Trends and predictors in methadone maintenance treatment dropout in Shanghai, China: 2005-2011

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Abstract

Background: The methadone maintenance treatment (MMT) program has been implemented in Shanghai since 2005. This study aims to portray the trend of MMT dropout and identify predictive factors that may influence dropout in Shanghai MMT clinics, which could assist in the intervention strategy development.

Methods: A retrospective evaluation was used in the Shanghai component of the National MMT data management system between January 1, 2005 and December 31, 2011. Cox model for recurrence events was employed to estimate hazard ratio (HR) predicting dropout during the follow-up period. **Results:** Of all 6169 participants, 63% dropped out of the program at least once (ranging from 0 to 10 times), and 74% of them did not return by the end of this study. The average monthly incidence rate of dropout was 4.4% with a range from 0 to 9.3%. Adjusted analyses demonstrated that the individuals with methadone tapering didn't have a greater probability of dropping out compared to those with stable dosage (HR=1.07, 95%CI: 0.90-1.27). However, there was a higher dropout rate among younger individuals (<30 years vs. ≥50 years old; HR=1.41, 95%CI: 1.16-1.71), among those who were less educated (HR=1.48, 95%CI: 1.17-1.87), among those who shared needles with others (HR=1.29, 95%CI: 1.06-1.58), among those whose urine tested positive for opiates (HR=1.69, 95%CI: 1.51-1.89), and among those who had a low average methadone dose at the initial stable stage of treatment (≤35mg/day vs. >65mg/day; HR=1.39, 95%CI: 1.19-1.63). **Conclusions:** Shanghai has been facing the challenge of keeping a high MMT retention rate. Methadone tapering after the stable treatment stage with sufficient dosage could be attempted to popularize in the MMT program, aside from considering comprehensive interventions among specific populations, such as the young, poorly educated, opiate-positive and needle sharing individuals.

Key words Methadone maintenance treatment; Dropout; Tapering off; Trend; Predictors; Survival analysis

1 Introduction

Opioid dependence has led to diverse social and health problems, such as poverty, violence, criminal behavior, discrimination and sexual transmitted disease epidemic. Due to the transmission of human immunodeficiency virus (HIV) and hepatitis C virus (HCV), the opioid dependent injecting drug user population is at highest risk of health problems.^{1,2} In China, injecting drug use was still the second single cause of HIV transmission although sexual transmission has become the primary mode of transmission since 2007.³ Up to 2010, over 1.4 million drug users were registered and the number is expected to grow annually;⁴ furthermore, some studies report the prevalence of HIV and HCV among heroin addicts were 1.1% and 53.9%, respectively.^{5,6} As of 2011, over three quarters of a million people with HIV infection were estimated among adults 15-49 years of age.³ More than 30 million HCV infected individuals were estimated in 1990s, and 17,632 new HCV infections were reported in 2011.^{7,8}

Methadone maintenance treatment (MMT) is one of the effective treatments for opiate addiction.⁹⁻¹¹ Previous studies have established that MMT programs reduce drug use, drug injecting behaviors, drug-related criminal behaviors, HIV infections, and improve relationships within families of heroin users.¹² A systematic review indicated that opiate substitution treatment was associated with a 54% reduction in risk of HIV infection among people who inject drugs.¹³ Therefore, eight MMT programs were pilot tested in five provinces within China in 2004 in order to reduce the opiate addiction rates and HIV epidemic health consequences attributed to addiction.¹⁴ Within six years, the MMT program expanded into a nationwide program involving more than 701 clinics serving approximately 295,000 participants.^{14,15}

The effectiveness of MMT is dependent upon timely entry into treatment, adequate medication dose, duration and continuity of treatment, and accompanying medical and psychosocial services.¹⁶ In order to effectively guide and manage the vast number of MMT clinics in the country, the Ministry of Health, the Ministry of Public Security and the State Food and Drug Administration jointly issued the *Temporary Scheme for Community-based Drug Maintenance Treatment for Heroin Dependents in 2003*, which was revised into the *Implementation Protocol for Community-Based Methadone Maintenance Treatment for Opiate Addicts* in 2006.¹⁴ However, many MMT clinics in China still experience high dropout and relapse rates.¹⁷ In Guangzhou, of those who are newly admitted MMT clients, 62% have exhibited poor adherence within the first 6 months since their admission.¹⁸

Shanghai, an economic center in the mainland of China, had a population of over 23 million in 2010.¹⁹ Owing to the challenges of controlling drug use and the HIV epidemic in this densely populated metropolis, 14 new MMT clinics were opened in Shanghai during the period of 2005-2009. However, little is known about the MMT compliance and retention in the Shanghai MMT clinics, limiting the development of valid management and intervention strategies. Therefore, the aim of this prospective study was to describe the trend of MMT dropout for those in Shanghai MMT clinics and identify predictive factors that may influence patient retention in Shanghai.

2 Methods

2.1 Study design

The study consists of an analysis of routinely collected data on all MMT users (n=6169) who came from the Shanghai component of the National MMT data management system between January 1, 2005

and December 31, 2011.²⁰ The cohort was used to observe the trend of enrollment and retention in MMT clinics over time. In order to estimate the hazard ratio for dropping out at differing time-points, and to analyze the predictive factors, a sub-cohort of individuals was defined to ensure there was at least three years of follow-up time after the initial evaluation. The sub-cohort (n=2463) included individuals attending MMT clinics between 01/01/2007 to 12/31/2008, Figure 1.

Figure 1 Overview of the prospective cohort study on methadone maintenance treatment

2.2 Data source and informed consent

The Shanghai component of the National MMT data management system records contain demographic information at enrollment, history of drug use, laboratory tests, methadone daily doses, reasons for withdrawal, referrals, clinic and physician information. The database is comprised of 8 datasets representing daily dose records, baseline surveys, follow-up surveys, withdrawal reasons, HIV tests, HCV tests, TB (tuberculosis) tests and urine (opiate) tests. There are 2.8 million daily dose records in the dataset. The participants recruited into the MMT included voluntary individuals, those required if released after arrest, and those seeking other medical care. All participants provided informed consent that their medical records could be used for scientific studies when they registered to MMT, and all the data in the study were de-identified.

2.3 Included and excluded criteria

Individuals were included in the study if their treatment codes were issued by Shanghai MMT clinics (the first three digits of treatment code were “310”) and if their dosing date was during the period of January 1, 2005 to December 31, 2011. The dropout events for each individual were followed over the study period. This study excluded those participants who were not initially registered in Shanghai MMT clinics, and considered their dropout events as missing values if the patients had a permanent referral to other provinces. Finally, there were 6169 individuals and 8398 dropout events in the total cohort. Individuals enrolled during the period of January 1, 2007 to December 31, 2008 established a sub-cohort

of the study population that had at least three years of available follow-up data. There were 2463 individuals and 2804 dropout events. A few of data entry errors (less than 0.2%) about age and dosage were found and corrected after checking with the local MMT clinics.

2.4 Study measures

The primary outcome of this study was dropout rate. An event with more than 30 suspended days was considered as one *dropout*. *Suspended days* was defined as a period of time that did not have methadone dosing records continuously recorded, except if there was a temporary or permanent referral to other provinces. A patient could have several dropout events. The duration of time (days) that was observed for each event was defined as either the time occurring between the enrollment and the dropout (survival time in survival analysis) or the duration of time occurring between the enrollment and the last date of the study (censor time in survival analysis). The monthly incidence rate of dropout was considered as the number of new dropouts per 100 current individuals in a given month.

Predictor covariates for dropout included age, sex, highest level of education achieved, employed status (yes/no), marital status, clinic (urban/suburban), past drug use history (heroin use, detoxification and needle sharing), most recent urine test (opiate), presence of infectious diseases (HIV/HCV/TB), and two derived variables based upon daily dosage records: 1) average methadone dose (mg/day) at the initial stable stage which was defined as 4-6 weeks after enrollment; 2) methadone tapering/increasing that is considered as the average methadone dose (mg/day) after the ninth week decreased/increased by more than 30% compared to the initial stable stage. See Table 1.

2.5 Statistical analysis

Descriptive statistics included mean (standard deviation), frequency and percentage. Multiple imputation (MI procedure) was used to cope with the missing values. Univariate Cox proportional hazards regression models (Cox model) were used to estimate hazard ratio (HR) predicting dropout during the follow-up period, for each variable in Table 1. All significant ($p < 0.05$) variables in the univariate analysis were selected as candidates for the forward stepwise multivariate Cox model analysis. Only variables making a statistically significant contribution to the fit of the model were retained for this analysis. A model for recurrent events data was used to conduct univariate and multivariate Cox models (see PHREG example 66.7 in SAS, Time-Dependent Repeated Measurements of a Covariate). All statistics were computed using SAS 9.3 (SAS Institute Inc., Cary, NC, USA).

3 Results

3.1 Participants' characteristics

From 2005 to 2011, a total 14 MMT clinics were established in Shanghai (1 in May 2005, 4 in September 2006, 3 in August 2007, 4 in September-December 2008 and 2 in October 2009). Of the 14 MMT clinics, seven were considered urban districts (Huangpu, Xuhui, Changning, Putuo, Zhabei, Hongkou and Yangpu), and seven were located in suburban districts (Minhang, Baoshan, Pudong, Songjiang and Qingpu).

As depicted in Table 1, the profiles of individuals representing the sub-cohort (2463 individuals) were very similar with that in the total cohort (6169 individuals). Therefore, the characteristics of individuals

representing the total cohort only are described here. Among the 6169 individuals, the average age was (40.9±8.5) years with a range of 18 to 72 years. Almost three-quarters of the population were between 30 and 49 years (71.8%). The majority of individuals were male (77.8%), Han nationality (98.4%) and from the urban clinics (75.5%). Only 37.1% were married and 18.1% had jobs when they started MMT. The majority of individuals (65.5%) were educated at junior high school level or below. The prevalence of HCV, HIV and TB infections at baseline were 68.8%, 0.9% and 0.8%, respectively.

The vast majority of individuals entering MMT were heroin users (98.9%), and the injection route was dominant (67.5%). Twenty nine percent were opiate-positive through urine test most recently. During the initial stable stage (4-6 weeks), the average methadone dose was (50.2±20.5) mg/day per patient, and 21.6% took the dosage over 65 mg/day. During treatment, 8% were tapering their methadone dosages. Within 7 days, 94% had at least one suspension, 36% had a continuous suspension of 8-14 days, 21% had a continuous suspension of 15-30 days, and 62.8% had at least one dropout (74% of them did not return by the end of this study period). The average dropout per patient was one (0.87±0.91, median was 1), ranging from 0 to 10 dropouts.

Table 1 Profiles of the participants of methadone maintenance treatment in Shanghai

Items	Sub-cohort (2007-2008)		Total cohort(2005-2011)	
	Num.(N=2463)	Pct. (%)	Num. (N=6169)	Pct. (%)
Age (year), $\bar{x} \pm s$	40.0±8.2		40.9±8.5	
<30	343	13.9	761	12.3
30-39	758	30.8	1805	29.3
40-49	1075	43.7	2622	42.5
≥50	287	11.6	981	15.9
Gender				
Female	615	25.0	1370	22.2
Male	1848	75.0	4799	77.8
Marital status				
Single	963	39.1	2462	39.9
Married	975	39.6	2287	37.1
Divorced	506	20.5	1360	22.0
Others(widow)	19	0.8	60	1.0
Ethnic nationality				
Han	2420	98.3	6072	98.4
Others	43	1.7	97	1.6
Clinic				
Urban	1937	78.7	4659	75.5
Suburban	526	21.4	1510	24.5
Employed				
No	2025	82.2	5053	81.9
Yes	438	17.8	1116	18.1
Education				
College and above	74	3.0	165	2.7
Senior high school	823	33.4	1963	31.8
Junior high school	1467	59.6	3757	60.9
Elementary and below	99	4.0	284	4.6
Detoxification history				
No	318	12.9	736	11.9
Yes	2145	87.1	5433	88.1
Heroin use at registration				
No	38	1.5	69	1.1
Yes	2425	98.5	6100	98.9

Drug-use route				
Only injection	1618	65.7	3893	63.1
Injection and oral	69	2.8	271	4.4
Only oral	776	31.5	2005	32.5
Needle sharing history (lifetime)				
No	2330	94.6	5699	92.4
Yes	133	5.4	470	7.6
Presence of HCV infection				
No	673	33.7	1572	31.2
Yes	1324	66.3	3462	68.8
Missing ¹	466		1135	
Presence of HIV infection				
No	1828	99.5	4812	99.1
Yes	10	0.5	42	0.9
Missing ¹	625		1315	
Presence of TB infection				
No	833	99.8	1913	99.2
Yes	2	0.2	15	0.8
Missing ¹	1628		4241	
Most recent urine test (opiate)				
Positive	647	27.5	1711	28.8
Negative	1708	72.5	4238	71.2
Missing ¹	108		220	
Average methadone dose at the initial stable stage (mg/day), $\bar{x} \pm s$				
	50.7±20.6		50.2±20.5	
≤35	572	25.9	1467	26.1
36-50	653	29.5	1716	30.6
51-65	463	20.9	1219	21.7
>65	524	23.7	1210	21.6
Missing ²	251		557	
Methadone dose change over time				
Stable	1343	54.5	3543	57.4
Tapering	217	8.8	498	8.1
Increasing	440	17.9	1035	16.8
Unknown ³	463	18.8	1093	17.7

¹ Not all of individuals received the tests of HCV, HIV, TB and urine.

² Missing dose values came from the patients without dosage records during the follow-up period of 4-6 weeks.

³ “Unknown” means that it was not available to identify the situation of methadone tapering due to their short follow-up period (less than 9 weeks).

3.2 Trend of dropout rate

Since the end of 2006, the number of enrolled individuals increased exponentially, especially during the period from 2006 to 2008. At the end of 2011, 6169 individuals had been cumulatively enrolled, however, only 61.3% (3063/6169) were still retained (regularly visiting MMT clinics). As shown in Figure 2, there was no clear periodic change in the dropout rate. However, the dropout rate was notably higher during the period from 2006 to 2008 coupled with a high enrolment rate, and became lower and more stable after 2009. The average monthly incidence of dropout was 4.4% with a range from 0 to 9.3%.

Overall, the participants with methadone tapering had similar dropout rates with those who kept stable doses from 2005 to 2011, and even had lower dropout rates at some particular time points (Figure 3).

Figure 2 Trend of monthly dropout in methadone maintenance treatment in Shanghai 2005-2011

Figure 3 Comparison of monthly dropout rate between methadone tapering and stable groups

3.3 Dropout predictors and multivariate analysis

The survival analyses were only conducted using the individuals represented in the sub-cohort (2463 individuals, 2804 events). As depicted in Table 2, the univariate cox model analysis demonstrated that nine candidate factors could be associated with dropout ($P<0.05$). Then, our multivariate stepwise Cox regression model involved the nine candidate factors. Finally, only six predictors (age, education, needle sharing, urine opiate test, average methadone dose at the stable stage, and methadone dose change over time) were selected into the final Cox model, however, marital status, drug-use route and HCV infection were excluded because their contributions were not significant any more ($P>0.05$).

As shown in Table 3, the individuals with methadone tapering didn't have a greater probability of dropping out compared to those with stable dosage (HR=1.07, 95%CI: 0.90-1.27). However, there was a higher dropout rate among younger individuals (<30 years vs. ≥ 50 years old; HR=1.41, 95%CI: 1.16-1.71), among those who were less educated (HR=1.48, 95%CI: 1.17-1.87), among those who shared needles with others (HR=1.29, 95%CI: 1.06-1.58), among those whose urine tested positive for opiates (HR=1.69, 95%CI: 1.51-1.89), and among those who had a low average methadone dose at the initial stable stage of treatment (≤ 35 mg/day vs. >65 mg/day; HR=1.39, 95%CI: 1.19-1.63).

Table 2 Univariate Cox model analysis with hazard ratios for dropout from methadone maintenance treatment

Factors	Hazard Ratio	95% CI	P value
Age (ref: ≥ 50 years)			
<30	1.53	1.26-1.84	<0.001
30-39	1.42	1.20-1.68	<0.001
40-49	1.17	0.99-1.38	0.061
Gender (ref: Male)			
Female	0.93	0.84-1.04	0.209
Marital status (ref: Married)			
Single	1.14	1.03-1.26	0.014
Divorced and others	0.96	0.85-1.09	0.518
Clinic (ref: Urban)			
Suburban	1.04	0.93-1.17	0.450
Education (ref: senior high school and above)			
Elementary & below	1.34	1.07-1.67	0.010
Junior high school	1.00	0.90-1.10	0.920
Employed (ref: No)			
Yes	1.12	0.99-1.26	0.074
Detoxification history (ref: No)			
Yes	0.96	0.84-1.11	0.598
Drug-use route (ref: Oral)			
Injection	1.13	1.02-1.25	0.021
Needle sharing (ref: No)			
Yes	1.40	1.16-1.69	0.001
HCV (ref: Negative)			
Positive	0.89	0.80-0.98	0.019
Urine test (ref: Opiate-negative)			
Positive	2.46	2.23-2.71	<0.001
Average methadone dose at the stable stage (ref: >65 mg/day)			
≤ 35	1.37	1.19-1.57	<0.001
36-50	1.54	1.35-1.76	<0.001
51-65	1.52	1.32-1.75	<0.001
Methadone dose change over time (ref: Stable)			
Tapering	0.98	0.83-1.15	0.77
Increasing	0.65	0.56-0.74	<0.001
Unknown	17.74	15.70-20.50	<0.001

*The factors (HIV, TB, heroin use and ethnic nationality) were not listed here due to too low prevalence to fit Cox model.

Table 3 Multivariate stepwise Cox model analysis with hazard ratios for dropout from methadone maintenance treatment

Factors	Hazard Ratio	95% CI	P value
Age (ref: ≥ 50 years)			
<30	1.41	1.16-1.71	0.001
30-39	1.37	1.15-1.63	<0.001
40-49	1.15	0.98-1.37	0.095
Education (ref: Senior high school and more)			
Elementary & below	1.48	1.17-1.87	0.001
Junior high school	1.00	0.90-1.10	0.925
Needle sharing (ref: No)			
Yes	1.29	1.06-1.58	0.012
Urine test (ref: Opiate-negative)			
Positive	1.69	1.51-1.89	<0.001
Average methadone dose at the stable stage (ref: >65mg/day)			
≤ 35	1.39	1.19-1.63	<0.001
36-50	1.36	1.18-1.56	<0.001
51-65	1.20	1.03-1.39	0.016
Methadone dose change over time (ref: Stable)			
Tapering	1.07	0.90-1.27	0.448
Increasing	0.57	0.49-0.67	<0.001
Unknown	12.77	11.09-14.71	<0.001

4 Discussion

Although the MMT program has been implemented in Shanghai since 2005, our study is the first to comprehensively report the longitudinal trends and predictors of dropout of individuals who attend the MMT clinics for treatment. This study found that both the rates of increasing enrollment and dropout have slowed since 2009. This may in part be due to the health authority and other governmental departments realizing that 14 clinics had satisfied the need in Shanghai and therefore no new MMT clinics were opened. In order to reduce the harm of drug use and to further control the HIV epidemic, the Chinese government has invested heavily in human resources and funds to run and manage the MMT programs. High dropout and relapse rates, however, have continued to be tough issues that challenge Chinese MMT clinics.^{17,18} In this study, 62.8% of individuals had dropped out, and only 61.3% were finally retained up until the end of 2011. Six factors including age, education, needle sharing, opiate urine test, average methadone dosage at the initial stable stage, and methadone dose change over time (tapering, stable or increasing), were found to be significantly associated with dropout from MMT according to adjusted multivariate analyses.

Prior studies have not demonstrated that age is an important predictor in MMT clinic dropout rates among other provinces of China,^{18,21} which may be attributed to inappropriate age grouping, such as 36-61 years or over 40 years. In our study, two age groups (less than 30 years, 30-39 years) were found to have higher likelihood for dropping out compared to the older group (over 50 years). It is well known that older drug users often age out of high intensity use and that younger individuals typically have riskier

profiles which interfere with their respective adherence to MMT. In addition, those with low levels of education may have poor understanding and acceptance of rules and regulations, and also reflect lower socio-economic status and other living conditions, so that they could be more likely to drop out from the MMT program.

Many studies have illustrated that higher methadone dose is associated with individuals remaining in treatment longer.²²⁻²⁶ This study also found that individuals that had low methadone doses (less than 65mg/day) during the initial stable stage, were more likely to drop out from MMT clinic as compared to those that had methadone doses of >65mg/day. Also, individuals with methadone increasing over time were less likely to dropout. However, timelessly increasing methadone dosage is not an optimal approach to prevent them from dropping out because it is not feasible and it could drive them to addict methadone. Fortunately, it was surprising to find that individuals with methadone tapering didn't have a higher probability of dropping out than those with stable dosage. In China, some of the service providers and individuals express concerns that methadone is 'yet another drug' and often request reduced dosages to avoid methadone addiction.^{27,28} It is true that "tapering off" methadone has been proposed in recent studies.^{29,30} But, people must be clearly aware of what is the appropriate stage for methadone tapering. Sufficient methadone dosage should be provided at the initial stable stage after the first two or three weeks adjusting stage. Then, tapering off methadone could be served to become an attempt among qualified individuals, which might benefit both participants and governments through saving the health resources. Therefore, it could be concluded that proper dosages prescribed at different stages would be crucial for MMT retention.

In our study, 29% of individuals were found to have positive-opiate at most recent urine tests. These individuals were more likely to dropout from MMT treatment as compared to those with negative-opiate urine tests (HR=1.66, 95%: 1.49-1.86). Also, individuals who shared needles with other injection drug users had a higher dropout hazard ratio compared to other individuals. Our findings support previous literature that the risk of early dropout among individuals living with other drug users was 2.71 times than other individuals in an MMT program.²¹ This study hypothesized that the addiction of these individuals was more serious and their relapse to drug use would cause a dropout because the relapse was a disruption to the MMT guideline. On the other hand, it could also reflect methadone doses were too low and they were taking other opiates to medicate withdrawal symptoms. Clearly, it is necessary to pay more attention to the risk factors experienced by those that access MMT and to the possible triggers different contexts and environments may produce.

The success of the MMT program can be partially attributed to the individual adherence to the daily treatment. The vast majority of individuals in this study suspended their treatments. Furthermore, some individuals had multiple repeated instances of dropout. The high proportion of people that suspend their daily methadone dose required guidelines to be revised to evaluate if different MMT clinic guidelines would decrease the frequency and duration of suspensions. According to the Chinese management guideline of MMT clinics: individuals must visit specific clinics every day and intake methadone at the sites; an extra prescription for the next day is prohibited; a small fee (\$1.5) is needed for methadone per day; and individuals with more than 7 continuously suspended days need to re-enroll. It is thought, that providing an extra prescription to the patient and allowing methadone doses to be carried out of clinics were permissible, some individuals would not consume their medicine but rather sell them in the market.

Therefore, it becomes being recognized that some individuals could cease treatment either temporarily or permanently as they could not tolerate these rigorous rules while strict management is implemented.

This is a valuable study using the long-term follow-up data based on the national MMT management system in China. However, there are limitations to consider when the results are interpreted. First, the dropout was defined as no-show (without dosing record) for 30 days continuously, which could misclassify individuals suspended temporarily into the dropout group, and vice versa. Second, relationship of family members, social network and psychological issues were not captured in the database. Third, it also should exercise caution in extrapolating the results of this study to MMT population in other areas because the characteristics of MMT population could be different.

Overall, MMT clinics have played an important role in controlling the HIV/HCV pandemic and drug abuse in China,³¹ but it is still a challenge to maintain a high MMT retention rate in Shanghai. Methadone tapering after the stable treatment stage with sufficient dosage could be attempted to popularize in MMT, aside from that comprehensive interventions including medical treatment, behavior education, psychological care, social and family support should be considered to address this issue, especially among specific populations, such as the young, poorly educated, opiate-positive individuals and injection drug users.

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