

Introduction

Methadone maintenance therapy (MMT) is the most effective evidence based treatment for opiate dependence. Most studies have shown reductions in illicit drug use and improvement on other psychosocial parameters such as legal issues, crime and risk behaviour^{1,3}. However, the problem of continuing drug use among MMT patients is long standing and widely acknowledged. Even in studies demonstrating the effectiveness of various interventions for improving treatment response among MMT patients, a subgroup of patients typically fails to respond. Ball & Ross² found rates of ongoing injection drug use as high as 57%. In Australia, Mattick et al⁴ found that patients maintained on about 55mg methadone tested positive for opiates in just over 50% of urine samples. In USA, Strain et al⁵ in 1999 found that patients on high dose methadone (over 80 mgs) tested positive for opiates in 53% of urine samples while patients on a moderate dose demonstrated 61.9% positive samples. Using similarly high methadone doses and enhanced psychosocial treatment supports, Avants et al⁶ achieved greater opiate abstinence but more than one third of samples were positive for illicit opiates with the most intensive treatment program. In a review of nine Veterans Administration clinics in USA treating an older client group, Willenbring et al⁷ in 2004, found that just 17% of samples provided by clinic attendees were opiate positive.

Although attempts to identify poor responders have failed to yield consistent predictors, several studies suggest various factors that might be associated with favourable outcomes. In most previous studies a higher dose of Methadone is associated with less illicit opiate abuse and longer retention rates in treatment^{5,8}. There is a significant amount of evidence that suggests poly-substance abuse seriously compromises treatment. Cocaine/crack abuse is a risk factor for continued heroin use^{9,10,11}. Contradictory results were obtained during investigation of the effectiveness of psychosocial programmes associated with Methadone treatment that varies widely among clinics. However, early and more frequent counselling contacts were associated with lower rates of drug use by patients on MMT¹². While it is generally recognised that patients who have a comorbid mental disorder in addition to an addiction have poorer treatment outcomes, there is limited research on the impact of mental disorders on the treatment of opiate dependence^{14,13,15}.

Identification of the factors that are predictive of outcomes, these might prove useful in modifying intervention strategies for improved responses. For this reason, we decided to investigate the factors supporting MMT effectiveness among patients attending drug treatment services at Drug Treatment Centre Board (DTCB) at Trinity Court in Dublin. DTCB is a central drug treatment service for the whole population of Dublin, which is approximately one million. This service also provides specialist advice and professional support to community based Methadone clinics and General Practices. The national advisory committee on drugs (NACD) estimates that there are over 12,500 opiate addicts in Dublin 24.

This is a retrospective study that aimed to measure rates of ongoing heroin abuse among patients on MMT in the Irish treatment context. We also sought to identify which patient and treatment characteristics are associated with an improved response to MMT.

Method

Setting

The DTCB is the longest established addiction treatment service in Ireland. The vast majority of clients have a primary diagnosis of opiate dependence. Treatment is provided by a multidisciplinary team led by a consultant psychiatrist. Addiction treatment services expanded substantially in Dublin during the 1990s. Many new addiction treatment clinics were opened and many general practitioners began providing treatment in the community setting to patients addicted to opiates. There are about eight thousand people on methadone maintenance in Dublin. At any one time, about 500 of these patients are being treated in DTCB. General practitioners in the community manage the most stable group of patients. More complex cases are managed in the local addiction treatment services. The most complex patients are managed in the DTCB. Patients are referred into and out of DTCB to and from other addiction services as their needs change. Patients attending the DTCB have higher rates of psychiatric comorbidity, serious physical illness, co-dependence on other substances, homelessness and violent behaviour than their counterparts in other services. The multidisciplinary team comprises of psychiatrists, nurses, counsellors, social work and outreach. Attendance at counselling is voluntary and many clients fail to attend following referral. The counselling approaches used draw upon Rogerian psychotherapy and cognitive therapy.

Data Collection

We included patients who were on MMT throughout a three-month period preceding data collection in 2004. Patients who dropped out of treatment were not included. Patients who were transferred back to community based addiction treatment during the three month period were also excluded. These patients were excluded because no, or very few, urine samples were available for these patients and the key outcome measure in this study was the proportion of the illicit opiate positive samples provided over a three month period. Patient characteristics including age, gender, duration in treatment and Methadone dose were obtained from the clinical notes. In order to examine rates of comorbidity, doctors managing patients identified those patient who had an affective disorder (Depression or Bipolar affective disorder) or a psychotic disorder (Schizophrenia, schizoaffective disorder or drug induced psychosis), according to ICD 10 criteria at the outset of the study.

Urine samples were collected from patients one or two times per week. In order to examine characteristics associated with better outcome, we created a dichotomous variable based on results of urinalysis screens for illicit opiate use. To maximise our statistical power to identify significant predictors of good outcome we sought to obtain groups of similar size. An earlier audit of outcome revealed that about half the clients on MMT were opiate positive in less than 20% of provided urine samples. Therefore we categorised patients as having a good outcome if less than 20% of their urine samples tested positive for opiates during the study period. Patients with more than 20% samples testing positive for opiates were categorised as having a poor outcome. There is no international consensus on the proportion of opiate positive urine samples that constitute a good outcome. As mentioned above, the mean proportion of the opiate positive samples found among the patients on MMT in the international studies ranges from 17% to 53%, with most studies at the upper end of this range. Consequently, we suggest that setting the cut-off at 20% has some face validity based on this international literature.

Urinalysis

Clients provided supervised urine samples between one and two times per week. Each sample is screened for opiates, cocaine metabolite (benzoylecgonine) and benzodiazepines using Syva® EMIT® II Plus homogenous enzyme immunoassay at the cut-offs of 300ng/ml, 300ng/ml and 200ng/ml respectively. Samples were also tested for amphetamines and ring substituted amphetamines (e.g. MDMA) using the microgenics CEDIA assay calibrated at a 1000ng/ml alpha amphetamine cut-off. The test for alcohol is a Microgenics® DRI® Ethyl Alcohol Enzymatic Assay at a cut off of 30mg%.

Statistical Analysis

Quantitative variables were converted into categorical variables for the purpose of analysis. Associations between categorical variables and good outcome were examined using Pearson's chi square test. Specifically we examined for the associations of good outcome with gender, age, duration in treatment, Methadone dose, attendance at counselling, psychiatric co-morbidity and illicit use of other drugs. Odds ratio and their 95% confidence intervals were reported to indicate the magnitude of associations. A logistic regression analysis was conducted to identify those variables independently predictive of a good outcome. Variables were chosen for inclusion in the final regression equation by using the forward and backward selection techniques, based on Wald statistic. All variables examined on univariate analysis listed above were considered for selection into the final regression equation. The selected variables were examined for evidence of interaction.

Results

Four hundred and ninety five patients were attending DTCB at the start of this study and 440 patients (89%) who remained in the treatment for full three month period were included in the study. Sixty-three per cent were male and their mean age was 32 years. Mean duration in treatment was 42 months. A comorbid psychotic illness was present in 26 (6%) patients and comorbid affective disorder was present in 121 (27%) patients. The average methadone dose prescribed to patients was 74mgs per day. The methadone dose was over 60mgs in 361 (82%) cases. One hundred and sixty-nine (38%) patients attended counselling during the study period. However, 47% of these attended counselling less than once per month. Urinalysis confirmed that 172 (39%) patients abused cocaine during the study period. Two hundred and eighty-one (65%) showed evidence of benzodiazepine (BZD) abuse (i.e. urinalysis demonstrated benzodiazepine use in the absence of benzodiazepine prescription). Seventy-five (17%) demonstrated evidence suggestive of alcohol misuse, with urine samples testing positive for the same. Twenty-two (5%) patients provided urine samples that were regularly positive for alcohol (i.e. more than one in five samples tested positive). Only 22 (5%) of the patients tested positive for amphetamines during the study period. Of these, fifteen patients demonstrated amphetamine use in just one urine sample over three month period of study.

Table 1. Characteristics associated with greater opiate abstinence among 440 patients on methadone maintenance treatment

Characteristic	Good outcome %	Odds ratio (95% confidence interval)	P value
Total	54		
Gender			

Male		52	1.0	
Female		58	1.3 (0.9-1.9)	0.21
Age				
<30 yrs		51	1.0	
=>30 yrs		58	1.3 (0.9-1.9)	0.15
Duration in treatment				
Under 24 month		48	1.0	
24-59 months		57	1.4 (0.9-2.3)	0.10
=> 60 months		59	1.6 (1.0-2.6)	0.06
Methadone dose				
Under 60mg		43	1	
At least 60mg		57	1.8 (1.1-2.9)	0.02
Counselling (%)				
None		56	1.0	
Some		51	0.8 (0.5-1.2)	0.3
Dual Diagnosis				
Not psychotic		55	1	
Psychosis		54	1.0 (0.4-2.3)	0.97
No affective disorder		53	1	
Affective disorder		59	1.3(0.8-2.0)	0.23
Illicit drug use				
Cocaine				
	abstinent	64	1.0	
	Infrequent use*	45	0.5 (0.3-0.7)	0.001
	Regular use*	34	0.3 (0.2-0.5)	<0.001
Benzodiazepine				
	abstinent	65	1.0	
	Intermittent use^	44	0.4 (0.2-0.7)	0.002
	Consistent use^	59	0.8 (0.4-1.4)	0.35
Alcohol				
	No samples positive	55	1.0	
	Infrequent use*	47	0.7 (0.4-1.3)	0.3
	Regular use*	68	1.8 (0.7-4.5)	0.22

* "Infrequent use" implies less than 20% of samples revealed presence of the substance and "Regular use" implies that more than 20% of samples revealed presence of the substance
^ "intermittent use" implies that some, but not all urine tests revealed

Of the 5686 urine samples collected from patients during the study period, 1616 (28%) were opiate positive. One hundred and forty-seven (34%) patients were abstinent from illicit opiates throughout the study period. A further 90 (20%) patients demonstrated infrequent illicit opiate misuse, testing positive for opiates in less than 20% of urine samples. Poorer outcome was significantly associated with lower methadone dose, cocaine abuse and intermittent benzodiazepine use on both univariate and multivariate analysis (see tables 1 and 2). Patients who were in treatment for a longer period (greater than 24 months) of time demonstrated lower levels of ongoing illicit opiate abuse (Mantel-Haenszel chi square test for trend, $p=0.05$). Outcome was not significantly associated with gender, age, counselling attendance or dual diagnosis.

Table 2. Factors associated with better outcome among 440 patients on methadone maintenance treatment, on multivariate analysis

Characteristic	Adjusted odds ratio (AOR)	95% confidence interval of AOR	P value
Methadone dose			
Under 60mg	1		
At least 60mg	2.2	1.3 - 3.7	0.005
Illicit drug use			
Cocaine			
	abstinent	1.0	
	Infrequent use*	0.4	0.3 - .07
	Regular use*	0.3	0.2 " 0.5
Benzodiazepine			
	abstinent	1.0	
	Intermittent use	0.5	0.3 " 0.8
	Consistent use	0.7	0.4 " 1.3

* "Infrequent use" implies less than 20% of samples are cocaine positive and "Regular use" implies that more than 20% of samples were cocaine positive

Thirty-three (43%) of the 77 patients who were receiving less than 60mg of methadone achieved a good outcome, with 22 demonstrating complete abstinence throughout the study period. Fifty patients were being prescribed more than 100 mgs of methadone. Fourteen (28%) of these failed to achieve a good outcome.

Discussion

Results of our study indicate that many patients were involved in ongoing illicit opiate misuse while on MMT. However, during the three months of study period one third of patients were opiate abstinent throughout. One in five patients demonstrated occasional opiate misuse while on MMT, with less than 20% of their urine samples testing opiate positive. Overall, 72% of urine samples provided by patients were opiate negative. Although findings from urinalysis vary in different studies^{4,5,7,17} these results from DTCB indicate a reasonable outcome for MMT patients in Dublin. Great caution is needed in evaluating methadone effectiveness reported in various studies as outcomes may be influenced by clinic policies, programme modalities and client characteristics. The DTCB clients, included in this study, are selected on the basis of being treatment resistant and difficult to manage in other clinics. Outcomes for patients on MMT in other treatment settings in Dublin are likely to be different, given the fact that the DTCB is effectively a tertiary referral service for other settings

Our findings that higher dose of methadone is associated with better outcome in terms of opiate abstinence strengthens previous evidence^{5,18}. This has been generally acknowledged in most treatment settings. Patients treated with inadequate doses of methadone commonly supplement their dose with illicit opiates. Treatment response can be maximised by titrating the dose of methadone in response to clinical signs and subjective distress. There is evidence from previous studies that most patients do not request inappropriate increases in methadone dosage⁸. On the other hand, higher doses alone may not solve the problem of illicit opiate use among methadone non-responders²¹. In this study, despite high doses of Methadone (greater than 100mg) more than one quarter of patients did not achieve good outcome. In a study by Belding¹⁸ 57% of non-responders were already on 80mg and 27% were on or above 100mg. In one study by Willenbring⁷ it was indicated that the percentage of patients that were successfully being maintained at doses less than 60mg ranged from 17 to 40%, with average across clinics of 29%. Therefore, simply providing higher doses to everyone will not guarantee a good outcome for all patients. Close monitoring of all patients who test positive for non medical opiates, regardless of current dosage, and reviewing the management plan based on individual needs may be a more appropriate approach than simply titrating up the dose.

This present study confirms previous findings that cocaine and benzodiazepines (BZD) abuse are linked with poorer outcomes^{18,20}. This study has shown that patients with positive cocaine samples were much less likely to have a favourable treatment response than those who avoided cocaine use. There is a need to develop and evaluate both pharmacological and psychosocial interventions for MMT patients who abuse cocaine²². This represents a growing challenge for treatment services as recent research has shown an increasing use of cocaine/crack in the opiate dependent population in Dublin^{11,13}. This has now become a growing challenge for services. One study²³ has shown that contingency intervention in conjunction with an intensive CBT protocol is effective in engaging and retaining patients with high levels of cocaine/crack use. BZD abuse in MMT patients was wide spread in our patient group, a finding that has previously noted in Dublin. It has been suggested that as a consequence of inadequate methadone dose, some patients

take BZD in order to handle heroin craving. If this is true than titration of methadone dose against use of BZD can be useful in eliminating BZD use in motivated patients. Contrary to our expectations we found increased opiate abuse among intermittent BZD users while the level of illicit opiate abuse among those constantly BZD positive were similar to those seen in the group who were BZD abstinent. . One explanation is that the intermittent BZD users are regularly seeking intoxication or experiencing difficult cravings. On some occasions, they take a handful of tablets and on other occasions they take heroin. The constant BZD users may be seeking a constant low grade sedation but do not particularly seek the euphoric effects from heroin anymore. Rates of abuse of amphetamines and ecstasy were low in this group during study period.

Another unexpected finding of this study was that patients with dual diagnosis tended to do well in terms of opiate abstinence. We speculate that patients with dual diagnosis were receiving more intensive treatment from the adult mental health teams and consequently fared as well as the other patients attending this specialist service. However, the amount of input from mental health teams was not measured. Enhanced and multidimensional services have been shown to demonstrate increased effectiveness in substance misuse treatment^{14,15,25}.

Unlike previous studies, this study failed to demonstrate any beneficial effects of counselling^{9,12}. However, these results should be interpreted cautiously. It is likely that this finding reflects the manner in which clients access counselling in DTCC. Out of 440 patients, only 87 attended counselling sessions on a regular basis. Patients with significant psychosocial problems and treatment resistance are prioritised for the referral to counselling, and many of them were consistently giving opiate positive samples before referral. Both our clinical experience and previous evidence suggest that the role of the counsellor is very important in treatment of substance misuse. In the study by Willenbring counselling frequency was positively correlated with better outcome. Counselling practices vary widely between different clinics. Outcome could be related to counselling skills, strategies and facilities. McLellan²⁶ has shown that adequate counselling including weekly sessions for first four weeks of treatment and monthly sessions thereafter improve outcomes compared to no counselling.

There was a positive correlation between opiate negative results and longer duration in treatment. Although results were not statistically significant, younger clients tended to demonstrate poorer outcome²⁷. There are a number of plausible explanations for poorer outcome among younger patients earlier in the treatment process. These include peer pressure, more chaotic life styles and lack of education and awareness in this group. There is a growing consensus regarding the need to develop specialist services tailored to suit the different needs of young drug abusers²⁸.

There are limitations to this study. The DTCC is a highly specialized drug treatment centre that has a multidisciplinary staff team and more resources than many other services. In general, patients attending this clinic have chronic substance misuse problems, complex mental health issues and more serious forensic, social and behavioural difficulties. In this respect, our cohort differs from those attending other community based substance misuse clinics and the outcome might be different in such settings. Also, in this study, counselling failed to show an improved outcome. As mentioned earlier, this could be due to the fact that only a minority of the patients with more serious psychosocial issues are prioritised for this service. A RCT design would be a more appropriate method to study the impact of counselling on outcomes. Urinalysis provides a very objective method for identifying ongoing illicit substance misuse during treatment. However, it is limited by the variability in elimination half-life of drugs. This can be weeks for benzodiazepines, days for opiates and cocaine and just hours for alcohol. With regard to alcohol abuse, some might consider it unreasonable to assume that alcohol detected in urine samples is indicative of problematic use. We did not use structured diagnostic instrument to identify patients with co-morbid psychiatric disorder. We relied on clinical diagnosis and this is likely to be less reliable in terms of consistency. We confined this study to patients who were on methadone treatment for the complete three month study period. In doing so, we cannot provide information on patients who dropped out of treatment, finished treatment or who transferred back to community based treatment during the study period.

The results achieved by patients in Dublin are quite good by international standards. Services providing MMT should monitor treatment outcome and develop interventions that strive to assist patients in achieving even higher rates of abstinence. MMT patients who abuse cocaine and BZD are at an increased risk of continuing opiate abuse and constitute a growing challenge to treatment services in Dublin.

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