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ORIGINAL ARTICLE

Comparison Between Urinalysis Results and Self-Reported Heroin Use Among Patients Undergoing Methadone Maintenance Treatment in China

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ABSTRACT

Background: The validity and concordance of two main measures of drug use behavior, self-report and urinalysis, has long been discussed. More understanding is needed about the underlying factors associated with discordance between these two methods. **Objectives:** Describe the pattern and associated factors of discordance between self-reported heroin use and the urinalysis results of opiate use among methadone maintenance therapy (MMT) patients in China. **Methods:** A total of 2,448 MMT patients from 68 clinics in five provinces of China participated in a survey, which collected information on demographics, drug use and MMT-related factors, depressive symptoms, and drug avoidance self-efficacy. The most recent urine morphine test result was obtained from medical records and compared with self-reported heroin use. Participants who had urinalysis within 14 days of the survey were included in the analysis. **Results:** Among the 1,092 participants, 70 (6.4%) self-reported heroin use and 195 (17.9%) had positive urinalysis results. The over-reporters group had significantly higher education, and the under-reporters had significantly higher level of drug-avoidance self-efficacy and lower level of depressive symptoms. Among the participants who either self-reported heroin use or had positive urinalysis results, being young, having higher education, and having lower level of depressive symptoms were associated with discordance between self-reports and urinalysis results. **Conclusion:** The combination of both measures in assessing drug use behavior seems necessary. The validity of self-report should be considered differently based on demographic and psychosocial characteristics.

KEYWORDS

Heroin use; methadone maintenance therapy; self-report; urinalysis

In drug use research literature, self-report and urinalysis are the two most commonly used methods to assess drug use behavior (Chermack et al., 2000; Denis et al., 2012). Although self-report is considered a convenient method, its validity is frequently questioned because of potential misreports influenced by factors such as concerns of confidentiality, negative consequences, and social-desirability (Chermack et al., 2000; Rehle, Lazzari, Dallabetta, & Asamoah-Odei, 2004). Urinalysis, in contrast, is regarded as a more accurate measure of drug use because it is not subject to the potential biases associated with self-reports (Ciesla & Spear, 2001; Lennox, Dennis, Scott, & Funk, 2006). However, in addition to the cost of urine screens (Ciesla & Spear, 2001), the accuracy of urinalysis depends on the sensitivity of the method, quantity of drug used or time since its use, and the retention time of the substance (Digiusto, Seres, Bibby, & Batey, 1996; Kilpatrick, Howlett, Sedgwick, & Ghodse, 2000).

Previous studies showed that the level of concordance between self-report and urinalysis, often reflected by the kappa value, varies by a wide range because of many factors, such as types of subjects studied, context of

assessment, and confidentiality of patient reports (Chermack et al., 2000; Denis et al., 2012; Digiusto et al., 1996; Solbergdottir, Bjornsson, Gudmundsson, Tyrfinngsson, & Kristinnsson, 2004). Two studies examining the validity of risk behavior assessment questionnaire indicated that self-report questionnaire could serve as a valid assessment of drug use behavior (kappa = 0.52 and 0.65 in two samples) (Dowling-Guyer et al., 1994; Needle et al., 1995). When comparing with urine test results, acceptable concordance was reported when confidentiality was ensured or there is no consequence (Grella, Anglin, & Wugalter, 1997; Magura, Nwakeze, & Densky, 1998; Weatherby, Needle, Cesari, & Chitwood, 1994; Zanis, McLellan & Randall, 1994). Under naturalistic treatment conditions where confidentiality was not ensured, Chermack et al. (2000) found higher rates of substance use based on urinalysis than patient self-reports and poor concordance between the two was reported. By contrast, Denis and his colleagues (2012) found that patients did not under-report their substance use in a naturalist clinical assessment setting and reported a high consistency between self-reported substance use and urinalysis results.

Several studies examined the underlying causes of concordance and discordance between self-report and urinalysis results with respect to demographic characteristics of patients, drug-use-related factors, and treatment-related factors. Among the patient demographic characteristics, age was associated with under-reporting; specifically, subjects aged over 30 years were more likely to under-report their substance use behaviors (Magura, Goldsmith, Casriel, Goldstein, & Lipton, 1987). Regarding drug-use-related factors, findings from the study by Wish and his colleagues (1997) revealed that self-reported substance use was more likely to be valid among extensive drug users, defined as those who use heroin or cocaine on daily basis. Regarding treatment-related factors, several studies in methadone maintenance therapy (MMT) settings reported that the patient's stage in treatment was an important factor influencing the report concordance. For example, MMT applicants had more accurate self-reports than those who had previously undergone treatment (Digiusto et al., 1996). Under-reporting also occurs more frequently at the follow-up stage than at the intake stage (Reilly, Twyman, & Williams, 1985). Poorer concordance among patients who have undergone MMT for a relatively long time compared with newly admitted patients was also reported (Chermack et al., 2000). One hypothesis is that at the follow-up stage, patients tend to conceal their drug use to maximize the benefit of the treatment they receive. In contrast, at the intake stage, applicants or newly admitted patients tend to disclose their substance behavior to justify their eligibility for treatment. Similar results were also reported for other addiction treatment settings (Buchan, Dennis, Tims, & Diamond, 2002; Wish, Hoffman, & Nemes, 1997). Nevertheless, another study reported no significant difference in concordance between the different treatment stages (Denis et al., 2012). Johnson and colleagues' study indicated that self-report could be considered reliable and valid among out-of-treatment drug users at six-month follow up. They also pointed out that the validity finding could be an overestimate of actual validity, since participants were prescreened and warned that an impending urinalysis would be conducted (Johnson et al., 2000).

Although MMT has been adopted as a national strategy to address the drug abuse problem and related human immunodeficiency virus (HIV) infections in China for more than ten years, one of the major barriers to addressing the problems is continued drug use among patients and the related low retention rates of MMT programs (Wu et al., 2013). Self-reported drug use and urinalysis are both used to monitor continued drug use in China's MMT program. Several previous studies on concurrent heroin use during MMT in China showed that the level of agreement

between the two measures was moderate ($\kappa = 0.40\text{--}0.47$; Landis & Koch, 1997; Li, Lin, Wan, Zhang, & Lai, 2012; Lin et al., 2010; Sullivan et al., 2014). However, there is a dearth of literature examining the associating factors of concordance/discordance between the two measures among MMT patients in China. The current study aimed to compare self-reported heroin use and urinalysis of opiate use among MMT patients in China, and to explore factors associated with discordance between the two assessment methods.

Methods

Participants

This study used the baseline data of a randomized controlled intervention trial implemented in five provinces in China, Sichuan, Guangdong, Shanxi, Hunan, and Jiangsu. The baseline data collection was conducted from September 2012 to August 2013. A total of 68 MMT clinics were randomly selected from the list of MMT clinics with more than 80 current patients in the five provinces. Thirty-six patients were randomly selected from each of the participating clinics using a systematic sampling approach. According to China's national guidelines (China Ministry of Health, China Ministry of Public Security & China Food and Drug Administration, 2006), all MMT patients must be: (1) at least 20 years old, (2) opiate dependent, (3) lacking severe psychosis and neurological damage, and (4) not under criminal or civil charges. These criteria were also applied to select eligible participants of the current study. With that said, this study only included patients who fulfilled the national criteria and were receiving MMT services at the participating clinics at the time of the study. MMT service providers referred the randomly selected patient to the project outreach staff. Following a standardized script, the project staff explained the study procedures and voluntary nature to the potential participants. During the recruitment process, the project staff particularly emphasized the fact that the data collected would be strictly confidential, and their name or identifiable information would not appear on assessment instruments. They were also informed that their responses to survey questions would not be shared with their service providers, and all the data will be stored in a secured centralized location and be available to research investigators only. All these confidentiality statements were communicated verbally and printed in the informed consent and provided to the potential participants. Written informed consent was obtained prior to the assessment. The refusal rate was less than 10%.

Clinical data collection

According to the national guidelines in China, MMT patients are required to provide urine samples to test for opiate use once a month on a random schedule (Cao et al., 2014). Urinalysis was performed by MMT providers to test for heroin use (detected as morphine). The manufacturer of the testing kit varies across clinics. To reduce the burden of frequent sample collection for both providers and patients, we did not conduct additional biomedical tests specifically for this study. The latest urinalysis and HIV serostatus results were obtained from the medical records with participant consent. The clinical data were merged with the behavioral data using a unique participant identification number.

Behavioral data collection

The assessment was administered using the computer assisted personal interview (CAPI) method. Assessment activities were conducted in a private room in the MMT clinic. Trained interviewers read survey questions to the participants and entered their responses directly into laptop computers. It took approximately 45–60 minutes to complete the process. Patients received 30 yuan (US: \$4.80) for participation in the assessment. The participating institutes in both China and the United States approved the study protocol.

Measures

In addition to the sociodemographic characteristics, such as age, gender, education, and household income (yuan), the questionnaire collected heroin use and treatment-related information. To measure MMT doses, participants were asked about the average dose of methadone they had received in the past 30 days. They were also asked in which year they started using heroin. A continuous variable of heroin lifetime use (in years) was generated by calculating the difference between the current year and the year in which the patient started using heroin. Similarly, the length to MMT (in years) was measured by asking participants the date of their admission to the MMT clinic and calculating the difference between the assessment date and the date of MMT admission. Self-reported heroin use was documented by asking participants whether they had used heroin in the past seven days (yes or no).

Depressive symptoms were measured using a shortened version of the Zung self-rating depression scale (Zung, 1965). This scale is widely used to measure levels of depressive symptoms in research (World Health Organization, 2015), and was validated among MMT patients in China (Yin et al., 2015). The scale is a nine-item

instrument consisting of six negatively worded items, such as “I feel down-hearted and blue,” “I get tired for no reason,” and “I have trouble sleeping at night,” and three positively worded items, such as “I feel hopeful about the future.” The participants were asked how often they felt each of the items. The response categories ranged from (1) “a little of the time” to (4) “most of the time.” After reversely coding the three positive items, a continuous variable was generated by summing the items. A higher overall score indicated a higher level of depressive symptoms (Cronbach’s $\alpha = 0.73$).

Drug avoidance self-efficacy was measured using questions from the drug-avoidance self-efficacy scale (DASES) (Martin, Wilkinson, & Poulos, 1995). Seven of the 16 questions were selected based on the relevance to the target population. The instrument was used previously to measure confidence and the perceived capability of self-drug avoidance among MMT patients (Li et al., 2013). In consideration of Chinese culture, we modified several questions from the original scale. For example, we used the question “Imagine it is Chinese New Year and you plan to do something special to celebrate, would you use drugs?” Each question was answered on a 5-point Likert-scale ranging from (1) “definitely” to (5) “definitely not.” The overall continuous score was constructed by summing the seven items with the three questions reversely coded. A higher overall score indicated a higher level of self-efficacy to avoid drug use (Cronbach’s $\alpha = 0.77$).

Statistical analysis

A total of 2,448 participants completed the survey and 2,444 had urinalysis results in the medical record. The time lag between the date of urinalysis and the self-report was calculated. Majority of the participants ($N = 1,973$; 80%) had their urinalysis conducted within 28 days of the survey; however, 22% ($N = 545$) of the participants had their time lag within seven days. To cleanly address our research questions of interest, our analysis sample included the participants who had their time lag between self-report and urine sample dates within 14 days ($N = 1,092$; about 45% of the original sample).

Four subgroups were defined based on the combination of self-reported heroin use in the past seven days and urinalysis results: (1) positive concurrent group, who self-reported heroin use and had positive urinalysis data; (2) over-reporters, consisted of participants who self-reported heroin use but had negative urinalysis results, (3) under-reporters, who had positive urinalysis results but self-reported no heroin use; and (4) negative concurrent group, who had negative urinalysis and self-reported no heroin use. First, descriptive statistics and frequencies for the demographic, clinical, and drug use characteristics

were summarized by group. Next, we reported the degree of agreement between the patients' self-reported heroin use during the past seven days and their urinalysis results using the observed agreement between the self-report and urinalysis as well as Cohen's kappa statistic. Third, the continuous and categorical characteristics of the over-reporters and under-reporters were compared with positive concurrent group using ANOVA and Chi-square tests, respectively. Lastly, we explored factors associated with the discordance between self-reports and urinalysis results among those who either reported using drugs in the past seven days or had positive urinalysis results using a logistic mixed-effects regression model with clinic-level random effects. The prespecified factors of interest were demographic characteristics (age, gender, and education), disease-related factors (HIV status), and drug use and MMT-related factors (years of heroin lifetime use, MMT dose, and length of MMT), adjusting for time lag between interview and urine date. The province was also included in the regression model to account for variability across provinces. The adjusted odds ratios (AOR) and corresponding 95% confidence intervals (CI) are presented. All statistical analyses were performed using the SAS System for Windows version 9.4 (Cary, NC).

Results

Sample description

The demographics, HIV status, heroin use, and MMT-related characteristics of the 1,092 participants are summarized in Table 1. Over half the patients (53.4%) were between 36 and 44 years old, and majority of them were males (77.9%). More than half of the patients were married or living with a partner at the time of the assessment, and 84.3% had received seven or more years of education. Forty-six percent of the patients reported a monthly household income of 2,000 yuan or lower. HIV prevalence among the study sample was 4.6%. About one third (31.6%) of the patients had daily methadone dosage above 60 mL. The average length of MMT of patients was about four years. The majority of the patients had used heroin for more than ten years.

Drug use characteristics

Regarding heroin use in self-report and urine sample within 14 days, 17.9% (195/1,092) of participants had positive urinalysis, where 6.4% (70/1,092) of them self-reported heroin use. There were 31 (2.8%) participants self-reported heroin use and had positive urinalysis (positive concurrent group). Less than 4% of participants

($N = 39$) self-reported heroin use but had negative urinalysis results, and they were categorized as over-reporters. Under-reporter group had 164 (15.0%) participants, who had positive urinalysis results but self-reported no heroin use. Almost 80% of the sample ($N = 858$) fell in the negative concurrent group, who had negative urinalysis and self-reported no heroin use (Table 1). Similar percentages of positive concurrent group, negative concurrent group, over-reporters, and under-reporters were found in various time lags. For instance, among 545 participants having their urine tests within seven days of the survey, 106 had either positive urinalysis results or self-reports (3.1% in positive concurrent group; 3.7% in over-reporter group; and 12.7% in under-reporter group).

Agreement between self-report and urinalysis

The overall observed agreement between the self-reported heroin use and urinalysis data was 81.4% (ranging from 74.9% to 89.9% across provinces), with relatively poorly consistent positive results (2.8%) and highly consistent negative results (78.6%). The overall Cohen's kappa statistic for agreement between the self-report and urinalysis data was 0.15 (range 0.05–0.25 across provinces), suggesting a fair level of agreement (Landis & Koch, 1997).

Comparison of under-reporters, over-reporters, and positive concurrent group

There were significant differences in education, drug avoidance self-efficacy, and depressive symptoms among positive concurrent group, under-reporters, and over-reporters (Table 1). The patients in the over-reporter group had significantly more years of education than those in the positive concurrent group (mean: 9.7 vs. 8.2; $P = 0.012$). The under-reporters had significantly higher level of drug-avoidance self-efficacy (mean: 27.6 vs. 23.7; $P = 0.0002$), but lower level of depressive symptoms (mean: 17.7 vs. 21.4; $P = 0.0008$) compared to positive concurrent group.

Factors associated with discordance between self-report and urinalysis

Among the patients who either self-reported heroin use or had positive urinalysis results, younger patients (AOR: 11.2 and 5.77 for 35 or younger and 36–45 years old, respectively), and patients who completed more years of education (AOR = 4.94, 95% CI: 1.57, 15.5) had higher odds of discordance between the self-report and urinalysis. Higher levels of depressive symptoms were associated with lower odds of discordance between the self-report and urinalysis (AOR = 0.89, 95% CI: 0.81, 0.98) (see Table 2).

Table 1. Sample characteristics, overall and by subgroups based on self-report and urinalysis results.

	Overall N = 1,092	SR+; U+ N = 31	SR+; U- N = 39	SR-; U+ N = 164	SR-; U- N = 858
Age					
Mean (SD)	40.4 (7.0)	40.8 (8.1)	37.8 (6.8)	39.8 (6.1)	40.6 (7.1)
35 or younger	268 (24.5)	7 (22.6)	14 (35.9)	38 (23.2)	209 (24.4)
36–44	583 (53.4)	15 (48.4)	18 (46.2)	102 (62.2)	448 (52.2)
45 or older	241 (22.1)	9 (29.0)	7 (18.0)	24 (14.6)	201 (23.4)
Male	851 (77.9)	21 (67.7)	30 (76.9)	130 (79.3)	670 (78.1)
Education ^{a,b}					
Mean (SD)	9.2 (2.7)	8.2 (3.2)	9.7 (2.6)	9.1 (2.4)	9.2 (2.7)
6 years or less	171 (15.8)	9 (29.0)	5 (12.8)	22 (13.4)	135 (15.9)
7–10 years	586 (54.0)	16 (51.6)	21 (53.9)	96 (58.5)	453 (53.2)
More than 10 years	329 (30.3)	6 (19.4)	13 (33.3)	46 (28.1)	264 (31.0)
Marital status					
Single	219 (20.1)	7 (22.6)	12 (30.8)	30 (18.3)	170 (19.8)
Married/Living with partner	612 (56.0)	13 (41.9)	14 (35.9)	85 (51.8)	500 (58.3)
Divorced/Separated/Widowed	261 (23.9)	11 (35.5)	13 (33.3)	49 (29.9)	188 (21.9)
Monthly household income (yuan)					
Mean (SD)	3,996 (5,823)	3,532 (3,750)	3,426 (4,515)	3,994 (6,363)	4,044 (5,847)
2,000 or less	504 (46.3)	11 (35.5)	19 (48.7)	90 (55.2)	384 (44.8)
2,001–5,000	378 (34.7)	16 (51.6)	14 (35.9)	39 (24.0)	309 (36.1)
5,001–10,000	153 (14.1)	3 (9.7)	4 (10.3)	24 (14.7)	122 (14.3)
10,001 or more	54 (5.0)	1 (3.2)	2 (5.1)	10 (6.1)	41 (4.8)
HIV positive	48 (4.6)	5 (16.1)	4 (10.5)	9 (5.6)	30 (3.7)
Methadone dose (More than 60 mL/day)	345 (31.6)	12 (38.7)	20 (51.3)	53 (32.3)	260 (30.3)
Length of MMT					
Mean (SD)	3.8 (2.1)	3.2 (2.5)	3.3 (2.1)	3.5 (2.1)	3.9 (2.0)
1 year or less	128 (11.7)	10 (32.3)	7 (18.0)	29 (17.7)	82 (9.6)
2–5 years	603 (55.2)	13 (41.9)	21 (53.9)	87 (53.1)	482 (56.2)
More than 5 years	361 (33.1)	8 (25.8)	11 (28.2)	48 (29.3)	294 (34.3)
Heroin lifetime use more than 10 years	873 (80.0)	23 (74.2)	30 (77.0)	129 (78.7)	691 (80.5)
Drug avoidance self-efficacy, M(SD) ^{a,c}	27.5 (5.3)	23.7 (5.1)	22.4 (5.0)	27.6 (5.3)	27.9 (5.1)
Depressive symptoms, M(SD) ^{a,c}	18.4 (4.4)	21.4 (6.0)	21.1 (6.1)	17.7 (5.3)	18.3 (5.4)

SR = Self-report; U = urinalysis.

^aSignificant group differences in education, drug avoidance self-efficacy and depressive symptoms were observed using ANOVA.^bSignificant difference between (SR+; U+) and (SR+; U-), $P < 0.05$;^cSignificant difference between (SR+; U+) and (SR-; U+), $P < 0.05$.**Table 2.** Logistic mixed-effects regression* on discordance between self-report and urinalysis data.

	Outcome = Discordance between self-report and urinalysis data	
	Adjusted odds ratio	95% CI
Age (REF: > 45 years)		
35 or younger	11.2	(1.82, 69.1)
36–45	5.77	(1.67, 19.9)
Male	2.55	(0.87, 7.44)
Education (REF: < 6 years)		
Primary school or higher	4.94	(1.57, 15.5)
Marital status (REF: Divorced/Separated)		
Single	0.96	(0.25, 3.60)
Married/Living with partner	1.98	(0.62, 6.35)
Monthly household income (REF: ≥ 5,000 or more)		
2,000 or less	1.70	(0.39, 7.38)
2,001–5,000	0.35	(0.08, 1.47)
HIV positive	0.25	(0.06, 1.08)
Heroin lifetime use (REF: > 10 years)		
Less than 10 years	3.08	(0.87, 10.9)
MMT dose (100 mL/day)	0.99	(0.97, 1.01)
Length of MMT (year)	1.10	(0.89, 1.38)
Drug avoidance self-efficacy	1.04	(0.96, 1.14)
Depressive symptoms	0.89	(0.81, 0.98)

*Controlling for province and time lag between interview and urine date.

Discussion

This study reported a low concordance between self-reported heroin use and urinalysis results among MMT patients in China. The discordance is mainly due to under-reporting, which is consistent with previous studies conducted under naturalistic conditions, in which confidentiality is not ensured (Chermack et al., 2000; Preston, Silverman, Schuster, & Cone, 1997). This provided further evidence that concurrent drug use in MMT clinics is underestimated even the interviewers emphasized the confidentiality prior to the data collection. Drug-use-related stigma, fear of legal repercussions, and avoidance of the negative consequences associated with continued heroin use in MMT could be the underlying causes for the unwillingness to report having used illicit drug (Chermack et al., 2000; Napper, Fisher, Johnson, & Wood, 2010). On the other hand, there were also a small proportion of the participants over-reported their heroin use. This could have been due to the recall bias or misunderstanding of the question. For example, the participants might mistakenly recognize the drug terminology used in the questionnaire and confuse other substance use with heroin (Falck, Siegal, Forney, Wang, & Carlson,

1992; Johnson et al., 2000). There also may have been some patients who exaggerated heroin use to impress the interviewer or to show rebellion (Macleod, Hickman, & Smith, 2005; Napper et al., 2010). In addition, it takes approximately 48 hours for heroin to be detected in the urine morphine test, depending on hydration, heroin dose and concentration, metabolism, body mass, urine pH, duration of use, and other factors (Moeller, Lee, & Kissack, 2008). While there is no gold standard in measuring drug use, it is recommended that in natural clinical settings, using a combination of self-reports and biological measures to monitor drug use behavior is necessary.

The study revealed that extent of discordance between self-report and urinalysis differs by patient's characteristic. The patients who are over 45 years were found to have a higher level of concordance between the two measures compared to their younger counterparts. The finding is supported by literature (Mackesy-Amiti, Fendrich, & Johnson, 2008; Magura et al., 1987), which suggested that MMT patients tend to discontinue concealing drug use behaviors as they mature, and social pressure on people who use drugs decreases with age (Mackesy-Amiti et al., 2008). Interestingly, we found that education is associated with discordance and particularly over-reporting. This finding is contradictory to Fendrich and Johnson's (2005) study, which reported that inadequate education and low literacy levels may result in increased survey errors. We speculate the over-reporting of heroin use with high education could be related to the fact that educational attainment reduces sensitivity or shame for individuals (Rivera et al., 2015).

This study contributes to the literature by considering psychological measures, including drug avoidance self-efficacy, in the comparison of self-report and urinalysis data. Self-efficacy is defined as the self-belief and confidence in one's ability to engage in behavioral change (Bandura, 1982) and has been demonstrated to influence behavioral outcomes associated with substance use and addiction (Kuerbis, Armeli, Muench, & Morgenstern, 2013). However, the outcome measures in the previous studies relied largely on self-reports (Brown, Seraganian, Tremblay & Annis, 2002; Sitharthan & Kavanagh, 1991; Sitharthan, Job, Kavanagh, Sitharthan, & Hough, 2003). Our study revealed that participants who reported a higher level of drug avoidance self-efficacy were also more likely to deny their heroin use behavior while their urinalysis results were positive. This finding suggests that one should be cautious when interpreting the correlation between self-reported drug avoidance self-efficacy and self-reported drug use behavior because the participants may have systematically overrated their self-efficacy and under-reported their drug use behavior. An objective measurement, such as urinalysis, is necessary for

assessing the relationships between self-efficacy and drug use behavior.

Findings should be interpreted within the context of the study limitations. In this study, the participants were asked to report their heroin use behavior in the past seven days, whereas the urinalysis results were obtained from their medical records. The time lag between the urinalysis and self-report may contribute to the discordance between the two measure. In addition, a false-positive urine test could be the result of cross-reactivity to other opiates or medications (e.g., poppy seeds, quinolones, rifampin, verapamil, quetiapine, and diphenhydramine). Nevertheless, the present study highlights the need to combine both self-reports and urinalysis to assess heroin use behavior in MMT settings. It is suggested that the validity of self-report in drug use assessment must be considered with demographical and psychosocial characteristics.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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