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Continued drug use during methadone treatment in China: A retrospective analysis of 19,026 service users☆,☆☆,★

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Abstract

This study examined nation-wide data from China to assess client outcomes after 6-months of methadone treatment. Data on 19,026 clients enrolled between April 2008 and March 2010 were reviewed for changes in HIV-risk behaviours and emergence of new HIV cases. Multivariable logistic regression was used to identify factors associated with illicit drug use while in MMT. Clients reported reduced drug use and related risk behaviours and improved social functioning. There were 24 newly-identified cases of HIV. Continued drug use was associated with low attendance (OR = 5.98, 95% CI = 4.69–7.63), frequently seeing drug using friends (OR = 3.72 for daily vs. never, 95% CI = 3.18–4.34) and having a difficult family relationship (OR = 2.03 for difficult vs. good, 95% CI = 1.63–2.52). Methadone dose was not associated with continued drug use while in treatment. The Chinese MMT programme appears to be having a positive influence on those clients who remain in treatment, but needs to explore strategies to increase accessibility.

Keywords

China; Methadone maintenance treatment; HIV/AIDS; Healthcare; Harm reduction

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☆☆Contributors: SGS conceptualized the study and conducted data analysis, interpreted results and drafted the paper and participated in revisions; ZW designed the National MMT Program, conceptualized the study design, participated in interpretation of the results and revising the paper; XC and EL contributed data analysis and interpretation of the results; RD participated in study design, interpretation of the results and revising the paper; all authors reviewed the final version of the manuscript and approved it for publication.

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1. Introduction

Methadone maintenance treatment (MMT) was introduced in the 1960s to help addicts reduce their dependence on illegal opiates and improve their social productivity (Dole & Nyswander, 1965; Hall, Ward, & Mattick, 1998; Joseph, Stancliff, & Langrod, 2000; Marsch, 1998). The use of MMT increased dramatically in the 1980s and 1990s when policy makers realised that it could help prevent the spread of HIV by reducing injecting drug users' engagement in HIV risk behaviours, especially the sharing of injection equipment as well as sexual risks (Ball, Lange, Myers, & Friedman, 1988; Gowing, Farrell, Bornemann, Sullivan, & Ali, 2006; Sorensen & Copeland, 2000; Ward, Mattick, & Hall, 1998). MMT is now recognised as an important component of any strategy to control HIV infection among injecting drug users (Beyrer et al., 2010). However, many clients never fully abstain from using opiates or other drugs while in treatment (Joseph et al., 2000; McLellan, Lewis, O'Brien, & Kleber, 2000) and may therefore continue to put themselves at risk of HIV and other infections. This is often tolerated by MMT programmes because ceasing treatment for this reason is associated with poorer client outcomes (Joseph et al., 2000; National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998). Current consensus is that doses between 60 and 100 mg/day are optimal for most clients (National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction, 1998), although the original trials which demonstrated methadone's efficacy used doses above 100 mg/day (Dole, Nyswander, & Kreek, 1966). While most programmes ostensibly follow this recommendation, suboptimal dosing (<60 mg/day) is extremely common (Lin & Detels, 2011; Pollack & D'Aunno, 2008). This may be due to strained human and financial resources which hinder clinics' abilities to meet care standards or because providers or clients prefer abstinence orientation (Fareed, Casarella, Amar, Vayalapalli, & Drexler, 2010; Lin & Detels, 2011). Conversely, clients may know that requesting lower doses can prevent withdrawal without overriding heroin's euphoria should they use it (Goldstein & Brown, 2003). There are also toxicity concerns about using higher doses of methadone (Fareed et al., 2010). Given the biological mechanisms involved, it is not surprising that the most consistent predictor of continued use of illicit opiates in MMT is methadone dose (Faggiano, Vigna-Taglianti, Versino, & Lemma, 2003).

China introduced MMT in 2004 in response to the rapidly rising number of heroin users and related increases in the prevalence of HIV (Sullivan & Wu, 2007). By March 2010 there were 684 clinics in 27 provinces. Until recently, unsafe behaviours associated with drug use were the biggest cause of HIV infections in the country, and continue to account for roughly 28% of new infections (Ministry of Health of the People's Republic of China, 2012). Sentinel data suggest that 66% of drug users use sterile equipment, but HIV prevalence among this group averages 6%, and is as high as 50% in Yili on the Kazakhstan border (Ministry of Health of the People's Republic of China, 2012). Previous analyses of the MMT programme isolated to selected clinics have suggested that clients do reduce their use of opiates, and this is associated with higher doses of methadone as well as higher education level (Li, Sangthong, Chongsuvivatwong, McNeil, & Li, 2011; Liu et al., 2008). The purpose of the present study was to see if these trends persisted across the country. We examined changes in illicit drug use and engagement in HIV risk behaviours among clients

across China who remained in MMT at least 6 months and identified factors associated with continued drug use while in treatment.

2. Methods

2.1. Client data

This study was approved by the IRB of the University of California, Los Angeles. Permission to use the data was granted by the National Center for AIDS/STD Control and Prevention in Beijing, which houses the MMT secretariat and oversees data collection. De-identified data were abstracted from their MMT Data System. Data collection and clinic management improved greatly in 2008 in terms of completeness and consistency, so these analyses are restricted to clients who began treatment between March 2008 and March 2010.

Clients were accepted into MMT if they were aged at least 20 years, were registered as a local resident, met the Chinese Classification of Mental Disorders 3 criteria for drug dependence, had no contra-indications for taking methadone and agreed to the clinics rules (Sullivan, 2011; Yin et al., 2010). Upon admission, clients are asked to provide basic demographic and drug use information for monitoring and evaluation purposes. Most clients are also asked to complete a detailed baseline survey to collect further information for monitoring and evaluation purposes. This survey is conducted face-to-face in a private room and includes data on drug-use, sexual and criminal histories, social functioning (i.e. involvement in crimes, employment and relationship with family and friends) and a blood sample is taken to assess HIV, hepatitis C and syphilis status. Those testing positive for HIV are referred to the National Free ART Program (Ma et al., 2010). A follow-up survey is scheduled for 6 months post-enrolment at which time these data are collected again and the clients' satisfaction with the service is measured. Only follow-up surveys taken within 1 month of the 6 month schedule were included. However, follow-up information was not always collected on time or at all. Reasons given for missing follow-up surveys included that clinic staff may have neglected to enter it into the data system; staff were too busy at the scheduled time of follow-up; or the client may have refused.

Roughly each month, on a random schedule, clients are requested to provide urine samples to assess continued opiate use. There is no standard test used by the programme, although only tests approved for use by the Chinese Food and Drug Administration are used by the clinics. Sensitivity and specificity of the test may vary, but typically they can detect opiates taken within the previous 7 days or to a concentration of 300 ng/ml.

Methadone is administered daily under the direct observation of staff. There are no options for take-home doses, nor any way to obtain methadone outside the clinics.

Clients can be ejected from the programme if they miss more than 7 consecutive days of treatment, if they cause trouble, or if they use alcohol or drugs (Yin et al., 2010). However, these criteria are not often enforced and clients may be permitted to re-enrol.

2.2. Clinic management

The programme is funded by the Chinese Central Government via the Ministry of Health, collaborating with the Ministry of Public Security and the State Food and Drug Administration, and local provincial governments who allocate funds for the establishment of clinics, but not their ongoing costs. Clients are charged a maximum of CN¥10 (US\$1.50) per day for treatment (irrespective of dose), although treatment is free for HIV-positive clients. Clinics use this money for the transportation and storage of methadone, the routine operation of the MMT program clinics, and to provide ancillary services.

Clinics are concentrated in areas of greatest need, with priority given to administrative areas (districts in cities and counties in rural areas) with more than 500 registered drug users (State Council of P.R. China, 2006). Since 2006, clinics in areas with as few as 300 registered drug users can also establish a clinic. The ideal clinic size is 300–500 clients, but clinics vary considerably in size, from a few dozen to nearly 1,500 clients. Clinics should have at least eight trained staff, but at times it may drop below this number; there are many barriers to finding and keeping well-trained staff (Lin et al., 2010). Clinics can be affiliated with either a Center for Disease Control (CDC), hospital, psychosocial health center, community-based medical service, voluntary detoxification center, or a hospital in the public security system. There are also mobile clinics, the first of which was introduced in 2006 to increase access for rural residents, and there were 26 vans in 10 provinces as of 22 March 2010. Transfers between clinics are permitted and are facilitated by a proximity card system, introduced in 2008, which records clients' information and can be used by clients to obtain methadone when they move or travel.

2.3. Continued drug use

Two variables indicated drug use: urine test results and self-reported use. Self-reported use is reported for the previous month, and the most recent urine test result was used. Discordance between the two indicators was examined using a kappa statistic, and the two variables were combined to create a composite variable, where drug use was indicated by either a self-report or a positive urine test or both.

2.4. Other treatment outcomes

Other drug-use-related behaviours measured included injection drug use, needle sharing and HIV status. Data on sexual HIV-risk behaviours were also available and included the numbers of sexual partners and condom use. Also examined were changes in measures of social functioning since improvements in these areas are also important outcomes of MMT. These included employment, criminal activity, client's relationship with their family, and how often they saw their drug-using friends.

2.5. Methadone dose and daily attendance

Clients attend the clinics daily to obtain their methadone dose, which is recorded in the data system. Doses were abstracted, and the median dose for the duration of treatment was calculated. The percentage of attendance was calculated based on the number of days a client received a dose over the 6-month period (182 days).

2.6. Statistical analyses

Changes in drug-use, HIV-risk behaviours, HIV status and social functioning after 6 months (+/- 1 month) of treatment were examined using paired t-test for continuous variables and McNemar's test for categorical variables. All p-values were 1-sided, since it was expected that MMT would have a positive influence on client's risk behaviours. Differences of >5% or 5 units were used to flag changes in the variables measured as potentially meaningful, since the size of the dataset meant that statistically significant effects for very small differences were likely. A sensitivity analysis was performed to see whether changes in clients' treatment outcomes were as profound if all those for whom follow up data was missing were included. We conservatively assumed a worse-case scenario where all those clients with missing data had the same values at follow-up as they did at baseline. For the urine test this meant that all those missing data were assumed to have a positive urine test at follow-up.

Factors associated with drug use after 6 months of treatment were examined by logistic regression. Separate models were constructed for three variables – urine-opiate test results, self-report and their composite – to see how the estimates varied according to these different outcomes. Predictors of drug use included median methadone dose during treatment (<60 mg versus 60 mg, as is commonly used), attendance (percent of days received a methadone dose during the first 182 days enrolled categorised as low (<30%), moderate (30–69%) and high (>70%)), gender, education level, the length of the commute to the clinic, years of using drugs, employment and relationship with family and friends. We included an interaction term for dose and attendance because we assumed, *a priori*, that these two variables would show effect modification. A random effect was included to account for the clustering of clients within clinics. Since the dataset was large, effect sizes of >2 or <0.05 were considered meaningful rather than examining statistical significance.

For the follow-up dataset, missing values were multiply imputed using the user-written programme, ICE (imputation by chained equations) in Stata 11 (Royston, 2005) (procedures for the imputation are described in detail in Sullivan, Detels, Wu, & for the National Methadone Maintenance Treatment Working Group, 2013, supplement 2). Values were missing for up to 15% of clients for some variables, except urine test results at follow-up for which 23% of results were missing (51% of baseline test results were missing because clinics either did not enter the result or assumed positive results based on self-reported drug use). Twenty imputed datasets were created for use in the logistic regression analysis. Clinics which were missing the entire baseline history (but not demographic information) for more than 10% of their clients were excluded.

3. Results

During the 2 year period studied, 107,740 clients enrolled, and 55,214 (51%) clients at 512 clinics were still actively in treatment 6 months after enrolment. Of these, only 19,026 (34%) at 428 clinics had completed a 6-month follow-up survey, of whom 14,709 had a urine test result (see Fig. 1). Baseline demographic characteristics of these clients are shown in supplementary Table 1. Those clients with follow-up surveys differed meaningfully from clients not surveyed in only two instances; 14% more people in the not-followed group had

experienced at least one treatment interruption of 30 days or more and 7.3% more people in the not-followed group had a positive opiate test at 6 months.

Changes in drug-use and social behaviours pre- and 6-months-post-MMT are shown in Table 1. Clients reported reduced drug use and related risk behaviours. Sexual behaviours (condom use, number of partners) changed little. Social functioning improved, with increases in the numbers of clients reporting a good relationship with their family, never seeing their drug using friends and employment. A large majority (94%) of clients thought that MMT was affordable, though 6% thought it too expensive. Similarly, most clients (98%) thought their dose was adequate, while less than 1% thought it was too high or too low. Nearly 97% of clients were satisfied or very satisfied with the service.

The sensitivity analysis of all 55,214 clients in treatment at 6 months, assuming missing risk behaviours had not changed since baseline indicated sustained improvements in many drug-use risk behaviours. As seen in Table 2, the proportion of clients who would have returned a positive urine opiate test, reported drug use or reported drug injection would have been reduced compared with baseline. However, these reductions in risk were not as spectacular as those seen in the complete case analysis (Table 1). For example, the proportion using drugs (either tested or reported) at 6 months had reduced by 17% in the sensitivity analysis compared with 60% in the complete case analysis. Similarly, the proportion reporting drug injecting decreased by 17% compared with 51%. Of note, while some social behaviours were observed to potentially improve, such as employment, family relationships and frequency of seeing friends showed little change.

Table 3 shows the concordance between self-reported drug use and the results of urine-opiate tests for those with both results and a urine opiate test conducted prior to the survey. Self-reported drug use did not concur with opiate test results in about 25% of cases, and the kappa statistic suggested poor concordance ($\kappa = 0.4$, $p < 0.0001$). Some 777 clients reported having used drugs in the month prior to interview but their urine-opiate test was negative, while 1127 claimed not to have used drugs in the previous month but returned a positive opiate test result. The composite variable suggested that nearly all clients had used drugs in the month prior to enrolment and 39% had done so at 6 months; this was 10% more than either the self-report or urine test variables had captured.

Factors associated with drug use at 6 month follow-up were estimated (Table 4). When predicting drug use as a composite variable, the strongest predictors of drug use during MMT were low (OR = 5.98, 95% CI = 4.69–7.62) as well as moderate attendance (OR = 2.43, 95% CI = 2.11–2.80), any frequency of seeing drug using friends (from OR = 3.72 for daily to OR = 3.05 for 1–4 times per week) and a poor relationship with family (OR = 2.03 for difficult vs. good, 95% CI = 1.63–2.52). When this model was compared to the model predicting a positive urine test result or the model predicting a positive self-report, the estimates changed little for most covariates, but had a profound effect on the estimates for contact with friends and relationship with family (Table 4). Specifically, for an outcome of a positive urine result, the strength of the effect of regularly seeing drug-using friends attenuated (OR = 1.90 for daily vs. never, 95% CI = 1.61–2.23) as did the effect of having a difficult family relationship (OR = 1.40 for difficult vs. good, 95% CI = 1.13–1.73).

Conversely, if self-reported drug use was the outcome, a difficult family relationship more than doubled the odds of drug use (OR = 2.68 for difficult family relationship vs. good, 95% CI = 2.12–3.39), while the strength of the effect of contact with friends increased by several orders of magnitude (OR = 10.43 for seeing friends daily vs. never, 95% CI = 8.80–12.38).

4. Discussion

For the clients who remain in treatment at least 6 months, it appears that MMT has had a positive influence. Clients reduced their drug use, injecting and sharing injecting equipment, and exhibited more socially desirable behaviours including increased employment, reduced drug-related crimes and improved relationships with their families. Twenty-three people appear to have been infected with HIV in their first 6 months of MMT, though it is possible that some of these people were infected prior to starting treatment and sero-converted during treatment. There was minimal change in sexual HIV-risk behaviours, but changes in these parameters can be difficult to interpret and may not reflect adoption of safer behaviours. For example, no condom use may indicate risky behaviour if the client has many partners, but not if they are in a monogamous relationship.

These findings are likely to be skewed in favour of positive outcomes for the MMT programme because it was limited to clients who had completed a survey. Moreover, a large number of clinics were excluded due to incomplete data collection. Without knowledge of the selection probabilities it is difficult to quantitate the influence of selection bias on our findings (Greenland & Lash, 2008). Our crude attempt to do so was by assuming that those without a follow-up survey had not changed any of their behaviours and this sensitivity analysis still indicated improvements in key HIV-risk behaviours, including drug use and injection, the size of effect was considerably attenuated. These improvements would likely be further reduced if those who dropped out of treatment had also been followed and if those excluded clinics had been included. Thus, while improvements may be observed for those remaining in treatment, especially those who comply with data collection procedures, it is unclear whether the programme is having a substantial impact on reducing drug-related harms in the community.

Discordance between clients' opiate test results and self-reported drug use was high, suggesting social-desirability bias in self-reporting, which may have been exacerbated by the use of face-to-face interviews. In the US, drug users seeking treatment were found to over-report drug use, possibly because they believed it would help them access treatment services (Weatherby et al., 1994). In our sample, reporting use with a negative urine test may reflect testing done at a time when the client had not recently used heroin. Clients can and do refuse to provide urine samples (Lin & Detels, 2011) and may avoid the clinic if prewarned by friends or staff. Those tested early in the month may know that it will be several weeks before they are tested again, so can freely use heroin or other drugs in the meantime (Goldstein & Brown, 2003). Such behaviour may not be typical of those clients who admitted to drug use and had a negative urine test result, but could be typical of clients who tested negative and also reported no drug use despite having done so. Clients may also be using non-opiate drugs, such as amphetamines or cannabis, which are not tested for in China for cost reasons. The majority of registered drug users in China use opiates (73.2%),

but amphetamine-type substances are rising in popularity (Ministry of Public Security, 2010). Ice and ketamine use has been reported among MMT clients (Darke, 1998; Li et al., 2011), and may be preferred since they are not blocked by methadone. For example, in Yunnan ephedrine use among clients nearly tripled from just 11.9% prior to enrolment to 31% after 1 year of MMT (Li et al., 2011). Thus, it may be time for the Chinese MMT programme to re-evaluate the need to test for drugs other than opiates as part of programme monitoring.

This study revealed a surprising lack of association between methadone dose and drug use during MMT. It is possible that those people with less severe addiction were able to do well in treatment on low doses, while those in need of higher doses were unable to remain in the programme. Both staff and clients have a preference for lower doses (Lin & Detels, 2011), but this may be unrealistic for some clients. The most spectacular effect was that of attendance, with lower percent-attendance associated with a 6-fold higher odds of drug use in treatment. The interaction term did not suggest any modification of this effect by dose. Treatment interruption and duration of treatment are associated with dose (Sullivan et al., 2013), so there may be an indirect effect of dose on drug use. Analytical strategies that can delineate this effect may provide a greater understanding of these pathways (VanderWeele, 2009; Vansteelandt, 2009). There is little flexibility allowed in the Chinese programme with regards to take home doses and clinic locations. The programme needs to consider strategies that enable, rather than deter, daily administration of methadone as barriers to accessing treatment appear to be harming the effectiveness of the programme.

The involvement of family in drug recovery has been emphasized (Pope, Wallhagen, & Davis, 2010; Yu & Stiffman, 2010) and may be even more important in collectivist societies than in western, individualistic cultures (Liu, Li, Lu, Liu, & Zhang, 2010), where most studies of methadone have been conducted. It has been suggested that drug prevention and treatment in China should increase the role of the family (Lin, Wu, & Detels, 2011; Liu et al., 2010), who can potentially encourage treatment participation and compliance. Conversely, families who are unsupportive of MMT may adversely affect recovery, so it is also important to involve these families in MMT to foster their understanding of treatment goals. Of greater influence than family was the frequency with which clients saw their drug-using friends. Even in collectivist cultures, the influence of friends on initiation or continuation of drug use can be substantial (Wu et al., 1996), particularly among adolescents and among those who live away from their families, which is the case for many MMT clients. Having been abandoned by most of their non-drug-using friends, MMT clients may only have friends who use drugs (Deng, Li, Sringeriyuang, & Zhang, 2007), some of whom may continue to use and encourage use by the client. There is a need to identify novel strategies to help clients establish new social networks that exclude their existing drug-using friends and help them to reintegrate into society. Significant stigma and discrimination towards drug users is likely to seriously impede such efforts (Liu et al., 2010; Yap, Wu, Liu, Ming, & Liang, 2002).

The strength of the estimates for both family and friends changed substantially depending on whether the analysis focussed on self-reported drug use or urine test results. Notably, this change was more than 5-fold for the estimate comparing seeing friends daily versus never if

the outcome was self-report (OR = 10.44) rather than a urine test result (OR = 1.9). It is unclear why this would be the case, although it is possible that clients who more readily admit to drug use might also be more likely to admit to seeing their drug-using friends, since both are undesirable behaviours. This finding illustrates the sensitivity of this analysis to the outcome specified, and similar outcome-measurement errors may explain some of the conflicting conclusions reported among studies.

5. Conclusions

This study demonstrated that the Chinese MMT programme appears to be having a positive influence on the drug-using behaviours of clients remaining in treatment for at least 6 months, with overall reduced harmful drug use and more socially desirable behaviours. However, the strength of these effects may be exaggerated because of the substantial proportion of clients not completing a follow-up survey. A major problem is the high proportion of drug users entering treatment who drop out early. We found that methadone dose was not associated with continued drug use while in treatment, but treatment attendance and clients' relationships with their family and friends had a strong impact on continued drug use. There thus appears to be a rationale for exploring strategies to increase the availability of methadone to clients, help clients establish new social networks and discourage socialisation with their drug-using friends, and emphasize the role of families in treatment. Finally, both biomarkers and self-reported measures may be useful indicators of drug use in MMT programmes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

- Ball JC, Lange WR, Myers CP, Friedman SR. Reducing the risk of AIDS through methadone maintenance treatment. *Journal of Health and Social Behavior*. 1988; 29:214–226. [PubMed: 3241064]
- Beyrer C, Malinowska-Sempruch K, Kamarulzaman A, Kazatchkine M, Sidibe M, Strathdee SA. Time to act: A call for comprehensive responses to HIV in people who use drugs. *Lancet*. 2010; 376:551–563. [PubMed: 20650515]
- Darke, S. The effectiveness of methadone maintenance treatment 3: Moderators of treatment outcome. In: Ward, J.; Mattick, R.; Hall, W., editors. *Methadone Maintenance Treatment and Other Opioid Replacement Therapies*. Harwood Academic Publishers; Amsterdam: 1998. p. 75-90.
- Deng R, Li J, Sringermyuang L, Zhang K. Drug abuse, HIV/AIDS and stigmatisation in a Dai community in Yunnan, China. *Social Science and Medicine*. 2007; 64:1560–1571. [PubMed: 17257727]

- Dole V, Nyswander M. A medical treatment for diacetylmorphine (heroin) addiction. A clinical trial with methadone hydrochloride. *JAMA*. 1965; 193:646–650. [PubMed: 14321530]
- Dole VP, Nyswander ME, Kreek MJ. Narcotic blockade. *Archives of Internal Medicine*. 1966; 118:304–309. [PubMed: 4162686]
- Faggiano F, Vigna-Taglianti F, Versino E, Lemma P. Methadone maintenance at different dosages for opioid dependence. *Cochrane Database of Systematic Reviews*. 2003 CD002208.
- Fareed A, Casarella J, Amar R, Vayalapalli S, Drexler K. Methadone maintenance dosing guideline for opioid dependence, a literature review. *Journal of Addictive Diseases*. 2010; 29:1–14. [PubMed: 20390694]
- Goldstein A, Brown BW. Urine testing in methadone maintenance treatment: Applications and limitations. *Journal of Substance Abuse Treatment*. 2003; 25:61–63. [PubMed: 14629984]
- Gowing LR, Farrell M, Bornemann R, Sullivan LE, Ali RL. Brief report: Methadone treatment of injecting opioid users for prevention of HIV infection. *Journal of General Internal Medicine*. 2006; 21:193–195. [PubMed: 16336624]
- Greenland, S.; Lash, TL. 19. Bias Analysis. In: Rothman, KJ.; Greenland, S.; Lash, TL., editors. *Modern Epidemiology*. 3rd ed. Lippincott, Williams & Wilkins; Philadelphia: 2008. p. 345-380.
- Hall, W.; Ward, J.; Mattick, R. The effectiveness of methadone maintenance treatment 1: Heroin use and crime. In: Ward, J.; Mattick, R.; Hall, W., editors. *Methadone Maintenance Treatment and Other Opioid Replacement Therapies*. Harwood Academic Publishers; Amsterdam: 1998. p. 17-58.
- Joseph H, Stancliff S, Langrod J. Methadone maintenance treatment (MMT): A review of historical and clinical issues. *Mount Sinai Journal of Medicine*. 2000; 67:347–364. [PubMed: 11064485]
- Li L, Sangthong R, Chongsuvivatwong V, McNeil E, Li J. Multiple substance use among heroin-dependent patients before and during attendance at methadone maintenance treatment program, Yunnan, China. *Drug and Alcohol Dependence*. 2011; 116:246–249. [PubMed: 21282020]
- Lin C, Detels R. A qualitative study exploring the reason for low dosage of methadone prescribed in the MMT clinics in China. *Drug and Alcohol Dependence*. 2011; 117:45–49. [PubMed: 21310554]
- Lin C, Wu Z, Detels R. Family support, quality of life and concurrent substance use among methadone maintenance therapy clients in China. *Public Health*. 2011; 125:269–274. [PubMed: 21414646]
- Lin C, Wu Z, Rou K, Pang L, Cao X, Shoptaw S, et al. Challenges in providing services in methadone maintenance therapy clinics in China: Service providers' perceptions. *The International Journal on Drug Policy*. 2010; 21:173–178. [PubMed: 19818591]
- Liu H, Li J, Lu Z, Liu W, Zhang Z. Does Chinese culture influence psychosocial factors for heroin use among young adolescents in China? A cross-sectional study. *BMC Public Health*. 2010; 10:563. [PubMed: 20858259]
- Liu EW, Wu ZY, Liang T, Shen LM, Zhong H, Wang B, et al. Risk factors associated with continued heroin use during methadone maintenance treatment in Guizhou province, China. *Zhonghua Yu Fang Yi Xue Za Zhi*. 2008; 42:875–878. [PubMed: 19141219]
- Ma Y, Zhang F, Zhao Y, Zang C, Zhao D, Dou Z, et al. Cohort profile: The Chinese national free antiretroviral treatment cohort. *International Journal of Epidemiology*. 2010; 39:973–979. [PubMed: 19556327]
- Marsch LA. The efficacy of methadone maintenance interventions in reducing illicit opiate use, HIV risk behavior and criminality: A meta-analysis. *Addiction*. 1998; 93:515–532. [PubMed: 9684390]
- McLellan AT, Lewis DC, O'Brien CP, Kleber HD. Drug dependence, a chronic medical illness: Implications for treatment, insurance, and outcomes evaluation. *JAMA*. 2000; 284:1689–1695. [PubMed: 11015800]
- Ministry of Health of the People's Republic of China. 2012 China AIDS Response Progress Report. Ministry of Health the People's Republic China; Beijing: 2012.
- Ministry of Public Security. Our country now registers 1.335 million drug users. Ministry of Public Security; Beijing: 2010.
- National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. Effective medical treatment of opiate addiction. National Consensus Development Panel on Effective Medical Treatment of Opiate Addiction. 1998; 280:1936–1943.

- Pollack HA, D'Aunno T. Dosage patterns in methadone treatment: Results from a national survey, 1988–2005. *Health Services Research*. 2008; 43:2143–2163. [PubMed: 18522665]
- Pope RC, Wallhagen M, Davis H. The social determinants of substance abuse in African American baby boomers: Effects of family, media images, and environment. *Journal of Transcultural Nursing*. 2010; 21:246–256. [PubMed: 20519728]
- Royston P. Multiple imputation of missing values: Update. *The Stata Journal*. 2005; 5:188–201.
- Sorensen JL, Copeland AL. Drug abuse treatment as an HIV prevention strategy: A review. *Drug and Alcohol Dependence*. 2000; 59:17–31. [PubMed: 10706972]
- State Council of P.R. China. Regulations on AIDS Prevention and Treatment. Beijing: 2006.
- Sullivan, SG. Implementation of the Chinese methadone maintenance treatment program: Analysis of national data. University of California; Los Angeles: 2011. p. 193
- Sullivan SG, Detels R, Wu Z, for the National Methadone Maintenance Treatment Working Group. Time to first treatment interruption in the Chinese methadone maintenance treatment programme. *Drug Alcohol Depend*. 2013; 133:427–432. [PubMed: 23896308]
- Sullivan SG, Wu Z. Rapid scale up of harm reduction in China. *The International Journal on Drug Policy*. 2007; 18:118–128. [PubMed: 17689354]
- VanderWeele TJ. Marginal structural models for the estimation of direct and indirect effects. *Epidemiology*. 2009; 20:18–26. [PubMed: 19234398]
- Vansteelandt S. Estimating direct effects in cohort and case–control studies. *Epidemiology*. 2009; 20:851–860. [PubMed: 19806060]
- Ward, J.; Mattick, R.; Hall, W. The effectiveness of methadone maintenance treatment 2: HIV and infectious hepatitis. In: Ward, J.; Mattick, R.; Hall, W., editors. *Methadone Maintenance Treatment and Other Opioid Replacement Therapies*. Harwood Academic Publishers; Amsterdam: 1998. p. 59-74.
- Weatherby NL, Needle R, Cesari H, Booth R, McCoy CB, Watters JK, et al. Validity of self-reported drug-use among injection-drug users and crack cocaine users recruited through street outreach. *Evaluation and Program Planning*. 1994; 17:347–355.
- Wu Z, Zhang J, Detels R, Duan S, Cheng H, Li Z, et al. Risk factors for initiation of drug use among young males in southwest China. *Addiction*. 1996; 91:1675–1685. [PubMed: 8972925]
- Yap L, Wu Z, Liu W, Ming ZQ, Liang S. A rapid assessment and its implications for a needle social marketing intervention among injecting drug users in China. *The International Journal on Drug Policy*. 2002; 13:57–68.
- Yin W, Hao Y, Sun X, Gong X, Li F, Li J, et al. Scaling up the national methadone maintenance treatment program in China: Achievements and challenges. *International Journal of Epidemiology*. 2010; 39:ii29–ii37. [PubMed: 21113034]
- Yu M, Stiffman AR. Positive family relationships and religious affiliation as mediators between negative environment and illicit drug symptoms in American Indian adolescents. *Addictive Behaviors*. 2010; 35:694–699. [PubMed: 20359830]

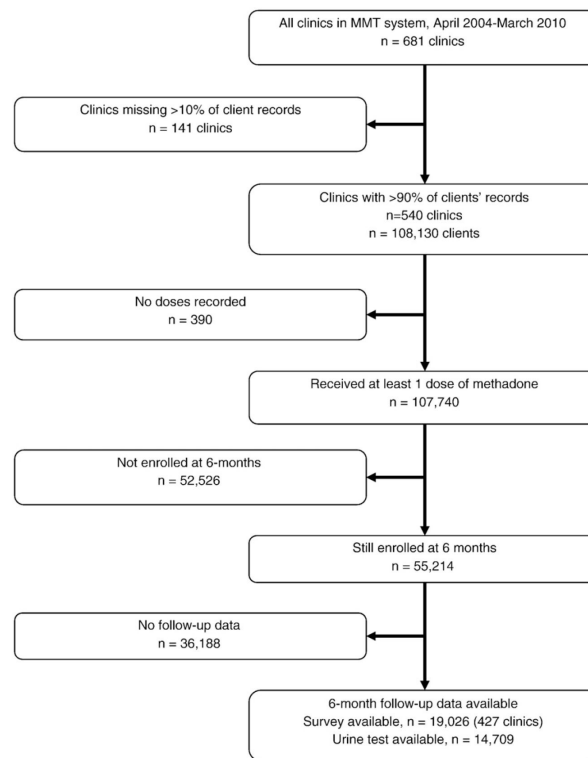


Fig. 1. Flow diagram of clients through the MMT system and included in the study. The number assessed for eligibility is not routinely assessed.

Table 1

Changes in drug use, HIV-risk behaviours, HIV status and social functioning among MMT clients at entry and 6 months after treatment.

| Variable | Entry | 6 months | p-value |
|---|----------------|----------------|---------|
| Positive urine opiate test | 6826 (97.9%) | 1957 (28.1%) | <0.0001 |
| Self-reported drug use in last month | 18,680 (99.6%) | 4665 (24.9%) | <0.0001 |
| Used drugs in last month (self-reported use or positive urine test) | 14,523 (99.7%) | 5745 (39.4%) | <0.0001 |
| Injected drugs in past month | 12,591 (67.4%) | 3128 (16.7%) | <0.0001 |
| Mean number of times injected, past month (SD) | 60.6 (63.5) | 3.0 (13.0) | <0.0001 |
| Shared needles in past month | 1174 (6.4%) | 229 (1.2%) | <0.0001 |
| Mean number of times shared needles, past month (SD) | 2.2 (17.5) | 0.1 (1.7) | <0.0001 |
| Mean number of needle partners (SD) | 0.2 (2.2) | 0.0 (0.2) | <0.0001 |
| Sexually active | 11,664 (62.8%) | 11,291 (60.8%) | <0.0001 |
| Used condom, last sex | 2358 (27.9%) | 2780 (32.9%) | <0.0001 |
| Mean number of sex partners, past 3 months (SD) | 0.7 (2.2) | 0.6 (0.9) | <0.0001 |
| HIV-positive | 1031 (5.9%) | 1054 (6.0%) | <0.0001 |
| Currently employed | 5375 (30.0%) | 7942 (44.3%) | <0.0001 |
| Recent drug-related crimes | 1558 (8.4%) | 571 (3.1%) | <0.0001 |
| Good/Normal relationship with family* | 17,243 (90.6%) | 18,245 (95.9%) | <0.0001 |
| Never sees friends [†] | 3898 (20.9%) | 9622 (51.6%) | <0.0001 |

Values are *n* (%) with p-value from McNemar's test or mean (SD) with p-value from the paired *t*-test. Percentages are for the column including the alternative (negative) state, which is not shown; e.g. at 6 months 28.1% had a positive urine opiate test, while 71.9% had a negative test. Samples do not always add to 19,026 because totals are only reported for clients with values at both time points.

* Negative state is "difficult".

[†] Negative state is "sometimes/often".

Table 2

Changes in drug use, HIV-risk behaviours, HIV status and social functioning among MMT clients at entry and 6 months after treatment including those clients with no follow-up data and assuming baseline behaviours persisted at 6 months for those with missing data.

| | Baseline | Follow up | p-value |
|---|-----------------|------------------|----------------|
| Positive urine opiate test | 25,858 (97.7%) | 20,989 (79.3%) | <0.0001 |
| Self-reported drug use in last month | 54,504 (99.7%) | 40,489 (74.1%) | <0.0001 |
| Used drugs in last month (self-reported use or positive urine test) | 50,489 (99.8%) | 41,711 (82.4%) | <0.0001 |
| Injected drugs in past month | 35,201 (64.7%) | 25,738 (47.3%) | <0.0001 |
| Mean number of times injected, past month (SD) | 57.5 (63.4) | 37.7 (57.6) | <0.0001 |
| Shared needles in past month | 3484 (6.4%) | 2539 (4.7%) | <0.0001 |
| Mean number of times shared needles, past month (SD) | 2.4 (18.3) | 1.7 (15.3) | <0.0001 |
| Mean number of needle partners (SD) | 0.2 (2.0) | 0.1 (1.6) | <0.0001 |
| Sexually active | 33,114 (61.5%) | 32,741 (60.8%) | <0.0001 |
| Mean number of sex partners, past 3 months (SD) | 0.7 (2.8) | 0.7 (2.5) | <0.0001 |
| Used condom, last sex | 8671 (29.3%) | 9093 (30.7%) | <0.0001 |
| HIV-positive | 4189 (7.6%) | 3202 (5.8%) | <0.0001 |
| Currently employed | 15,704 (30.7%) | 18,271 (35.7%) | <0.0001 |
| Recent drug-related crimes | 4189 (7.6%) | 3202 (5.8%) | <0.0001 |
| Good/Normal relationship with family [*] | 50,187 (92.3%) | 51,183 (94.1%) | <0.0001 |
| Never sees friends [†] | 10,143 (18.7%) | 15,867 (29.2%) | <0.0001 |

Values are *n* (%) with p-value from McNemar's test or mean (SD) with p-value from the paired *t*-test. Percentages are for the column including the alternative (negative) state, which is not shown; e.g. at 6 months 79.3% had a positive urine opiate test, while 20.7% had a negative test. Samples do not always add to 19,026 because totals are only reported for clients with values at both time points.

* Negative state is "difficult".

† Negative state is "sometimes/often".

Table 3

Discordance between urine opiate tests and self-reported drug use at 6-month follow-up (opiate test within 1 month prior to survey).

| Opiate test result | Self-reported drug use in last month | | |
|--------------------|--------------------------------------|--------------|--------------|
| | No | Yes | Total |
| Negative | 5035 (62.8%) | 777 (9.7%) | 5812 (72.5%) |
| Positive | 1127 (14.0%) | 1083 (13.5%) | 2210 (27.5%) |
| Total | 6162 (76.8) | 1860 (23.2) | 8022 |

Values for clients who had completed a urinary opiate test prior to the survey and had a result for both variables. A further 6586 clients had a urine test after their survey. Kappa = 0.36, $p < 0.0001$.

Table 4

Factors associated with drug use after 6 months of methadone treatment.

| Complete-case analysis, for 19,026 clients in 427 clinics (1–550 clients per clinic) | | | | | | | |
|---|-----------------------------------|---------------------------------------|-----------|-----------------------------------|-----------|-------------------------------|------------|
| | Category | <u>Composite drug use^a</u> | | <u>Positive urine test result</u> | | <u>Self-reported drug use</u> | |
| | | OR | 95%CI | OR | 95%CI | OR | 95% CI |
| Median dose/day (vs. 60 mg) | <60 mg | 0.96 | 0.86–1.07 | 0.96 | 0.85–1.08 | 0.95 | 0.83–1.09 |
| Attendance (vs. high (70%)) | Moderate (30–69%) | 2.43 | 2.11–2.80 | 2.33 | 2.00–2.71 | 2.29 | 1.94–2.70 |
| | Low (<30%) | 5.98 | 4.69–7.63 | 5.72 | 4.50–7.28 | 5.11 | 3.90–6.71 |
| Dose*attendance | Dose <60 mg × moderate attendance | 1.07 | 0.90–1.26 | 1.03 | 0.87–1.23 | 1.07 | 0.88–1.30 |
| | Dose <60 mg × low attendance | 1.14 | 0.86–1.51 | 1.12 | 0.86–1.47 | 1.17 | 0.86–1.60 |
| Gender (vs. female) | Male | 1.13 | 1.03–1.25 | 1.08 | 0.97–1.20 | 1.06 | 0.95–1.20 |
| Ethnicity (vs. non-Han) | Han | 0.90 | 0.77–1.04 | 0.85 | 0.73–0.98 | 0.98 | 0.82–1.18 |
| Education level (vs. illiterate) | Primary school | 0.94 | 0.66–1.35 | 1.02 | 0.70–1.49 | 1.03 | 0.68–1.55 |
| | Junior high school | 0.91 | 0.64–1.29 | 0.97 | 0.67–1.41 | 0.96 | 0.64–1.45 |
| | Middle or high school | 0.81 | 0.56–1.17 | 0.85 | 0.58–1.26 | 0.94 | 0.62–1.42 |
| | Junior college or higher | 0.87 | 0.57–1.33 | 0.83 | 0.52–1.31 | 1.06 | 0.64–1.74 |
| Employed (vs. unemployed) | Yes | 0.89 | 0.82–0.97 | 0.90 | 0.83–0.98 | 0.90 | 0.82–1.00 |
| How often saw drug-using friends in last month (vs. never) | 1–4 times per week | 3.05 | 2.76–3.37 | 1.68 | 1.51–1.87 | 7.53 | 6.67–8.51 |
| | 5–6 times per week | 3.53 | 3.10–4.01 | 1.99 | 1.74–2.28 | 9.47 | 8.15–11.00 |
| | Daily | 3.72 | 3.18–4.34 | 1.90 | 1.61–2.23 | 10.44 | 8.80–12.38 |
| Relationship with family (vs. good) | Normal (not good, not bad) | 1.28 | 1.17–1.39 | 1.22 | 1.11–1.34 | 1.38 | 1.24–1.53 |
| | Difficult | 2.03 | 1.63–2.52 | 1.40 | 1.13–1.73 | 2.68 | 2.12–3.39 |
| Number of years using drugs | | 0.99 | 0.98–1.00 | 0.99 | 0.98–1.00 | 1.00 | 0.99–1.01 |
| Length of commute | | 1.00 | 1.00–1.00 | 1.00 | 1.00–1.00 | 1.00 | 1.00–1.00 |

^aComposite drug use means drug use recorded either through urine test or self-report or both.