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Outcome evaluation of the opioid agonist maintenance treatment in Iran

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Abstract

Introduction and Aims. *Methadone maintenance treatment and buprenorphine maintenance treatment are the two main therapeutic options considered for opioid replacement therapy. This study was conducted to examine the effectiveness of methadone maintenance treatment and buprenorphine maintenance treatment in Iran under usual clinical conditions.* ***Design and Methods.*** *In this outcome research, 311 patients consented to participate in the study (77.8% response rate). The Opioid Treatment Index, General Health Questionnaire and WHOQOL-BREF questionnaire were used to assess the effectiveness of the therapeutic programs. Drop-out rate was calculated after two and six months of treatment.* ***Results.*** *Mean dose of methadone was in an acceptable range; however, doses for buprenorphine maintenance treatment patients seemed low. The rates of attrition after two and six months of treatment were 24.2% and 44.0% in the methadone maintenance treatment group and 41.3% and 65.4% in the buprenorphine maintenance treatment group, respectively ($P < 0.001$). Drug use, HIV risk-taking behaviour, and mental and physical health improved in both groups at six months of treatment, while quality of life improved only in the methadone maintenance treatment group.* ***Discussion and Conclusions.*** *The retention seen in the buprenorphine group may in part be related to the low buprenorphine doses used. As a whole, the positive results provide support to continuation of maintenance programs.* [Esmaeili H-R, Ziaddinni H, Nikravesh M-R, Baneshi M-R, Nakhaee N. Outcome evaluation of the opioid agonist maintenance treatment in Iran. *Drug Alcohol Rev* 2014;33:186–193]

Key words: Iran, harm reduction, human, opioid-related disorders/rehabilitation, patient dropout/statistics and numerical data.

Introduction

Opiates are the third most used class of drugs in the world [1] and Iran has one of the highest prevalence of opioid use [2]. Several hundred years of history of opioid use and its proximity to the largest opium-producing country in the world (Afghanistan) are key causes [3]. Although statistics related to drug abuse in Iran differ, according to some reports 1 in every 17 people in Iran is a drug abuser, and it has been suggested that drugs are the most lethal threat to Iranian society today [4]. Opioids, in addition to increasing mortality and morbidity, affect quality of life [5] and place a financial burden on society due to the cost of law enforcement, unemployment and other related social outcomes [6].

Iranian anti-drug laws treat drug addiction as a crime, but all addicts are permitted to refer themselves to licensed centres affiliated with the Ministry of Health for treatment and rehabilitation, and they are not subject to legal prosecution during this period. Substance abuse control in Iran has focused on decreasing supply, demand and harm. With regard to reducing harm, substance abuse treatment centres have been

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operating in Iran since 2005 [7]. Previously, detoxification from opiates was primarily performed using clonidine in outpatient departments. Before 2005, the emphasis was placed on drug law enforcement and the 'war on drugs'. However, since then the focus has gradually shifted towards harm reduction [4]. Patients referred to substance abuse treatment centres at their own request and according to national protocols undergo one of the two treatment interventions: detoxification and/or maintenance treatment. Maintenance treatment itself is either methadone maintenance treatment (MMT) or buprenorphine maintenance treatment (BMT). Reported outcomes of maintenance treatment vary between studies [5] and effects such as improved health status, decrease in substance use, decrease in the rate of drug injection and decrease in criminal behaviours have been reported thus far [8]. Most studies on opioid maintenance therapies have been performed in developed countries, with few studies in developing countries [6].

In light of the complexity of opioid dependency treatment and the growing number of patients undergoing drug addiction treatment, it is necessary to evaluate the efficacy of treatment programs [9]. Despite the importance of program evaluation, no comprehensive study assessing the performance of substance abuse treatment centres in Iran has been conducted in the 10 years of their existence; the only relevant study conducted to date was only performed on intravenous drug users [10]. The present study aimed to evaluate the outcomes of these clinics in a real-world setting in an Eastern Mediterranean country.

Studies in which treatment outcomes are evaluated in real-life conditions instead of controlled conditions are known as effectiveness studies or outcome research [9]. The aim of clinical trials is to aid in clinical decision making, whereas effectiveness studies are primarily aimed at helping with health policy decision making. In many cases, effectiveness studies may complement clinical trials to aid in health policy decision making [11].

Method

Study setting

This effectiveness study was performed in 2012 in Kerman, the centre of the largest province in Iran. The study protocol was approved by the Ethics Committee of Kerman University (K/89/517). According to the national protocol for initiating maintenance therapy, it is necessary that the opioid user fulfils at least one of the following criteria: intravenous drug use; heroin consumption; opium consumption having had at least three failed attempts to quit drugs; history of imprisonment; being HIV positive and being female [12]. In the course of MMT, the opiate-dependent patient received 30–40 mg methadone on the first day followed by a daily increase of 10 mg up to 120 mg/day. Methadone in the form of syrup (5 mg/ml) must be swallowed under the daily supervision of the clinic staff during the first two months of treatment and take-home medication is only provided on holidays. After two months of treatment methadone patients were able to receive every-other-day or three-times-weekly supervised doses for the next two months. In the fifth month they were allowed to have five unsupervised doses per week. Finally, in the sixth month six-day take-homes were authorised. In buprenorphine maintenance treatment, the patient begins on an initial dose of 2–4 mg. During the first four weeks of treatment, the maintenance dose may be increased to a maximum of 16 mg per day or every other day, based on individual patient response and tolerability. Buprenorphine was provided in the form of sublingual tablets that were administered under once weekly supervised dosing condition for the whole six months.

For methadone treatment, doses between 1 and 39 mg were classified as low, those between 40 and 59 as medium and those between 60 and 120 mg as high [6]. For buprenorphine treatment, the corresponding doses were 2–6 mg (classified as low), 7–15 mg (classified as medium) and 16 mg (classified as high) [13].

The cost of monthly opioid agonist treatment for both regimens was the same at approximately 30–35 dollars, and the patients themselves selected either MMT or BMT under real-world conditions.

Participants

Of the 49 treatment centres, seven were randomly selected. A total of 400 persons referred for buprenorphine or methadone maintenance therapy were consecutively selected from these centres and, after explaining the purposes of the study and obtaining their informed consent, they were invited for an interview and to fill out questionnaires. No subject was on antiretroviral therapy for HIV infection. All participants were opioid dependent. Opioid dependence was established using a semi-structured interview based on DSM-IV criteria. To keep the situation representative of the real world scenario, the participants were not paid to participate in the study.

Assessment

Evaluations were performed at three time points: before treatment, two months after treatment and six months after treatment. Interviews were performed at two time points: before treatment initiation and six months after

the treatment. In the second month, percentage lost to follow-up (in addition to the sixth month) was calculated. Retention was defined as the proportion of participants known to be receiving MMT or BMT at the end of each follow-up period (i.e. two and six months after treatment onset), whereas attrition was defined as loss to follow-up.

The following questionnaires were used to measure the outcomes of the two maintenance treatment programs:

Opioid Treatment Index (OTI). This included questions on six dimensions of HIV risk-taking behaviour, drug use, criminality, social functioning, physical health and mental health. In addition to 11 drug classes examined in the OTI, we also asked participants about *Sukhteh* (half-burnt opium) and *Shireh* (refined opium extract) consumption. Collectively, they are referred to as opium residue with purity 4–5 times more than opium. The validity and reliability of the Persian version of this questionnaire had previously been tested and shown to be adequate [14]. In all dimensions, higher score indicates more significant drug abuse-related problems. Except for the dimension of social functioning, questions relate to the previous month. The questionnaire was completed through interview.

WHOQOL-BREF questionnaire. This included 26 questions assessing quality of life. The validity and reliability of the Persian version of the questionnaire have previously been tested and shown to be adequate [15]. Higher scores indicate a higher quality of life.

General Health Questionnaire. This included 12 questions assessing the general health of subjects. The validity and reliability of the Persian version of this questionnaire have been previously tested and shown to be adequate [16]. A higher score indicated poorer mental health.

Urine test. At six months of follow-up, a urine test was performed to assess if the participants were positive for opium, heroin or morphine (Behmedico, Tehran, Iran).

Demographic variables including age, sex, educational level, employment status, marital status and history of imprisonment were also recorded. Retention was defined as the proportion of participants known to be receiving MMT or BMT at the end of each follow-up period, while attrition was defined as lost to follow-up. Retention at two and six months of treatment was considered to be the sole objective indicator of program effectiveness [9]. Interviews were conducted by qualified psychologists who had passed a training course held by the last author (N.N). The quality of data gathering was supervised continuously.

Data analysis

Chi-square test was used for comparison of categorical data between the two groups. Wilcoxon test was conducted in order to assess differences in OTI scores before the intervention and six months after the intervention. In order to evaluate the relationship between independent variables and drop-out rate, multivariate logistic regression was conducted.

Results

In total, 400 individuals were invited to participate in this study, of whom 311 agreed (response rate = 77.8%). Of those, 207 underwent MMT and 104 underwent BMT. Demographic features of the two groups are presented in Table 1. This shows that, except for previous history of imprisonment being higher in the MMT group ($P < 0.001$), there was no significant difference between the groups for other demographic features. The proportion of cases receiving high-dose maintenance therapy was significantly higher in the MMT group (75.9%) than the BMT (1.0%) group ($P < 0.001$) (Table 1). At baseline, three cases in the MMT group and one case in the BMT group were intravenous drug users. Mean doses of methadone and buprenorphine at the sixth month of treatment were 70.8 ± 22.5 and 5.8 ± 3.1 mg, respectively.

At the second month of treatment 29.9% (n = 93) of participants had dropped out, and 51.1% (n = 159) of participants had dropped out by the sixth month of treatment. The drop-out rates at two and six months of treatment were 41.3% and 65.4% in the BMT group and 24.2% and 44.0% in the MMT group, respectively ($P < 0.001$) (Table 2).

According to the OTI questionnaire, which asks about recent use of 11 drug categories, nobody reported using cocaine, hallucinogens or inhalants at the time of admission (Table 3). The most commonly consumed substances (excluding tobacco) were opium and heroin; heroin consumption was significantly greater in the MMT group (44.9%) compared with the BMT group (19.2%) ($P < 0.001$). Changes in the scores for six independent outcomes on the OTI and quality of life between basal time and the sixth month are shown in Table 4. Mental and physical health improved in both groups, and all subdomains of quality of life showed significant improvement in the MMT group. The two groups had negative urine screening tests (116 and 36 individuals in MMT and BMT groups, respectively) for all the three drugs checked (i.e. opium, morphine and heroin) at six months of

Table 1. *Baseline characteristics in MMT and BMT groups*

Characteristics		MMT group (%) $n = 207$	BMT group (%) $n = 104$	*P* value
Age	<30 years	74 (35.7)	44 (42.3)	0.261
	≥ 30 years	133 (64.3)	60 (57.7)	
Sex	Male	184 (88.9)	87 (83.7)	0.193
	Female	23 (11.1)	17 (16.3)	
Education	Illiterate/Primary	50 (24.2)	28 (26.9)	0.564
	Secondary	95 (45.9)	39 (37.5)	
	Diploma	43 (20.8)	26 (25.0)	
	College	19 (9.2)	11 (10.6)	
Marital status	Married	61 (29.5)	29 (27.9)	0.337
	Unmarried	122 (58.9)	68 (65.4)	
	Divorced	24 (11.6)	7 (6.7)	
Job	Unemployed	34 (16.4)	14 (13.5)	0.266
	Part time	72 (34.8)	46 (44.2)	
	Full time	101 (48.8)	44 (42.3)	
Imprisonment	Yes	71 (43.3)	10 (9.6)	<0.001
	No	136 (65.7)	94 (90.4)	
Dose level	Low	17 (8.2)	70 (67.3)	<0.001
	Medium	33 (15.9)	33 (31.7)	
	High	157 (75.9)	1 (1.0)	

BMT, buprenorphine maintenance treatment; MMT, methadone maintenance treatment.

Table 2. *Number of participants retained in the opioid maintenance programs*

		Retention at 2-month follow-up		Retention at 6-month follow-up	
Maintenance treatment	N at baseline	Yes (%)	No (%)	Yes (%)	No (%)
Methadone	207	157 (75.8)	50 (24.2)	116 (56.0)	91 (44.0)
Buprenorphine	104	61 (58.7)	43 (41.3)	36 (34.6)	68 (65.4)
P value		<0.001		<0.001	

treatment. As shown in Table 4 drug use decreased in both groups, at six month follow-up in comparison with baseline ($P < 0.001$).

According to the multivariate logistic regression, type of treatment was related to risk of drop out; treatment with buprenorphine increased the probability of drop out by 2.35 times [95% confidence interval 1.11–4.98, $P = 0.026$], whereas most of the demographic variables (including age, sex, educational level and marital status) and maintenance dose of drugs were not significantly related to risk of drop out. Having a full-time job lowered the risk of drop out and heroin use and history of imprisonment increased the risk of attrition (Table 5).

Discussion

Treatment evaluation helps to recognise how often a program achieves its goals. According to our results, attrition is an area of concern for both types of maintenance treatment, especially BMT. Although opioid addiction is known to be a chronic relapsing disorder, experience in other countries has shown that maintenance treatment, especially MMT, is effective in retaining patients in treatment and reducing harm [13,17]. MMT and BMT are based on substitution of methadone or buprenorphine with the drug being consumed. In this way, not only is the user freed from the control of the previously consumed drug but they also regain control over their addiction. Even though the user becomes physically dependent upon another substance, drug-related behaviours improve and eventually the user may return to a drug-free life [6]. Review studies relating to the efficacy of MMT and BMT have shown that these treatments are effective. In the case of MMT, evidence of its efficacy is more compelling [6,18].

Before interpreting the results, we should point out the aim of our study was not to compare MMT and

Table 3. *Drug used by respondents during 4 weeks before enrolment*

Substance	MMT group (%) $n = 207$	BMT group (%) $n = 104$	*P* value
Opium	84 (40.6)	52 (50.0)	0.114
Heroin	93 (44.9)	20 (19.2)	<0.001
Opium residue	38 (18.4)	34 (32.7)	0.005
Other opioids[a]	8 (3.9)	11 (10.6)	0.02
Cannabis	8 (3.9)	1 (1.0)	0.281
Amphetamine	12 (5.8)	3 (2.9)	0.258
Sedatives	35 (16.9)	7 (6.7)	0.013
Barbiturates	1 (0.5)	0 (0)	1.00
Alcohol	5 (2.4)	0 (0)	0.173
Cocaine	0	0	
Hallucinogens	0	0	
Inhalants	0	0	
Tobacco (cigarette/waterpipe)	135 (65.2)	53 (51.0)	0.015

[a] Illegal methadone, diphenoxylate, morphine, codeine

Table 4. *Mean (±SE) OTI and QoL scores before and 6 months after treatment in MMT and BMT groups*

Variable	MMT group ($n = 116$)			BMT group ($n = 36$)		
OTI subscale	Baseline	Follow-up	*P* value	Baseline	Follow-up	*P* value
Drug use	14.0 (1.0)	6.5 (1.1)	<0.001	9.0 (1.0)	5.6 (1.6)	<0.001
Social functioning	16.3 (0.3)	15.3 (0.4)	0.216	16.1 (0.5)	16.9 (0.8)	0.608
HIV risk-taking behavior	8.0 (0.8)	0.4 (0.2)	<0.001	6.7 (1.2)	0.0 (0.0)	0.005
Mental health	6.5 (0.2)	4.0 (0.3)	0.001	5.0 (0.4)	2.3 (0.5)	0.006
Physical health	10.1 (0.5)	6.1 (0.5)	<0.001	10.0 (0.7)	7.2 (0.9)	0.022
Criminality	0.04 (0.02)	0.03 (0.03)	0.180	0.0 (0.0)	0. (0)	1.000
QoL domains						
Physical health	3.2 (0.05)	3.6 (0.06)	<0.001	3.2 (0.1)	3.6 (0.1)	0.555
Psychological health	2.6 (0.05)	3.1 (0.06)	<0.001	2.8 (0.1)	3.2 (0.1)	0.357
Environmental health	2.9 (0.04)	3.1 (0.05)	<0.001	3.0 (0.1)	3.1 (0.1)	0.964
Social relationships	2.9 (0.06)	3.2 (0.06)	0.001	2.9 (0.1)	3.3 (0.1)	0.150
Overall QoL	2.9 (0.04)	3.2 (0.04)	<0.001	3.0 (0.1)	3.2 (0.1)	0.608

BMT, buprenorphine maintenance treatment; MMT, methadone maintenance treatment; OTI, Opiate Treatment Index; QoL, quality of life.

BMT since the patients were not randomised to the treatment conditions, which may introduce bias, and further, the groups had different baseline characteristics. The main advantage of the present study is the fact that it evaluated the efficacy of treatment programs in a real world setting. However, both subjective criteria such as self-reported health and perceived quality of life and objective criteria such as retention rate have been evaluated. Disadvantages of the present study include the absence of a control group and not measuring factors that might affect retention such as social support, family relationships and patient's motivation, as well as evaluation of quality and treatment satisfaction. Another limitation was the lack of specific laboratory tests to confirm self-reported drug use and urine screening tests. Although urine collection was supervised, the possibility of false negative results and urine tampering could not be ruled out [19]. Confirmatory testing using methods such as gas chromatography/mass spectrometry (GC/MS) are needed to verify the results [19]. Meanwhile, it is possible (not likely) that some of the individuals who discontinued medication may have sustained their abstinence after medication discontinuation. Therefore assuming that retention is comparable to success may be a study limitation as well, as additional bias may be introduced into the study by only looking at treatment outcomes of those still in treatment at follow-up. The relatively low sample size in BMT group resulted in decrease in power. Post hoc power analysis showed that the lack of difference between baseline and follow-up quality of life was related to low sample size.

Table 5. *Logistic regression analysis to identify factors associated with treatment dropout at 6-month follow-up*

Characteristics		Adjusted odds ratio	CI 95%	*P* value
Age	< 30 years	1		
	≥ 30 years	0.82	0.48-1.41	0.482
Sex	Male	1		
	Female	1.30	0.60-2.73	0.530
Education	Illiterate/Primary	1		
	Secondary	0.79	0.43-1.47	0.471
	Diploma	1.33	0.65-2.73	0.435
	College	0.84	0.34-2.11	0.718
Marital status	Unmarried	1		
	Married	1.10	0.61-2.00	0.750
	Divorced	0.64	0.25-1.62	0.342
Job	Unemployed	1		
	Full time	0.44	0.22-0.91	0.027
	Part time	0.55	0.26-1.15	0.111
Imprisonment	No	1		
	Yes	2.12	1.14-3.92	0.017
Heroin use at baseline	No	1		
	Yes	1.80	1.05-3.06	0.032
Type of treatment	MMT	1		
	BMT	2.35	1.11-4.98	0.026
Dose level	Low	1		
	Medium	1.23	0.59-2.57	0.576
	High	1.01	0.44-2.30	0.988

BMT, buprenorphine maintenance treatment; MMT, methadone maintenance treatment.

In the MMT group, probabilities of retention at two and six months of treatment were 76% and 56%, respectively. The retention rate in the BMT group at the end of the study was 21% lower than in the MMT group (Table 2). In a nationwide study of a US veteran's affairs population, the rates of retention were 40% and 30% at two and six months of MMT, respectively [20]. In China, retention rate at six months was shown to be 57% for one program [21]. In a study of intravenous drug users performed in collaboration between the World Health Organization and some Asian and Eastern European countries, 70% of MMT patients remained in treatment at the six-month interview [22]. Although the rate of treatment continuation in the present study was similar to several previous studies, it should be mentioned that premature drop out is the main barrier for maintenance treatments [23]. Several studies have already been performed that assess the causes of attrition from maintenance treatments, but on the whole there is no agreement on these factors [19,23]. Factors such as the patient's age, mental illness and race have been known to be important factors in risk of drop out in some studies [20,23] but not relevant in others [6]. Although the majority of studies have reported higher probability of retention in higher doses of maintenance treatments [6], we did not find any such relationship. This may be due to high rates of attrition in both groups [6]. In the present study, regression analysis showed no significant relationship between the probability of retention and demographic variables (except for full-time job) or maintenance dose of methadone or buprenorphine (Table 5). The probability of drop out in the BMT group was 2.4 times higher than that in the MMT group. A Cochrane review has also shown that BMT is less effective than MMT [18]. Another probable reason for lower success rate in BMT is related to the utilisation of lower maintenance doses in BMT compared to MMT. It should be noted that, while most of the subjects in the MMT group received high doses of methadone, in the BMT group only one patient was categorised as receiving a high dose of buprenorphine (Table 1). So use of a lower range of buprenorphine doses in BMT group comparing to methadone in MMT group may contribute to the superior outcomes associated with methadone treatment. Mattick *et al.* provided insights into the importance of adequate dosage levels in decreasing the rate of drop out [18]. Low dosage in the early stage of BMT may also be worth considering [24], as low doses of BMT in the early stages of treatment may be related to attrition from clinics. Therefore the importance of adequate dosage of buprenorphine should be highlighted in the education of physicians working in drug rehabilitation clinics. Heroin users had poorer outcomes and were 1.80 times more likely to drop out of maintenance treatment.

According to Gossop *et al.*, in many cases outcome is not the most important determinant and some factors such as problems with social support and family relationships can negatively affect the results of treatment [17]. In the present study we did not collect any data relating to family support and so could not assess its role in the risk of drop out. Anecdotal evidence suggests that patients undergoing maintenance therapy receive no formal or regular support from government agencies.

In the present study, both maintenance treatments improved self-reported physical and mental health. As shown in Table 4, the difference between baseline and follow-up data in subdomains of quality of life seems to be comparable between MMT and BMT groups but in only MMT group the differences showed statistically significant difference. The small sample size in the buprenorphine group at follow-up may generally make it difficult to detect statistically significant changes. There was no significant change in criminality or HIV risk behaviours that may be caused by a low baseline level. According to the Substance Abuse and Mental Health Services Administration, recovery is defined as 'a process of change through which an individual achieves abstinence and improved health, wellness and quality of life' [5]. Therefore, improvement in health (both physical and mental) and quality of life could be included as a measure of success for MMT programs in Iran.

Considering the aforementioned results, policy-makers should consider the following two points in assessing the effectiveness of maintenance treatments in Iran. First, the prevalence of opioid dependency in Iran is high [2] and any effort to reduce the harm of drug use would be appreciated. Second, it has been proven that in middle-income countries such as Iran, opioid agonist maintenance treatment has a significant role in decreasing the risk of HIV and HCV [1,10]; therefore, the continuity of maintenance treatment programs seems to be logical.

In conclusion, considering the rate of retention in maintenance treatment programs, particularly in MMT, and improvements in quality of life after this therapeutic intervention, it can be said that this program has been successful in Iran. More studies are needed that consider all of the factors required to identify the predictors of drop out and consequently to perform necessary interventions for increasing the rate of retention. A higher buprenorphine dose is recommended during BMT.

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