P=0.3 P= 0.10 P=0.005 P=0.05	Non-randomised. Small numbers	None
12.			Observational	(85%) of in-prison treatment entered community treatment post-release.		Treatment only	None
13.	Treatment retention	METH dose	Observational	≥80mg on release, 6 month follow up (61.5%) vs. (21.4%), One month attrition <80mg, (64%) vs. (15.4 %)	P<0.01	No p value for attrition	None
4.	Treatment retention	BUP versus METH	RCT	BUP (48%) vs. METH (14%). Intended to continue treatment BUP (93%0) vs. METH (44%)	P<0.001 P< 0.001	Small numbers	None
5.	Treatment retention	NLT versus METH	RCT	6 month NLT (69.6%) vs. METH (23.8%)	P= 0.003		

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LAAM= levo-alpha acetyl methadol

ral post-release and those without showed better outcomes in the structured referral group [27, 38-40]. BUP showed better outcomes than METH for immediate post-release retention with retention rate of 48% for BUP and 14% for METH (p< 0.001) [53]. NLT had better outcomes than METH at six months

Table 5. Non-Fatal Overdose (NFODs)

Ref	Out-come	Intervention	Study type	Outcome	Positive outcome at $p < 0.05$	Comments	Possible impact of bias on treat-ment effect (from on Table 4)
6.	NFODs	METH versus no treatment	RCT	8/ 62 experienced non-fatal overdose- occurring across all arms.		Small num-bers, self report,	underestimate
7.		BUP versus no treatment	Non ran-domised trial	3/36 – all in the no tx pre-release	P=0.23	Small num-bers	underestimate

METH=methadone, BUP=buprenorphine, NLX=naloxone, NLT=naltrexone, LAAM= levo-alpha acetyl methadol

follow up with 70% still in treatment compared to 24% of the METH control group (p=0.003) [50]. The only study reporting on METH dose showed less than one month's treatment attrition in those receiving ≥80mg and a statistically significant differences in six month's treatment retention for those on higher doses (p<0.01) [71]. One observational study [51] showed that receiving METH in prison increased community treatment entry compared to those not on AOT (85% vs. 37%) (p< 0.01) reducing significantly at six

Table 6. Overdose Mortality

Ref	Out-come	Interven-tion	Study type	Outcome	Positive outcome at $p < 0.05$	Comments	Possible impact of bias on treatment effect (from on Table 4)
3.	Over-dose deaths/ mortal-ity	METH versus no treatment	RCT	One overdose death in the no treatment group at one month, 8 deaths at 12 months. 7 in the no treatment groups, 4 overdoses and 3 others. The overdose death in treatment group was cardiovascular related.		Small numbers	No effect
5.				No deaths at 6 months follow up for 41/44 followed up patients		Small numbers, Pre-treatment dropout	None
6.				2 died of drug overdose within days of release in no treatment control group			
11.			Observa-tional	17 deaths all while not in treatment. No difference between those initiated onto AOT in prison and those not.		4 year follow on RCT	None
14.		AOT (METH and BUP)	Observa-tional	AOT in (51%) of releases-AOT post-release 4 week CMR = (6.4 per 1000 PY, CI= 5.2- 7.8). No AOT CMR = (36.7 per 1,000 PY CI= 28.8- 45.9) reduced by 75%. Short term protective factor.	No p value but sta-tistically signifi-cant.	Large –data linked almost 100% follow up	Low risk- large population based study/good general-izability
4.		BUP vs. no treat-ment	RCT	No reported deaths at 3 months follow up.		Descriptive-small study size	No effect

METH=methadone, BUP=buprenorphine, NLX=naloxone, NLT=naltrexone, LAAM= levo-alpha acetyl methadol

months (27% vs. 9%) (p<0.01).

3,2,2, Non-fatal overdoses (NFOD)

This outcome was only reported in two of the included studies (Table 4). McKenzie et al. [56] reported that 14% of those included in the study experienced NFODs on release and found that these were distributed evenly across those receiving METH on release and those in the referral for treatment group. Zaller et al. [75] showed that 8% of the study group reported at least one episode of NFODs post-release and all of these were not on BUP treatment at the time of release. On analysis this was not found to be statistically significant (p=0.23). See Table 5.

3.2.3. Overdose Mortality

This primary outcome was reported in six of the included studies. Kinlock et al. [38] reported one overdose death in the no treatment group in the first month post-release, and reported eight deaths at 12 months. 50% of these deaths were overdose related and all occurred in the no treatment arm of the study [40]. The other deaths in this group were cardiovascular and HIV related. The single death in the treatment group was cardiovascular in nature. McKenzie et al. [56] reported two deaths immediately post-release in those not receiving METH. Dolan et al. [19] reported 17 deaths at four years follow up, none receiving METH at the time of their death and this was independent of having received METH at the time of release from prison. Degenhardt et al. [16] found a statistically significant difference in four week post-release crude mortality ratio (CMR) between those on AOT and those not on AOT, with AOT reducing it by 75% (AOT 4 week CMR= 6.4 per 1000 PY, CI=5.2-7.8, no AOT CMR = 36.7 per 1000 PY, CI = 28.8-45.9). See Table 6.

3.3. Synthesis of Secondary Outcomes

3.3.1. Continued use of heroin and other illicit drugs

Four studies reported on post-release heroin use in the METH vs. no METH group. These showed a significant reduction in heroin use both by drug screen and self-report at one month follow up (p<0.05) but this effect reduced over three, six and 12 months and became statistically not significant (ns.) [20, 27, 38-40 51, 56]. Two studies showed differences in self-report heroin use for both BUP vs. no BUP or BUP vs. METH but these differences were not statistically significant [53,75]. For the NLT vs. no pharmacotherapy, four-week post-release opioid relapse rates were significantly lower among the experimental group: 36% vs. 87% (p < 0.02) [44]. There was limited data available on other drug use both for self-report and drug screen. Kinlock et al. [38, 40] reported on cocaine use (drug screen and self-report) and found less cocaine use in the METH group vs. the control (45% vs. 65%); however this difference was not statistically significant. This was similar at three, six and 12 month follow-up. McKenzie et al. [56] also found reduced cocaine use in the METH group (19% vs. 67%) (p= 0.05). See Table 7.

3.4. Assessment of Quality

Quality was assessed as good in five studies [16, 20, 28, 38, 53], adequate in six [37, 50, 51, 56, 71, 75] and inadequate in two [19, 26]. See Table 8.

Selection bias: Randomisation: all included trials were described as randomised. Lee et al. [44] (RCT) was not included for risk of bias assessment since only data from an abstract was available for inclusion. Tables 8 and 9. Only in one of the RCTs [19] was the randomisation process not described (rated unclear). Two studies [53, 50] reported that the allocation process was concealed (low risk). The remaining five were rated as unclear. In six studies baseline data between the control and experimental data were comparable. In Kinlock et al., [37] group comparability was unclear since many of those randomised to the experimental arm withdrew and were added to the control arm. Logistic regression analysis controlling for baseline between the group differences was used when testing outcome between groups.

Performance and detection bias: Blinding was assessed across four dimensions considering performance and detection bias across subjective and objective measures. Six studies were rated as unclear as providing no information on blinding across all domains. Lobmaier et al. [50] was considered high risk of bias for participant and performance blinding.

Attrition bias: Three of the seven studies dealt with incomplete data and were rated as low risk [20, 28,38]. Magura et al. [53] was rated as unclear as the loss to follow up may have overstated treatment. Kinlock et al. [37] was rated as high risk as follow up groups were not comparable due to high attrition, especially in the experimental group after randomisation and before treatment. The original design was revised in this study and analysis controlled for baseline differences between the groups. Four of the studies included did not carry out intention-to-treat analysis [20, 28, 37, 53].

Table 7. Continued use of heroin and other illicit drugs

Ref	Out-come	Intervention	Study type	Outcome	Positive outcome at p < 0.05	Comments	Possible impact of bias on treatment effect (from on Table 4)
3.	Heroin Use - Drug Screen	METH versus no treatment	RCT	1 month Urine positive for morphine METH (28%) vs. control (41%) and (63%) 3 months ,39%, 39%, 48%, 6 months 65%, 48%, 28%, 12 months odd ratio (OR) 0.57 vs. 4.046 vs. 7.07	P< 0.05 n.s. P= 0.002 P<0.01 and P<0.001	Small size, loss to follow up in non-treatment group	None
1.	Heroin use – Self Report	METH versus no treatment	RCT	METH 0/12 re-addicted, 10/12 intermittent, 2/12 none vs. control 18/20 re-addicted.	P= 0.008	Patient records	underestimate
3.				One month experimental (40%) vs. (39%) and (60%), 3 months (55%) vs. (60%) and (77%), 6months (86) days vs. 49 days, 12 month (106.2) vs. (120.7) vs. (167.1)	P< 0.02 P= 0.014 P=0.009		underestimate
6.				(14%) of pre-release treatment groups relapsed vs. (56%) and (44%)	P = 0.008	As treated n.s	
7.		BUP versus no treatment	Non-randomised trial	None in the pre-release group, heroin 23.1% of the post-release group reported heroin use	P=0.08		Underestimate
4.		BUP vs. METH	RCT	Heroin or non prescribed opiate use: BUP (53%) vs. METH (66%)	n.s.		
9		NLT vs. no treatment	RCT	NLT vs. no AOT, 4 week follow up for opioid relapse (36%) vs.(87%)	p < 0.02	Preliminary findings on only 29	unsure
3.	Other drugs – Drug Screen	METH versus no treatment	RCT	One month for cocaine use 45% vs. (65%), 3 months (42%) vs. (39%) and (65%),	n.s. n.s.		
6.		Other Drugs – Self Report	RCT	Cocaine use at 6 months: control (19%) vs. (41%) and (67%)	P=0.05		underestimate

METH=methadone, BUP=buprenorphine, NLX=naloxone, NLT=naltrexone, LAAM= levo-alpha acetyl methadol

Reporting bias: Unclear reporting of the methodology was evident in six of the studies. Kinlock et al. [37] was assessed as high risk due to the extensive lack of information provided regarding those who dropped out. Of the original 145 randomly assigned only 64 were followed up, with 55% attrition in the experimental arm.

Other potential sources of bias: All seven were rated high as regards other potential sources of bias.

3.4.1. Assessment of the Quality of Non-Randomised Trials

Quality assessment of the one non-randomised trial [75] was conducted using Transparent Reporting of Evaluations with Nonrandomized Designs (TREND). Zaller et al. [75] arose from a feasibility study with an experimental study occurring due to the non-availability of BUP for those enrolled in the early part of the study. Whilst not randomised, both

Table 8. Risk of Bias Assessment for RCTs

Ref. No.	Sequence generation adequate	Allocation concealment	Baseline data/selection basis	Incomplete outcome data adequately addressed	Intent to treat analysis	Other limitations discussed by authors
1.	Yes – allocation by lottery Risk = low	Unclear Risk = unclear	Groups comparable Risk = low	Yes – no missing data on outcomes. Risk = low	No	Small sample size, no urine drug screens available on controls. Risk = high
2.	Unclear Risk = unclear	Unclear Risk = unclear	Unclear: baseline data only given for follow up group Risk = unclear	Follow up group's not comparable, high drop out by experimental group post-randomisation and pre treatment. Study design revised to include this. Those who withdrew before treatment were allocated to the experimental group. Analysis controlled for baseline difference. Risk = low	No	Small sample, males only, one site and urine drug screens and treatment records only available for the experimental arm. Risk = high
3.	Yes - block randomisation Risk = low	Unclear Risk = unclear	Groups comparable Risk = low	Yes –high follow up rates for all groups. Risk = low	Yes	Male only, one jurisdiction. Risk = high
4.	Yes- block randomisation Risk = low	Yes- allocation process was concealed Risk = low	Groups comparable Risk = low	Significant pretreatment drop out in the control group and in post-release follow up. Risk = high	Yes	High dropout rates in METH group, small number of participants, urine drug screens not available, large amount of inmates chose not to be considered for the trial. Risk = high
5.	Yes – random number generator Risk = low	No Risk = high	Groups comparable Risk = low	Unclear – loss to follow up may overstate treatment effect- likely to similar for experimental and control arm. Risk = unclear	Yes	Male only, one site, and suboptimum doses of METH. Risk = high
6.	Yes-computer generated random permutation Risk = low	Unclear Risk = unclear	Groups comparable Risk = low	70% follow up at 6 months, no significant differences found between follow up groups Risk = high	Yes	Self report for drug use, standard of care changed mid-study with two of the control arms becoming one, restrictive inclusion criteria. Risk = high
8.	Yes – block randomisation Risk = low	Unclear Risk = unclear	Groups comparable Risk = low	95 % follow up post-release Risk = low	No	Single location-reduced generalizability/restrictive exclusion criteria/ small numbers of female prisoners/geographical barriers to accessing community treatment not addressed

experimental and control groups were comparable at base line. The control arm was much larger than the experimental arm (32 vs.12) but had 25% attrition at six month follow up. While not impacting on the outcome of treatment retention outcomes may have underestimated NFODs and continued use of heroin and other illicit drugs in the control group and the treatment effect of BUP on these outcomes. See Table 9.

3.4.2. Assessment of the Quality of Observational Studies

The quality of observational studies was as-

Table 9. Risk of Bias for Non Randomised Trials

Ref. No.	Sequence generation adequate	Allocation concealment	Baseline data/ selection basis	Incomplete outcome data adequately addressed	Intent to treat analysis	Other limitations discussed by authors
7.	No – arose from feasibility study	No	Groups comparable	82% follow up at 6 months. More loss to follow up in referral group. No analysis done on loss to follow up group.	No	Small sample size, no data on those who refused to participate, single site, reliance on self report for drug use.
	Risk =high	Risk = unclear	Risk = low	Risk = unclear	Risk = high	Risk = high

sessed using a checklist of preferred reporting items for systematic reviews (PRISMA statement) [45]. See Table 10.

3.4.3. Bias across Studies

The inclusion of randomised, non-randomised and observational studies made the assessment of bias across the studies difficult. Bias across the included experimental studies arose mainly from: treatment dropout post-randomisation and allocation, failure to describe the methodology for the blinding of outcome assessor and the management of incomplete data and dropout both from participants and, particularly, from those who dropped out at the allocation phase. In the observational studies systematic bias may have occurred if those receiving the pharmacological interventions had more severe dependence than those not receiving the intervention and may then underestimate the effect of the pharmacotherapy cumulatively across the studies. This may have occurred on three of the included observational studies, since no description is included on the baseline difference between cohort and controls [16, 26, 51]. The difference in variables such as age, HIV status and history of mental illness may also have impacted negatively on outcomes. For both experimental and observa-

Table 10. Quality of Observational Studies

Ref No.	Methodology explained	Inclusion criteria described	Variables defined	Number of individuals at each stage reported/ descriptive data	Main results clearly presented	Follow up rate	Limitations/bias discussed by authors	Evaluation of bias/limitations
10.	Yes	Yes	Yes	Yes	Yes	AOT = 67% Detox = 47%	Pre–study differences between groups and controls (adjusted for statistically), loss to follow up bias, poor records for community follow up group.	Non response bias (no important base line differences in interviewed versus not interviewed; lower treatment contact rates for not interviewed) may understate treatment effect.
11.	Yes	Yes	Yes	Yes	Yes	Mortality 100%	No data available for drug use.	Study is a follow up study of almost 4 years, so doesn't reflect the effect of post-release from pharmacotherapy.
12.	Yes	Yes	Yes	Yes	Yes	Overall 93%	Feasibility rather than outcome study, no control group, small sample size, short follow up.	Selection bias: significant pre-incarceration differences between groups, higher levels of heroin use and injecting in those completing treatment

Table 10. Quality of Observational Studies

Ref No.	Methodology explained	Inclusion criteria described	Variables defined	Number of individuals at each stage reported/ descriptive data	Main results clearly presented	Follow up rate	Limitations/bias discussed by authors	Evaluation of bias/limitations
13.	Yes	Yes	Yes	Yes	Yes	Not relevant Only looking at treatment retention.	Small sample size, male only, one site.	Very restrictive entry criteria limiting its generalizability. No analysis of difference between groups which may have affected both dose and retention outcomes.
14.	Yes	Yes	Yes	Yes	Yes	100%	Inconsistencies may arise from data linkage process because two different agencies involved, unable to indentify unexpected releases that may have been released without a prescription, unable to determine differences in characteristics between those entering/not entering AOT post-release.	Very large data linkage study with almost 100% follow up, very low risk of bias related to mortality outcome. No randomisation bias since entire population included. High generalizability.

tional studies, the small numbers of female prisoners, the exclusion of prisoners with severe mental health problems, the unique post-release arrangements and the preponderance of studies from the USA reduces their generalizability to other jurisdictions and the general prisoner population.

Loss to follow up is a major problem in prison-based research where post-release outcomes are being researched. Losses to follow-up tend to have more negative outcomes than those who are followed-up and this may impact on findings. The primary outcomes of retention in treatment or post-release mortality (if national death register is used) should not be affected by loss to follow-up but all other outcomes may be affected. The use of intention-to-treat analysis in RCTs reduces this potential source of bias but may negatively affect some outcomes if the assumption is made that those lost to follow-up have relapsed. Failure to conduct intention-to-treat analysis could underestimate the treatment effect. Response bias of self-reported data (due to social acceptability) is also possible for the primary outcome of NFODs and the secondary outcome of continued use of heroin and other illicit drugs. The small sample size in all the RCTs and in most of the observational studies may limit the studies' ability to assess differences between the study groups.

4. Discussion

The review investigated effectiveness of commonly used pharmacotherapies in treating opioid dependence in prisons in relation to treatment retention, levels of NFODs and mortality rates; and continued heroin and other illicit drug use in different post-release timeframes. Factors complicating the interpretation of the effectiveness of pharmacotherapy interventions and their impact on post-release overdose mortality centre on the wide regional differences in post-release overdose rates which are accounted for by difference in prison populations studied, loss of follow-up, local variation in heroin purity, regional variation in drug injecting versus non-injecting routes, regional difference in poly-drug use (particularly benzodiazepines and alcohol), differences in availability and type of community treatment.

Limitations of the review centred on the following. Most studies included in this systematic review had small numbers, excluded female prisoners and those with a history of major mental illness. Most

had limited geographical variation (the majority were USA based) and they did not evaluate the effect the transfer of care process itself or community treatment had on the studies' outcomes. Most of the included studies had important methodological shortcomings. Given the difficulties in conducting experimental studies in the prison population, particularly when community follow-up is required, the inclusion of both experimental and observational studies increased the available evidence to draw conclusions from, but limited the synthesis of data on outcomes. The inclusion of observational studies significantly increased the population of prisoners included in the systematic review. The synthesis of data was also impeded by the heterogeneity of the included studies and the unique design of many of the RCTs even made synthesis across RCTs difficult. A notable limitation of this review is that only one study compared different types of AOT therapies [53]. The increasing evidence for the effectiveness of AOT in prison, on release and in the community makes it increasingly difficult to conduct prison-based RCTs which, by their design, involve withholding treatment to a cohort which fit the criteria for AOT. The limited use and the lack of research in prison populations for both NLT and NLX, mean that these could still be considered experimental or novel approaches to opioid dependence treatment in pre-release prisoners, particularly for those who wish to be drug-free on release or those with a history of injecting.

Findings underscore that AOT (METH, BUP, LAAM) initiated pre-release was associated with significant post-release treatment retention on discharge into the community, and post-release reduction in heroin use. Unfortunately no study compared AOT for the period of incarceration with AOT initiated pre-release. Prisoners on AOT at release were more likely to attend community treatment compared to prisoners not on AOT but with a referral to community treatment organised post-release [20, 53]. This improved retention was shown immediately post-release and was retained at one month, three months, six months and twelve months [27, 39, 40]. All of the agonist pharmacotherapies reviewed showed similar results for improved retention when compared to no AOT on release but, interestingly, prisoners released on BUP reported to their designated post-release community placement significantly more often than those on METH [53]. These differences could be explained by the less restrictive and flexible community-based BUP programmes compared with highly regulated METH programmes requiring daily attendance and full supervision of medication. Release from prison is a stressful and busy period for the former inmate and daily attendance for pharmacotherapy is one of many competing needs and one which is difficult to maintain [43]. Attempted diversion of BUP among prisoners while incarcerated was reported in one study [28] and is a weakness in the widespread use of this medication as a prison based AOT. The success of both LAAM and BUP in treatment retention increase AOT options for pre-release treatment [37, 28, 53]. The long-acting nature of LAAM gives a further 24-48 hour time frame for patients to engage with community services before experiencing withdrawal. Given the increasing concerns related to METH's effect on the QT interval and the increased risk assessment and cardiac evaluation of patients before starting METH replacement treatment (MRT), it may be timely to review the utility of this forgotten AOT. The ability to double-dose prisoners with BUP could be utilised to extend the timeframe (48 hours) for prisoners to attend community AOT services which may have a further positive impact on treatment retention. The impact of requiring medical insurance for on-going treatment is a factor addressed in a number of the US studies [28, 75]. It is noted that this is not an issue in Europe or Australia where drug treatment services are largely publicly funded.

In terms of additional therapeutic supports, the recent development of long-acting NLT formulations is an exciting option in the use of antagonist pharmacotherapy in pre-release prisoners, particularly for those who choose to undergo detoxification and wish to remain drug abstinent on release. NLT achieved higher treatment retention than METH at six months follow up (70% vs. 24%) (p=0.003) and is showing a promising reduction in one month post-release drug use when compared to no pharmacotherapy in preliminary results from a recently completed RCT [44]. While these results are promising, NLT should be used in a context of augmenting existing AOT services and not as an alternative. Patient choice had a major impact on acceptance of this treatment option [50]. The pharmacodynamics of the slow-release formulation ensures treatment retention and overdose protection for the duration of its effectiveness (3-6 months) but delayed treatment fallout and overdose can occur once its antagonist effect wears off [10,17]. The long-acting formulations allow for immediate protection in the early post-release phase and for a comprehensive community-based relapse prevention programme to be put in place, which may also include continuation of NLT therapy.

The review identified a paucity of significant data on NFODs. Internationally there is an incidence of NFODs of between 25%-50% among IDUs with a history of incarceration [35, 36] and a previous history of NFODs in associated with increased risk of future overdose (fatal and non-fatal) [13, 36]. Any overdose prevention strategies should target this increased risk group particularly in jurisdictions where AOT and other drug treatment resources are limited. Prisoners on BUP or METH on discharge had significantly reduced mortality risks in the immediate four weeks post-release. Of interest is that no NFODs were reported by those on BUP which may support its potential to be safer than METH in overdose situations because of the ceiling effect on respiratory depression. This review did not identify any data on the use of THN in prisoners released into the community since no studies were found that satisfied the inclusion criteria. The EMCDDA [21] and World Health Organisation [73] recommend a number of interventions to reduce post-release overdose deaths. These include: pre-release education on overdose risks and prevention, continuation of, and initiation of, replacement treatment and improved referral to aftercare and community services. There was evidence that AOT on release had a positive impact on post-release drug use with significant reductions in heroin use (both on self-report and drug screens) compared to those not receiving AOT [20, 38, 75] . These follow-up periods ranged from one to twelve months. NLT also showed reduced heroin use in a four week post-release follow up compared with those receiving no pharmacotherapy [44].

5. Conclusions

There is evidence that AOT (dose dependent) is effective in reducing heroin use, injecting and syringe sharing while in prison and that it increases retention in post-release treatment where arrangements are in place for its continuation in the community. The considerable excess mortality risk in the two-four weeks on post-release following cessation of prison based-treatment indicates that any disruption to treatment needs to be carefully considered and detoxification from AOT should include relapse prevention and overdose management techniques. Prisoners should ultimately be afforded the same quality and level of care that is available in the community [46]. Also given the benefits of continuity of treatment and the difficulties with re-induction of low or non-tolerant patients, particularly with METH [28, 38, 56], there is also a strong argument for the continuation of AOT in prison. Given the heterogeneity of the prison population and their complex medical and social needs, different pharmacotherapies may be more effective in different prisoner groups and those with a higher risk of overdose (mental illness, previous suicide attempts, history of drug use, female prisoners) may require different approaches to treatment provision. Further research is warranted.

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Contributors

DC designed the study and wrote the protocol, managed the literature searches and analyses, undertook the statistical analysis. MCVH wrote the first draft of the manuscript. The authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest

The authors have no conflict of interest.

Ethics

This study does not require ethics committee approval because is a systematic review.

Note

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