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REGULAR ARTICLE

Factors associated with illicit opioid use in methadone maintenance treatment clients in 5 Provinces, China

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Abstract
Objectives To investigate factors associated with illicit opioid use among methadone maintenance treatment (MMT) population.
Methods Participants were recruited from Beijing (2 clinics), Shanghai (2 clinics), Guangdong (2 clinics), Chongqing (2 clinics) and Gansu (1 clinic) provinces. Information about heroin use and MMT was obtained from a self-reported questionnaire, illicit opioid use was obtained from monthly medical records. Binary logistic regression was used to investigate factors associated with illicit opioid use.
Results Five hundred ninety-eight eligible MMT participants were used for data analysis. Variables such as age, gender, route of heroin use and daily MMT dosages were associated with illicit opioid use. Compared with MMT participants aged <40 years, participants aged 40–44 years ($P = 0.027$, OR = 0.57, 95 % CI 0.35–0.94), 45–49 years ($P < 0.001$, OR = 0.41, 95 % CI 0.24–0.67) and ≥50 years ($P = 0.008$, OR = 0.52, 95 % CI 0.33–0.85) were more likely not to have illicit opioid use. Compared with male participants, females were more likely to have illicit opioid use ($P = 0.044$, OR = 1.53, 95 % CI 1.01–2.32). Compared with inhalation heroin abusers, abusers with route of inhalation + injection heroin use were more likely to have illicit opioid use ($P = 0.009$, OR = 2.00, 95 % CI 1.19–3.36). Compared with daily MMT dosages <60 mg participants, participants with daily MMT dosages >80 mg were more likely to have illicit opioid use ($P = 0.003$, OR = 2.37, 95 % CI 1.35–4.15).
Conclusions Age, gender, route of heroin use and daily MMT dosages were associated with illicit opioid use. A tailored intervention is needed for a promotion of MMT.

Keywords MMT · Heroin use · Urine morphine test · Risk factors · Methadone maintenance treatment

Introduction

Methadone is a long-acting synthetic opioid-receptor agonist, which has been first synthesized in Germany as a substitute analgesic for morphine prior to World War II. In 1949, Americans discovered that it could be used to treat heroin withdrawal symptoms [1]. Methadone maintenance treatment (MMT) is a methadone substitution maintenance treatment. After methadone orally administrated once, it can last 24–36 h for heroin addicts without evident methadone euphoria. Currently, it has been proven to be an important and effective substitution treatment for opioid abusers especially for heroin addicts [2]. MMT can avoid withdrawal symptoms induced by heroin abstention, suppress heroin use [3, 4], decrease needle-syringe sharing practices, lower risks of HIV and other blood-borne diseases transmission and infection [5–8], reduce harm and criminalities [9], help heroin abusers return to society earlier [10]. So, it has been accepted and used in some regions and nations especially in most developed countries

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[11]. However, worldwide MMT coverage is very low. By 2009, MMT had been implemented in 61 countries, with only 8 % injecting opioid abusers receiving opioid substitution treatment (OST). Regional and national MMT coverage varied substantially, 61 % injecting drug users (IDUs) received OST in western Europe while only ≤1 % IDUs received OST in central Asia, Latin America, and sub-Saharan Africa [11].

In China, MMT program was initiated in 2004, with first 8 MMT clinics piloted [10, 12, 13]. Study showed that it was effective in the reduction of drug use, drug injecting behaviors, drug-related criminal behaviors, HIV infection, and improved relationships within family members [10]. After that, MMT clinics have been scaled up nationwide rapidly. Data from national methadone maintenance treatment progress report in December, 2015 showed that, this program had encompassed 785 MMT clinics in 29 provinces, benefited tens of thousands of opioid addicts by the end of 2015.

Clients who met MMT criteria admitted MMT clinic for MMT. According to China national MMT guidelines [14], urine morphine test was randomly performed every month by clinician in MMT clinics in China during MMT, as well as other countries did in the world. The positive urine morphine test outcome indicated a recent opioid use.

MMT is good for clients and society. However, the progress of MMT may be hampered due to various aspects, such as drop out, heroin use and methadone side effects, etc. During MMT, illicit substance use is one of the important indicators that influences MMT effects. Studies [15–17] showed that not all MMT participants can fully abstain illicit opioid use during MMT. The existence of a concurrent illicit opioid use during MMT discounted the MMT effect. To take effective intervention measures to promote MMT, to identify factors associated with concurrent illicit opioid use during treatment is necessary. However, fewer studies about the investigation of factors associated with concurrent illicit opioid use during MMT can be searched.

In this study, we used a self-reported questionnaire to investigate factors associated with illicit opioid use among MMT clients in China, with the aim of knowing factors associated with concurrent illicit opioid use, for a further promotion of MMT in China.

Methods

Participants

This study was one part of our substance abuse investigation among MMT clients. Participants were recruited from Beijing (2 clinics), Shanghai (2 clinics), Guangdong (2 clinics), Chongqing (2 clinics) and Gansu (1 clinic) provinces. In this substance abuse investigation, participants met the following criteria were included: (a) met the criteria of Chinese Classification of Mental Disorders version 3 for opioid dependence, (b) aged ≥20 years, (c) local resident or reside for more than 6 months, (d) having been in MMT clinic for a continuous MMT for at least 1 month, (e) no mental illness, can fully be responsible for his/her act. In this study, participants with no other illicit substance use before MMT, who reported a urine morphine test outcome, were included for a further data analysis.

This study was done during the period from January 2015 to July 2015. Peking University Health Science Center Ethics Committee approved the study. A written informed consent was obtained from each participant before enrolment. Participants took this participation voluntarily.

Questionnaire

In this study, a self-designed questionnaire was used to investigate factors associated with urine morphine test outcome during MMT. The questionnaire included baseline characteristics, heroin use before MMT, MMT and urine morphine test outcome during MMT. Baseline characteristics included gender, age, education and marital status. Heroin use before MMT included four items: cumulative years of heroin use, dosages of heroin use per time (g), frequency of heroin use in one-day and route of heroin use. MMT included two items: daily MMT dosages (mg) and cumulative years of methadone treatment. Urine morphine test outcome was obtained from electronic medical records. Any of positive urine morphine test outcomes excluded the outcome induced by medical use was defined as illicit opioid use.

Based on research objects, frequency distribution and related expertise, we divided variables into several groups. Age was divided into 4 categories: <40 years, 40–44 years, 45–49 years and ≥50 years. Education was divided into 4 categories: educated ≤6 years, 7–9 years, 10–12 years and >12 years which represented that MMT participants had a primary school, middle school, high school and post-high school education, respectively. Daily MMT dosages was divided into 3 categories: <60 mg, 60–80 mg and >80 mg.

Investigation

A face to face interview was performed by experienced clinicians. All investigators were trained before investigation. The investigation was performed anonymously.

Statistical analysis

SPSS Statistics Software 20.0 (IBM Corporation) was used for data analysis. Data were expressed as number (%), OR (95 % CI). Chi-squared test was used to compare baseline characteristics between urine morphine test negative and positive outcome participants. Binary logistic regression was used to explore factors associated with positive urine morphine test outcome. Variables which were significant in a univariate logistic regression were used as candidate variables for a multivariate logistic regression analysis (To control the effect of time in treatment on the outcome, we selected cumulative years of methadone treatment as candidate variable). Hosmer–Lemeshow test was used to evaluate the goodness of fit of the logistic model. All variables entered simultaneously, the entry and removal criteria were 0.05 and 0.10, respectively. A two-tailed p value <0.05 was regarded as significant.

Results

In all, 1004 eligible MMT clients finished our substance abuse investigation. Of whom, 598 MMT participants had no other illicit substances use before MMT, and reported urine morphine test outcome, who were eligible for data analysis. In these 598 MMT participants, 166 (27.8 %), 147 (24.6 %), 73 (12.2 %), 87 (14.5 %), 125 (20.9 %) participants finished their investigation in Beijing, Shanghai, Guangdong, Chongqing and Gansu, respectively.

Baseline characteristics

Table 1 showed the difference of baseline characteristics between urine morphine test negative and positive outcome groups during MMT. Variables of education and marital status were comparable between urine morphine test negative and positive outcome groups. However, there were significant differences ($P < 0.01$) in variables of gender and age between urine morphine test negative and positive outcome groups.

Univariate analysis outcome

Univariate analysis outcome showed that Route of heroin use and daily MMT dosages (mg) were significantly associated with illicit opioid use ($P < 0.05$, Table 2).

Compared with inhalation only heroin abusers, abusers with route of inhalation + injection heroin use were more likely to have illicit opioid use ($P = 0.003$), with an odds ratio of 2.10 (95 % CI 1.28–3.43). Compared with daily MMT dosages <60 mg participants, participants with daily MMT dosages >80 mg were more likely to have illicit opioid use ($P = 0.001$), with an odds ratio of 2.52 (95 % CI 1.48–4.30).

Table 1 Baseline characteristics of MMT clients between positive and negative urine morphine test outcome

Variable	Negative	Positive	Total
Gender**			
Male	277 (81.0 %)	184 (71.9 %)	461 (77.1 %)
Female	65 (19.0 %)	72 (28.1 %)	137 (22.9 %)
Age (years)**			
<40	62 (18.2 %)	81 (31.6 %)	143 (24.0 %)
40–44	82 (24.1 %)	58 (22.7 %)	140 (23.4 %)
45–49	85 (24.9 %)	48 (18.8 %)	133 (22.3 %)
≥50	112 (32.8 %)	69 (26.9 %)	181 (30.3 %)
Missing	1	–	1
Education (years)			
≤6	25 (7.3 %)	27 (10.6 %)	52 (8.7 %)
7–9	169 (49.4 %)	127 (49.8 %)	296 (49.6 %)
10–12	125 (36.6 %)	85 (33.3 %)	210 (35.2 %)
>12	23 (6.7 %)	16 (6.3 %)	39 (6.5 %)
Missing	–	1	1
Sexual partner			
No sexual partner	138 (41.9 %)	112 (44.3 %)	250 (43.0 %)
Have sexual partner	191 (58.1 %)	141 (55.7 %)	332 (57.0 %)
Missing	13	3	16

** $P < 0.01$

Multivariate analysis outcome

Data showed that age, gender, route of heroin use and daily MMT dosages were associated with illicit opioid use in multivariate logistic regression model (Table 3).

Compared with participants aged <40 years, participants aged 40–44 years, 45–49 years and ≥50 years were more likely not to have illicit opioid use [$P = 0.027$, OR = 0.57 (95 % CI 0.35–0.94); $P < 0.001$, OR = 0.41 (95 % CI 0.24–0.67); $P = 0.008$, OR = 0.52 (95 % CI 0.33–0.85), respectively]. Compared with male participants, female participants were more likely to have illicit opioid use [$P = 0.044$, OR = 1.53 (95 % CI 1.01–2.32)]. Compared with inhalation only heroin abusers before MMT, abusers with route of inhalation + injection heroin use were more likely to have illicit opioid use [$P = 0.009$, OR = 2.00 (95 % CI 1.19–3.36)]. Compared with daily MMT dosages <60 mg participants, participants with daily MMT dosages >80 mg were more likely to have illicit opioid use [$P = 0.003$, OR = 2.37 (95 % CI 1.35–4.15)].

Table 2 Factors possibly associated with positive urine morphine test in MMT participants

Variable	N	Number of urine test positive (%)	OR (95 % CI)	*P*
Cumulative years of heroin use				
<5	101	40 (39.6 %)	1	
5–9	134	56 (41.8 %)	1.10 (0.65–1.85)	0.736
10–14	190	85 (44.7 %)	1.24 (0.76–2.02)	0.400
≥15	168	73 (43.5 %)	1.17 (0.71–1.94)	0.536
Missing	5	2 (40.0 %)	–	–
Dosages of heroin use per time (g)				
<0.5	197	94 (47.7 %)	1	
0.5–0.9	212	85 (40.1 %)	0.73 (0.50–1.09)	0.121
≥1.0	187	77 (41.2 %)	0.77 (0.51–1.15)	0.198
Missing	2	0 (0.0 %)	–	–
Frequency of heroin use in one-day				
<3	285	111 (38.9 %)	1	
≥3	312	144 (46.2 %)	1.34 (0.97–1.86)	0.076
Missing	1	1 (100.0 %)	–	–
Route of heroin use				
Inhalation	315	123 (39.0 %)	1	
Inhalation + Injection	82	47 (57.3 %)	2.10 (1.28–3.43)	0.003
Injection	196	86 (43.9 %)	1.22 (0.85–1.75)	0.280
Missing	5	0 (0.0 %)	–	–
Daily MMT dosages (mg)				
<60	336	140 (41.7 %)	1	
60–80	191	71 (37.2 %)	0.83 (0.58–1.19)	0.312
>80	70	45 (64.3 %)	2.52 (1.48–4.30)	0.001
Missing	1	0 (0.0 %)	–	–
Cumulative years of methadone treatment				
≤1	65	22 (33.8 %)	1	
>1–3	156	68 (43.6 %)	1.51 (0.83–2.76)	0.180
>3–6	223	100 (44.8 %)	1.59 (0.89–2.83)	0.116
>6	152	65 (42.8 %)	1.46 (0.80–2.68)	0.221
Missing	2	1 (50.0 %)	–	–

Discussion

Though MMT made benefits to opioid abusers and society, the controversy exists since it was performed. This controversy is at least indirectly related to pharmacological properties of methadone itself [18]. Methadone use and MMT may have several serious side-effects, such as respiratory depression, QT prolongation, methadone dependence and withdrawal symptoms, etc. Respiratory depression is the most serious side-effect among MMT participants, which usually occurs in the induction phase, a longer duration of MMT can develop tolerance, an individualized step by step methadone doses increase in induction phase will help to lower methadone overdose death [19, 20]. QT prolongation occurs in about 10–15 % MMT participants, especially for clients with a history of unexplained loss of consciousness or with family history of sudden cardiac death. Screening clients with these histories is important [21]. As a replacement substance, medical methadone use does not produce a sharp euphoria [20]. In some extent, it alleviates illicit opioid dependence. Methadone withdrawal may last a number of weeks, a tapered methadone doses or buprenorphine substitution treatment may alleviate these withdrawal symptoms [22]. Due to its high relapse rates after cessation of methadone use, a longer duration of maintenance treatment is recommended. These side effects may hamper the implementation of MMT. To evaluate illicit opioid use during MMT, randomly urine morphine test every month in MMT clinic is used, which is an objective, operational, measurable indicator. In this study, we used a self-reported questionnaire to investigate the possible biological factors associated with positive urine morphine test outcome in MMT clients who had no other illicit substance use before MMT,

Table 3 Factors associated with positive urine morphine test outcome in a multivariate binary logistic regression

Variable	β	OR (95 % CI)	*P*
Age (years)			
<40		1	
40–44	−0.557	0.57 (0.35–0.94)	0.027
45–49	−0.903	0.41 (0.24–0.67)	<0.001
≥50	−0.646	0.52 (0.33–0.85)	0.008
Gender			
Male		1	
Female	0.427	1.53 (1.01–2.32)	0.044
Route of heroin use history			
Inhalation		1	
Inhalation + Injection	0.693	2.00 (1.19–3.36)	0.009
Injection	0.089	1.09 (0.74–1.61)	0.650
Daily MMT dosages (mg)			
<60		1	
60–80	−0.250	0.78 (0.53–1.14)	0.200
>80	0.862	2.37 (1.35–4.15)	0.003
Cumulative years of methadone treatment			
≤1		1	
>1–3	0.303	1.35 (0.72–2.55)	0.349
>3–6	0.472	1.60 (0.87–2.94)	0.128
>6	0.301	1.35 (0.71–2.58)	0.361
Constant	−0.329		0.310

with the aim of identifying factors currently associated with illicit opioid use, for a further intervention to promote MMT effect. Our findings showed that variables of age, gender, route of heroin use and daily MMT dosages were associated with illicit opioid use.

Age and illicit opioid use

In our study, we observed that older MMT clients (aged ≥40 years) were more likely not to have illicit opioid use compared with MMT clients aged <40 years. That meant younger MMT clients were more likely to have illicit opioid substance use during MMT. The possible reasons were inferred as follows.

Age represented separate stage of participants' lifetime. First, younger MMT clients were full of curiosity about fresh things, they preferred to try new things, seeking amusement and excitement. Second, the surroundings around younger MMT clients precipitated illicit opioid use; that is, younger MMT clients met more illicit opioid abusers and had more opportunity to get illicit opioid. Third, after a period of heroin use, addicts might gradually lose the sense of heroin use. Therefore, MMT clients aged <40 years had more possibility to use illicit opioid. One study [17] in Dehong prefecture of Yunnan, China observed that MMT patients aged 40–49 years were more likely to have negative urine morphine test outcomes compared with MMT patients aged 18–29 years in a unadjusted logistic regression model though this correlation disappeared in an adjusted logistic regression model, which partly supported our result. The more possibility of illicit opioid use in younger MMT clients indicated that younger MMT clients were the population needed to be paid more attention in current MMT circumstances.

Gender and illicit opioid use

The relationship between gender and illicit opioid use differed [15, 17]. One study [17] did not observed the gender difference in urine morphine test outcome. However, another study [15] observed that female MMT clients seemed to be more likely to have a concurrent heroin use than male MMT clients in family members and friends drug use group (71.4 vs 50.0 %); male clients seemed to be more likely to have a concurrent heroin use than female clients in no family members or friends drug use group (34.8 vs 20.8 %), though there was no significant difference.

In our study, we observed that female MMT clients were more likely to have illicit opioid use than male MMT clients. There was slightly gender difference. The reason of this gender difference might be complicated and the mechanism of this gender difference needed a further study. However, this gender difference illustrated that female clients seemed to be more likely to have illicit opioid substances use during MMT in our study population. A tailored gender-specific MMT is more appropriate.

Route of baseline heroin use and illicit opioid use

Abusers with route of baseline injection only or route of baseline inhalation + injection heroin use suffered a more severe extent of heroin addiction [23]. MMT is effective to relieve withdrawal symptoms but less effective to suppress craving of heroin abusers [24, 25], this indicates that other factors may play a role in heroin craving [26]. Therefore, relapse seems inevitable among some heroin addicts during MMT. Our study showed that, compared with baseline inhalation only heroin abusers, heroin addicts with route of baseline inhalation + injection use were more likely to have illicit opioid use. This result showed that MMT clients with route of baseline inhalation + injection heroin use could not suppress heroin use as well as baseline inhalation only heroin use MMT clients.

Compared with baseline inhalation only heroin use MMT clients, abusers with route of baseline injection only

heroin use showed no significance in illicit opioid use in this study population. The possible explanation was that baseline injection only heroin abusers had a longer period of heroin use, abusers with route of baseline injection only heroin use could not get extra heroin euphoria, gradually lost the interest of heroin use. Therefore, they might not increase their heroin use during MMT, and the urine morphine test outcome might not be significantly different from baseline inhalation only heroin use MMT clients.

Daily MMT dosages and urine morphine test outcome

Studies [17, 27–29] about daily MMT dosages and heroin use/urine morphine test outcome varied. Some studies [17, 29] reported a positive effect of methadone use on decreased heroin use. Other studies [27, 28] showed no significant association between daily MMT dosages and urine morphine test outcome. Our study showed that compared with daily MMT dosages <60 mg, MMT clients with daily MMT dosages >80 mg were more likely to have illicit opioid use after balance the variable of MMT duration. The reason might be that MMT was less effective to suppress heroin craving [16]; furthermore, in our study, participants were in a steady state of MMT, they used their daily MMT dosages highly depended on individualized methadone dosages to avoid heroin withdrawal symptoms, which made participants of daily MMT dosages <60 mg differ from participants of daily MMT dosages >80 mg; participants of daily MMT dosages >80 mg might suffer a more severe illicit opioid craving than participants with daily MMT dosages <60 mg. Our results suggested that more efforts should be paid on participants with daily MMT dosages >80 mg to suppress the illicit opioid use during MMT compared with daily MMT dosages <60 mg group.

Strengthens and limitations

One strengthen of this study was to use the variable of monthly urine morphine test outcome, which was a more operational, measurable and objective indicator, to reflect illicit opioid use (mainly heroin use). The other strengthen included a better control of other variables, such as in a population of no other illicit drug use at baseline, dosages of heroin use, cumulative years of heroin use, etc. However, there were some limitations. First, this was a cross-sectional study, which confined it to draw a causal-effect conclusion. Second, these data were self-reported investigation, and, therefore, a reporting bias was inevitable. Despite these limitations, we tried to illustrate our data in compared groups, not to draw a causal-effect conclusion. Our illustration will help knowing current factors associated with illicit opioid use, which is important for a promotion of MMT.

Conclusions

Our study illustrated that age, gender, route of heroin use before MMT, and daily MMT dosages were associated with illicit opioid use. To know these factors associated with current illicit opioid use, take tailored intervention will further promote MMT.

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Compliance with ethical standards

Conflict of interest All authors declare that there are no conflicts of interest.

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