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Adherence to substitute opioid prescribing: survey of inner-London drug services

AIMS AND METHOD

To investigate non-adherence to substitute opioid treatment, using a cross-sectional study design, with 630 patients from three London community drug services. Adherence was measured as the number of doses collected from the pharmacy as a proportion of the total number of doses stipulated on the prescription during a 28-day period and was further investigated through laboratory urine drug screens.

RESULTS

Overall, 30.5% (n = 191) of individuals failed to pick up at least one dose of medication from the pharmacy over 1 month, but only 1.6% (n = 10) missed 50% or more of their doses. Non-adherence was associated with supervised consumption, more frequent pick-up, shorter duration of treatment, younger age, a lower dose of methadone and a recent urinalysis result positive for opiates.

CLINICAL IMPLICATIONS

Treatment services need to monitor levels of adherence to treatment and develop strategies to improve it so that treatment can be optimised effectively.

There is widespread agreement that poor adherence to treatment leads to poorer clinical outcomes in chronic medical conditions.[1] Typical adherence rates for prescribed medications are about 50%,[2] with rates found in the treatment of alcohol and opiate dependence being comparable to those for diabetes, hypertension and asthma.[3] Objective measures of adherence, such as collection of medication at the pharmacy, cannot confirm medication consumption or consumption of the right dose at the right time. More objective tests such as urinalysis can be tampered with.[4] Plasma drug levels may be difficult to interpret owing to varying inter-individual rates of metabolism and drug–drug interactions.[5] Subjective measures such as patient self-report are subject to recall bias and untruthfulness, and patients and physicians may have a different concept of what constitutes a 'missed dose'.[6] Of wider concern is the risk of unused methadone being diverted onto the black market,[7] and the increased risk of it being taken by non-tolerant individuals with fatal results.[8]

The new *Drug Misuse and Dependence – UK Guidelines on Clinical Management* place a strong emphasis on optimising treatment,[9] but if individuals are not taking their medication as prescribed there is a risk that it will be less effective. Currently there is a lack of data on adherence to substitute opioid prescribing. The aims of this study were to quantify one aspect of non-adherence, the extent to which patients miss picking up doses of prescribed opioid medication, and to investigate the factors associated with it.

Method

The inner-London boroughs of Camden and Islington have a combined population of 397 000 – a diverse community with areas of significant deprivation alongside areas of relative affluence. Camden and Islington have a high proportion of people using drugs who are recorded as being in treatment.[10] Substance misuse prescribing services are provided through a network of National Health Service (NHS) clinics, which are consultant-led, multidisciplinary teams offering a range of specialist treatment services, including maintenance opioid prescribing, detoxification, a crack cocaine programme, primary care services, care management and criminal justice interventions. The three treatment services included in the study each cover different geographic

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areas of the two London boroughs. The majority of referrals are self-referrals (54%), followed by those from primary care (10%) and the criminal justice system (7%).

Procedures

Most individuals begin substitute opioid treatment on supervised consumption either at the clinic (on-site) or at a community pharmacy. This may continue for at least 3 months. The next step is for the person to collect the medication daily from a community pharmacy without supervised consumption. Stable patients may progress to less frequent pick-up, such as three times a week, twice weekly or even weekly. Individual prescriptions run for a maximum of 14 days and FP10(MDA) prescription pads allow medication to be dispensed in instalments up to daily. The pharmacist signs the prescription and writes the amount dispensed on each occasion. If the person fails to pick up some of the medication, the pharmacist writes 'not dispensed' or 'not administered'. Until recently, the original prescriptions were returned to the NHS Trust, where they were stored for 5 years before being destroyed. On-site dispensing takes place at one of the drug services and each dose dispensed is recorded on an out-patient prescription chart.

Participants

All patients in receipt of a prescription for a controlled drug (methadone, buprenorphine or diamorphine) were eligible for the study. The ethics committee gave 'chairman's action' authorisation to this study because it was considered to be an audit.

Data collection and measures of adherence

Demographic details and information regarding drug use were collected for each patient from the service's minimum data-set, a spreadsheet which is sent monthly to the National Drug Treatment Monitoring Service (www.ndtms.net). We hand-checked the returned FP10 prescriptions and the out-patient prescription record sheets to see whether each dose had been dispensed on each of the days specified. We chose the month of September in 2003 as the audit month. Non-adherence was defined as the number of doses not collected by the patients over a 28-day period as a proportion of the total number of doses specified on the prescription – a measure of missed doses. Thus a patient on a weekly pick-up who missed one pick-up out of four in a 28-day cycle would have an adherence of 0.75 (75%), as would a patient on a daily pick-up who missed seven pick-ups over 28 days. If a patient on daily dispensing misses a pick-up from the pharmacist, the next dose that can be dispensed will be on the following day – this will count as one missed pick-up. If three or more consecutive days are missed, patients have to re-present to the treatment service and be titrated back onto their opioid medication with a replacement prescription. If patients on weekly dispensing miss a pick-up, the remainder of that pick-up cannot be issued and they will need to re-present to the treatment service for a replacement if they have missed fewer than 3 days or for titration if 3 or more days have been missed. Where replacement prescriptions were issued, only the missed days were counted. For instalment prescribing on FP10(MDA) prescriptions, each pick-up has to occur on the date specified; missed pick-ups cannot be dispensed after this date. Adherence data were available for 99.5% of patients ($n = 627$).

Urine samples were sent to two local laboratories for analysis, both of which provided results for all the urinalyses that had been undertaken during the audit month and 1 month either side. We chose this window to maximise the number of urine test results available for statistical analysis, as patients may have tests at frequencies varying from monthly to 3-monthly – despite this, 217 individuals (34%) had no urinalysis result available. Urine was tested for opiates (morphine), cocaine, benzodiazepines, methadone, amphetamines and cannabis using immunoassay tests followed by confirmatory tests for metabolites using thin layer chromatography and gas chromatography. Results for opiates and methadone were recorded as positive or negative.

Statistical analysis

Adherence was measured as a percentage, but for the purposes of analysis the results were dichotomised into adherent (100% of doses collected) and non-adherent (<100% collected). The reason for this was that the results were extremely skewed towards 100% adherence. Non-parametric tests were not used as 69.5% of patients shared the same value for this variable (100% adherent). Results were analysed using the Statistical Package for the Social Sciences (SPSS) version 15.0 for Windows. Continuous variables were analysed using parametric tests (*t*-test and one-way analysis of variance) and categorical data were analysed using the chi-squared test. Binomial logistic regression was performed using candidate predictors of non-adherence. This analysis was performed only on data for individuals prescribed methadone because of the difficulty of estimating methadone dose equivalents for those prescribed buprenorphine or diamorphine.

Results

The demographic and prescribing characteristics of the sample are listed in Table 1. Its members were predominantly male and White British, and most had had previous contact with drug treatment services. Methadone was the main opioid prescribed and the majority were taking it in mixture form. Just under half were on supervised consumption and three-quarters were on 5 days to 7 days per week pick-ups. Of those who had had a recent urine drug screen, over half had an opiate-positive result (morphine), suggesting recent heroin use. Just over 7% of patients being prescribed methadone had a negative methadone urinalysis, indicating either non-adherence with the prescribing regimen or that the sample had been taken prior to commencing treatment.

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Table 1. Characteristics of patients in an inner-London prescribing programme ($n = 630$)

Age, years	
Mean (s.d.)	39.1 (9.0)
Range	18.5–76.4
Gender, *n* (%)	
Male	441 (70)
Female	189 (30)
Ethnic group, *n* (%)	
White British	431 (68.4)
Irish	49 (7.8)
Black (African–Caribbean)	29 (4.6)
Asian	23 (3.7)
Other	98 (15.5)
Previous treatment,[a] *n* (%)	359 (90.7)
Duration of treatment, months	
Mean (s.d.)	31.9 (42.8)
Range	0.2–378.2
Mental health history, *n* (%)	150 (23.8)
Past injecting drug use,[b] *n* (%)	114 (48.9)
Client has dependent children,[c] *n* (%)	135 (21.7)
On supervised consumption, *n* (%)	278 (44.1)
Methadone dose, mg	
Mean (s.d.)	61.3 (25.8)
Range	5–200
Opioid prescription, *n* (%)	
Methadone mixture	572 (90.8)
Methadone tablets	29 (4.6)
Methadone ampoules	14 (2.2)
Diamorphine ampoules	3 (0.5)
Buprenorphine	12 (1.9)
Pick-up frequency, *n* (%)	
5–7 days per week	478 (75.9)
2–4 days per week	82 (13.0)
Weekly/twice-weekly	70 (11.1)
In receipt of other FP10,[d] *n* (%)	107 (17)
Opiate-positive urine in past month,[e] *n* (%)	228 (55.2)
Methadone-negative urine in past month,[f] *n* (%)	27 (7.5)

a. Missing data for 234 patients.

b. Missing data for 397 patients.

c. Missing data for 8 patients.

d. Prescription for other non-opioid medication.

e. Missing data for 217 patients, excluding those taking diamorphine.

f. Missing data for 193 patients, excluding those taking diamorphine or buprenorphine, and those whose urinalysis results pre-dated start of treatment.

Levels of non-adherence

Overall, 30.5% ($n = 191$) of patients receiving a substitute opioid prescription missed at least one dose of their medication from the pharmacy in the preceding month. For most patients this was an infrequent occurrence, with only 1.7% missing 50% or more of their doses. For the whole sample the mean number of missed doses was 1.4 (range 0–26).

Associations with non-adherence

Table 2 shows the associations between the variables studied and two measures of adherence: non-adherence to doses of substitute opioid medication, and having a recent opiate-positive urine test. Neither measure of adherence was associated with ethnicity, previous drug treatment, having a mental health history, having dependent children or being in receipt of another FP10 prescription for a non-opioid medication. For non-adherence the strongest associations were with supervised consumption, more frequent pick-up and an opiate-positive urine sample. The second measure, a recent opiate-positive urinalysis, was most strongly associated with supervised consumption and a history of injecting drug use.

Three continuous variables (age, methadone dose and duration of treatment) were analysed in relation to adherence. For adherent *v.* non-adherent patients the results were as follows: mean age 39.7 years *v.* 37.6 years ($t = 2.7$, d.f. = 625, $P = 0.007$); mean methadone dose 62.2 mg *v.* 56.9 mg ($t = 2.2$, d.f. = 624, $P = 0.027$) and mean duration of treatment 36.2 months (interquartile range (IQR) 4.7–61.4) *v.* 22.5 months (IQR 3.3–24.3) ($t = 3.7$, d.f. = 619, $P < 0.001$). The same variables were analysed in relation to patients who had had a recent opiate-positive urine result, but only duration of treatment showed a significant difference: opiate-positive patients 24.0 months *v.* opiate-negative patients 33.6 months ($t = -2.3$, d.f. = 398, $P = 0.023$) – this analysis was only undertaken on data for patients prescribed methadone.

Multivariate analysis

In the binary logistic regression analysis of variables associated with non-adherence to methadone doses ($n = 606$), only three variables were retained in the final model: supervised consumption (adjusted odds ratio (OR) = 1.65, 95% CI 1.11–2.45, $P = 0.01$), duration of treatment episode (adjusted OR = 0.99, 95% CI 0.98–0.99, $P = 0.01$) and methadone dose (adjusted OR = 0.99, 95% CI 0.98–1.00, $P = 0.08$).

Discussion

In this study of patients on substitute opioid prescribing programmes, almost 70% were fully adherent in collecting all their prescribed doses of medication from the pharmacy, which compares favourably with studies of other chronic diseases. In a study by McLellan *et al*, only 60% of patients with type 1 diabetes and less than 40% of patients with hypertension and asthma adhered fully to their medication regimens.[3] The strongest associations with non-adherence were more frequent pick-up of medication, supervised consumption, an opiate-positive urine result, a lower dose of methadone, having been in treatment for a shorter period and being younger.

Because of the cross-sectional nature of the study, the interpretation of these associations needs to proceed with caution because of the risk of 'reverse causality'. One might anticipate that supervised consumption and more frequent pick-ups would be associated with better adherence to treatment. The fact that these interventions are associated with non-adherence highlights the

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Table 2. Variables associated with adherence to opioid medication and use of illicit opiates ($n = 630$)

	Adherent, %			Opiate urine results, %		
	Yes	No	χ^2 (P)	Positive	Negative	χ^2 (P)
Gender						
Male	71.9	28.1	3.89 (0.05)	55.1	44.9	NS
Female	64.0	36.0		55.3	44.7	
Past injecting use						
Yes	79.9	28.1	NS	74.3	25.7	9.4 (0.002)
No	74.8	25.2		49.3	50.7	
Opioid medication[a]						
Mixture	68.2	31.8	6.74 (0.03)	55.1	44.9	NS
Tablets	78.1	21.9		54.5	45.5	
Ampoules	94.1	5.9		44.4	55.6	
Supervised consumption						
Yes	60	40	21.04 (<0.001)	65.1	34.9	14.7 (<0.001)
No	77	23		46.3	53.7	
Frequency of pick-up						
5–6 times weekly	63.8	36.2	30.94 (<0.001)	58.5	41.5	8.4 (0.015)
2–4 times weekly	85.4	14.6		44.0	56.0	
Weekly/twice-weekly	90.0	10.0		34.6	65.4	
Opiate-positive urine test in past month						
Yes	63.0	37.0	6.77 (0.009)			
No	75.0	25.0				
Methadone urine test in past month[b]						
Negative	53.8	46.2	2.46 (0.13)	70.1	29.9	4.65 (0.043)
Positive	68.8	31.2		52.6	47.4	

NS, not significant.

a. Does not include patients taking diamorphine.

b. Patients prescribed methadone only and attempted exclusion of those whose urinalysis results clearly pre-dated the start of prescribed treatment.

selection process whereby individuals end up on these treatment modalities. Patients assigned to supervised consumption and daily pick-up are likely to comprise people just starting treatment who are in the process of stabilising, people who have failed to stabilise in treatment, previously stabilised patients who are going through a chaotic phase, and patients who have stabilised and are about to move on to unsupervised consumption and less frequent pick-ups. The finding that over half of patients who were non-adherent had been in treatment for over 10 months suggests that they were not predominantly in the early phases of treatment. A potentially confounding factor in this scenario is methadone dose, and our results confirm that patients who did not adhere tended to receive lower doses. Furthermore, if patients collecting their dose daily miss one pick-up they can go back to the pharmacy the next day and continue to collect their medication; however, if patients on a weekly schedule miss a pick-up, they potentially lose a week's supply of medication unless they are able to go back to the treatment service and have a new prescription issued. Therefore, the consequences of missing a pick-up are quite different depending on the frequency of the pick-up.

Multivariate regression analysis suggested that supervised consumption and a shorter duration of treatment were the most significant independent predictors of non-adherence. These findings are consistent with another recent investigation which used a self-report measure, and found missed pick-ups the most prevalent type of non-adherence for those patients on supervised consumption.[11] So although supervised consumption of methadone reduces the risk of diversion and methadone-related deaths,[12] it may increase the risk of non-adherence.

The association between missing doses of methadone, being on lower doses and using illicit opiates is consistent with other published research in this area, especially in relation to 'on-top' illicit heroin use.[13] Research from the National Treatment Outcome Research Study has shown that for every 1 mg increase in methadone dose there is a 2% reduction in the level of illicit heroin use.[14]

The main measure of adherence used in this study tells us only whether patients collected their medication and not whether they consumed it all, which is a limitation. However, the majority of patients prescribed methadone had a recent drug screen that confirmed the drug's presence. Furthermore, those who did not pick up all their medication were more likely to use illicit heroin, suggesting that their treatment was less effective. The relationship between levels of adherence and treatment outcome has yet to be fully revealed in the substance misuse field. In the treatment of HIV, levels of adherence to antiretroviral agents needs to be of the order of 97% to suppress viral replication and reduce the risk of drug-resistant strains developing.[15] Using missed pharmacy pick-ups as a proxy for adherence, Nachega *et al* found

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that virological outcomes improved in a linear dose–response manner as adherence to treatment increased beyond 50%.[16]

A further limitation of this study is that it was undertaken in just two inner-London boroughs across three treatment services and may not be generalisable to other parts of the UK or to other parts of the world where prescribing practices may differ significantly. However, the large sample and objective nature of the measures of adherence are the main strengths of this study.

From a clinical governance point of view, one needs to ask to what extent were clinicians aware of the degree to which some of their patients were failing to pick up their medication. The local agreement with community pharmacies is that they should contact drug treatment services if a patient misses three consecutive doses. However, we were unable to confirm whether this had always happened.

We conclude that adherence to treatment should be an integral part of the regular cycle of review of treatment effectiveness. Obtaining feedback from pharmacists and incorporating it into the clinical review process is essential if treatment is to be optimised effectively.

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Declaration of interest

None.

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