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The SUMMIT Trial: A field comparison of buprenorphine versus methadone maintenance treatment

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Abstract

This prospective patient-preference study examined the effectiveness in practice of methadone versus buprenorphine maintenance treatment and the beliefs of subjects regarding these drugs. A total of 361 opiate-dependent individuals (89% of those eligible, presenting for treatment over 2 years at a drug service in England) received rapid titration then flexible dosing with methadone or buprenorphine; 227 patients chose methadone (63%) and 134 buprenorphine (37%). Participants choosing methadone had more severe substance abuse and psychiatric and physical problems but were more likely to remain in treatment. Survival analysis indicated those prescribed methadone were over twice as likely to be retained (hazard ratio for retention was 2.08 and 95% confidence interval [CI] = 1.49–2.94 for methadone vs. buprenorphine), However, those retained on buprenorphine were more likely to suppress illicit opiate use (odds ratio = 2.136, 95% CI = 1.509–3.027, $p < .001$) and achieve detoxification. Buprenorphine may also recruit more individuals to treatment because 28% of those choosing buprenorphine (10% of the total sample) stated they would not have accessed treatment with methadone.

Keywords: Buprenorphine; Methadone; Maintenance; Treatment retention; Opiate dependence

1. Introduction

Opiate maintenance treatment with both methadone (MMT) and buprenorphine (BMT) has been shown to reduce the negative consequences of opiate dependence: reducing mortality, illicit drug use, criminal behavior, and spread of blood borne viruses and improving physical and mental health and social functioning (National Institute for Clinical Excellence [NICE], 2007).

NICE guidance (NICE, 2007) in the UK recommends the availability of both and states that where both are "equally appropriate," methadone should be first-line, based on its reduced cost and evidence from existing trials (summarized in the recently updated Cochrane review by Mattick, Kimber, Breen, & Davoli, 2008) that retention with methadone is better; whereas suppression of illicit opiate use is equivalent with either treatment.

However, many of the trials on which the Cochrane review was based (Fischer et al., 1999; Johnson et al., 2000; Lintzeris et al., 2004; Mattick et al., 2000; Neri et al., 2001; Petitjean et al., 2001; Strain, Stitzer, Liebson, & Bigelow, 1994) used relatively low doses of buprenorphine with slow inflexible induction, and this may have skewed the retention rates in favor of methadone. In addition, there is virtually no research identifying features that predict a better outcome with either drug or directly examining other outcomes, such as social functioning or psychological health, to guide the

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clinician in deciding whether indeed both drugs are equally appropriate. The decision as to which drug to prescribe is therefore currently based on predicted differential effects based on the known pharmacology of the drugs and clinicians' opinions and patient choice, about which very little is known.

Methadone is a long-acting full agonist at the mu opiate receptor. Consequently it can offer a degree of persisting intoxication (including a degree of sedation), which may be attractive to some and limiting to others. Continued use of illicit heroin is common, limiting the reduction in harm associated with treatment. It is capable of producing fatal respiratory depression and prolongs the QTc interval (Fanoe, Hvidt, Ege, & Jensen, 2007), contributing significantly to opiate-related deaths (Auriacombe, Franques, & Tignol, 2001). Withdrawal from methadone is believed by many opiate users to be worse than heroin withdrawal. This, in addition to the requirement for daily dosing, leads some to view methadone simply as an "alternative addiction" that prolongs dependency. These beliefs form part of a negative "lore" among some heroin users regarding methadone, which has been shown to inhibit some individuals from engaging with treatment (Kayman, Goldstein, Deren, & Rosenblum, 2006; Schwartz et al., 2008).

Buprenorphine's receptor profile as a partial agonist with high affinity at the opiate receptors should in theory predict superiority over methadone in terms of safety (due to a ceiling effect on respiratory depression; Walsh, Preston, Stitzer, Cone, & Bigelow, 1994), suppression of illicit opiate use (due to increased receptor blockade), improvements in social functioning (due to reduced sedation), and progression to detoxification (due to greater ease of withdrawal).

Translation of theory into practice has however been patchy. To date, studies have shown no consistent benefit in terms of suppression of illicit opiate use or social functioning. Progression to detoxification has not been examined. Buprenorphine does appear to be safer than methadone for those individuals who remain in treatment (Auriacombe et al., 2001; Bell, Butler, Lawrence, Batey, & Salmelainen, 2009), but the impact of reduced retention rates cannot be ignored in this context, as mortality rates of injecting drug users are considerably higher when not in treatment (Gronbladh, Ohlund, & Gunne, 1990) as are levels of criminal activity and chaotic social functioning that impact on their immediate families (including their children) and society in general.

Negative aspects of buprenorphine include the potential to precipitate withdrawal symptoms at induction. In addition, the sublingual tablet tastes unpleasant and dissolves slowly, reducing its acceptability and making supervision of its use more difficult. The practice of crushing and injecting the tablets also leads to significant harm.

Whether the availability of an alternative has attracted into treatment individuals averse to methadone has not been examined; however, since the introduction of BMT to the UK, the number of prescriptions for both drugs has increased (NTA, 2007), implying that more individuals are being treated rather than that buprenorphine has replaced methadone in existing patients.

There are no existing trials comparing BMT and MMT based in the UK, which differs in important respects to many other countries, partly due to the free availability of both treatments in most areas and a comprehensive benefit system. These factors contribute to difficulty recruiting to randomized controlled trials to the extent that their generalizability can be severely compromised. A local pilot study found that the number of eligible subjects prepared to accept randomization constituted less than 2% (Pinto, Rumball, Maskrey, & Holland, 2008). Randomization and effective blinding also (in theory) divorce the results from patients' expectations about the effectiveness, for them as individuals, of the two alternative treatments. This could be predicted to have a powerful effect on their outcome in routine clinical practice where patients do know which treatment they are receiving.

The authors were therefore interested to explore the effectiveness of BMT versus MMT in UK clinical practice where treatment is freely available, and patient choice is now supported (NICE, 2007), outside the narrower confines of a randomized control trial. Effectiveness was measured in terms of retention, achievement of opiate detoxification, and suppression of illicit opiate use. Secondary outcomes included measurement of social functioning and psychological health. Uniquely, comprehensive baseline data were gathered regarding participants' history, detail on reasons for choice, and beliefs about both treatments to explore the basis on which patients chose between these drugs and establish whether any preexisting features or expectations predicted outcomes in treatment.

2. Materials and methods

2.1. Subjects and setting

Participants were recruited between October 2005 and October 2007 from three sites within one community drug service covering a large rural area and two urban centers in Norfolk. All new patients who were opiate dependent (based on clinical assessment and at least two urine toxicology screens), not prescribed either study drug for the preceding month, requesting maintenance treatment (and for whom it was appropriate) were invited to participate.

2.2. Interventions

Treatment occurred according to usual clinic practice and was not influenced by participation in the trial. Patients chose either methadone or buprenorphine in collaboration with the treating clinician. Induction in line with national guidance (Orange book) on to the drug of choice occurred over a titration period of 3 days during which the patient attended daily for monitoring. Doses were given under

supervision, and multiple doses could be given over the course of a day. Following titration, most patients continued to receive their medication under supervision on most days either in the clinic or a community pharmacy. In line with normal UK practice, take-home doses were introduced on an individual basis when it was felt appropriate and safe to do so. Alteration to doses either up or down could be negotiated with the treating clinician at any point. Where general practitioners were willing, prescriptions for stable subjects were transferred to primary care.

Patients were discharged from the trial if they failed to take their prescription for more than 7 days or were discharged from the service. Criteria for discharge were production of a tampered urine sample; serious aggressive behavior to staff or on the premises; illicit drug use on the premises; and failure to engage constructively with therapy after appropriate attempts by workers to facilitate engagement.

In addition to pharmacological treatment, subjects were seen individually by key workers, initially weekly then at a frequency negotiated with the subject according to their needs. Key workers act as care coordinators, providing individual support sessions that are not structured therapy. This includes signposting and assistance with a range of needs, for example, accessing housing support, education and employment advice, and finance and benefits advice. They act as advocates for the patients and monitor physical and mental health, making referrals to additional services as appropriate. Medical review occurs in the service six monthly or on request of the key worker.

2.3. Measures

Detailed baseline data were collected on a very wide variety of demographic and background variables (>50). In addition, at entry, participants completed a detailed questionnaire regarding their knowledge and beliefs about the two alternative drugs and their reasons for their treatment choice. The following beliefs or knowledge were explored: taste of drug, likelihood of experiencing withdrawals when starting on the drug, effect on craving, blocking effect on heroin use, overdose risk, level of intoxication (sedation, clear headedness, emotional numbing), stigma, ease of detoxification, and degree to which the drug was perceived as an alternative addiction.

The primary outcome was retention in treatment at 6 months or successful detoxification (i.e., a "positive" outcome). Successful detoxification was defined as patients who were recorded to be opiate-free at the point of discharge from the service during the trial. Subjects were considered as "not retained" in the trial if they failed to take their maintenance drug for seven consecutive days. A secondary outcome was suppression of illicit drug use evidenced by urine toxicology. The frequency of urine sample testing in the service is flexible according to the level of engagement and suspected or reported illicit drug use. This could have led to a wide variation in the numbers of available samples for patients in the trial. To eliminate this discrepancy and prevent possible bias, it was decided at the outset to obtain copies of the first urine toxicology report each month only from the clinical notes. Christo inventories (a measure of social functioning, addictive and risk behavior, and treatment engagement; Christo, Spurrell, & Alcorn, 2000) were completed by key workers at baseline, 3 months, and 6 months. Additional self-report data on alcohol use (brief Alcohol Use Disorder Identification Test, brief AUDIT), illicit drug use (adapted Office for National Statistics questionnaire), and psychological health (Brief Symptom Inventory [BSI]) were collected at baseline, 3 months, and 6 months.

2.4. Sample size

A pilot study ($n = 42$) demonstrated approximately equal numbers chose each drug and suggested that methadone retained about 15% more subjects at 6 months (68% vs. 55%)[13]. A total sample size of 326 was calculated to be sufficient, with 80% power, to detect a difference of 55% versus 70% using the chi-squared test at a 5% significance level. After the trial began (at $n = 109$), recruitment demonstrated that methadone was the more popular choice (2:1 ratio). We therefore recalculated the sample size at that point taking account of this imbalance, which raised the sample size required to 363 patients.

2.5. Analysis

Because this was a nonrandomised study, baseline data were compared to investigate differences between groups. Retention was compared between groups using Fisher's exact test. To control for possible confounders, all variables measured at baseline that exhibited both (a) a p value less than .2 when tested for bivariate association with the primary outcome and (b) a p value less than .2 when tested between groups were included as independent variables in a logistic regression to obtain an adjusted odds ratio (OR). In addition, the Cox proportional hazards model was used to compare time retained between groups, using the same potential confounders as in the logistic regression to provide adjusted estimates. Analyses were conducted on an intention-to-treat basis, classifying participants according to the drug they first chose, then repeated on a per-protocol basis analyzing participants according to the drug they completed the study on. Finally, a sensitivity analysis was conducted, broadening our definition of retention to include those who were transferred on a prescription to another drug treatment service.

Urine results were analyzed as repeated measures to allow for correlation between results on each patient. In addition, sustained abstinence from illicit use was investigated by comparing groups in terms of the proportion providing six negative urines, or five negative and one missed urine. Changes in Christo, BSI, and drug and alcohol use scores for those retained at follow-up were

compared using a linear regression model to adjust for the corresponding baseline measure.

Within each drug category, we also investigated the effect on outcome of participants' baseline knowledge, beliefs, and reason for choice of drug. Initially, this was by a univariate analysis for each drug to explore whether those with a positive outcome had different beliefs to those with a negative outcome. We then planned to undertake a multivariate analysis if a number of beliefs appeared potentially predictive of success.

2.6. Ethical approval

Ethical approval for this study was obtained from the Norwich District Research Ethics Committee. Informed consent was obtained from all participants.

3. Results

3.1. Participants

A total of 555 clients presented for maintenance treatment, of whom 105 were excluded (see Fig. 1) and 44 were not approached by our study researcher due to logistical difficulties covering three sites. Of the remaining 407 clients, 361 (89%) agreed to enter the study. Of these, 227 (63%) chose methadone, and 134 (37%) chose buprenorphine (Fig. 1).

3.2. Baseline comparison

The two groups appeared to be well matched (Table 1). Most were White, unemployed, male polydrug users involved in criminal activity who had been dependent on heroin (which most injected) for an average of 10 years. Most described a history of childhood adversity, with more than one third reporting some form of abuse and two thirds reporting a parent with an alcohol problem. Most participants also had poor physical and mental health.

Some differences were noted. Those choosing MMT were more likely to be female (28% vs. 19%), to have resident children (23% vs. 14%), to have a drug-using partner (62.6% vs. 49.4%), to express a higher level of psychological distress (BSI's Global Symptom Index 53.6 vs. 50.3), to have a physical diagnosis (51% vs. 41%), and to be taking some medication for that condition. They had slightly poorer social functioning reflected in higher average Christo scores (11 vs. 9.7), were more likely to be using heroin intravenously (68% vs. 55%) at a higher reported dose (0.8g vs. 0.5g), and to have positive urine toxicology for cocaine.

3.3. Doses

Mean dose of buprenorphine at the end of Day 1 of titration was 6.9 mg (range = 2–12 mg), 9.9 mg (range = 2–20 mg) at the end of Day 2, and 11.3 mg (range = 4–20) at the end the Day 3. This compared to a mean of 50.7 mg Day 1 (range = 0–135 mg), 63.8 mg Day 2 (range = 5–160 mg), and 69.6 mg at the end of Day 3 for methadone (range = 5–170 mg). Mean maximum doses throughout the trial were 73.3 mg of methadone (range = 10–170 mg) and 11.7 mg of buprenorphine (range = 4–20 mg). More patients on buprenorphine chose to reduce their dose during the trial rather than to increase it.

3.4. Positive outcome (i.e., retention or detoxification)

At 6 months, significantly fewer of those selecting BMT (50%), than those selecting MMT (70%), achieved a positive outcome ($p < .001$; Fisher's exact test). This equates to a relative risk of a positive outcome for BMT of 0.71 (i.e., a reduced probability of a successful outcome) or an OR of 0.43 (95% confidence interval [CI] = 0.20–0.67, $p < .001$). This OR decreased (i.e., worsened) to 0.34 (95% CI = 0.20–0.59, $p < .001$) after adjusting for potential confounders. Almost identical results were found in a per-protocol analysis adjusting for seven participants who swapped from buprenorphine to methadone soon after entering the study. The difference in positive outcome observed, favoring methadone, was wholly due to the difference in retention rates as detoxification was achieved by more of those receiving buprenorphine (10/134, 7.5%) than those receiving methadone (1/361, 0.3%).

3.5. Survival analysis

A survival analysis to 6 months further demonstrated the marked difference in retention (see Fig. 2). A log-rank test comparing methadone to buprenorphine indicated markedly different survival functions ($p < .001$). The unadjusted hazard ratio for retention on methadone compared with buprenorphine over the 6 months of the study was 2.08 (95% CI = 1.49–2.94, $p < .001$). Adjusting for the same potential confounders as in the main analysis raised this hazard ratio to 2.27 (95% CI = 1.56–3.30, $p < .001$). Reasons for noncompletion are shown in Table 2.

3.6. Investigating the relationship between dose of drug and retention

Fig. 3 shows the relationship observed between the dose prescribed and the retention rates. Doses of methadone greater than 60 mg appeared most effective, with increasing dose yielding improved retention. In contrast, although a dose of at least 8 mg of buprenorphine appeared necessary, further increases above this level did not appear to improve retention.

3.7. Analysis of predictors for retention in treatment at 6 months

We undertook an analysis to identify which baseline factors predicted retention in treatment at 6 months.

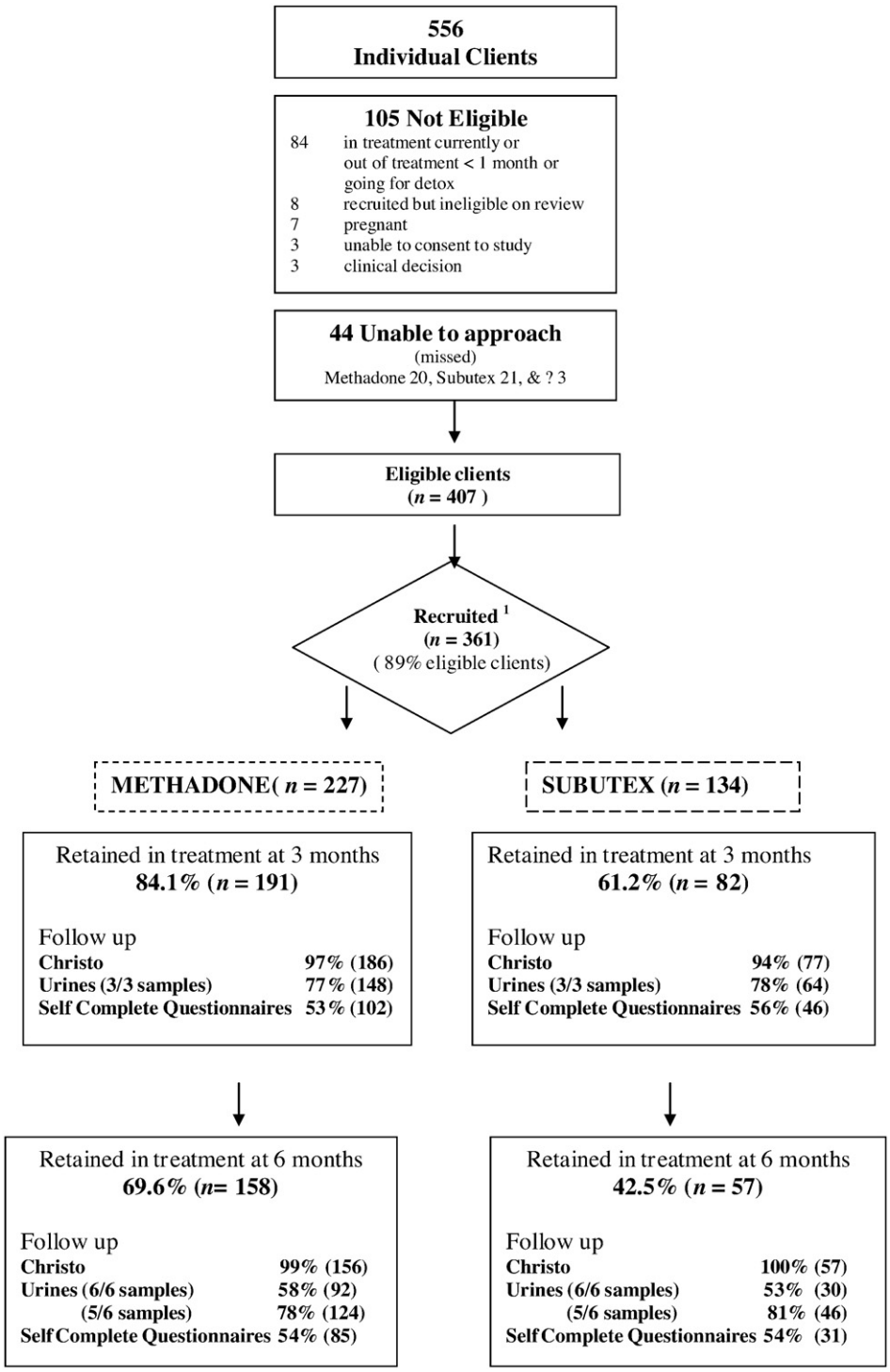

Fig. 1. CONSORT statement: flowchart describing progress of participants through the SUMMIT trial.

Bivariate analysis identified 15 baseline variables that appeared to be related to retention, in addition to preferred drug. When these were incorporated simultaneously into a multiple logistic regression, 7 were significant. The predictor of retention with greatest OR was preferred drug (MMT), this was also highly statistically significant

Table 1
Baseline comparison

	Methadone (n = 227) n (%) or M (SD)	Buprenorphine (n = 134) n (%) or M (SD)	p value (Fisher's exact or Mann–Whitney test)
Male	163 (71.8%)	108 (80.6%)	.08
Age	33.1 (7.9)	32.4 (7.7)	.48
White	217 (96.9%)	128 (95.5%)	.57
Age left education	15.6 (1.7)	15.8 (2.6)	.98
In a relationship	113 (49.8%)	72 (53.7%)	.51
Resident children	52 (23.2%)	18 (14.0%)	.04
Accommodation			
Stable	151 (66.8%)	94 (70.2%)	.73
Temporary	68 (30.1%)	35 (26.1%)	
Homeless	7 (3.1%)	5 (3.7%)	
Employed	26 (11.5%)	18 (13.5%)	.62
Any previous convictions	206 (90.8%)	115 (86.5)	.22
Any previous custodial sentences	147 (64.8%)	85 (63.4%)	.82
Parent drug user	38 (17.0%)	19 (14.7%)	.65
Parent had alcohol problem	146 (65.2%)	79 (60.3%)	.36
Parent had psychiatric disorder	77 (34.5%)	41 (31.5%)	.64
Parents separated	114 (51.4%)	74 (57.4%)	.32
Time in care as a child	58 (25.8%)	42 (31.6%)	.27
Abused as a child	83 (37.1%)	51 (38.9%)	.74
Current psychiatric diagnosis	122 (54.0%)	61 (45.9%)	.16
Current physical diagnosis	115 (50.7%)	54 (41.2%)	.10
No. medications	1.5 (2.0)	1.1 (1.5)	.02
On BDZ or Z drug	67(30.0%)	32 (24.2%)	.27
Taking any psychotropic drug	101 (44.9%)	48 (36.4%)	.12
BSI T scores			
Global Severity Index	53.6 (11.8)	50.3 (13.7)	.07
Positive Symptom Distress Index	51.7 (11.0)	48.7 (12.8)	.07
Positive Symptom Total	54.6 (12.5)	51.7 (14.7)	.12
Age first used heroin	19 (16–25)	20 (17–25)	.21
Ever injected	200 (88.5%)	107 (79.9%)	.03
Ever shared injecting equipment	97 (42.9%)	57 (42.9%)	1.0
Current route of use intravenous	144 (68.3%)	64 (54.7%)	.02
Previous methadone script	145 (64.4%)	76 (56.7%)	.18
Previous buprenorphine script	89 (39.2%)	65 (48.5%)	.10
Previous detoxification	120 (53.6%)	77 (58.3%)	.44
DRR/DTTO [a]	41 (18.1%)	23 (17.2%)	.89
DIP [b]	49 (21.6%)	40 (29.9%)	.10
Partner drug user	72 (62.6%)	38 (49.4%)	.08
Christo baseline	11.0 (0.24)	9.7 (0.32)	.001 [c]
Brief AUDIT	3.6 (3.5)	3.5 (3.3)	.84
No. illicit drugs used	4.0 (1.7)	3.5 (1.8)	.01
Baseline urine test			
Positive for opiate [d]	211 (94.6%)	122 (96.1%)	.62
Positive for cocaine	97 (43.7%)	41 (32.5%)	.05
Positive for amphetamine	10 (4.5%)	9 (7.1%)	.33
Positive for benzodiazepine [e]	57 (25.6%)	26 (20.5%)	.30
Positive for cannabis	90 (46.6%)	59 (56.2%)	.15

[a] Drug rehabilitation or drug treatment and testing order.
[b] Drug intervention program.
[c] T test.
[d] Some opioids (e.g., street methadone/buprenorphine) give a negative opiate test on EMIT screen.
[e] Considering those known to be prescribed benzodiazepines as negative.

($p < .001$). Other predictors were older age, fewer custodial sentences, not having a drug-using parent, being on a higher number of other medications, and the absence of illicit benzodiazepines and cocaine from the baseline urine (Table 3).

3.8. Beliefs and knowledge regarding buprenorphine and methadone

When participants' own beliefs about buprenorphine and methadone were compared (i.e., within-subject comparison),

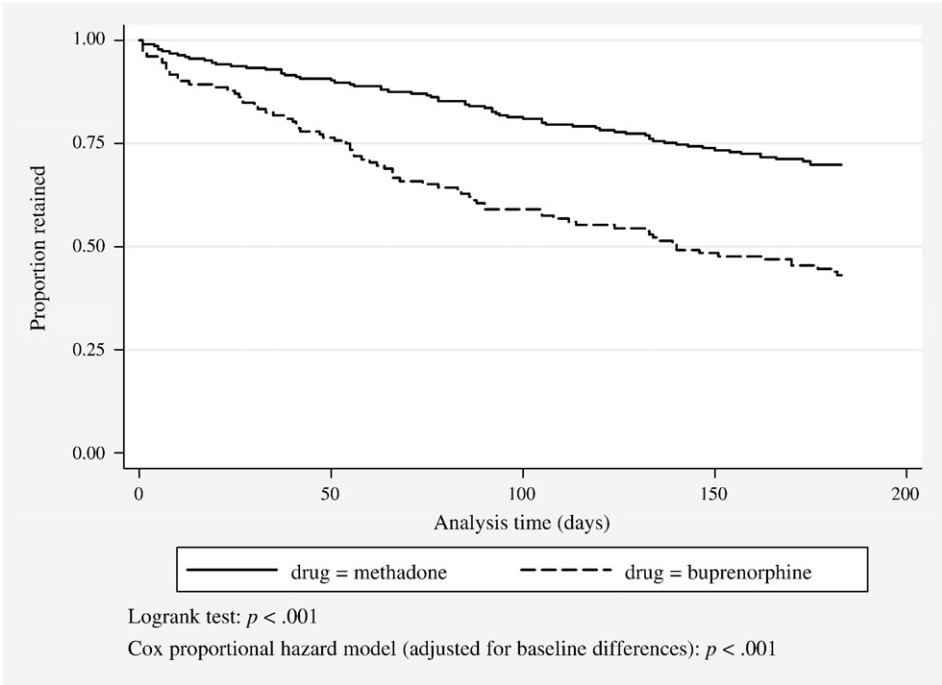

Fig. 2. Survival analysis showing retention in treatment for methadone versus buprenorphine.

it was clear that they believed these drugs to be very different (see Table 4). Most marked differences (>1 point difference, on each 1- to 5-point Likert scale) were taste (buprenorphine worst), blocking effect on heroin use (buprenorphine more effective), risk of overdose (buprenorphine safer), ease of stopping (buprenorphine easier), and time to stop (buprenorphine less). Because this was a pragmatic study, we did not have direct control over the information clinicians discussed with subjects prior to treatment initiation. However, subjects were asked about their sources of information and to identify that which they considered to be the main source in making their treatment choice. Eighty-one percent identified their own experience as their primary source of information (vs. 1% who identified drug workers as their primary source). In addition, subjects were asked separately whether they felt free choose their treatment; 92% responded that they did.

Table 2
Reasons for participants not completing study

Reasons	Methadone noncompleters (n = 69) n (%)	Buprenorphine non-completers (n = 77) n (%)
Planned detox' attempt	1 (1.5)	10 (13.0)
Transferred to other service	3 (4.3)	4 (5.2)
Client dropped out	33 (47.8)	40 (51.9)
Discharged by service		
Aggression	2 (2.9)	0 (0)
Tampered urine	3 (4.3)	3 (3.9)
Persistent on-top use	4 (5.8)	4 (5.2)
Other reason	3 (4.3)	3 (3.9)
Detained (police/prison)	18 (26.1)	13 (16.9)
Death	2 (2.9)	0 (0)

We then investigated whether those choosing buprenorphine as a group differed in their beliefs about the two drugs to those choosing methadone. This analysis demonstrated that those choosing buprenorphine appeared to have a consistently more negative view of methadone than those choosing methadone, whereas participants were reasonably consistent in their view of buprenorphine irrespective of their drug choice. In particular, those choosing buprenorphine, as a group, believed that if they used methadone, then they would be more likely to crave heroin, be less clear headed, be more drowsy, and experience more emotional numbing. They felt methadone would be harder to stop, that using methadone was more like swapping one addiction for another, and that they would be viewed more negatively by others. In contrast, the only areas where there was a difference between the two groups in views about buprenorphine were that those choosing methadone believed titration on to buprenorphine would be more uncomfortable than titration on to methadone and that craving would be less reduced on buprenorphine (see Table 5).

Next, the relationship between beliefs and retention was investigated. A small number of these were potentially significant on a univariate analysis ($p < .1$). However, when these were entered together into a multivariate analysis, only one variable (belief as to whether buprenorphine blocked the effect of heroin) remained significant after adjusting for group, age, previous custodial sentences, parental drug user, and cocaine use. The adjusted odds of retention were 5.21

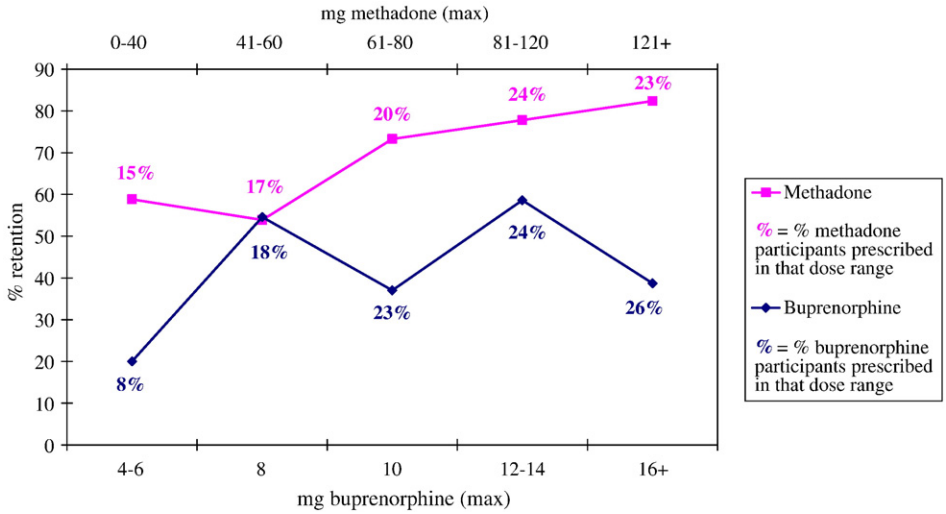

Fig. 3. Comparing retention at 6 months by maximum dose of drug prescribed.

(95% CI = 1.71–15.85, p = .004), with those believing that buprenorphine acted as an effective blocker being more likely to be retained than those who did not. However, it should be noted that more than 70% of participants considered it to be an effective blocker (retention = 63%), whereas only 6% thought it was not (37% retention).

3.9. Reasons for choice of treatment

Reasons for choice of drug were stated by 127 of 134 (95%) of those choosing BMT and 227 of 361 (61%) of those choosing MMT. For those stating a reason in the BMT group, the most commonly cited reasons for choice of drug were a negative view of methadone (52%), issues around the drug's ability to block the effect of heroin (46%), previous experience with buprenorphine (17%), beliefs about ease of detoxification (12%), and issues around intoxicating effects or a desire for clearheadedness (12%). Cited reasons did not appear to differ between those with a positive outcome and those with a negative outcome. For methadone, the reasons for choice showed greater variation with by far the most commonly cited reason being previous experience (39%), followed by fear of withdrawal at induction (8%), issues around intoxicating effects (8%) and believing that they were on too much heroin to use buprenorphine (7%). Those citing previous experience appeared to have a negative outcome more often than a positive outcome (53% vs. 33%). Of interest, all those choosing methadone because they felt they could not take buprenorphine (due to their high level of heroin use) dropped out of treatment (16 participants, 24% of methadone losses).

Table 3
Baseline variables predicting retention at 6 months on multivariate analysis

Variables	OR for retention at 6 months	95% CI	p value
Buprenorphine preferred	0.29	0.17–0.48	<.001
Age	1.05	1.01–1.08	.005
No. previous custodial sentences	0.92	0.88–0.97	.001
Parent was drug user	0.51	0.27–0.97	.04
No. of medications, M (Mdn)	1.25	1.06–1.47	.008
Baseline cocaine positive	0.56	0.34–0.93	.03
Baseline benzodiazepine positive	0.53	0.30–0.93	.03

3.10. Impact of buprenorphine availability on recruitment

Subjects choosing BMT were asked at recruitment if they would have come into treatment if methadone were the only treatment available, 38 (28% of the BMT group—10% of the total sample) answered "no" to this question.

3.11. Urine results

Those prescribed buprenorphine showed evidence of using less illicit opiate than those prescribed methadone. The odds of having opiate-negative urine samples were significantly higher for the buprenorphine group whether considering all patients (OR = 2.14, 95% CI = 1.51–3.03) or only those retained at 6 months (OR = 2.74, 95% CI = 1.77–4.22; Table 6). Evidence of sustained abstinence from heroin was also significantly more likely in the BMT group. Two proxy measures for this were used. First, a complete set of six opiate-negative urine results, and then less stringent criteria including those with five negative and one missing urine result. On either of these measures, the buprenorphine group was more likely to achieve sustained abstinence. This difference was most marked in those retained at 6 months (OR = 6.08, 95% CI = 2.15–17.16; Table 6). No significant difference was found in urine levels of other illicit drugs, which appeared to be unaffected by treatment (Table 6).

Table 4
Comparing within-participant differences in views

Views	Buprenorphine, *M* (*Mdn*)	Methadone, *M* (*Mdn*)	No. for matched pairs analysis (% subjects)	*p* value (Wilcoxon matched pairs)
Taste	1.7 (1)	2.9 (3)	290 (80)	<.001
Withdrawal at start (5 = bad withdrawal)	3.5 (3.5)	3.0 (3)	252 (70)	<.001
Hold (5 = no withdrawals)	4.2 (5)	4.4 (5)	246 (68)	.05
Craving for heroin (5 = craving stopped)	3.6 (4)	3.0 (3)	248 (69)	<.001
Change effect of heroin (5 = total block)	4.3 (5)	1.7 (1)	285 (79)	<.001
Risk of overdose (5 = low)	3.3 (3)	1.6 (1)	173 (48)	<.001
Clearheaded (5 = not at all)	1.7 (1)	2.6 (3)	258 (71)	<.001
Drowsiness (5 = very sleepy)	1.8 (2)	2.8 (3)	252 (70)	<.001
Emotional numbing (5 = emotional numbing)	1.9 (1)	2.8 (3)	214 (59)	<.001
Others' views of addiction (5 = not addict)	2.2 (1)	1.3 (1)	308 (85)	<.001
Ease of stopping drug (5 = very hard)	3.0 (3)	4.3 (5)	245 (68)	<.001
Time to stop (% days/weeks vs. months)	49.3%	12.8%	219 (61)	<.001 [a]
Swapping one addiction for another (5 = not true)	3.3 (4)	2.4 (2)	286 (79)	<.001

[a] McNemar test for matched pairs.

3.12. Christo, BSI, and brief AUDIT scores

Christo data were available for almost all retained clients at baseline, 3 months, and 6 months (94%–100% of retained subjects). Although both groups showed an improvement in Christo and BSI scores over follow-up, the changes adjusted for baseline values were not significantly different between groups. Regarding alcohol consumption, at 6 months the BMT group showed an improvement (decrease in AUDIT scores), whereas the MMT group demonstrated deterioration (increased scores; $p = .052$ between groups; see Table 7).

3.13 Side effects

A greater proportion of those receiving methadone complained of side effects than those receiving buprenorphine

Table 5
Comparison of participants' views by group about buprenorphine and methadone treatment

Views	Buprenorphine group, *M* (*SD*)	Methadone group, *M* (*SD*)	*p* value (Mann–Whitney test)
Buprenorphine taste (5 = great)	1.8 (0.9)	1.7 (0.8)	.05
Methadone taste (5 = great)	3.1 (1.1)	2.8 (1.1)	.006
Importance of taste (5 = not at all)	4.2 (1.3)	3.8 (1.3)	.01
Withdrawals experienced when starting buprenorphine (5 = yes, badly)	3.2 (1.1)	3.7 (1.3)	<.001
Withdrawals experienced when starting methadone (5 = yes, badly)	2.5 (1.3)	3.2 (1.2)	<.001
Buprenorphine stop withdrawals (hold; 5 = no withdrawals)	4.2 (1.0)	4.1 (1.1)	.55
Methadone stop withdrawals (holds; 5 = no withdrawals)	4.2 (1.0)	4.4 (0.9)	.19
Heroin craving when on buprenorphine (5 = expect cravings to stop)	3.9 (1.1)	3.4 (1.5)	.001
Heroin craving when on methadone (5 = expect cravings to stop)	2.6 (1.3)	3.2 (1.3)	<.001
Change effect of heroin when on buprenorphine (5 = totally blocked)	4.5 (0.9)	4.3 (1.1)	.15
Change effect of heroin when on methadone (5 = totally blocked)	1.5 (0.9)	1.8 (1.1)	.04
Risk of overdose on buprenorphine (5 = low)	3.4 (1.5)	3.2 (1.5)	.46
Risk of overdose on methadone (5 = low)	1.7 (1.0)	1.6 (1.0)	.40
Clearheaded on buprenorphine (5 = not at all)	1.7 (0.8)	1.7 (1.0)	.84
Clearheaded on methadone (5 = not at all)	3.1 (1.2)	2.3 (1.0)	<.001
Drowsiness on buprenorphine (5 = very sleepy)	1.9 (0.9)	1.7 (1.0)	.14
Drowsiness on methadone (5 = very sleepy)	3.4 (1.2)	2.5 (1.1)	<.001
Emotional numbing effect of buprenorphine (5 = disconnected from emotions)	1.9 (1.1)	1.8 (1.1)	.19
Emotional numbing effect of methadone (5 = disconnected from emotions)	3.4 (1.3)	2.5 (1.2)	<.001
View of other people about buprenorphine (5 = not a drug addict)	2.2 (1.4	2.2 (1.5)	.63
View of other people about methadone (5 = not a drug addict)	1.2 (0.7)	1.4 (0.9)	.04
Ease of stopping buprenorphine (5 = very hard)	2.8 (1.2)	3.1 (1.3)	.09
Ease of stopping methadone (5 = very hard)	4.6 (0.8)	4.2 (0.9)	<.001
How long to stop buprenorphine (% days or weeks vs. months)	50.5%	48.1%	.71
How long to stop methadone (% days or weeks as opposed to months)	11.2%	17.3%	.16
Buprenorphine is swapping one addiction for another (5 = not true)	3.4 (1.4)	3.2 (1.5)	.37
Methadone is swapping one addiction for another (5 = not true)	1.9 (1.2)	2.7 (1.5)	<.001
Importance of receiving a drug experienced before	3.0 (1.6)	2.7 (1.6)	.11

Table 6
Urine test results: repeated measures analysis and analysis of opiate abstinence

	All subjects			Subjects retained at 6 months		
Variables	No. of tests	OR of a negative urine sample for the BMT vs. MMT group (95% CI)	*p* value	No. of tests	OR of a negative urine sample for the BMT vs. MMT group (95% CI)	*p* value
Opiate	1,400	2.136 (1.509–3.027)	.000	1,122	2.735 (1.771–4.224)	.000
Cocaine	1,400	1.514 (0.989–2.318)	.056	1,122	1.331 (0.766–2.313)	.311
Amphetamine	1,395	0.809 (0.364–1.794)	.601	1,121	0.771 (0.260–2.290)	.640
Benzodiazepines	1,395	1.262 (0.745–2.137)	.388	1,120	1.350 (0.670–2.718)	.401
Cannabis	1,199	1.166 (0.722–1.884)	.529	969	1.432 (0.782–2.624)	.245
		OR BMT vs. MMT groups (95% CI)			OR BMT vs. MMT groups (95% CI)	
Opiate abstinence (6 negative urines)		2.693 (1.071–6.767)	.04		6.079 (2.153–17.163)	.001
Opiate abstinence (6 negative urines or 5 negative + 1 missing)		2.391 (1.122–5.096)	.02		4.748 (2.081–10.831)	.03

(55% vs. 44%, $p = .01$). The most common side effects in the MMT group were sweating (19%), sedation (12%), and constipation (10%). Side effects most frequently reported in the BMT group were sedation (9%) and constipation (8%).

3.14. Adverse events

Two patients died during the trial period, both in the methadone group. One death was due to a heroin overdose shortly after the start of treatment related to adverse social circumstances. The second was recorded as methadone toxicity in combination with two other sedative drugs in a patient prescribed the same dose for some time.

4. Discussion

This is the first large study to compare the effectiveness of buprenorphine maintenance with methadone maintenance in ordinary UK clinical practice. The results demonstrate that those treated with buprenorphine are more than 50% less likely to remain in treatment for 6 months than those receiving methadone (adjusted hazard ratio = 0.47, 95% CI = 0.32–0.69, $p < .001$). This is considerably greater than the effect size pooled from randomized controlled trials (relative risk = 0.85) by Mattick et al. (2008) and similar to that Burns et al. (2009) found in a large (nonrandomized) retrospective cohort study. However, this poorer retention needs to be balanced against a finding of superiority in suppression of illicit opiate use by buprenorphine in those who were retained. This was demonstrated in several ways including an overall reduction in the number of urine samples positive for opiates, increased rates of sustained abstinence from illicit use, and increased rates of progression to detoxification. These findings are in contrast to previous randomized trials but similar to the results that Vigezzi et al. (2006) found in another nonrandomized, nonblinded field trial. In addition, our results suggest that BMT may be associated with reduced alcohol use but did not demonstrate any difference in social functioning or psychological health.

The hypothesis that poor retention is due to slow titration or inadequate dosing is not supported by the results of this trial. Rapid titration was achieved, and although loss during titration was more common in the BMT group and made a small contribution to the overall outcome, an increased rate of loss was seen throughout the trial. The mean maximum doses of buprenorphine achieved (11.7 mg) were slightly below the current UK guidelines (12–16 mg for most patients; DOH, 2007) but in the upper range of the doses used in the flexible dosing trials Mattick et al. (2008) included in the Cochrane review, almost identical to estimated average doses found in Australian clinical practice by Burns et al. (2009) but above the average dose (8.9 mg) found in a recent national audit of actual prescribing 2004–2005 by the NTA (2007). Dosing was flexible, and subjects did not appear to seek higher doses. In fact, more of those on buprenorphine chose to reduce their dose than to increase it. Furthermore, our results suggest that above 8 mg increasing doses for buprenorphine did not improve retention. No studies to date have specifically compared retention for doses greater than 8 mg, but four studies, which examined dose of buprenorphine as a predictor of retention in a secondary analysis, failed to find a relationship (Gerra et al., 2004, 2006; Soyka, Zingg, Koller, & Kuefner, 2008; Vigezzi et al., 2006). Kakko et al. (2007) reported 78% retention using a very high mean dose (29 mg), but this was an intention-to-treat analysis where only 35% of the BMT group actually remained on buprenorphine at 6 months.

Examination of predictors of retention in the sample as a whole revealed treatment of choice as by far the strongest factor. Additional predictors (older age, fewer custodial sentences, and absence of drug-using parents), although less powerful, made intuitive sense. Additional use of benzodiazepines and cocaine/crack is known to negatively effect prognosis (Marsden et al., 2009; Rooney, Kely, Bamford, Sloan, & O'Connor, 1999). The use of more prescribed medications was surprising but could imply more engage-

Table 7
Comparison of Christo, AUDIT, and BSI scores over follow-up

Measures		Baseline, *M* (*SD*)	*p* value[a]	3 months, *M* (*SD*)	*p* value[a]	6 months, *M* (*SD*)	*p* value[a]	Mean change 0–3 months (*SD*)	*p* value[b]	Mean change 0–6 months (*SD*)	*p* value[b]
Christo	Bup	9.7 (3.7), *n* = 133	.044	5.9 (3.8), *n* = 77	.014	5.5 (3.5), *n* = 57	.121	3.9 (3.6)	.098	4.4 (3.8)	.205
	Meth	11.0 (3.6), *n* = 227		7.1 (4.0), *n* = 187		6.5 (3.8), *n* = 156		3.6 (4.3)		4.2 (4.2)	
Audit	Bup	3.5 (3.3), *n* = 134	.843	3.9 (3.5), *n* = 46	.546	3.0 (3.3), *n* = 31	.193	0.0 (3.6)	.863	0.8 (3.9)	.052
	Meth	3.6 (3.5), *n* = 227		3.5 (3.0), *n* = 101		3.9 (3.3), *n* = 84		0.5 (2.9)		–0.7 (3.0)	
GSIT	Bup	50.3 (13.7), *n* = 133	.066	50.2 (12.1), *n* = 46	.649	50.2 (13.4), *n* = 31	.779	2.3 (11.9)	.995	2.0 (12.5)	.852
	Meth	53.6 (11.8), *n* = 227		51.5 (13.3), *n* = 101		51.7 (14.1), *n* = 85		2.8 (10.1)		2.0 (11.7)	
PSDIT	Bup	48.7 (12.8), *n* = 133	.071	47.9 (11.0), *n* = 46	.759	45.2 (11.6), *n* = 31	.197	2.3 (11.1)	.970	5.2 (12.0)	.362
	Meth	51.7 (11.0), *n* = 227		49.3 (12.5), *n* = 101		49.0 (13.6), *n* = 85		3.0 (9.9)		3.9 (10.7)	
PSTT	Bup	51.7(14.7), *n* = 133	.122	52.4 (13.0), *n* = 46	.818	52.5 (13.4), *n* = 31	.808	1.1 (12.1)	.468	0.5 (14.1)	.878
	Meth	54.6 (12.5), *n* = 227		52.1 (12.6), *n* = 101		53.5 (13.95), *n* = 85		3.0 (10.7)		0.6 (13.0)	

Note. Those retained at time of measurement only. Sample sizes for changes correspond to those of corresponding follow-up period. Changes for all measures are baseline minus follow-up, positive is improvement as in all cases higher scores = worse health state. GSIT = Global Severity Index T score; PSDIT = Positive Symptom distress index T score; PSTT = Positive Symptom Total T score.

[a] Wilcoxon Mann–Whitney.

[b] Linear regression including baseline measurement as independent variable.

ment with treatment systems or experience of more negative consequences of drug use leading to greater motivation to engage. The numbers retained were too small to confidently examine baseline predictors of retention in the buprenorphine group separately. Previous studies, which have examined baseline factors, identified comorbid depression and chronicity of dependence, but these have not been successfully replicated (Gerra et al., 2004, 2006; Poirier et al., 2004; Schottenfield, Pakes, & Kosten, 1998; Soyka et al., 2008).

Rather than any simple demographic variable, an alternative hypothesis is that the disparity in retention between methadone and buprenorphine is more closely related to the match between individuals' needs, treatment aspirations, and expectations.

Firstly, with regard to aspiration, maintenance treatment is usually considered as a route to abstinence from illicit drug use. However, for some injecting drug users, it may be seen as a means to reestablish control over their use, allowing them to comfortably forgo alternative opiates (usually heroin) but retain the option to use occasionally, either recreationally or as a coping strategy. Although possible, this is less easy for those using buprenorphine, a drug that blocks opiate receptors. It is possible, therefore, that more of those choosing methadone did so with these more achievable aspirations. The finding that retention was prolonged in those who expressed stronger baseline beliefs about buprenorphine as a "blocker" with less intoxicating effects, and chose not to take it, supports such a hypothesis. Furthermore, those choosing methadone commonly cited fear of withdrawal and issues around desire for expected opioid effects as reasons for choosing it.

In contrast, apart from a dislike of methadone, those choosing buprenorphine commonly cited its ability to block heroin use, ease of detoxification, and lack of intoxicating effects as reasons for their choice. This may reflect higher aspirations around elimination of illicit opiate use and detoxification. A previous study (Pinto, Rumball, & Holland, 2008) found that buprenorphine is often viewed as a drug for those who are "serious" about treatment. Although this would explain the better performance in this group regarding illicit opiate use, it would also leave those individuals who failed to achieve these more challenging goals vulnerable to disillusionment and disengagement. Secondly buprenorphine is intrinsically less rewarding than methadone and provides less sedative effect. This might have been expected to be of particular value to those expressing more psychological distress, but BSI scores did not predict retention in this study. Finally, because of its reduced potency, a prescription for buprenorphine may simply be easier for subjects to disengage from than high-dose methadone.

The numbers lost to treatment on BMT are of concern, and the authors suggest that further research should focus on the relationship between treatment aspirations, treatment choice, and retention in treatment.

Exploration of subjects' views about the drugs revealed that they are generally very well informed, with the largest perceived differences between the drugs being in taste, ability to block heroin use, and ease of coming off the drug. The stated reasons for choice, in addition to aspirations, revealed more about what is perceived to be important. Past experience was commonly cited by both groups, but safety was rarely mentioned, highlighting the mismatch in priorities between patients and their clinicians.

The pragmatic, open-label design of this study has strengths and weaknesses. A very high recruitment rate was achieved (89% of the eligible population), and subjects received the treatment available in ordinary National Health Service (NHS) community drug services. This makes the results highly generalizable. However, the limitations must be acknowledged. The absence of randomization is one limitation. Although the groups appeared similar on most baseline variables, there were some differences between groups. These differences suggested that the methadone group had more risk factors for poor retention. Despite this, adjustment for baseline differences only increased the gap in retention rates between BMT and MMT. Nevertheless, we cannot be certain that unmeasured differences did not favor the methadone group. No measures were taken to reduce the possible impact of the views and expectations of treating staff and subjects because these are inevitably present and contribute to effectiveness in real clinical practice. In addition, we deliberately included an exploration of subjects' beliefs and expectations as a part of our study. Furthermore, because of the pragmatic nature of the trial, we were unable to dictate the frequency of urine sampling. As a result, our data are restricted to one per month, which gives only a limited picture of possible drug use and therefore weakens the findings regarding suppression of illicit use.

The marked difference in retention rates raises important issues regarding the use of buprenorphine for maintenance in the UK, where commissioners have imposed targets of 80% retention at 3 months, linked to funding (BMT falls below this at 61.2%, whereas MMT reaches 84.1%). In addition, buprenorphine is more expensive than methadone. However, the extra cost may be offset for services (treatment is free for NHS patients) if BMT increases progression to abstinence and detoxification allowing shorter episodes of treatment. Our results also provide evidence that the availability of buprenorphine recruits additional individuals into treatment. Not only did 10% of the sample state that they would not have entered treatment where methadone is the only available option, but all of those accepting MMT because they thought they could not be titrated on to BMT dropped out of treatment. In addition, the group choosing BMT expressed a more negative view of methadone, and more than half cited dislike of methadone as the reason they chose buprenorphine. This would suggest that although buprenorphine should, as per NICE Guidance, be an available option for all, services should closely monitor those on this drug for the first 3 months and maintain a low threshold for conversion to methadone for those not achieving illicit abstinence.

In conclusion, this study has shown that in a UK drug treatment context, those choosing methadone maintenance are considerably more likely to be retained in treatment at 6 months than those choosing buprenorphine. This difference appears unrelated to dose, titration procedure, or subjects' beliefs and expectations about the drugs. Those retained on buprenorphine appear more able to suppress illicit opiate use and progress to detoxification. In addition, provision of buprenorphine has merits in increasing recruitment to treatment.

5. Addresses of sites

Trust Alcohol and Drug Service, NWMHPT, Norfolk, England:

- 7 Unthank Road , Norwich NR2 2PA,
- 22-24 Colgate, Norwich NR3 1BQ
- The Weavers Centre, Hellesdon Hospital, Drayton High Road, Norwich and
- The Willows Centre, Northgate Hospital, Northgate, Great Yarmouth.

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