

Drug use and long-term methadone maintenance treatment in Yunnan province

Yinfeng Xu¹, Xintong Wang¹, Mingjiao Wang², Xinyue Li², Jiucheng Shen^{2,*}

¹Medical School of Yunnan College of Business Management, Yunnan, China

²Yunnan Institute for Drug Abuse, Kunming, Yunnan, China

*Corresponding Author

Abstract: Yunnan has been launching methadone maintenance treatment (MMT) since 2004 to combat heroin use and HIV epidemics. **Objectives:** To describe the concurrent drug use and severity of drug use among MMT clients, and to identify its associated factors. **Methods:** A cross-sectional study was performed in 2020-2021 in Yunnan, and 975 subjects were recruited through stratified cluster sampling. Information about drug use and other covariates were collected by self-development questionnaire and urine test. **Results:** The overall percentage of any drug use in Yunnan MMT population was 15.9% in the past 3 months, and was 10.7% in the past 7 days. Zero of heroin users and 5.4% of amphetamine type stimulants users were identified as high-risk group and need intensive interventions. Longer treatment, higher dose and influenced by peer were strongly associated with drug use. **Conclusion:** MMT has been a successful treatment in Yunnan, which could greatly reduce drug use. only very few of users were identified as high-risk group and need intensive interventions. Methadone dose, treatment period and peer influence were strongly associated with drug use, and strategies focus on these factors should be valuable for a successful achievement of MMT services.

Keywords: MMT; Yunnan; HIV Epidemics

1. Introduction

Methadone maintenance treatment (MMT) is internationally recognized as one of the most effective programs for heroin use, which can reduce or eliminate drug use and help drug users back to normal life in various culture context (1-2). China has been piloting and scaling up MMT since 2004 combating the increasing heroin use and HIV epidemics. According to government statistics, the number of heroin users

in China rose sharply from 7,000 in 1990 to 1.14 million in 2004 (3-4). Heroin was the primary drug in China, and injecting drug use was the most common route of HIV transmission and spread. Injection drug users accounted for 79.2% of the total HIV/AIDS patients in 2001 and 43.2% in 2004 in China, (3,5).

By 2016, a total of 788 MMT clinics have been set up in 29 provinces (including autonomous regions and municipalities) in china (6). Yunnan province has always been the hardest hit area by heroin and the HIV epidemic due to the geographical proximity to the “Golden Triangle” (7). In 2005, Yunnan officially launched MMT program. There were 68 MMT clinics in total by the end of 2021, more than 50,000 heroin addicts have been treated and 12,000 people were under treatment annually (data from the Yunnan Provincial Working-group of Methadone Maintenance Treatment).

Many studies have shown that MMT can significantly reduce drug use. A trial study conducted in New York city found that heroin users with no treatment were 92 times more likely to be using heroin and 53 times more likely to have been reincarcerated, than those in MMT (8). Another 12-year follow-up study showed opioid abuse decreased gradually to about 40% after 6 years in MMT and stabilizing at that level (9). Several studies in China have shown that drug use rate decreases to about 27% after 1 year and to 24% after 4-5 year in MMT, while increased to 43.9% for 10 years or more (10-15). This shows a small number of MMT clients which continued to use drugs after a certain period or even a long term of MMT. Drug use not only had a negative impact on the physical and psychological health of MMT clients, but also makes the treatment more complex or difficult. It will also raise concerns or even confusions for the effectiveness of MMT.

We conducted this province-wide survey to describe the concurrent drug use behavior and

severity of drug use among MMT clients, and to identify the associated factors for drug use, so that we can further understand the impact of MMT on the reduction of drug use, and hopefully to provide clinical evidence for future policy considerations and possible interventions.

2. Material and Methods

2.1 Study Design and Setting

A cross-sectional study was performed from Oct 2020 to May 2021 to calculate the percentage of concurrent drug use among MMT clients in the MMT clinics of Yunnan province, and to describe the severity and negative outcomes of drug use. A case-control study was designed based on this cross-sectional investigation to identify the associated factors for the outcome of drug use in the last 3 months, people who used any drugs from the data of urine tests or questionnaire were categorized as case group.

2.2 Study Subjects and Sampling

The study subjects were the heroin users who enrolled and remained in MMT when this study was performed. The exclusion criteria were: (1) those who had serious physical and mental illness; (2) those who have serious language or hearing impairments and unable to communicate; (3) those who were unable to provide informed consent.

The stratified cluster sampling was employed for the recruitment of study subjects. There are 68 MMT clinics in the 14 cities/prefectures of Yunnan province. Firstly, 9 cities/prefectures were randomly selected including Kunming city which is the capital city of Yunnan, from 14 cities/prefectures. Then 2 clinics in Kunming city and 1 clinic in each of the other 8 cities/prefectures were selected based on convenience sampling with the consideration of the willingness and abilities for the implementation of our research. For each clinic, All the clients came for medication on any a day in Oct, 2020, will be asked for the recruitment of study subjects to minimize selection bias. A total of 975 subjects were included in this study.

2.3 Data Collection and Measurement

Outcome variables were concurrent drug use behaviors in the last 7 days and 3 months, and the severity of concurrent drug use. Confounding factors included the following 7 items: demographics, marriage and family status,

history of drug use before the enrollment of MMT, dosage and duration in MMT, accessibility and availability of MMT, social function, health status of subjects and other individual factors.

The information of concurrent drug use was collected through self-development questionnaire for drug use in the last 3 months and urine test for drug use in the last 7 days. Urine test was done by using a detection kit (Colloidal Gold) to detect morphine Methamphetamine, Ketamine, MDMA, and cannabis from human urine sample. The severity of drug use in the last 3 months was assessed through The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) Chinese version. The ASSIST Chinese version was developed from ASSIST, and is an easily, brief, valid and reliable screen instrument for identifying the severity of 8 groups of psychoactive substance use in individuals within the past 3 months. The score of ASSIST are graded 3 classes to identify the risk of progressing to dependence linked to the different intervention strategies in primary care and other health settings. Score of 0-3 (0-10 for alcohol) is classified as a low-risk group and need no intervention, score of 4-26 (11 to 26 for alcohol) is a moderate risk group and need brief intervention, and scores of 27 or higher is as high-risk group and need intensive intervention. Other covariates were collected through self-development questionnaire by face-to-face interview.

2.4 Data Analysis

Univariate analysis was performed to describe the distributions of variables, and to check if there were any implausible values. Bivariate analysis by using T tests, X² square tests, or non-parameter tests was performed to assess the crude associations between potential confounders and outcome variable. Independent variables, which have a significant ($P < 0.1$) crude association with outcome variable, were included in the initial multivariate logistic model. Model building was done by using stepwise estimation in STATA and setting $p \geq 0.15$ as the significant level for removal from the initial model.

Odds Ratios and their correspondent 95% confidence intervals were computed as the estimates of associations. P values represented were from 2-tailed test and $P < 0.05$ was considered significant. All statistic analysis was done by using STATA 14.0 (Stata Corp, College

Station, TX, USA).

3. Results

3.1 Demographics and Other Characteristics of Study Subjects

Among the 975 subjects, the majority were males (80.7%) and Han people (84.4%). The median age was 45 years (P25-P75: 40-49 years), with a range of 20-78. There were 539 subjects (55.7%) married or common law, 199 (20.6%) were single and 229 (23.7%) were divorced/separated/widowed. For the education level of subjects, 257 (26.4%) were primary school or below, 494 (50.7%) were junior school and the other 257 (23.0%) were high school or above. There were 358 (36.8%) employed subjects, 428 (44.0%) unemployed subjects and 187 (19.2%) peasants. For the average monthly income in the last year, there were 148 subjects (15.2%) having 0 RMB, 286 (29.4%) having 1,000 RMB or less, 271 (27.9%) having 1,000-3,000 RMB, and 267 (27.5%) having 3,000 RMB or more per month. There were 141 (14.5%) subjects living alone.

3.2 Type of Drugs Used

The most drug used was heroin. There were 97 subjects (10.0%) from urine tests only, and 146 subjects (15.0%) from urine tests and questionnaire used heroin respectively, (Table 1). Among study subjects, the percent of any drug use was 10.7% in the last 7 days from the results of urine tests, and was 15.9% in the last 3 months from the data of questionnaire. The percent of polydrug use 10.6% from the urine test and 11.6% from the data of questionnaire.

Table 1. Types of Concurrent Drug Used

Types of drugs	Urine tests		Urine test + self-report	
	n	%	n	%
Heroin	97	10.0	146	15.0
Methamphetamine(Meth)	15	1.5	25	2.6
Ketamine	0	0.0	0	0
MDMA	1	0.1	2	0.2
Cannabis	2	0.2	2	0.2
Synthetic drugs (Meth, MDMA, Ketamine)	15	1.5	25	2.6
Any drug use	104	10.7	155	15.9
Polydrug use	11	1.1	18	1.8
Heroin only	89	9.1	130	13.3
Synthetic drugs only	6	0.6	9	0.9
Heroin + synthetic drugs	8	0.8	16	1.6

3.3 Severity of Concurrent Drug Use

There are 2 subjects and 15 subjects used cannabis and methamphetamine separately, all the subjects for these 2 categories of substance use were at moderate risk to dependence. For subjects who use heroin, 94.6% of whom were at moderate risk and 5.4% were at high risk.

Table 2. Risk Groups to Dependence Based on the Score of ASSIST Screen

	Cannabis (n, %)	Methamphetamine (n, %)	Heroin (n, %)
Low risk	0(0.0)	0(0.0)	0(0.0)
Moderate risk	2 (100.0)	15 (100.0)	123(94.6)
High risk	0 (0.0)	0 (0.0)	7 (5.4)

3.4 Concurrent Heroin Use Behaviors in the Past 3 Months

Among the 146 users, 3.6% were everyday drug use, and 15.2% were every week use, they were basically regular drug use. The costs on drugs were relatively low, 9.1% subjects spent more than 1000 RMB (about 143 USD) per month. There were 43.2% subject's injection drug use, only 1.8% shared syringes. There were 11.7% subjects had a strong craving for heroin and 13.5% subjects experienced a strong euphoria when drug use. There were 14.4% subjects experienced great impact of drug use on financial conditions and 14.6% on health.

Table 3. Heroin Use Behaviors in the Past 3 Months

Variables	frequent	percent(%)
Frequency of heroin use	frequent	percent(%)
Everyday	4	3.6
Every week	17	15.2
1-3 times per month	49	43.8
Less than every month	42	37.5
Costs on drugs per month		
<200 RMB	32	29.1
200-499 RMB	46	41.8
500-999 RMB	32	29.1
>=1000 RMB	6	9.1
injection drug use		
Yes	63	43.2
No	83	56.8
Sharing syringes with peer		
Yes	2	1.8
No	109	98.2
Drug use along with peer		

Yes	18	16.2
No	93	83.8
How soon do you use drug after getting up in the morning		
In the 10 min	4	3.6
Between 10-30 min	9	8.0
30-60 min	18	16.1
After 1 hour	81	72.3
Score of craving for drugs (0-10)		
No(0)	3	2.7
mild(1-3)	35	31.5
Moderate(4-6)	60	54.1
Strong(7-10)	13	11.7
Score of the pleasure or euphoria of drug use (0-10)		
No(0)	10	9.1
mild(1-3)	35	40.5
Moderate(4-6)	51	46.0
Strong (7-10)	0	0.0
Time spent on drug use		
Very little time	48	43.2
A small part of time	57	51.4
Most of time	6	5.4
Almost all the time	0	0.0
Impact of drug use on your financial status		
Little or none	43	38.7
Have some impact	52	46.9
Have great impact	16	14.4
Impact of drug use on your health		
Little or none	61	55.0
worse	32	28.8
Much worse	18	14.6

3.5 Crude Associations Between Outcome of Drug Use and Characteristics of Subjects

Table 4 shows the distribution of characteristics of subjects, and the crude association with the outcome of any drug use in the past 3 months. Covariates of education level, occupation, monthly income, time on getting to MMT clinics, social communication abilities had a statistic relationship with outcome of drug use ($P<0.05$), covariates of marriage status, main ways of drug use, cumulative months in MMT, average daily dose of methadone (figure 1 and figure 2), ever have at least 1 year of drug clean after the enrollment of MMT, contact or stay with peer who use drugs in the past 3 months had a

significant relationship with drug use ($P<0.001$).

Table4. Characteristics of Study Subjects and Crude Association with Outcome Variable

Characteristics	Any drug use in the past 3 months (n,%)		X ²	P
	No	Yes		
Gender				
female	161 (19.5)	27 (18.1)	0.15	0.696
male	665 (80.5)	122 (81.9)		
minorities				
Yes	136 (16.5)	16 (10.7)	3.15	0.076
No	690 (83.5)	133 (89.3)		
Age group (years)				
<40	184 (22.3)	35 (22.8)	1.19	0.552
40-49	447 (54.2)	74 (49.7)		
>=50	193 (23.4)	40 (26.8)		
Education level				
Primary school or below	212 (25.7)	45 (30.2)	7.90	0.019
Junior school	411 (49.8)	83 (65.9)		
Senior school or higher	203 (24.6)	21 (16.7)		
occupation				
employed	316 (38.3)	42 (28.2)	6.34	0.042
unemployed	350 (42.5)	78 (52.3)		
peasants	158 (19.2)	29 (19.5)		
Monthly income (RMB)				
<1000	358 (43.5)	76 (53.0)	6.76	0.034
1000-2999	226 (27.5)	45 (30.2)		
>=3000	239 (29.0)	28 (18.8)		
Marriage status				
Married or common law	454 (55.5)	56 (37.6)	16.62	0.000
single	184 (22.5)	44 (29.5)		
divorce/separate/widowed	180 (22.0)	49 (32.9)		
Relationship with family members				
Good	600 (84.0)	96 (80.0)	2.50	0.286
Average	110 (15.4)	22 (18.3)		
poor	4 (0.6)	2 (1.7)		
Live alone				
Yes	112 (13.6)	29 (19.5)	3.56	0.059
No	714 (86.4)	120 (80.5)		
Years of drug use before the enrollment of MMT (years)				
<5	243 (29.5)	47 (31.8)	0.97	0.617
5-9.9	232 (28.2)	36 (24.3)		
>=10	348 (42.3)	65 (43.9)		
Main ways of drug use				
Smoking	310 (37.6)	44 (29.5)	20.86	0.000
Injection	182 (22.1)	59 (39.6)		
Both	333 (40.4)	46 (30.9)		
Cumulative months in MMT				
<24	46 (5.7)	23 (15.6)	43.30	0.000
24-59	155 (19.0)	47 (32.0)		
60-119	263 (32.3)	47 (32.0)		
>=120	350 (43.0)	30 (20.4)		
Average daily dose (mg)				

<30	156 (18.9)	16 (10.8)	15.70	0.001
30-59	240 (29.1)	64 (43.2)		
60-99	229 (27.8)	43 (29.1)		
>=100	200 (24.2)	25 (16.9)		
Ever have at least 1 year of drug clean after the enrollment of MMT				
Yes	719 (87.5)	73 (50.0)	124.19	0.000
No	103 (12.5)	76 (51.0)		
Time on getting to MMT clinics				
<= 15 minutes	294 (35.8)	37 (25.3)	6.03	0.014
> 15 minutes	527 (64.2)	109 (74.6)		
How do you feel about the expense on MMT				
Light	186 (22.5)	29 (19.7)	1.35	0.509
Reasonable	516 (62.5)	91 (61.9)		
Heavy	124 (15.0)	27 (18.4)		
Social communication ability				
Good, able to keep a good relationship with people	539 (65.3)	80 (53.7)	8.39	0.01
Average, able to keep a basic relationship with people	241 (29.2)	55 (36.9)		
Poor, had little/no interact with people	45 (5.5)	14 (9.4)		
Contact or stay with peers who use drugs				
Yes	50 (6.1)	37 (24.8)	53.95	0.000
No	768 (93.9)	141 (94.6)		
Ever went to hospital for physical or mental illness in the past year				
Yes	203 (24.6)	44 (29.5)		
No	623 (75.4)	105 (70.5)	1.64	0.201
Ever experience a misfortune negative event in the past year				
Yes	49 (5.9)	8 (5.4)		
No	777 (94.1)	141 (94.6)	0.07	0.787

We categorized methadone dose at 20mg as group interval. There is a strong crude and dose-dependent association between length in MMT, prescribed methadone dose and

concurrent drug use behaviors (figure 1 & 2).

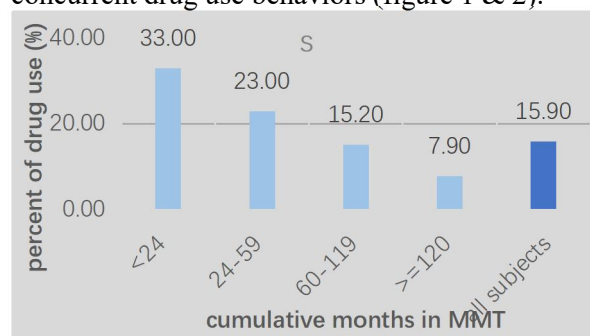


Figure 1. Treatment Period and Drug Use Behavior

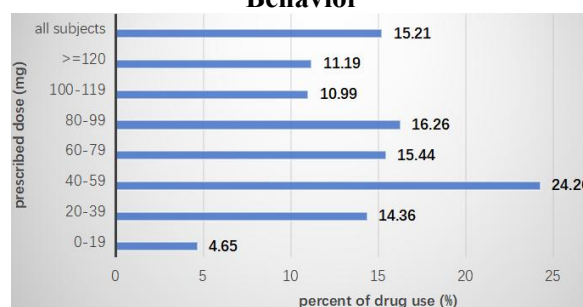


Figure 2. Prescribed Methadone Dose and Drug Use Behaviors

4. Multivariable Analysis

Multivariable analysis shows that variable of “Ever have at least 1 year of drug clean after the enrollment of MMT” (OR:0.16, 95% CI:0.10-0.25, $p<0.001$) and “Cumulative months of 120 or more in MMT” (OR:0.30, 95% CI:0.14-0.63, $p<0.01$) were the significant protective factors for outcome variable of concurrent drug use; while variable of “social connect with peers who use drugs in the past 3 months” (OR:4.32, 95% CI:2.47-7.57, $p<0.001$) was a strong risk factor, and variable of “Main ways of injection for drug use” (OR:1.86, 95% CI:1.11-3.12, $p<0.05$) and “Marriage status of divorce/separate/widowed” (OR:1.91, 95% CI:1.15-3.15, $p<0.05$) was the significant risk factors for outcome variable of concurrent drug use.

Table 5. Adjusted Odds Ratios of Factors for Drug Use

Variables	Odds Ratio	Std. Err.	z values	P values	95% CI
Ever have at least 1 year of drug clean after the enrollment of MMT	0.16	0.04	-8.16	<0.001	(0.10 - 0.25)
Social connect with peers who use drugs in the past 3 months	4.32	1.24	5.13	0.002	(2.47 - 7.57)
Cumulative months in MMT					
<24	ref				
24-59	0.77	0.28	-0.73	0.468	(0.38 - 1.56)
60-99	0.64	0.23	-1.25	0.21	(0.21 - 1.29)
>=120	0.30	0.11	-3.15	0.002	(0.14 - 0.63)

Average daily dose (mg)					
<30	0.53	0.19	-1.76	0.078	(0.26 -1.07)
30-59	1.46	0.38	1.45	0.146	(0.88 -2.42)
60-99	Ref.				
>=100	0.82	0.25	-0.65	0.517	(0.44 -1.51)
Main ways of drug use					
Smoking	ref				
Injection	1.86	0.49	2.36	0.018	(1.11 -3.12)
Both	0.84	0.23	-0.63	0.527	(0.49 -1.44)
Marriage status					
Married or common law	ref				
single	1.49	0.40	1.48	0.139	(0.88 -2.53)
divorce/separate/widowed	1.91	0.49	2.52	0.012	(1.15 -3.15)
Monthly income (RMB)					
<1000	ref				
1000-2999	1.16	0.29	0.58	0.564	(0.71 -1.88)
>=3000	0.63	0.18	-1.58	0.114	(0.36 -1.12)
cons	0.69	0.29	-0.87	0.385	(0.30 -1.59)

Note: CI. Confidence interval

5. Discussion

Concurrent drug use is a universal issue for global MMT program and raises a lot of public concerns on MMT effectiveness. This study is one of the few studies on the concurrent drug use behaviors and its associated factors in Yunnan province, after 15 years of Yunnan MMT initiation.

Our data shows a great number of subjects were older or single people, have a lower social competitive power and lower economic status. Previous studies also show MMT entrants were more likely to have a lower social well-being, even in MMT for years (16-17). This characteristics of MMT population could raise various problems including aging, survive, health, psychological issues, and of course the drug use (16-20). All that may lead to unsuccessful treatment outcomes.

The overall percentage of any drug use in Yunnan MMT population was 15.9% in the past 3 months, and was 10.7% in the past 7 days. This is a key indicator for the impact of MMT on the reduction of drug use in Yunnan province, where still is one of the most serious area of heroin epidemics. Most MMT services in Yunnan primarily delivery medications with few social-psychology interventions. Our result is significantly lower than other studies done in and outside of China, with the results varied between 15%- 43.9% over various treatment periods from 3 months to 10 years or more. (9-15, 21-22). Possible explanations for this lower result are: (1)

drug use in Yunnan was significantly decreased in the context of covid-19 pandemic. Studies based on waste-water epidemiology in 129 counties of Yunnan, showed that in 2021 in Yunnan, there was a decrease of 50% for the consumption of drugs, and a decrease of 30% for new drug users compared that in years before covid-19 (23). (2) Our study was done after 15 years of MMT initiations, most addicts had been educated on drug preventions for years by MMT and other facilities.

For subjects who used drugs, a small number of them (zero of heroin users and 5.4% of amphetamine type stimulants users) were identified as high-risk group and need intensive interventions. The majorities, about 80% or more, were generally not the regular/compulsive-use pattern, have no strong craving for drugs or feeling of pleasure when use, and did not lead to great impact on their health, financial status and social functions. There were 1.8% users shared syringe or needles. Therefore, there was limited impact on STIs transmission for themselves and public. This needs to be fully demonstrated to the public, for a better understanding of the drug use behaviors in MMT and the effectiveness of MMT in real world.

Our study indicates that MMT could greatly reduce, but not eliminate drug use behaviors in the whole MMT population. The common reasons for drug use we learned from interview were: (1) drug use seems to be a kind of habitual behaviors or “instinctive reaction” when frustrated, which they learned or did many years

before. (2) mutual influence with peers. (3) poor social well-being in MMT population.

There is a strong crude association between longer treatment period and lower percentage of drug use, and multivariable analysis also shows that "10 year or more in MMT" (OR:0.30, 95% CI:0.14-0.63, $p<0.01$) were the significant protective factors for drug use; Previous studies showed the similar results with varied effect size (9,14,22,24). Many studies well documented that longer treatment is a key to MMT efficacy (29-30) and no studies support to set a fix limit on treatment period. Strategies to keep patients remaining in MMT is a potentially valuable for improving treatment outcomes.

Prescribed methadone dose was strongly associated but not a factors with/for drug use: 10.99%-11.19% in higher dose group of 100mg or above VS. 15.44%-16.26% in moderate dose group of 60-99mg VS. 14.46%-24.26% in lower dose group of 20-59mg. However, the extremely low dose of 1-19mg group has the lowest percentage (4.65%) of drug use. Generally, the dose of 40-59mg is the most risk dose, while dose of 1-19mg was most protective dose for drug use in our practice. For the people who took the extremely low dose, we observed this population were more likely to successfully experience the process of dose reduction to hopefully stop any drug intake including methadone, and have better performance in treatment, e.g. better motivations, compliance or social functions. This dose-dependent association between prescribed dose and drug use in our study, is consistent with other studies (25-27). Possible mechanism was that adequate dose could achieve the minimal craving, cross tolerance for the effect of drug use, and better retention (24,28). However, some researchers argued for this finding, because they believed dose should be individual rather than simply "lower" or "higher". with the respect to dose, there should be 3 considerations: (1) individual and adequate dose may be a crucial factor for those who have better performance in MMT. (2) Dose may not be the most crucial factor for all patients. (3) higher dose may be insufficient for some patients (28).

Variable of "Contact or connect with drug use peers" (OR:4.32, 95% CI:2.47-7.57, $p<0.001$) was a strong predictor for drug use. other studies have shown consistently that peer influence closely linked to substance use (31-32). The underlying process for peer influence included

socialization and selection, people who continuously were influenced by peer were more likely to have problem in the process of social acceptability (32).

"Marriage status of divorce/separate/widowed" (OR:1.91, 95% CI:1.15-3.15, $p<0.05$) was the significant risk factors for drug use, because being single may have poor social support system. we failed to find the accessibility of MMT as a predictor of drug use, probably because of the "survive bias" of study subjects.

There are some limitations in our study. The recruitment of study subjects was not completely randomly, which may bias the generalization of study results. The reject rates of 5-10% for subjects' recruitment in each clinic, however, the drug use behaviors may be underestimated because people who refuse to be recruited were more likely to be users. Third, other important factors for drug use, e.g. psychological, family or community factors, were not included in this study, this may be bias our findings.

In conclusion, MMT in Yunnan has been a successful treatment services for opiates users, which could greatly reduce drug use, longer treatment could achieve better outcomes. There were a few MMT entrants who continuously use drugs when in MMT, but most of them were not regular or compulsive drug users, and had little impact on themselves and society. Better understanding of concurrent drug use and MMT services should be developed in public and others who concern MMT program. Methadone dose, treatment period and peer influence were strongly associated with drug use, and strategies focus on these factors should be valuable for a successful achievement of MMT services.

Ethics statement: The study was approved by the Institutional Review Board of Yunnan Institute for Drug Abuse. All information Data was used only for this study, inform consent was provided by all subjects.

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