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Comparison of methadone and buprenorphine for opiate detoxification (LEEDS trial):

a randomised controlled trial

Abstract

Background

Many opiate users require prescribed medication to help them achieve abstinence, commonly taking the form of a detoxification regime. In UK prisons, drug users are nearly universally treated for their opiate use by primary care clinicians, and once released access GP services where 40% of practices now treat drug users. There is a paucity of evidence evaluating methadone and buprenorphine (the two most commonly prescribed agents in the UK) for opiate detoxification.

Aim

To evaluate whether buprenorphine or methadone help to achieve drug abstinence at completion of a reducing regimen for heroin users presenting to UK prison health care for detoxification.

Design

Open-label, pragmatic, randomised controlled trial in three prison primary healthcare departments in the north of England.

Method

Prisoners (n = 306) using illicit opiates were recruited and given daily sublingual buprenorphine or oral methadone, in the context of routine care, over a standard reduced regimen of not more than 20 days. The primary outcome measure was abstinence from illicit opiates at 8 days post detoxification, as indicated by urine test (self-report/clinical notes where urine sample was not feasible). Secondary outcomes were also recorded.

Results

Abstinence was ascertained for 73.7% at 8 days post detoxification (urine sample = 52.6%, self report = 15.2%, clinical notes = 5.9%). There was no statistically significant difference in the odds of achieving abstinence between methadone and buprenorphine (odds ratio [OR] = 1.69; 95% confidence interval [CI] = 0.81 to 3.51; P = 0.163). Abstinence was associated solely with whether or not the participant was still in prison at that time (15.22 times the odds; 95% CI = 4.19 to 55.28). The strongest association for lasting abstinence was abstinence at an earlier time point.

Conclusion

There is equal clinical effectiveness between methadone and buprenorphine in achieving abstinence from opiates at 8 days post detoxification within prison.

Keywords

opiate substitution treatment; prison; randomised controlled trial.

INTRODUCTION

Around 75 000 drug users with complex problems enter the UK prison estate per year, with up to 80% of offenders testing positive for class A drugs on arrival.[1] Class A drugs include heroin, crack, and cocaine. Those addicted to illicit opiates such as heroin require medical help in reducing and stopping their use.[2] When entering prison, they are typically offered pharmacological interventions, such as an opiate maintenance or detoxification.[3] Detoxification is 'a clearly defined process supporting safe and effective discontinuation of opiates while minimising withdrawals',[4] while maintenance is 'suitable for patients who want to stop using illicit opioids but are unable to achieve abstinence from all opioids'.[5] The value of maintenance prescribing in the community is well established,[6,7] and there is an evolving evidence base for its use in prison.[8–10] Many drug users express a wish to detoxify from opiates while in prison,[11,12] and it is within this context that this research was undertaken.

Drug users are nearly universally treated for their opiate use within a primary care setting in the prison, and primary care clinicians are employed widely within the prison estate. In 2006, the Department of Health, via primary care trusts, was devolved of all responsibility for the health care of prisoners — previously it had been provided by the Prison Service — in order to bring the standards of primary care for prisoners to the equivalent standards that patients received in the community.[13] Since 2006, prisoners accessing health care are now viewed as general practice patients.

Over the last decade there has been a significant increase in the numbers of GPs in the community who will treat drug users,[14] with almost 40% of practices now involved, highlighting a rise of 25% in just 5 years.[15] Fifty per cent of all GPs practising in the community will have seen a drug user in the preceding month, and half of these will have offered a prescription for the treatment of drug misuse.[16]

As most prisoners are eventually released from prison, it is important that GPs are informed of the evidence base surrounding detoxification. This has become particularly pertinent, as a recently published survey of GPs practising in Scotland and offering treatment to drug users found that there had been a drop from approximately 40% to 25% in GPs offering short-term community detoxification and referral to residential services.[17]

In the past, no 'drug of choice' for opiate detoxification in UK prisons was stipulated and the decision was left to the discretion of the prescribing clinician,[11,12] resulting in a variety of agents being used, including methadone, dihydrocodeine, buprenorphine, lofexidine, and clonidine. Prior to the mid-

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How this fits in

Although almost 40% of GPs are now involved in the treatment of drug users, and almost all drug treatment in prisons is delivered in primary care, there is a scant evidence base on which to guide GPs as to which detoxification agents to use. This randomised controlled trial conducted in the primary healthcare departments of three UK prisons shows equal effectiveness between methadone and buprenorphine. As far as the project team are aware, this is the only randomised controlled trial of a medicinal product — in any specialty — conducted in the UK prison estate in the past decade.

2000s, the most commonly used drug was dihydrocodeine. There was a move away from prescribing dihydrocodeine due to diversion potential in the prison shadow economy (because of the number of tablets required to cover withdrawal). In line with community prescribing, buprenorphine has been increasingly prescribed, in the form of sublingual tablets.[18] Despite previous reluctance to prescribe methadone, following a small number of methadone-related deaths in custody, policy initiatives in 2004 recommended increasing its provision within UK prisons,[19] and it was reintroduced into the estate. Subject to clinician discretion, buprenorphine or methadone are now recommended as first-line agents for prisoners requesting opiate detoxification.[3]

This research was undertaken in response to a need to evaluate the first-line agents for detoxification in UK prison-based primary care services, given the paucity of empirical evidence comparing the effectiveness of methadone with buprenorphine for detoxification. The authors are aware of only six published studies.[20–25] A Cochrane Review of buprenorphine detoxification and maintenance studies concluded that completion of withdrawal treatment is possibly more likely when managed with buprenorphine compared to methadone.[26] However, the difference was not statistically significant and no data were reported on post-detoxification outcomes, leading the authors to conclude that more research was needed to evaluate possible differences in effectiveness between the two medications.

METHOD

Study design and randomisation

The study was a pragmatic, open-label, randomised controlled trial (RCT), comparing sublingual buprenorphine and oral methadone (see Figure 1 for CONSORT diagram).

A blinded study would have necessitated commercial funding to develop dummy preparations, and while there is potential for bias when participants and service providers are not blind to the intervention, there is also potential for bias in study findings where there is a commercial funder.[27] Hence an objective primary outcome was designed, identified by a biochemical urine test. Previous research has shown that the results of unblinded RCTs tended to be biased toward beneficial effects only if outcomes were subjective as opposed to objective.[28]

Randomisation sequence (with random block size) was generated using Microsoft Excel RAND function. Sealed, opaque, consecutively numbered envelopes concealing the name of the allocated intervention were prepared by a researcher who had no contact with participants.

Setting and approvals

The setting was three prison healthcare departments in remand prisons in the north of England (two male, one female). All prisons are security category B (high but not maximum security), with prisoners aged over 21 years. The research was subject to a number of ethical approvals, as described fully elsewhere.[29]

Sample size

The study protocol was devised to detect a 15% difference in the proportion of opiate-free patients within the detoxification period.[30] For a percentage abstinent of 35% in one group and 50% in the other group, the researchers expected to recruit 340 participants, yielding at least 80% power (1–β error) of detecting an absolute difference of 15% between the proportion of opiate-free patients in each group, at a two-sided 5% level of significance (α error).

Eligibility criteria

Inclusion criteria

- 21–65 years old;
- using illicit opiates as confirmed by urine test;
- expressing a wish to detoxify and remain abstinent;
- willing to give informed consent; and
- remaining in custody for at least 28 days.

Exclusion criteria

- contraindications to methadone or buprenorphine;
- medical conditions requiring emergency

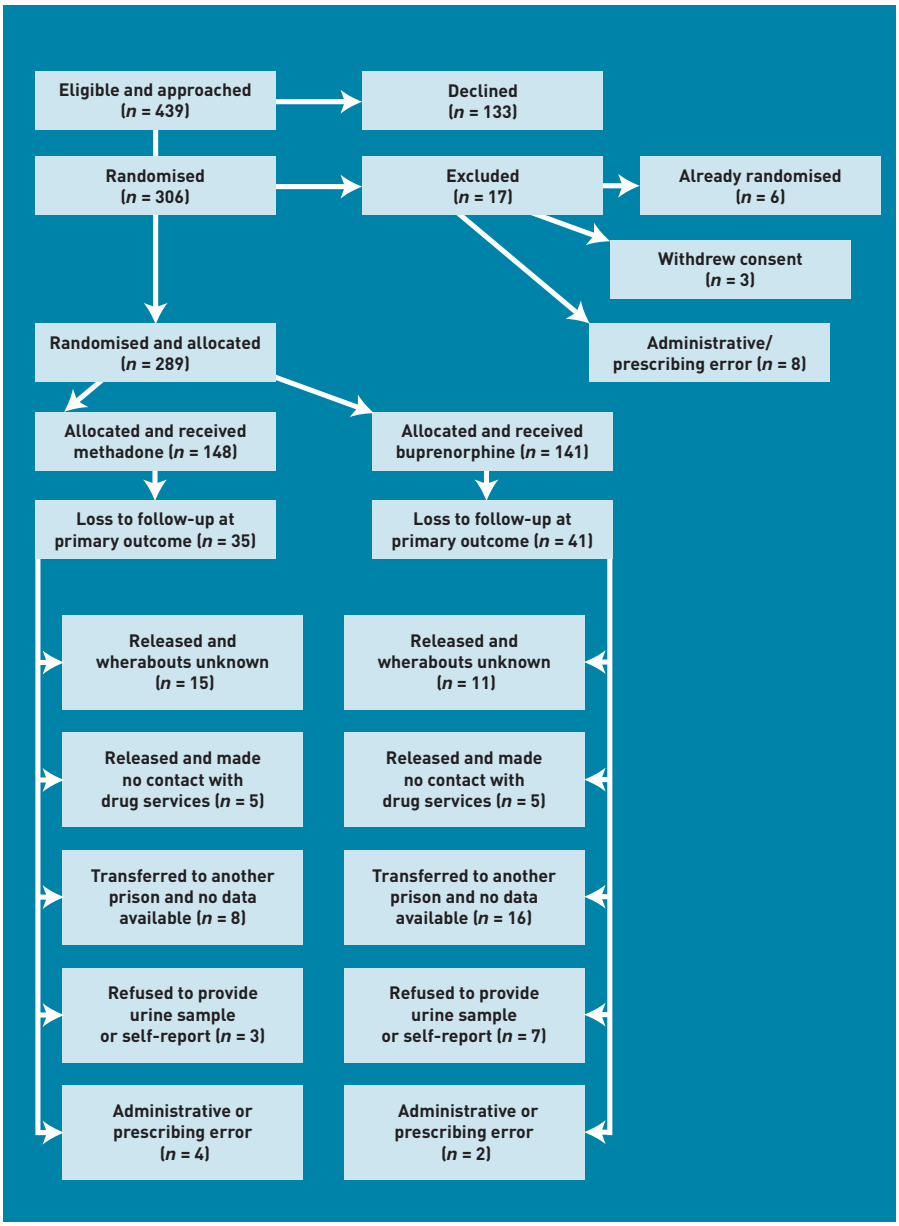

Figure 1. CONSORT diagram.

admission to hospital, thus precluding detoxification;

- currently undergoing detoxification from other addictive drugs whereby concurrent opiate detoxification would not be clinically indicated; and
- previously randomised into the trial.

Recruitment and consent

Between January 2006 and June 2008, participants were recruited from medical reception areas on first arrival into prison. Eligible prisoners were approached by a researcher who gave a detailed verbal explanation of the trial, alongside a patient information sheet. Written consent was obtained after the prisoner had made an informed decision to take part. The prescribing doctor randomised by opening the next envelope and prescribing the intervention named inside. Both prisoner and doctor were blind to the intervention until this point. Standard clinical care then continued. Data collection commenced in February 2006, ceasing in July 2009.

Prisoner participation was incentivised with £5 credited to prisoners' prison phone accounts, given when the primary outcome was gained.

Interventions and outcomes

Participants were randomly allocated to either a methadone or buprenorphine detoxification regime (both administered openly, in the context of standard prison doctor and drugs-worker support). The protocol made provision for prescribing regimes to be at the discretion of the prescribing doctor. However, in practice, prescribing was within the dose limits highlighted in Table 1. The primary outcome was abstinence from illicit opiates at 8 days post detoxification, as indicated by a urine test. Eight days was selected following discussions with biochemists regarding the time period required for the agents to be eliminated from urine. Participants who did not complete the detoxification or refused to provide urine were excluded from analysis. If participants were released before the date of the urine test, the primary outcome was based on self-report in the community, or from clinical notes. Loss to follow-up was noted if self-report data were unobtainable.

Secondary outcomes included abstinence status at 1, 3, and 6 months post detoxification, ascertained via urine test if the participant was still in prison. If the participant had been released, local community drugs service records were accessed to verify abstinence. Adverse events were recorded and a researcher was informed immediately of any serious adverse events, which were then reported to the regulatory authorities. These included overdose, self-harm, or suicide attempt; inappropriate use of prescribed medication; or admission as a prison healthcare inpatient. Leaving the study early and reasons for withdrawal from the trial were recorded.

Analysis

Analysis was undertaken using Stata 11. Logistic regression models were constructed for abstinence at each time point, considering all variables of interest. It was anticipated that the number of participants would decrease over time, so

the analysis determined only statistically significant associations with abstinence, to build more parsimonious models with sufficient power to estimate the effect of any associations. These are the 'best-fit' models, and as such give the best estimates of the effect of associations. A sensitivity analysis on full intention-to-treat (ITT) data was undertaken to ascertain any differences in interpretation, assuming that where no abstinence information was available, the participant was no longer in prison and no longer abstinent.

RESULTS

Three-hundred and six participants consented to take part in the trial. Four-hundred and thirty-nine eligible prisoners were invited, with an acceptance rate of 69.7%. Seventeen participants were excluded after randomisation but before the primary outcome, due to administrative or prescribing errors, meaning 289 prisoners received one of the two interventions (Figure 1).

Continuous variables (age, duration of use, longest abstinence, and mean daily use of opiates) were found to be positively skewed, so medians rather than means are reported. The median age was 30.8 years (interquartile range [IQR] = 26.9 to 34.9). The median duration of using opiates was 10 years (IQR = 6 to 13). Of the 289 prisoners, 148 were randomly allocated to methadone and 141 to buprenorphine. Table 2 illustrates the integrity of the randomisation process, as possible independent confounding variables were not over-represented in either of the intervention arms.

Overall, 152 out of the 289 participants (52.6%) gave a urine sample at 8 days post detoxification. Self-report was provided by 44 (15.2%) and clinical notes were accessed for 32 (11.1%). For 15 (5.2%) participants, clinical notes were traced but the outcome of abstinence at 8 days post detoxification was unknown or unclear, meaning that the abstinence outcome was ascertained for 213 (73.7%). Table 3 shows the numbers of participants available for analysis at each time point, and an unadjusted odds ratio (OR) comparing the detoxification arms. The primary analysis was based on complete data.

Table 4 shows results prior to determination of the 'best-fit' models, as highlighted in Table 5. At 8 days post detoxification, there was no statistically significant difference in the odds of achieving abstinence between the methadone and buprenorphine arms (OR = 1.69; 95% confidence interval [CI] = 0.81 to 3.51; $P = 0.163$). Similarly, there was no statistically significant difference at 1 month (OR = 0.38; 95% CI = 0.13 to 1.10; $P = 0.074$) or 3 months (OR = 0.38; 95% CI = 0.13 to 1.10; $P = 0.074$), and insufficient data at the 6-month time point to undertake statistical analysis.

These results are increasingly based on smaller numbers, so confidence intervals may be large and estimates of effect may differ widely across time points. While some variables may initially show statistical significance in these tables, this does not remain after model fit is improved. However, it should be emphasised that the 'best-fit' logistic regression model was

Table 1. Detoxification regime schedules

Day	Buprenorphine, mg	Methadone, 1 mg/1 ml mixture
1	8	30
2	8	30
3	8	30
4	8	30
5	8	30
6	6	25
7	6	25
8	4	22
9	4	22
10	4	20
11	3.6	20
12	3.6	18
13	3.2	16
14	2.8	14
15	2.4	12
16	2.0	10
17	1.6	8
18	1.2	6
19	0.8	4
20	0.4	2

Table 2. Descriptive data pertaining to the distribution of variables across the two interventions

	Methadone, *n* = 148	Buprenorphine, *n* = 141
Previous successful detox, *n* (%)	71 (48.0)	74 (52.5)
Ethnicity, *n* (%)		
White British	133 (89.9)	132 (93.6)
Asian	4 (2.7)	4 (2.8)
Black	6 (4.1)	1 (0.7)
Mixed race	1 (0.7)	1 (0.7)
White other	4 (2.7)	1 (0.7)
Route of administration		
Injected	84 (56.8)	70 (49.6)
Smoked	51 (34.5)	59 (41.8)
Both injected and smoked	3 (2.0)	5 (3.5)
Longest abstinence (months), median (IQR)	8 (0.5 to 24)	8 (0 to 21)
Age (years), median (IQR)	30.7 (27.0 to 34.8)	31.0 (26.4 to 34.9)
Length of opiate use (years), median (IQR)	10 (6 to 13)	10 (6 to 13)
Daily amount (£) of opiate use, median (IQR)	45 (25 to 60)	50 (30 to 60)

Table 3. Post detoxification abstinence across time

Outcome — abstinent	Buprenorphine	Methadone	Total *n* (%)	OR (95% CI)
At 8 days				
Urine sample only[a]	57/71	62/81	152 (53)	1.25 (0.54 to 2.96)
Complete data[b]	74/100	79/113	213 (74)	1.22 (0.64 to 2.34)
ITT data[c]	74/141	79/148	289 (100)	0.96 (0.59 to 1.57)
At 1 month				
Urine sample only[a]	38/50	47/56	106 (37)	0.61 (0.20 to 1.77)
Complete data[b]	45/72	64/87	159 (55)	0.60 (0.29 to 1.24)
ITT data[c]	45/141	64/148	289 (100)	0.62 (0.37 to 1.02)
At 3 months				
Urine sample only[a]	24/28	13/22	50 (17)	4.15 (0.91 to 21.58)
Complete data[b]	31/46	27/48	94 (33)	1.61 (0.64 to 4.06)
ITT data[c]	31/141	27/148	289 (100)	1.26 (0.68 to 2.35)
At 6 months				
Urine sample only[a]	17/22	8/13	35 (12)	2.13 (0.36 to 12.18)
Complete data[b]	21/33	16/27	60 (21)	1.20 (0.37 to 3.88)
ITT data[c]	21/141	16/148	289 (100)	1.44 (0.68 to 3.11)

[a]Urine sample provided. [b]Urine sample or self-report or clinical notes. If no data available, participant excluded. [c]Urine sample or self-report or clinical notes. If no data available, assumed 'not abstinent' and analyse by intention to treat. ITT = intention-to-treat.

developed upon completion of data collection and did not form part of the original study protocol. In agreement, however, across both Table 4 and Table 5, abstinence was found to be primarily associated with whether or not the participant is still in prison at that time point (at 8 days and 1 month) and whether or not the participant was abstinent at the previous time point (at 1 month and 3 months). ORs differ somewhat between the tables but directions of effect are the same and these differences are therefore likely to be due to the smaller sample sizes. Interpretation of the effect sizes should be taken from Table 5.

At 8 days post detoxification, Table 5 shows that participants still in prison have 15.22 times the odds (95% CI = 4.19 to 55.28) of being abstinent. At 1 month, participants previously abstinent at 8 days post detoxification have 4.50 times the odds (95% CI = 1.96 to 10.34) of remaining abstinent, and participants still in prison have 7.03 times the odds (95% CI = 2.22 to 22.25) of being abstinent. At 3 and 6 months, abstinence depends solely on whether or not the participant was abstinent at the previous time point. At 3 months, participants who were abstinent at 1 month have 8.65 (95% CI = 3.22 to 23.24) the odds of being abstinent. At 6 months, participants who were abstinent at 3 months have 32.86 (95% CI = 6.11 to 176.62) the odds of being abstinent. Due to small numbers at the 6-month stage (52/289 participants, 18.0%), these confidence intervals are very wide. As expected, the number of participants that can be included in the analysis reduced over time, and so the models become increasingly lacking in power.

Results from the sensitivity analysis with ITT data are shown in full (Tables 6 and 7). Results are broadly similar and interpretation of the key variables remains the same. However, by ITT analysis, whether or not the participant remains in prison at each time point has a much larger impact on their abstinence status, as expected due to the study's ITT

Table 4. Logistic regression model of abstinence at 8 days, 1 month, and 3 months, considering all variables of interest

	Abstinence at 8 days (*n* = 170)		Abstinence at 1 month (*n* = 122)		Abstinence at 3 months (*n* = 70)	
Variable	**Odds ratio (95% CI)**	***P*-value**	**Odds ratio (95% CI)**	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Buprenorphine versus methadone	1.69 (0.81 to 3.51)	0.163	0.38 (0.13 to 1.10)	0.074	1.50 (0.37 to 6.04)	0.571
In prison versus not in prison at timepoint	18.44 (3.69 to 92.05)	<0.001	13.48 (2.69 to 67.50)	0.002	5.94 (0.61 to 58.13)	0.126
Abstinence at 8 days	n/a	n/a	8.03 (2.51 to 25.73)	<0.001	0.50 (0.08 to 3.09)	0.457
Abstinence at 1 month	n/a	n/a	n/a	n/a	16.87 (2.82 to 101.02)	0.002
Previous success versus no previous success	0.94 (0.44 to 2.02)	0.882	0.38 (0.12 to 1.16)	0.089	4.71 (0.94 to 23.54)	0.059
Ethnicity versus white British						
Asian	2.72 (0.29 to 25.72)	0.658	0.04 (0.00 to 0.57)	0.051	52.46 (0.37 to 7520.23)	0.429
Black	Insufficient data		0.12 (0.01 to 0.98)		1.65 (0.06 to 47.36)	
Mixed race	Insufficient data		Insufficient data		Insufficient data	
White other	0.77 (0.07 to 8.34)		0.55 (0.03 to 9.68)		7.01 (0.14 to 352.40)	
Type of use versus injected:						
Smoked	0.74 (0.34 to 1.61)	0.666	1.36 (0.43 to 4.27)	0.871	0.60 (0.12 to 3.09)	0.442
Injected and smoked	1.52 (0.16 to 14.42)		1.18 (0.11 to 12.53)		0.24 (0.02 to 2.24)	
Longest abstinence, per month increase	1.00 (0.98 to 1.03)	0.955	1.02 (0.98 to 1.06)	0.428	0.98 (0.95 to 1.02)	0.299
Age, per 1 year increase	0.97 (0.92 to 1.04)	0.402	1.14 (1.01 to 1.29)	0.030	1.05 (0.92 to 1.20)	0.469
Years using, per year increase	1.04 (0.96 to 1.14)	0.315	0.85 (0.73 to 1.00)	0.046	1.10 (0.92 to 1.31)	0.300
Amount using, per £ increase	1.00 (0.99 to 1.01)	0.743	1.01 (0.99 to 1.02)	0.489	0.98 (0.95 to 1.00)	0.108

Table 5. Logistic regression best-fit models for abstinence at all time points

Outcome/association	Odds ratio (95% CI)	*P*-value	*n* (%)
Abstinence at 8 days:			213 (73.7)
In prison at 8 days versus not	15.22 (4.19 to 55.28)	<0.001	
Abstinence at 1 month:			148 (51.2)
Abstinent at 8 days versus not	4.50 (1.96 to 10.34)	<0.001	
In prison at 1 month versus not	7.03 (2.22 to 22.25)	0.001	
Abstinence at 3 months:			89 (30.8)
Abstinent at 1 month versus not	8.65 (3.22 to 23.24)	<0.001	
Abstinence at 6 months			52 (18.0)
Abstinent at 3 months versus not	32.86 (6.11 to 176.62)	<0.001	

n = number of participants included in the analysis (participants with missing values in outcome or associated factor excluded).

Table 6. Best-fit models for abstinence at all time points (ITT analysis)

Outcome/association	Odds ratio (95% CI)	*P-value*	*n* (%)
Abstinence at 8 days:			289 (100)
In prison at 8 days versus not	97.83 (29.56 to 323.75)	<0.001	
Abstinence at 1 month:			289 (100)
Abstinent at 8 days versus not	3.74 (1.73 to 8.05)	0.001	
In prison at 1 month versus not	77.84 (28.98 to 209.11)	<0.001	
Abstinence at 3 months:			289 (100)
Abstinent at 1 month versus not	3.88 (1.61 to 9.32)	0.002	
Abstinent at 3 months versus not	54.94 (20.98 to 143.86)	<0.001	
Abstinence at 6 months			289 (100)
Abstinent at 3 months versus not	20.63 (4.35–97.93)	<0.001	
Abstinent at 6 months versus not	193.01 (41.45–898.68)	<0.001	

n = number of participants included in the analysis (participants with missing values in outcome or associated factor excluded). ITT = intention-to-treat.

assumptions. The effect of abstinence at previous time points was reduced, but the direction of effect remained the same.

DISCUSSION

Summary

This study suggests there is equal clinical effectiveness between methadone and buprenorphine in achieving abstinence from opiates at 8 days post detoxification. The strongest association for lasting abstinence was a user being abstinent at an earlier time point. This finding has clinical utility in that users should be encouraged to remain in drug treatment. Those who failed to achieve abstinence at 8 days post detoxification were unlikely to be abstinent at a later time point.

The fact that none of the variables relating to mean daily use, length of use, administration route, previous successful detoxifications, or length of previous abstinence was associated with achieving abstinence raises important issues for clinical practice. Patients should not be discouraged from undertaking detoxification purely on current or past drug history and treatment success. The strongest association with achieving abstinence was residence within prison. Therefore, the authors recommend that prison healthcare staff are supported to offer detoxification programmes for those wishing to become abstinent.

Recent policy initiatives have made provision for the widespread introduction of opiate maintenance programmes across the UK prison estate, to achieve equivalence with community standards of drug treatment.[2,3] It is important that while such

Table 7. Abstinence at 8 days, 1 month, and 3 months; considering all variables of interest (ITT analysis)

	Abstinence at 8 days (*n* = 170)		Abstinence at 1 month (*n* = 122)		Abstinence at 3 months (*n* = 70)	
Variable	**Odds ratio (95% CI)**	***P*-value**	**Odds ratio (95% CI)**	***P*-value**	**Odds ratio (95% CI)**	***P*-value**
Buprenorphine versus methadone	1.74 (0.84 to 3.61)	0.136	0.42 (0.17 to 1.05)	0.065	2.14 (0.74 to 6.18)	0.159
In prison versus not in prison at timepoint	119.48 (27.28 to 523.38)	<0.001	186.88 (45.59 to 765.94)	<0.001	87.99 (24.63 to 314.29)	<0.001
Abstinence at 8 days	N/A	N/A	4.67 (1.77 to 12.34)	0.002	0.67 (0.20 to 2.22)	0.515
Abstinence at 1 month	N/A	N/A	N/A	N/A	4.42 (1.44 to 13.55)	0.009
Previous success versus no previous success	0.92 (0.43 to 1.98)	0.837	0.42 (0.15 to 1.15)	0.090	1.36 (0.46 to 3.96)	0.578
Ethnicity versus white British						
Asian	2.72 (0.31 to 23.89)	0.652	0.16 (0.02 to 1.41)	0.186	3.41 (0.27 to 42.50)	0.822
Black	Insufficient data		0.18 (0.02 to 1.31)		1.15 (0.07 to 18.44)	
Mixed race	Insufficient data		Insufficient data		Insufficient data	
White other	0.81 (0.07 to 9.29)		0.50 (0.04 to 6.31)		1.12 (0.05 to 23.70)	
Type of use versus injected						
Smoked	0.73 (0.34 to 1.55)	0.647	0.97 (0.36 to 2.61)	0.994	0.47 (0.15 to 1.54)	0.181
Injected and smoked	1.37 (0.16 to 11.69)		0.89 (0.08 to 9.28)		0.17 (0.02 to 1.43)	
Longest abstinence, per month increase	0.262 1.00 (0.98 to 1.03)	0.836	1.01 (0.98 to 1.05)	0.519	0.99 (0.96 to 1.02)	0.406
Age (per 1 year increase)	0.98 (0.92 to 1.04)	0.460	1.10 (1.01 to 1.20)	0.034	1.06 (0.96 to 1.16)	0.262
Years using (per year increase)	1.05 (0.96 to 1.14)	0.302	0.92 (0.82 to 1.04)	0.170	1.09 (0.96 to 1.24)	1.198
Amount using (per £ increase)	1.00 (0.99 to 1.01)	0.819	1.00 (0.99 to 1.02)	0.565	1.00 (0.98 to 1.02)	0.924

N/A = not available. ITT = intention-to-treat.

activity takes place, prisoners who express motivation to undergo detoxification from opiates are supported in their treatment choice. However, the period after release from prison is a high-risk time for drug-related death in individuals who have undergone detoxification in the prison setting and then relapsed upon release from prison. Therefore it would be prudent to offer such a detoxification regime only to patients who have made a planned decision to undergo detoxification and where their care can be handed over to community primary care services upon release, to minimise the risk of relapse.

Detoxification guidance for UK prisons is not prescriptive and suggests that either methadone or buprenorphine should be offered as first-line treatment, taking into account the preference of the user.[31] However, previous research has highlighted the risk of buprenorphine diversion and misuse in some UK prisons,[32] leading some commentators to suggest that methadone should be used in preference to buprenorphine as a first-line agent for detoxification.[33] The present research, in demonstrating equal clinical effectiveness between the two medications, would concur that where buprenorphine diversion is a problem, methadone should be offered as first line.

Strengths and limitations

There is a paucity of prison-based RCTs, due in part to the significant logistical challenges presented by conducting this type of research among prisoners.[34] The prison population crisis, which occurred in the midst of recruitment, resulted in prisoners being unexpectedly transferred to serve their remaining sentences at other establishments, with little prior warning, making follow-up problematic and significantly more time consuming. Many were unexpectedly transferred or released before their primary outcome could be determined by urine sample, and therefore the outcome was identified by self-report or from clinical records. While not ideal, this constituted a minority of participants. An outcome of abstinence from drugs should not be prone to self-reporting bias, as there was no apparent gain to the participant who had already left the treatment provider in which the intervention had been delivered.

Improvements in community maintenance prescribing during the life course of the trial meant less demand for detoxification in prison health care; therefore, fewer people than anticipated were recruited in the original time frame. Neither of these issues could have been foreseen by the project team. Data collection was slow at times, due to access issues with key personnel at drug intervention programmes, who had to prioritise their own workload before undertaking trial tasks. It was due to the perseverance of the research team that the data collection was completed as fully as possible, with a follow-up rate of almost 75% for the primary outcome. Inevitably, it was not possible to collect 100% of follow-up data and this presents a challenge to statistical analysis aiming to ensure that erroneous conclusions are not drawn from an incomplete dataset. To minimise this risk, two sets of analysis of the data were undertaken. The first entailed analysis by intention to treat and the second by analysis after excluding missing data. Table 3 shows the findings of the two analyses did not differ, thus improving confidence in the validity of the research conclusions.

Comparison with existing literature

Over 300 participants were recruited to this RCT, and the primary outcome was ascertained for almost 75% in this complex, transient patient group. The authors believe the findings have made a significant contribution to the international literature regarding detoxification from opiates. Only six previous studies have been undertaken evaluating the effectiveness of methadone versus buprenorphine, all outside prison. The mean number of participants per study was just 36. At the time of writing the protocol for the research, there was no published meta-analysis of these studies. A Cochrane Review published in 2009 included the findings of four of these studies, a total of just 182 participants.[26] Only three studies had a primary outcome of abstinence from opiates evidenced by biochemical urine sample.[20,21,24] Only two studies used comparative statistics and one acknowledged small sample size as a limitation that affected significance. Both community-based studies demonstrated no significant difference between buprenorphine and methadone, for either abstinence[20] or retention in drug treatment.[24] Both studies acknowledged a substantial dropout rate. The present prison-based trial would concur with these findings.

Implications for practice and research

The findings of this study have implications for both prison and community-based general practice, as the vast majority of prisoners are, in time, released back into

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the community and subsequently may receive detoxification from their GP. Therefore, GPs treating drug users — regardless of their setting — need to be aware of the results of one of the few trials that compared the two most commonly used detoxification agents used in the UK. The findings of the present study would suggest that prison GPs can offer either methadone or buprenorphine as a treatment for opiate detoxification, as both are equally effective in helping users achieve abstinence. The study has also highlighted the positive association between imprisonment and achieving abstinence. However, detoxification is only one part of treatment, and many such users will subsequently be released into the community. Therefore, to minimise the risk of relapse there needs to be strong coworking between prison-based and community-based primary care services for the benefit of drug users.

As regards future research practice, the logistic regression analysis suggested that, compared to community settings, patients may be more successful in undergoing detoxification in the prison setting. Obviously, it would not be feasible to randomise participants to detoxification in either the prison or community setting, as the powers to confer a custodial sentence rest with the courts. However, future research activity could consider randomising participants presenting in either the prison or community setting to either a detoxification or a maintenance programme. Outcomes of abstinence from illicit drugs, abstinence from prescribed drugs, and reoffending rates could then be considered, in addition to considering the mortality and morbidity associated with each type of intervention. The present study was underpowered to detect whether those with a previous history of smoking opiates were more likely to achieve abstinence than those with a history of smoking and injecting. Such an important clinical question merits future research activity.

The authors are unaware of any other clinical trials of a medicinal product — in any specialty — being carried out in the UK prison estate in the past decade. Methodological challenges are probably the reason for this, as previous commentators seeking to conduct RCTs in secure environments have highlighted.[34] Only two previous UK prison studies evaluated the effectiveness of differing medications for detoxification. The first evaluated the withdrawal severity of methadone and lofexidine,[35] but the rates of completion were not sufficient to detect a statistically significant difference (sample size of 74). In the authors' previous trial, buprenorphine and dihydrocodeine (90 participants) were compared.[36] A higher proportion of people allocated to buprenorphine provided a urine sample that was negative for opiates (abstinent) compared with those who received dihydrocodeine. The main methodological implication of this current project is the demonstration that an RCT can be conducted in the British prison estate. If there are important unanswered clinical questions that relate specifically to the prison population, then clinical researchers should not be discouraged from implementing further RCTs in the prison setting.

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