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Research Article

Buprenorphine/Naloxone and Methadone Opioid Replacement Therapy: A 2-Year Follow-Up Study and Health Economic Analysis

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Abstract

Background

Opioid Replacement Therapy (ORT) is the main UK treatment for opiate dependency. Both methadone and buprenorphine-based drugs are licensed for this purpose in the UK with over 25,000 people prescribed in Scotland, mostly receiving methadone. Choice of ORT agent reflects historic guidance that methadone was the 'first line' recommendation if both were suitable. Now, evidence suggests that both are equally effective, although concerns regarding a higher risk of methadone overdose have been raised. Many factors, including higher costs and time commitment to dispense buprenorphine-based products, however, may have affected their wider use in the UK. Clinicians require better evidence to inform their clinical decisions. This study considers a cohort of treatment-seeking opiate-dependent individuals in a single health board area in Scotland, prescribed methadone or buprenorphine/naloxone ORT, comparing 2-year retention rates with the costs of treatment delivery and health care utilization.

Methods

We compared 62 patients receiving buprenorphine/naloxone (as Suboxone©) with 175 receiving methadone ORT (Total N=237). The health economic component reports only those for whom a complete dataset was available (n=212). Administrative NHS data was used to assess treatment retention and costs over a two year period. Costs included those associated with ORT delivery as well as broader healthcare utilization.

Results

No statistically significant differences were found with respect to retention rates or healthcare costs though the Cost Effectiveness Plane (CEP) showed considerable uncertainty in these results implying that retention may be greater in the methadone group.

Conclusion

This study suggests that, when combining all treatment delivery and additional healthcare costs, buprenorphine/naloxone is broadly equivalent in cost effectiveness to methadone ORT when delivered in the NHS system. Retention rates over 2 years were also comparable. These data may support the view that buprenorphine/naloxone represents a cost-neutral alternative ORT to that of methadone.

Keywords: Buprenorphine; Health economic analysis; Methadone; Opioid dependency

Introduction

The prevalence of opiate dependency in the UK is estimated at 1.1% (ages 15-54) with over 130,000 patients reported to be receiving clinical treatment for this disorder [1]. Though other substances are more commonly used, the most prevalent illicit drug associated with opioid dependence is heroin. In Scotland, prevalence is higher than the rest of the UK. It is estimated that there were 61,500 people, aged 15-64 years, using opiates in 2012/13, reflecting 1.74% of the general population, an increase of 3% from 2009-10 [2]. Heroin dependence is associated with many harms, including premature deaths (usually from overdose), which have fluctuated around an upward trajectory over the last twenty years [1]. In 2015 there were 3674 deaths reported in England and Wales-a record high [3]. In the same year there were 706 drug-related deaths in Scotland, 15% more than in 2014, with 86% of these potentially attributed to one or more opioids [4]. As well as the risk associated with the pharmacological properties of opioids, opioid users are more likely to experience comorbid physical and mental health problems which may impact on risk and recovery potential [5]. Indeed, concern about Blood Borne Virus (BBV) infections in injecting drug users has driven the development of interventions to reduce harm-including the increased access to Opioid Replacement Therapy (ORT). Drug use also carries a wide range of social consequences which may be positively influenced by engagement in effective treatment [6]. Opioid misuse contributes significantly to social exclusion with users experiencing high rates of homelessness, unemployment and imprisonment resulting from acquisitive crime or prostitution [1]. In this context, it has been estimated that annual costs associated with drug misuse in the UK could be as high as £21 billion in the UK [7].

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Choice of ORT agent

For thirty years, treatment for illicit drug misuse has focused on reducing drug-related harms. Opioid Replacement Therapy (ORT), using the drugs methadone and buprenorphine, are effective treatments that can reduce these harms [5]. Availability of ORT shows considerable variation across the UK [8]. Since the mid noughties, however, it has also been recognised that services should offer greater choice and personalised/tailored care to match an individual's aspirations and risks, with the aim of delivering an improved likelihood of progress and "recovery". Clinically, this has proven a difficult balance to achieve-with some changes in the commissioning of treatment in England and Wales, aiming to encourage progress towards a drug-free lifestyle, potentially being associated with increases in drug-related risks and death [9]. The mainstay UK ORT drug-methadone mixture-has also become a focus of concern with some commentators, arguing that its pharmaceutical effects could reduce recovery potential [10]. Consequently, the selection of ORT drug has remained the focus of debate.

Methadone ORT has been the most common UK treatment for opioid dependence since the 1980s and it is now estimated that some 25,569 people are prescribed this treatment in Scotland [8]. At the turn of the millennium, after successful introduction in mainland Europe, pharmaceutical products based on the opioid agonist/antagonist agent buprenorphine were promoted as an alternative treatment in the UK [11]. Both agents have been associated with a range of positive health, social functioning and criminal justice outcomes. Overall, the accumulated evidence is now felt to support the view that these treatments are equally effective [8,12]. Until recently, however, UK guidance, suggested a hierarchy of use-with methadone preferred if both were clinically indicated [13]. Reflecting the developing evidence-base, the most recent UK treatment guidance, however, has now put both agents on a more equal footing [5].

But these treatments have key clinical differences in terms of patient-experience and delivery. Because of partial antagonist activity, buprenorphine induction presents clinical challenges and potentially more early drop-outs [12]. Additionally, until recently, buprenorphine-based agents were available only as sub-lingual tablets that require longer pharmacy visits, increasing associated costs when supervised dispensing is required. This may be one reason that, while the relative proportions fluctuate, buprenorphine prescribing remains less common than methadone [8]. Also, in urban community pharmacies, where there may be large numbers of patients receiving supervised ORT, the additional time commitment may limit access to ORT if sub-lingual buprenorphine-based products are preferred.

On the other hand, epidemiological studies in the UK have queried increased overdose risk associated with methadone prescribing when compared to buprenorphine [14]. As UK drug deaths are now a major concern, this phenomenon may be one reason that more recent national data has shown an increase in the proportion of buprenorphine prescribing in Scotland [8].

Health economic evaluations

International studies have suggested that methadone ORT may deliver better retention than buprenorphine [15-18]. However, none was set in a UK treatment setting. Although evidence has shown methadone to be broadly less expensive to deliver than buprenorphine-based ORT, one UK health economic evaluation suggested that buprenorphine/naloxone was actually less costly than methadone. This study also found that, while methadone was associated with better rates of 6 month retention in treatment, buprenorphine/naloxone was more likely to support achieving abstinence [19].

There is little evidence on the difference in wider health care costs between ORT with methadone and any of the standard buprenorphine-based treatments (generic, Subutex© or Suboxone©). As more varied formulations of buprenorphine-such as depot preparations - have become available in the UK recently [20], more valid evidence is required to help direct clinical care delivery, ensuring that patients receive the most appropriate ORT.

Aims and objectives

This study aimed to:

1. Assess treatment and wider health care costs associated with methadone and buprenorphine/naloxone ORT;
2. Assess the relative rates of retention in treatment at two years;
3. Compare the cost-effectiveness of these drugs.

Methods

Sample

In 2014, an audit sample had been derived from a community-based National Health Service (NHS) addiction treatment service in a Scottish region-NHS Fife Addiction Services (FAS). This sample comprised of 62 opiate-dependent ORT cases prescribed the buprenorphine/naloxone product Suboxone® and 175 who were prescribed methadone. Representativeness of the study sample at baseline was evaluated by comparing key characteristics with those of the total FAS treatment population.

Data acquisition process

This study used patient-identifiable baseline data from a 2014 service audit. These data were then linked, using unique identifiers, with a range of validated health informatics datasets describing prescribing information, clinical contacts and outcomes over the study period. Informatics techniques were then used to deliver an anonymised dataset to researchers for analysis.

Datasets accessed

The datasets utilised included: Locally compiled datasets, including NHS Fife Addiction prescribing (FA); national datasets, including: Community Prescribing (CP)-all prescribed medications by case; A&E attendances; out-patient attendances by service-SMR (Scottish Morbidity Record) 00; General Hospital admissions (SMR01); Psychiatric Hospital admissions (SMR04) and General Register Office for Scotland (GROS) records for deaths.

Cost estimation

A micro-costing exercise was conducted following the methods of technology appraisal recommended by the Scottish Medicines Council (SMC) [21]. Treatment costs included: Costs of the drugs themselves; dispensing fees (to pharmacists associated with dispensing controlled drugs); instalment fees (relating to daily dispensing); supervision costs(relating to supervision responsibilities);and visits to the drug service (staff time). The financial year of 2012/13 was used for all unit costs. For costs occurring in the second year a discount rate of 3.5% was applied. Costs used are shown in table 1.

Treatment	Unit Cost		Reference
	Methadone	Buprenorphine/ Naloxone	
Dispensing fee	£2.15	£2.15	(ISD Scotland 2012/13)
Instalment fee	£1.79	-	Recorded by study
Supervision fee	£1.40	£3.40	Recorded by study
Drug service visit	£60.00	£60.00	(ISD Scotland 2012/13)

Table 1: Unit costs of treatment.

In order to cost the treatment, two datasets were combined: The NHS Fife Addiction (FA) and the Community Prescribing (CP) data. Start dates were chosen for each cohort member as the closest date in either file to October 2011. The NHS Fife Addiction (FA) dataset provided prescription cycles (28 days) as well as a record indicating when pharmacist supervision was required. However, as this local dataset was incomplete, the national Community Prescribing (CP) data was used to address any gaps. This CP dataset contained no indication of prescription cycles or supervision, and did not have accurate prescribing initiation dates (as in these records these were rounded up or down to the nearest month), but was used only to fill gaps in the FA data. Assumptions were made as to the presence of duplicated data based on the dates and doses recorded. In cases where it was not possible to tell if prescriptions were duplicates or not, the CP data was kept in the final combined dataset. Although this may lead to overestimating of the treatment costs overall, it kept the calculation method consistent across the two drug groups and ensured no underestimation of costs. The FA dataset was also found to contain some overlapping dates on prescription records. When identified, these records were assessed by two clinicians in the study team who advised these anomalies were likely due to changes in doses mid 28 day cycle (reflecting more urgent dose adjustments during this phase of treatment). The cycles were adjusted accordingly to reflect shorter cycles on different doses of the ORT drug.

Treatment delivery costs

The treatment was costed using cost per unit of drug, calculated from the Prescription Cost Analysis 2012/13, multiplied by the total dosage for each cycle [22]. The chemical name, dosage and form were used to calculate a weighted average. To each individual prescription an average dispensing cost of £2.15 was then added [23]. Methadone (but not buprenorphine/naloxone) incurred an instalment cost of £1.79. FA data for that participant was used to estimate whether the prescriptions were supervised or not. The FA data, however, did not inform us on how many days the participant was supervised. Therefore, following expert clinical review (and reflecting local standard practice) it was agreed that we should normally assume 6/7 days supervision in a 28 day cycle. The CP data also had no recorded prescription length, so we costed supervision/instalments by counting the number of days in a block of entries from the community data for either supervision or instalments. This pragmatic solution could be applied consistently throughout the whole dataset. Supervision costs were calculated from NHS Fife Pharmacy Services for the period 2011 to 2013 with supervision costing £3.40 per visit for Suboxone© (the form of buprenorphine/naloxone used exclusively in the study area) and £1.40 for methadone.

Regarding service attendances, the FAS standard was that an ORT patient would be seen at clinic on a monthly basis-whatever drug was prescribed. Additional visits may be organised at times of higher risk, when contact may be escalated. We therefore costed one monthly visit with a nurse as the minimum that would have occurred. This was costed using the average nurse-led outpatient clinic visit unit cost (£60), since no specific drug service costs were available.

Healthcare resource utilization

In order to cost the 2 year healthcare resource use, a predicted end date was generated for each participant by adding 730 days to their start date. The administrative files were then filtered using the start and predicted end date. Any NHS resource use within this period was then costed (with the second year discounted at 3.5%). For baseline adjustment, the six month period before the participants' start date was also costed.

Out-patient clinic attendances: Outpatient visits at the addiction service were categorised as either a consultant or nurse-led clinic and then separated into different specialities. The costs book, compiled by ISD, was applied using clinic type and speciality [23]. Within the outpatient data, some visits were classed as Did Not Attend (DNA), with no prior warning. For this we costed full amount, assuming staff time could not be reallocated.

Hospital attendances: For A&E attendances, visits were costed using the cost book giving an average unit cost for an attendance at A&E. Ambulance transport incurred an additional cost. Any subsequent hospital admission was costed within the inpatient data. Inpatient data was split into three categories: Inpatient days, day cases and inpatient days-less than one (representing a short stay). These were then costed by speciality. For inpatient days - more than one, the cost per bed day was multiplied by the number of days. For day cases, a cost per case was applied. For those inpatient days - less than one, the one day cost was applied as a conservative estimate, since no standard short stay costs were available [24]. The cost per speciality came from patient-level data (including procedures) acquired from NHS Scotland [25].

Outcome measure

Our primary outcome measure was 2 year retention in treatment. If the participant had a gap greater than 28 days at any point, they were considered not retained and treatment data was not costed from then. If the treatment duration was less than two years by more than 28 days, they were also considered not retained.

Cost-Effectiveness Analysis (CEA)

Incremental cost-effectiveness analysis was performed to combine the identified costs with the outcome. Where applicable a Cost-Effectiveness Ratio (ICER) was calculated. The mean difference in costs between the two groups was compared with the mean difference in effectiveness. The below formula is for the ICER, whereby Δ represents difference, E represents effects, C represents the cost of the intervention, while subscripts 'I' and 'UC' refer to intervention and usual care, respectively.

$$\mathrm{ICER} = \frac{\Delta C}{\Delta E} = \frac{C_I - C_{UC}}{E_I - E_{UC}}$$

If, however, one treatment was both more effective and less costly, this treatment was said to be 'dominant' and an ICER deemed unnecessary.

Handling uncertainty

The non-parametric bootstrap re-sampling technique was employed to explore the sensitivity of calculated costs and effect [26]. Cost and outcome data were bootstrapped to account for skewness, sampling with replacement and observation 5000 times to generate a new population of sample means with an approximate normal distribution. These bootstrap results were then displayed graphically using a Cost-Effectiveness Plane (CEP) to show the uncertainty surrounding the mean estimates of incremental costs and effects.

Sensitivity analysis

In addition to the primary analysis, a sensitivity analysis was undertaken to repeat the cost-effectiveness using mean imputation for missing variables. Since there were 19 participants who crossed over to another treatment during the study period, a sensitivity analysis excluding these participants was also conducted. Once more, the outliers for wider health care resource use at baseline were explored and those more than three times the group standard deviation were excluded from the analysis.

Information and research governance

Standard operating procedures at HIC Services, University of Dundee, were followed to ensure anonymization of the dataset. HIC Services is a University of Dundee/NHS research support unit within the Tayside Medical Science Centre (TASC). It operates a secure "safe haven" environment with robust data governance for the provisioning of clinical data to academics for research (http://medicine.dundee.ac.uk/hic). Relevant permissions were obtained prior at the inception of the 2014 audit as was NHS Research and Development (R&D) permission - obtained through NHS Research Scotland (NRS). Ethical approval was obtained from the East of Scotland Ethics Committee. The Fife Caldicott Guardian granted permission to access NHS Fife electronic extractions. Updated permissions were subsequently obtained for the 2 year follow up study.

Results

Representativeness of sample

The study population was found to be representative of FAS total population with regard to age, gender profile and stability of housing. There were significant differences, however, regarding employment status at baseline, with high rates of unemployment observed in the study sample population (92%) compared to the overall FAS population (81%). This reflected particularly high levels of unemployment in the study methadone group (99%) while the buprenorphine/naloxone group had a lower unemployment rate (79%). Also, while self-reported mean heroin use in the study sample was representative of the FAS population as a whole, the proportion reporting injecting was significantly higher in the sample population (11%) than in the FAS total population (4%). The study sample therefore had higher levels of unemployment and intravenous drug use when compared to the total service population, reflecting significantly higher rates in the methadone treated sample.

Exclusions

Of the 244 participants included at study inception (FAS audit), three were excluded from this analysis. One was missing from the FA dataset; one had conflicting data in the CP and FA dataset; one was represented in both the buprenorphine/naloxone and methadone cohorts. Of the remaining 241 participants, 29(12%) were missing other key data and so were excluded. Subsequently, 212 participants were included within the basecase analysis. The baseline characteristics following this exercise are shown in table 2.

Comparison of baseline characteristics following these exclusions showed that buprenorphine/naloxone and methadone groups did not differ by age (t-test: p=0.522), gender (χ2test: p=0.474) in the basecase, nor in the mean imputation analysis (Table 2). Figure 1 reports the scores at baseline for both groups and analyses using the Scottish Index of Multiple Deprivation [27], which is divided into quintiles from 1 (most deprived) to 5 (least deprived). There were no statistically significant differences between groups in the basecase analysis (ANOVA: p=0.224) nor the mean imputation analysis (ANOVA: p=0.130).

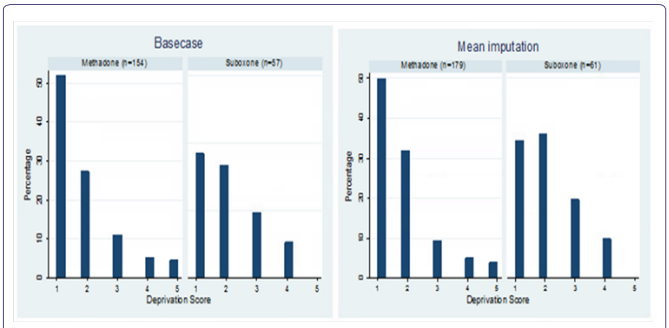

Figure 1: Baseline deprivation scores by treatment group.

Outcome-retention in treatment

One participant in the buprenorphine/naloxone group successfully completed treatment before the two-year study period, indicated by a recorded change in medication to the opioid blocker Naltrexone. This participant was therefore inputted as retained. Those that died during treatment were inputted as not retained. Some 57% of buprenorphine/naloxone and 69% of methadone cases were retained. The adjusted difference was calculated using a logistic regression as the outcome was binomial and is reported as an odds ratio. This difference was not statistically significant in the basecase analysis [OR=0.64 (95% CI=0.34 to 1.21, p=0.171)] nor the mean imputation sensitivity analysis [OR=0.58 (95% CI=0.31 to 1.05, p=0.073)].

Treatment delivery costs

Costs reflected drug cost, dispensing fees, instalment cost and supervision fee where applicable as well as costs associated with a monthly drug service review visit. The basecase analysis revealed the buprenorphine/naloxone group had a greater number of dispensed items, but was subject to significantly less supervision (T-test: p<0.001). Although the buprenorphine/naloxone group did not incur an instalment cost, some participants crossed over to methadone during the study, incurring instalment costs in 30 cases. Service attendances were the same for both groups. The mean imputation analysis revealed similar results to the basecase. The mean treatment costs of the two groups were compared using a Generalised Linear Model (GLM) with a gamma distribution (Table 3).

	Basecase			Mean Imputation		
	Methadone (n=154) (SD)	**Buprenorphine/ Naloxone (n=57) (SD)**	**p-value**	**Methadone (n=179) (SD)**	**Buprenorphine/ Naloxone (n=61) (SD)**	**p-value**
Age	36 (8)	37 (10)	0.5217	36 (8)	37 (10)	0.5694
% Female	35%	30%	0.474	34%	31%	0.675

Table 2: Baseline characteristics.

	Basecase		Mean Imputation	
	Methadone (n=154) (SD)	**Buprenorphine/ Naloxone (n=57) (SD)**	**Methadone (n=179) (SD)**	**Buprenorphine/ Naloxone (n=61) (SD)**
Pharmaceuticals	£425 (£324)	£2381 (£1500)	£426 (£324)	£2382 (£1501)
Dispensing	£1337 (£348)	£1373 (£273)	£1337 (£352)	£1348 (£298)
Instalments	£1113 (£322)	£52 (£207)	£1106 (£331)	£49 (£200)
Supervisions	£405 (£308)	£356 (£554)	£427 (£331)	£401 (£596)
Visits	£1337 (£361)	£1327 (£298)	£1343 (£353)	£1327 (£298)
Total	£4612 (£1212)	£5552 (£1819)	£4639 (£1256)	£5507 (£1848)
Adjusted difference (95% CI)	£918 (£406 to £1430)		£854 (£361 to £1347)	
	p<0.001		p=0.001	
Unadjusted difference (95% CI)	£938 (£432 to £1446)		£868 (£372 to £1364)	
	p<0.001		P=0.001	

Table 3: Summary of mean treatment costs.

Note: *GLM model adjusted for age, sex and deprivation score (baseline characteristics).

The adjusted difference in mean total treatment costs was £918 greater for buprenorphine/naloxone, driven by the mean cost of the drug formulation (Suboxone©). This difference was statistically significant. The mean imputation analysis results showed buprenorphine/naloxone treatment costs to be £854 greater than for those with methadone. Again this difference was statistically significant (p<0.001).

Wider health care costs

Regarding use of healthcare services, participants prescribed buprenorphine/naloxone were found to have fewer A&E attendances (0.9 vs. 1.7); fewer acute hospital inpatient days (0.4 vs. 1.4) and psychiatric hospital inpatients days (0.481.3 vs. 1.30.48); the same number of outpatient visits (2.6 vs. 2.6) and more day case attendances (0.2 vs. 0.0). The most widely used outpatient facility was for mental illness and the most widely used inpatient facility was for acute medicine. For buprenorphine/naloxone, 26% and for methadone 33% of outpatient visits were recorded as DNAs. The mean imputation analysis showed very similar results to that of the basecase, with just marginally greater inpatient days and psychiatric days for the methadone group. The associated wider health care costs are presented in table 4. Total health care costs were -£1258 (95% CI=-£2502 to -£13, p=0.048) lower for the buprenorphine/naloxone group after adjusting for baseline costs and characteristics. The mean imputation analysis did not reach statistical significance with the adjusted regression (p=0.197).

Total costs

Total costs of treatment delivery and healthcare utilization are summarised in table 5. The primary analysis results showed no statistically significant differences in costs between the methadone or buprenorphine/naloxone ORT groups.

Cost-effectiveness analysis and uncertainty

The degree of uncertainty relating to any differences is reflected in the Cost-Effectiveness Plane (CEP) presented in figure 2. This cost-effectiveness scatter plot was produced from the bootstrapping results for the difference in retention (presented as an odds ratio) and difference in cost. The results of the 5000 re samples were plotted on a cost-effectiveness plane, visually displaying any uncertainty surrounding the mean differences in costs and retention between buprenorphine/naloxone and methadone. The majority of the plots are concentrated in the bottom right and bottom left quadrants, suggesting there was considerable uncertainty about which treatment was less costly. The finding that there are fewer results in the northern quadrants may imply that methadone is more effective at retaining participants. Through bootstrapping the results, 95% confidence intervals were also generated for both incremental cost and retention. The results were an incremental cost of-£121 (bootstrapped 95% CI=-£1498 to £1053) and retention odds ratio of 0.64 (bootstrapped 95% CI=-0.33 to 1.29).

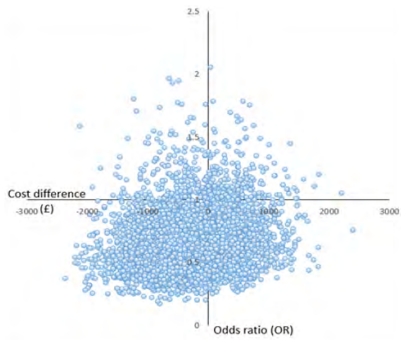

Figure 2: Cost Effectiveness Plane (CEP).

	Basecase		Mean Imputation	
	Methadone (n=154) (SD)	**Buprenorphine/ Naloxone (n=57) (SD)**	**Methadone (n=179) (SD)**	**Buprenorphine/ Naloxone (n=61) (SD)**
Outpatient cost	£368 (£611)	£397 (£825)	£356 (£587)	£397 (£801)
A&E cost	£381 (£559)	£161 (£350)	£383 (£547)	£160 (£468)
Inpatient cost	£1330 (£4476)	£466 (£1650)	£1652 (£6991)	£445 (£1620)
Psychiatric hospital cost	£547 (£3173)	£201 (£1410)	£917 (£5994)	£202 (£1365)
Community prescribing cost	£513 (£725)	£728 (£1261)	£501 (£695)	£730 (£1248)
Total	£3147 (£5766)	£1956 (£3103)	£3811 (£9934)	£1935 (£3008)
*Adjusted Difference (95% CI)	-£1258 (-£2502 to -£13)		-£1207 (-£3039 to £625)	
	p-value=0.048		p-value=0.197	
**Unadjusted Difference (95% CI)	-£1383 (-£2617 to -£148)		-£1570 (-£2869 to -£272)	
			p-value=0.018	

Table 4: Wider health care costs.

Note: *GLM model adjusted for baseline cost/characteristics; **GLM model adjusted for baseline cost.

	Basecase		Mean Imputation	
	Methadone (n=154) (SD)	**Buprenorphine/ Naloxone (n=57) (SD)**	**Methadone (n=179) (SD)**	**Buprenorphine/ Naloxone (n=61) (SD)**
Treatment	£4612 (£1212)	£5552 (£1819)	£4639 (£1256)	£5507 (£1848)
Healthcare	£3147 (£5767)	£1956 (£3103)	£3811 (£9934)	£1935 (£3008)
Total	£7760 (£5875)	£7508 (£3631)	£8450 (£9828)	£7443 (£3579)
*Adjusted Difference	£-121 (-£1341 to £1098)		-£697 (-£1957 to £581)	
	p=0.846		p=0.285	
**Unadjusted Difference	£-257 (-£1580 to £1067)		-£894 (-£2429 to £641)	
	p=0.704		p=0.254	

Table 5: Cost per participant during two year study period.

Note: *GLM model adjusted for baseline cost/characteristics; **GLM model adjusted for baseline cost.

Sensitivity analysis

Sensitivity analyses were carried out to test the robustness of the results. This included: Excluding the 19 participants who crossed to the other ORT treatment during the follow up period; excluding outliers in terms of health care costs at baseline and excluding those who died during the study. Regarding cross over, more Suboxone© participants (10 cases-18% of sample) crossed over than Methadone (9 cases-6%) and their mean age was slightly lower than the average of the whole group at baseline. The percentage of females was similar in both groups (50% Suboxone, 44% methadone). Their SIMD scores are reported in figure 3.

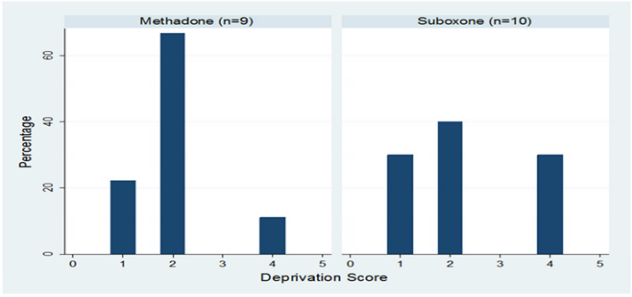

Figure 3: Crossover deprivation scores.

Results are shown in table 6. Excluding crossovers had little effect on the headline results, with slightly higher cost difference -£434 in favor of Suboxone© (95% CI=-£2134 to £1265), and marginally less difference in retention, with those in the Methadone group 1.49 times more likely to be retained. Excluding healthcare cost outliers at baseline (those greater than three times the standard deviation of the whole group) and the four deaths (all in the methadone group) also had little effect. All sensitivity analyses gave non-statistically significant results, highlighting further the uncertainty surrounding these findings.

Discussion

Opiate dependency is prevalent in the UK with drug related death a common and increasing concern [3,4]. Engaging and retaining people in treatment are vital and Opioid Replacement Therapy (ORT) is effective at achieving this goal [5]. Both methadone and buprenorphine (the agents currently licensed for ORT in the UK) are effective drugs [12]. In the UK, however, buprenorphine-based ORT has remained less popular for many reasons [8]. Little research of relevance to the UK has explored cost-effectiveness differentials between buprenorphine and methadone. If buprenorphine-based ORT is found to be as effective as methadone (as systematic reviews suggest) and also brings potential to reduce drug deaths, then it is important that we understand potential barriers to its more widespread use.

	Adjusted Difference in Retention (95% CI)	p-value	Adjusted Difference in Cost (95% CI)	p-value
Excluding crossovers	0.67 (0.34 to 1.34)	0.26	-£434 (-£2134 to £1265)	0.616
Excluding outliers at baseline	0.72 (0.37 to 1.375)	0.316	-£327 (-£1938 to £285)	0.691
Excluding deaths	0.59 (0.30 to 1.12)	0.105	-£40 (-£1382 to £1302)	0.624

Table 6: Sensitivity analysis.

Using informatics techniques, we have compared patients on methadone and buprenorphine/naloxone (as Suboxone©) ORT over two years and have assessed the ability of both agents to retain people in treatment. We have assessed the cost associated with delivering this treatment and have also considered broader healthcare costs incurred, reflecting these patients' use of NHS services. A Health Economic Analysis has been undertaken to determine which ORT agent is most cost effective at delivering retention in treatment.

We found no statistically significant difference in cost effectiveness between methadone and buprenorphine/naloxone ORT with regard to retention in treatment at 2 years. There was, however, considerable uncertainty in these results with the Cost Effectiveness Plane (CEP) showing most points below the line.

The biggest driver of cost for buprenorphine/naloxone was the total treatment cost, which, at £918 (95% CI=£406 to £1430) was more costly than methadone and statistically significant ($p<0.001$). This finding is unsurprising due to the much higher pharmaceutical costs of the form of drug used in the study region during the study period-Suboxone©. The greatest driver of cost for methadone, however, was that of inpatient hospital care, reflecting greater healthcare utilisation- potentially reflecting less reduction in harms-in this group.

Strengths and weaknesses of the study

This study has used informatics techniques to create an anonymised dataset, giving us access to data not otherwise available for research purposes. This has allowed a more detailed assessment of the factors that may influence clinical decision making. However, there are many weaknesses in this study.

One weakness is the potential bias in the creation of the original audit sample. The statistically significant difference between the groups at baseline in terms of deprivation status and living conditions suggests they may reflect patient groups whose dependency is at a different stage of development associated with different degrees of harm. The buprenorphine/naloxone sample consisted of all patients prescribed the drug at the index date. The methadone group, however, was opportunistically recruited over a similar time period from a larger population on methadone ORT in the same Scottish region. The demographic analysis showed the methadone group to be living in more urban environments and more deprived areas at baseline. This feature alone could have driven some of the differences in "cost" as the more deprived group may be more likely to require to access healthcare [28]. The groups may also have already been "selected" and matched to each treatment in the fife service-as many services report using buprenorphine-based ORT in patients who are more stable or are felt to have more recovery potential. We have not been able to determine whether this difference may further skew our results and conclusions. Finally, the study did not use a randomised sample and we cannot therefore remove the potential effects of confounders.

As reflected in the methods section, many assumptions were made due to the quality and complexity of the available, routinely-collected, administrative data used. Regarding the costs, the greatest uncertainty lay with the combining of the two prescribing datasets. It would be beneficial in future to improve the quality assurance of the NHS Fife Addiction dataset, so that this one dataset-with richer data - can be used for research purposes. The costs we used in the analysis included the use of administrative data (the Scottish Morbidity Record or SMR). These data are not collected for research purposes and, though they contain valuable information, recorded by clinicians and administrators, they inevitably bring further uncertainty. Non-NHS costs – such as social care or criminal justice costs - were not included within this analysis as the data available were not sufficient to give accurate estimates of these wider societal costs, all of which are affected by substance use. This information would have strengthened the analysis considerably.

Regarding outcomes, it has been argued that retention is a valuable "proxy" measure of clinical outcomes – as it is strongly associated with the clinical goals of reduced risk-taking, less drug use and improved health and social functioning. As such, retention can be a helpful indicator of successful treatment and has been reported as such in numerous previous publications. However, in this study, there were no data available to examine those who were not retained. Instead expert clinical advice was sought and it was felt most prudent to assume that any participants leaving treatment before the two year end point should be classed as "not retained". One participant who stopped ORT but started naltrexone before leaving the treatment service had objectively achieved abstinence so was classed as "retained".

The overall uncertainty around our findings is a concern. These issues would benefit from further investigation, such as through a well-designed prospective Randomised Controlled Trial (RCT) using a more robust outcome measure such as Quality Adjusted Life Years (QALYs) [29]. QALYs is a generic health outcome measure that can be compared across all intervention types and is recommended in the UK by NICE and SMC for economic evaluations aiming to advice on cost-effectiveness. An RCT may also help to explore further the wider healthcare costs associated with ORT in a more robust fashion.

This study has shown how real life data extraction can be used in an economic evaluation of treatment for opioid dependency and that buprenorphine-based ORT remains a viable alternative to methadone in a UK community treatment setting. In the context of increasing drug death in the UK, more well-designed prospective studies, using robust data, are required to aid clinical decision-making and improve patient choice.

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Declarations of Interest

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References

1. EMCDDA (2012) Annual Report on the State of the Drugs Problem in Europe 2012. EMCDDA, Lisbon, Portugal.
2. ISD Scotland (2014) Estimating the National and Local Prevalence of Problem Drug Use in Scotland 2012/13. ISD Scotland, Edinburgh, UK.
3. Office for National Statistics (2016) Deaths related to drug poisoning in England and Wales: 2015 registrations. Office for National Statistics, London, UK.
4. National Records of Scotland (2016) Drug-related deaths in Scotland in 2015. National Records of Scotland, Edinburgh, UK.
5. Department of Health and Social Care (2017) Drug misuse and dependence: UK guidelines on clinical management. Department of Health and Social Care, London, UK.
6. United Nations office on Drugs and Crime (1995) The Social Impact of drug Abuse. United Nations office on Drugs and Crime, Vienna, Austria.
7. Public Health England (2018) Alcohol and drugs prevention, treatment and recovery: Why invest? Public Health England, London, UK.
8. ScotPHO Public Health Information for Scotland (2016) Drug misuse: Treatment for drug misuse. ScotPHO Public Health Information for Scotland, Edinburgh, UK.
9. Advisory Council on the Misuse of Drugs (2015) How can opioid substitution therapy (and drug treatment and recovery systems) be optimised to optimise recovery outcomes for service users? Advisory Council on the Misuse of Drugs, London, UK.
10. White WL (2010) Recovery-Oriented Methadone Maintenance. Jointly published by the Great Lakes Addiction Technology Transfer Center, the Philadelphia Department of Behavioral Health and Mental Retardation Services, and the Northeast Addiction Technology Transfer Center, in part under a cooperative agreement with the Substance Abuse and Mental Health Services Administration's (SAMHSA) Center for Substance Abuse Treatment (CSAT), Chicago, USA.
11. SUBUTEX et génériques.
12. Mattick RP, Breen C, Kimber J, Davoli M (2014) Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane Database Syst Rev 3.
13. Connock M, Juarez-Garcia A, Jowett S, Frew E, Liu Z, et al. (2007) Methadone and buprenorphine for the management of opioid dependence: A systematic review and economic evaluation. Health Technol Assess 11: 1-171.
14. Marteau D, McDonald R, Patel K (2015) The relative risk of fatal poisoning by methadone or buprenorphine within the wider population of England and Wales. BMJ Open 5: 007629.
15. Mattick RP, Ali R, White JM, O'Brien S, Wolk S, et al. (2003) Buprenorphine-Naloxone versus methadone maintenance therapy: A randomised double-blind trial with 405 opioid-dependent patients Addiction 98: 441-52.
16. Canadian Agency for Drugs and Technologies in Health (2013) Suboxone versus methadone for the treatment of opioid dependence: A review of the clinical and cost-effectiveness. Canada.
17. Hser YI, Saxon AJ, Huang D, Hasson A, Thomas C, et al. (2014) Treatment retention among patients randomized to buprenorphine/naloxone compared to methadone in a multi-site trial. Addiction 109: 79-87.
18. Gouveia M, Sousa R, Costa J, Borges M (2015) Economic evaluation of Suboxone® for substitution treatment of opioid drug dependence in Portugal. Heroin Addiction & Related Clinical Problems 17: 43-50.
19. Maas J, Barton G, Maskrey V, Pinto H, Holland R (2013) Economic evaluation: A comparison of methadone versus buprenorphine for opiate substitution treatment. Drug Alcohol Depend 133: 494-501.
20. Public Health england (2018) National intelligence network on drug health harms briefing: July 2018. Public Health England, London, UK.
21. Scottish Medicines Council (2016) Working with SMC-A Guide for Manufacturers. Scottish Medicines Council, Glasgow, Scotland.
22. Curtis L, Burns A (2015) Unit Costs of Health and Social Care 2015. Personal Social Services Research Unit (PSSRU), Canterbury, UK.
23. ISD Scotland (2013) Prescription Cost Analysis for financial year 2012/13. ISD Scotland, Edinburgh, UK.
24. ISD Scotland (2015) IRF- NHS Scotland expenditure-Hospital inpatient and day cases mapping sections, 2013/14. ISD Scotland, Edinburgh, UK.
25. NHS Scotland (2015) Methods and Sources-NHS and Social Care. NHS Scotland, Edinburgh, UK.
26. Severens JL, De Boo TM, Konst EM (1999) Uncertainty of incremental cost-effectiveness ratios. A comparison of Fieller and bootstrap confidence intervals. Int J Technol Assess Health Care 15: 608-614.
27. ISD Scotland (2016) The Scottish Index of Multiple Deprivation (SIMD). ISD Scotland, Edinburgh, UK.
28. MacLeod, M, Graham, E, Johnston, M, Dibben, C, Morgan I (1999) How does relative deprivation affect health? Health Variations 3: 12-13.
29. Richardson G, Manca A (2004) Calculation of quality adjusted life years in the published literature: A review of methodology and transparency. Health Econ 13: 1203-1210.

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