doi:10.1111/j.1360-0443.2006.01603.x

Addressing the efficacy of dihydrocodeine versus methadone as an alternative maintenance treatment for opiate dependence: a randomized controlled trial

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ABSTRACT

Aim The aim of this study is to define the efficacy of dihydrocodeine as an alternative to methadone in the maintenance treatment of opiate dependence. **Design** A pragmatic open-label randomized controlled study of patients recommended for opiate maintenance treatment to test equivalence of the two treatment options with follow-up continuing for up to 42 months after recruitment. **Setting** Assessment at either Edinburgh's Community Drug Problem Service or at two general practitioner practices with specialist drug community psychiatric nurses, then with shared care follow-up. **Participants** Two hundred and thirty-five subjects (168 male, 67 female) with opiate dependence syndrome were recruited. Subjects selected were suitable for opiate maintenance treatment. Routine treatment was offered throughout. **Intervention** Patients were randomized to receive either methadone mixture 1 mg/ml or dihydrocodeine, 30 mg or 60 mg tablets. **Measurements** The primary outcome measure was retention in treatment. Eight secondary outcomes included total illicit opiate use, reported crime, physical health, mental health, injecting drug use, overdoses, selling drugs and being in education or work. Measures were compared over 42 months follow-up. **Findings** There was no difference in groups for retention in treatment at follow-up and there was improvement in all secondary outcomes from baseline. No significant difference in outcomes was found between randomized groups over time. Compliance with randomized treatment differed by randomized group and was affected by experiences in custody during follow-up. Those randomized to dihydrocodeine were more likely to switch treatments. **Conclusions** These results, combined with existing clinical experience, provide evidence that dihydrocodeine is a viable alternative to methadone as a maintenance treatment for opiate dependence. Indirect comparisons with other studies show dihydrocodeine (and methadone) to be superior to placebo.

Keywords Dihydrocodeine, methadone, randomized controlled trial.

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Submitted 21 December 2005; initial review completed 7 March 2006; final version accepted 5 June 2006

INTRODUCTION

Dihydrocodeine (DHC) has been used as an oral opioid for maintenance treatment of opioid dependence in a number of European countries [1–5]. It has been identified in at least one study [6] as the most commonly prescribed drug after methadone by general practitioners (GPs) in the United Kingdom, despite an absence of evidence from any randomized controlled trials (RCTs) of its safety and efficacy.

Given the limited choice of existing opioids approved for maintenance (methadone and buprenorphine), it would be desirable to increase patient choice by adding DHC if the evidence warrants it [7]. The most suitable comparator is oral methadone, the best-supported form of opioid maintenance treatment.

Previous studies suggest that there is at least a subset of individuals dependent on opioid drugs, including heroin, who prefer to avoid treatment with methadone. Reasons include the sedative effect of methadone, its potential side effects, dangers of toxicity, the stigma and regulations surrounding its prescription and dispensing arrangements. Others indicate that a shorter-acting drug such as DHC is not only tolerated but desirable. DHC is

much shorter-acting than methadone, requiring more than one daily dose for pain management, with consequent potential for withdrawal between doses, something that methadone aims specifically to avoid.

On the accepted hierarchy of agents to treat pain, the World Health Organization (WHO) pain ladder, DHC is included with tramadol among the weaker agents to be tried prior to resorting to morphine-like agents [8]. The short action of DHC corresponds to its much lower affinity of binding to the mu-opioid receptor. Dihydrocodeine is metabolized to several compounds by the cytochrome P450 enzyme CYP2D6. The most active metabolite is dihydromorphine, which is more strongly bound to the mu-opioid receptor than the parent compound. About 7% of the Caucasian population are poor metabolizers, which may give rise to intolerance in the same way as those intolerant to morphine [9]. Methadone is metabolized mainly in the liver; the main step consists in the N-demethylation by CYP3A4 to EDDP(2-ethylidene-1,5-dimethyl-3,3 diphenylpyrrolidine), an inactive metabolite [10]. The activity of CYP3A4 varies considerably among individuals, and such variability is responsible for the large differences in methadone bioavailability. Differences in pharmacokinetics and pharmacodynamics of DHC and methadone may explain some of the subjective differences and the variation in tolerance seen in treatment groups.

The principle outcome measure in this study was retention in treatment. This is one of the most widely reported outcomes for indicating success with prescribed opiate substitute therapy. Secondary outcomes included reduction in illicit opiate use and injecting behaviour, stability of life-style as measured by criminal behaviour and employment potential, improvement in physical and mental health, selling drugs and overdoses [11].

Urinalysis for the presence of opioids and other drugs of dependence were used to validate prescribing and to confirm compliance, but were not considered as an outcome measure. This study was designed to test equivalence between two treatments and not the superiority of one over the other. The hypothesis that dihydrocodeine is a suitable treatment comparable to methadone is therefore addressed.

METHODS

Recruitment

Ethical approval was obtained from the Lothian Research Ethics Committee. Subjects were recruited between August 2000 and December 2003 from patients assessed at the Edinburgh and Lothian Community Drug Problem Service (CDPS), and at two GP practices with specialist drug community psychiatric nurses (CPNs) attached. Opiate dependency was established using local procedures which included at least one opiate-positive urine toxicology result.

Baseline data were obtained from these assessments using a modified Maudsley Addiction Profile (MAP) [12]. Assessments were conducted prior to, and independent of, entry into the trial.

All patients had been recommended for opiate substitution therapy before being invited to participate in the study and were excluded from consideration only if a coexisting condition, such as pregnancy or psychiatric morbidity, meant that randomization would be undesirable.

Of the 570 patients who began treatment during the trial, 51% ($n = 291$) were eligible for inclusion and 81% ($n = 235$) of this group were recruited. Those who declined to take part were either reluctant or unable to comply with the twice-daily supervised dosing requirement during the double-blind phase of the trial, or (more frequently) preferred to start the methadone treatment they expected and were consequently unwilling to risk the possibility of randomization to dihydrocodeine. Patients who consented to randomization agreed to be interviewed at 6-monthly intervals, irrespective of factors such as non-retention in treatment, abstinence, loss of contact with services or imprisonment.

The study was not blinded after an initial 29 patients provided statistically significant evidence that both patients and clinical staff were able to distinguish between treatments.

Randomization and intervention

The pharmacist held lists of treatment assignments, stratified by sex and randomized in blocks of varying size. Staff entered patients without knowing their assignments, and in the blinded phase double-dummy treatments were used. This information was not available to medical staff. Treatment was initiated with methadone mixture drug tariff formula 1 mg/ml or dihydrocodeine (30 mg or 60 mg) tablets. This was modified from the national guidelines [7]. A starting dose of methadone was agreed in all cases and converted for the DHC group (2.5 mg methadone = 30 mg dihydrocodeine). A stabilizing dose was titrated during a 3-week induction phase involving daily supervised consumption, with Sunday's dose dispensed on Saturday and consumed unsupervised. Once a stabilizing dose was attained, dispensing and supervising arrangements were determined individually according to prevailing clinical practice, and were not influenced by participation in the trial. It was recommended that patients remained with their assigned treatment for the duration of the trial, or for as long as prescribing continued. All other aspects of subsequent clinical management proceeded independently of the study.

Follow-up

Urine samples for toxicology analysis were taken whenever possible. Most interviews were conducted in patients' homes, while a smaller number were conducted at other locations such as prisons, GP surgeries, CDPS, hospitals, rehabilitation clinics and bed-and-breakfast hostels. Many patients changed address frequently, or spent very little time at their recorded address. Those in treatment were traceable through their prescriber or pharmacy. Subjects who were not still in treatment and not at their last known address were often traced by other means, such as through relatives or associates, the prison service, contact with other drug agencies or via the health board's GP–patient registration records. Follow-up was continued until the last patient had been followed for 6 months, when the earliest recruit had been followed for over 3 years.

Statistical methods

Initial power calculations indicated that a total of 400 patients might be required based on approximate calculations, as the distribution of the outcomes measures were not known. An interim power calculation was carried out after the 6-month data were available for 64 patients and scores for illicit opiate use could be calculated. Overall retention in treatment or abstinence from all opiates was estimated to be around 90%. Interim power calculations at this point indicated that a total of 250 patients would give 80% power to identify that DHC retained 10% fewer patients in treatment than methadone and to detect a difference of 0.5 points increase on the score for illicit opiate use (see below for definition).

An analysis protocol was developed using outcome data for the whole group without reference to the treatment assignment. All analyses compared randomized groups by intention-to-treat (ITT). Some extremely skewed outcomes were categorized.

Outcomes at 6 months were compared by *t*-tests or exact tests. Repeated-measures analysis was used to compare treatments over the follow-up period using SAS PROC MIXED [13], which allowed an average difference between treatments to be calculated from all available data for each outcome. Treatment comparisons were adjusted for the following baseline characteristics: age group, sex and (for women) whether any dependent children, severity of addiction scale, psychological problems score and baseline level of outcome (if appropriate). The main outcome measure was retention in treatment and others were based on those in the NTORS report [14], and those available from the completed MAP. Details of the scores are in the footnote to Figure 2.

RESULTS

General

A total of 235 patients (168 male, 67 female) were recruited, with 17 patients failing to attend their first stabilization appointment. Figure 1 shows that 18 of the 108 patients who were allocated to dihydrocodeine and attended treatment were prescribed methadone at 3 weeks follow-up. Two patients changed from methadone to dihydrocodeine at 3 weeks, and in later stages of follow-up more patients moved treatment group. A change from dihydrocodeine to the standard treatment (methadone) was achieved more easily than a change to dihydrocodeine, because many clinicians were unwilling to prescribe dihydrocodeine unless the trial patient had been randomized to receive it.

Follow-up rates for the 218 patients who attended for initial treatment are shown in Table 2. In all 6-month follow-up categories more than 90% of patients were contacted and interviewed and in the final (36 months) category 84% were seen.

Baseline characteristics of the study sample are presented in Table 1, along with comparable data from the Scottish Drug Misuse Database 2003/4. This database collates information from treatment centres across Scotland and data in the table represent new treatment episodes. Treatment doses for patients were determined by clinicians responsible for individual patients and ranged

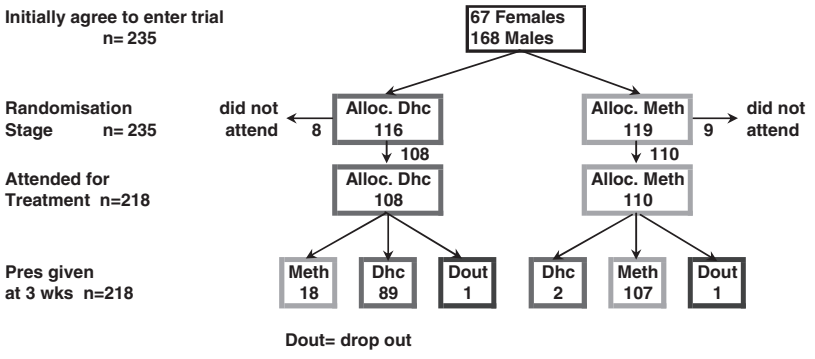

Figure 1 Consort diagram

Table 1 Treatment allocation alongside ISD data for 'new patients' presenting to services in Scotland in 2003/4 ($n = 10\,910$) on selected variables.

	Dihydrocodeine		*Methadone*		*ISD*
	n	*%*	*n*	*%*	*n = 10 910*
Overall	116	100	119	100	100%
Age at entry to study (years)					
16–25	45	39	53	45	34%
26–35	47	41	53	45	48%
36–45	21	18	12	10	16%
46–55	3	3	1	1	2%
Gender					
Female	32	28	35	29	35%
Male	84	72	84	71	65%
Main illicit opiate					
Heroin	61	53	57	48	
Dihydrocodeine	48	41	40	34	
Methadone	6	5	22	18	
None	1	1	0	0	
Level of use of illicit opiates					
Low (< 60 ml meth equiv./day)	62	53	75	63	
Medium (60–100 ml meth equiv./day)	40	34	34	29	
High (> 100 ml meth equiv./day)	14	12	10	8	
Other illicit drugs and alcohol					
Benzodiazepines	91	78	92	77	34%
Amphetamines or MDMA	25	22	21	18	2%
Cocaine or crack	21	18	23	19	10%
Cannabis	77	66	85	71	25%
Alcohol	20	17	31	26	
Drug-related risky behaviour					
Ever injected drugs?	61	53	76	64	73%
Injected in the last 30 days?	39	34	44	37	45%
Risky injecting last 30 days?	26	22	29	24	
Overdosed in the last 6 months?	10	9	8	7	
Offending					
Have you ever been in prison?	71	61	65	55	
Been in prison in the past 6 months?	27	23	31	26	
Been arrested in the past 6 months?	44	38	48	40	
Crimes committed in last 30 days					
Selling drugs	30	26	42	35	
Fraud/forgery	24	21	22	18	
Shoplifting	49	42	59	50	
Other theft	35	30	32	27	
Other	9	8	10	8%	
No crimes committed	41	35	30	25	
Health					
Ever tested for HIV, HBV or HCV?	70	60	68	57	
HIV positive	1	1	0	0	
HBV positive	2	2	5	4	
HCV positive	11	9	9	8	
Maudsley Addiction Profile	Mean	SD	Mean	SD	
Physical health score/115	56.1	13.0	57.2	12.6	
Psychological health score/50	27.2	7.7	29.7	7.7	
Dependency					
*SDQ opiates/15	9.9	4.0	10.4	4.0	
SDQ alcohol/20	1.7	3.3	2.1	3.3	

*SDQ = sum of the score of responses to five severity of dependency questions.

Table 2 Follow-up rates by time from randomization calculated for the 218 patients who attended for treatment initiation by randomized treatment. Patients were 'eligible' if they were entered early enough to be followed-up each time.

	Methadone			*Dihydrocodeine*			*All*		
	Followed-up			*Followed-up*			*Followed-up*		
	Eligible	*n*	*%*	*Eligible*	*n*	*%*	*Eligible*	*n*	*%*
6 months	110	107	97	108	105	97	218	212	97
12 months	100	91	91	95	89	94	195	181	92
18 months	69	64	93	76	69	91	145	136	92
24 months	54	51	94	59	53	90	113	104	92
30 months	40	39	98	46	44	96	86	83	97
36 months	29	24	83	28	24	86	57	48	84

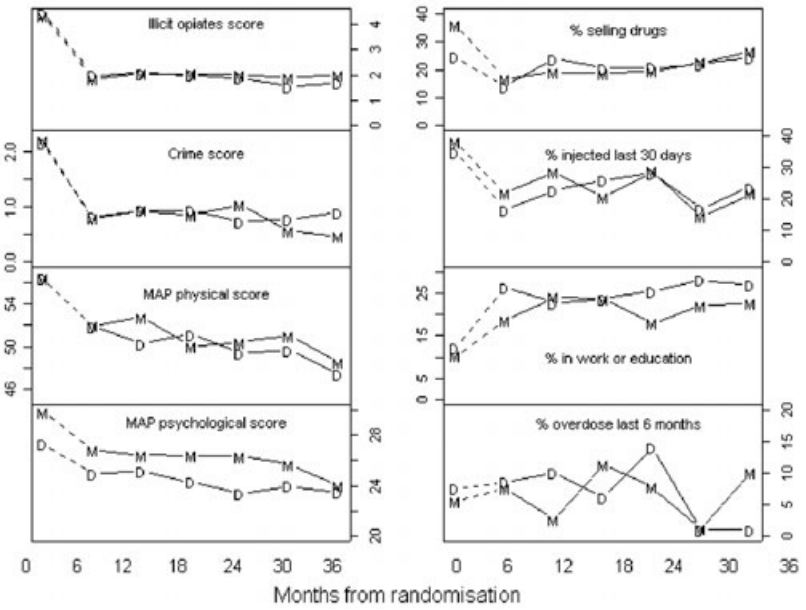

Figure 2 Mean of outcome measures over follow-up period, estimated from the repeated-measures analysis. (i) The MAP physical and psychological scores were calculated as recommended [12]. (ii) The crime score was calculated as described in the NTORS study [14]. Given its highly skewed nature, it was recoded into a score (in brackets) as follows: (0), > 0–10 (1), > 10–30 (2), > 30–60 (3), > 60–100 (4), > 100–200 (5), > 200 (6). (iii) Total reported illegal opiate use, reported in a variety of formats, was converted to mls of methadone per day by an algorithm that is available from the authors. This was then recoded into groups to give the recoded scores (in brackets) no illegal opiate use (0), 0–1 ml (1), 1–10 ml (2), 10–30 ml (3), 30–60 ml (4), 60–100 ml (5), 100 + ml (6)

from 40 to 150 mg methadone or the equivalent dihydrocodeine. Thirty mg dihydrocodeine was taken to be roughly equivalent to 2.5 mg methadone. Doses were determined by clinicians and were independent of conversion factors.

Prescribed doses of dihydrocodeine were slightly higher than those of methadone at 3 weeks ($P = 0.04$) and 6 months ($P = 0.08$).

Outcomes by intention-to-treat

Retention in treatment or abstinence was high and not significantly different between randomized assignment at any follow-up [at 6 months 95/97 (90%) on DHC 93/107 (87%) on methadone, difference 3.6%, CI (–5.2%, 12.6%); at 12 months 76/89 (86%) on DHC 78/91 (86%) on methadone, difference –0.3%, CI (–10.8%, 10.3%); and at 18 months 61/69 (88%) on DHC 49/64 (77%) on methadone, difference 11.9%, CI (–1.1%, 25.0%)]. The majority of retained patients were on substitute opiate prescriptions. At 6 months only three patients (one DHC and two methadone) were abstinent and only 12 reports of abstinence were recorded during the 572 later follow-up visits.

The repeated-measures analyses of the secondary outcomes showed that there was no evidence of differences between randomized groups in the mean levels of any outcomes. Fitted values from the repeated measures analyses are shown in Fig. 2. The differences in scored outcomes, DHC minus methadone groups averaged over all available follow-ups, were: illicit opiate score –0.01 95% CI (–0.31, 0.29), crime score 0.03 95% CI (–0.29,0.36), physical health score –0.72 95% CI (–4.12, 2.68), psychological health score, –1.79 95% CI (–4.08,0.50). For outcomes expressed as percentages, the differences (DHC

minus methadone) were selling drugs 0.9% 95% CI (−0.5%,2.3%) injecting −2.4% 95% CI (−11.0%, 6.3%) in work or education 3.7% 95% CI (−5.8%,13.1%) overdosing 1.7% 95% CI (−2.8%,6.1%). Adjustment for covariates did not alter any of these differences substantially.

Significant improvements from baseline were seen for all measures for both groups except for overdoses, where the numbers were small. The crime score and use of illicit opiates showed the most pronounced improvement and this was sustained over the full 36 months of the study. Both physical and psychological health had a significant improving trend over the duration of the study ($P < 0.05$ in each case), with no significant trends observed for other outcome measures after 6 months.

Retention in treatment and compliance

Overall compliance with some form of maintenance therapy was high. A *post-hoc* analysis investigated influences on compliance and retention. The main factors associated with these were randomized treatment, older age and imprisonment. Older age groups were more likely to be compliant and to remain in treatment at follow-up. Figure 3 presents the proportions on different treatments over time by randomized group and by whether there had been any period of custody during follow-up. Patients randomized to dihydrocodeine were more likely to cross over to the other treatment. For patients with some experience of custody during follow-up, dropout from maintenance was more common and did not differ by randomized group. For patients not in custody during follow-up only two of the 53 patients randomized to DHC used opiates and were not in treatment at any follow-up, while comparable data for those randomized to methadone was 10 of the 54 ($P < 0.03$, Fisher's exact test). This was not a planned comparison, so it needs to be interpreted with caution.

A indirect comparison of dihydrocodeine with placebo was carried out using published data from methadone trials (Fig. 4) and is discussed later.

Overdoses and adverse events

A similar rate of overdose problems (self-induced harm situations) was observed in the two treatment groups: 22.6% and 17.6% in the methadone and dihydrocodeine groups, respectively. There was only one death (a methadone overdose) in a total of 399.5 person-years of follow-up. The death occurred in a recently detoxified patient.

Toxicology results

Urine tests were not used as a principle outcome measure as it was expected that availability of samples at follow-up might be compromised. For example, at 6 months, 38 of the 212 patients (18%) followed-up had missing toxicology results. Reasons included person in custody (14), home interview, telephone follow-up (16), and interview in public places or hospital (one). At 6 months follow-up 96% of those prescribed dihydrocodeine tested positive for dihydrocodeine and 99% of those prescribed methadone tested positive for methadone.

This suggests that compliance with prescribed opiate was very strong. Of the 37 patients who claimed to be using no illicit opiates at 6 months, at least six (16%) were taking illicit opiates.

DISCUSSION

This may be the first RCT of opiate dependence treatment involving dihydrocodeine. At 6 months the follow-up rate was 97% and the retention-in-treatment rate was 89%. By comparison, a Glasgow study [15] had a retention-in-treatment rate of 29% at 6 months. This low retention rate may reflect the low doses of methadone prescribed and the policy that patient continuation on the

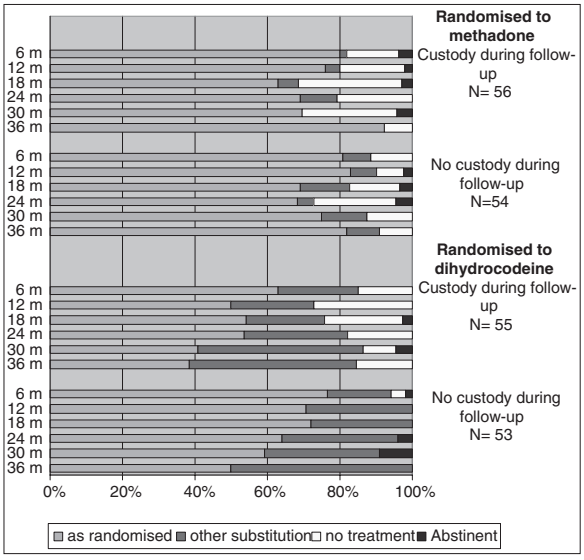

Figure 3 Actual treatment at follow-up by randomized groups and custody

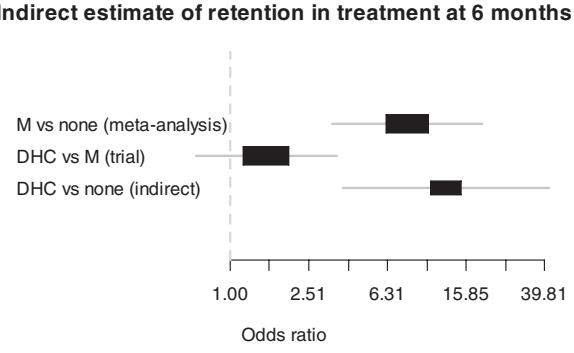

Figure 4 Indirect estimate of retention in treatment at 6 months

maintenance programme was dependent on opiate-negative urine samples. The DATOS (Drug Abuse Treatment Study) cohort study showed retention in methadone maintenance programmes varying between 15% and 76% at 1 year [16].

Reservations concerning previous research include studies with fixed doses, research settings with atypical routine practice (e.g. highly motivated and specifically trained staff with close supervision and regulatory control), small sample size and short duration of follow-up for what is a chronic relapsing condition. The present study has accommodated flexible dosing, routine care as delivered in specialist and community general practice settings and a reasonable sample size. Results of comparisons between doses removes the possibility that one group might be responding to treatment better than the other simply because treatment was greater in terms of opiate dosage. It also suggests that the clinical titration of dose is effective, if the equivalence values are correct. Comparisons between doses depends, critically, on conversion factors. Results here suggest that the correct equivalence is between 2.5 and 3.0 mg of methadone to 30 mg dihydrocodeine.

The finding that patients randomized to dihydrocodeine were more likely to change treatments almost certainly reflects the wider availability of methadone as substitution therapy. Similarly, the better retention in treatment for patients randomized to dihydrocodeine who stayed out of prison may reflect the fact that the dihydrocodeine arm offered the choice of two regimens, while those in the methadone arm were largely denied the opportunity of trying dihydrocodeine. Every attempt was made to make the study sample of patients for this RCT a typical clinical sample, with patients receiving no additional attention or treatments other that those required to record baseline and follow-up data. The comparison of the study sample with patients in the Scottish Drug Misuse Database confirms that the sample enrolled in the current study has similar characteristics to opiate users presenting to services in Scotland (Table 1). It would appear, however, that our sample injected less but were more often multiple-drug users. The HIV prevalence rate in the study sample was low in comparison to other groups researched in Edinburgh [17,18].

Only one death occurred (in the methadone group) with a total of 399.5 person-years of follow-up. This gives us a rate of 0.25 per 100 person-years of follow-up, much lower than that found in previous studies with similar populations which have typically found a rate of around two per 100 person-years. Based on this typical rate, we would have expected 7.2 deaths to have occurred. This observed rate is significantly different ($P < 0.01$, using a Poisson distribution). The expectation that there might be a large preference for dihydrocodeine did not transpire. This compromised recruitment to the study as some of the referrals preferred to commence methadone.

There was a clear and highly significant agreement with findings from other RCTs using methadone maintenance. In particular, similar findings were reported for the reduction of illicit opiate use, crime rates and injecting [19]. In addition, the study showed that with either treatment there were significant and progressive improvements in both physical and psychological health as rated by patients over the follow-up period. These health improvements were comparable with the NTORS cohort study, in which patients at one follow-up had a 20% improvement in both physical and psychological health for a range of treatments [20]. With the recent introduction of alternatives to methadone for maintenance treatment such as buprenorphine, sustained-released morphine and injectable heroin there is a need for research into the relative benefits and distinctive characteristics of these medications as well as the patient group and characteristics of individuals most suited to different treatment options [21].

Dihydrocodeine has been used in reduction regimens, may be less toxic and may be useful in achieving a satisfactory short-term relief of withdrawals in a custodial situation where treatment is expected to be short-term. The importance of minimizing periods of relative withdrawal between doses is frequently stressed [22]. There is, however, case report information to support the trial evidence which indicates a patient preference for a short-acting agent as an alternative to methadone. The process of matching the patient to the treatment through therapeutic testing or informed patient choice is widely practised and this study suggests that it should also be available for opiate-dependent patients in treatment [23]. The existence of evidence of the effectiveness of methadone allowed us to calculate an indirect comparison between dihydrocodeine and placebo [24,25] A recent Cochrane review [26] presented evidence for retention in treatment on methadone compared to no active treatment, based on pooling results from three RCTs.

The retention rate in the methadone group was 68% (173/254) compared to 25% (63/251) in the untreated group. The combined odds ratio for retention in treatment on methadone compared to placebo is 7.93 (95% CI 3.25,19.33). We combined this estimate with our estimate of the odds ratio for retention on dihydrocodeine compared to methadone at the 6-month follow-up. Figure 4 shows these odds ratios and the indirect odds ratio comparing dihydrocodeine with no treatment. The combined estimate is 12.45 (95% CI 3.64, 42.6) for the odds of retention on dihydrocodeine compared to no active treatment, good evidence that it can be an effective substitution therapy.

Acknowledgements

The project was funded by the Chief Scientist Office of the Scottish Executive, grant number K/opr/2/2d3999. We are grateful to NAPP Pharmaceuticals for providing dummy dihydrocodeine tablets to allow the double dummy phase of the trial to be conducted. Trial registration: International Standard Randomized Controlled Trial Number ISRCTN63574530.

Declaration of interest

Dr Robertson is on an occasional advisory committee at NAPP Pharmaceuticals, Cambridge, UK.

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