ORIGINAL ARTICLE

The Proportion of Non-retention and Its Associated Factors Among Clients Receiving Methadone Maintenance Therapy in Kelantan, Malaysia

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ABSTRACT

Introduction: Methadone maintenance therapy (MMT) requires a client to take a daily dose of methadone to reduce cravings for opioid and suppress withdrawal syndrome. Non-retention in the MMT will seriously expose more risk rather than the benefits of the program. Hence, determining the factors associated with non-retention to the MMT is essential. Thus, the present study was conducted to determine the proportion of non-retention and its associated factors among clients receiving MMT in Kelantan, Malaysia. **Methods:** By using a retrospective record review analysis, the required information of the clients was obtained from fourteen MMT clinics in Kelantan, Malaysia. A total of 155 clients were selected in this study using systematic random sampling. Multiple logistic regression analysis was performed to determine the factors associated with non-retention among clients receiving MMT. **Results:** It was found that the proportion of non-retention to the MMT in Kelantan, Malaysia was 21.9%. Clients with advanced age, taking daily direct observed therapy, and no underlying HIV were the predictors of non-retention among clients receiving MMT in Kelantan, Malaysia. **Conclusion:** The findings highlight a relatively high proportion of non-retention among the MMT clients. There is a need for an integrated, culturally relevant approach towards tackling the factors associated with non-retention in the future to keep this program sustainable and effective.

Keywords: Methadone maintenance therapy, Non-retention, Opioid, Malaysia

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INTRODUCTION

Methadone maintenance therapy (MMT) is a drug replacement therapy to reduce the craving among opioid use disorder patients (1). It was first used as a treatment for heroin use disorder in New York during the post World War II (2). Methadone, which acts as a potent synthetic long-acting opiate agonist, has pharmacological actions similar to morphine but less damaging effect compared to the injection of morphine (3). There are eighty countries around the world practising MMT as their strategy to reduce the prevalence of opioid use disorder (4).

The introduction of naltrexone in 1995 through medication assisted treatment (MAT) program was the first initiative by Malaysia health ministry for the treatment of opioid-dependent. This opioid antagonist, however, has been replaced with buprenorphine due to strong withdrawal effect among patient with a history of taking heroin. The limited availability of buprenorphine in government clinics urges the government to start methadone maintenance therapy (MMT) to expend the service (5). The current practice of MMT in Malaysia requires a client to take daily maintenance therapy at a clinic with strict supervision by health care staff. Some of them had a privilege to take-home doses of methadone with strict rules.

The increasing trend of opioid use disorder creates an opportunity to promote and increase the number of clients enrolled in MMT. Retention is essential for a good treatment outcome. The clients require a daily dose of opioid as their body developed tolerance and physical dependence (6). They need a higher dose to achieve the same physiological and psychological effects. Clients in this program are strictly required to take a daily dose of methadone to reduce cravings for opioid and suppress withdrawal syndrome (7).

Determining the factors associated with non-retention is essential to ensure the program is cost-effective. It also

helps the ministry of health to create new strategies in reducing the proportion of non-retention among MMT clients. The main objectives of the MMT program are to increase the quality of life, improved psychosocial function and reduce the risk of infection acquired by sharing needles likes Hepatitis C and HIV (8, 9). Retention to the therapy is essential in managing HIV patients to comply with other harm reduction programs like antiretroviral therapy and treatment related to co-infection diseases of HIV like tuberculosis and Hepatitis C (10). Effective treatment outcomes with a low proportion of non-retention will reflect a good governance money-spending strategy to reduce drug abusers (11). Hence, the present study was conducted to determine the proportion of non-retention and its associated factors among clients receiving MMT in Kelantan, Malaysia.

MATERIALS AND METHODS

Study design and location

A retrospective record review was conducted among MMT clients enrolled from January to December 2017. Those clients were registered at fourteen MMT clinics in Kelantan, Malaysia. All of them required to be registered at least 14 days before enrolled in this study to ensure stable maintenance dose and only clients with high commitment were selected. Also, we included only those clients who were more than 18 years old in the present study. We excluded those clients with missing data for more than 30% of the interested variables.

Using a single proportion formula, with the proportion of non-retention to MMT from the previous study as 38% (12) and precision was set at 0.08, the required sample size was 155. Systematic random sampling was applied to select the clients to be included in the study. In the present study, those who defaulted to follow up for more than 14 days consecutively were considered as non-retention to the MMT. A client was required to be screened for HIV and tuberculosis. Meanwhile, urine analysis for drugs was also performed to determine for any drug used before the treatment was started. The validated WHO Quality of Life Questionnaire BREF (WHOQOL-BREF) was used to measure the quality of life among clients on the registration day (5, 12).

A low dose of methadone (30mg) was given as an initial dose, tapering up two weekly until no more craving symptoms present. Then, each client was kept on a maintenance dose and required a monthly follow up to monitor for any withdrawal symptoms. Random urine analysis for drugs was performed on follow up to look for any concurrent drugs taken during the treatment. All clients had formal counselling sessions before they enrolled in this treatment to ensure their preparedness and six-monthly session to keep them motivated. Defaulted of at least one formal session was considered as not completed to the counselling session in the present study.

Data Collection

Records on the sociodemographic information, treatment history, and daily attendance to monitor their performance in this program were kept in every client's folder. All data were recorded using a designed proforma. The outcome variable in the present study was non-retention to the therapy. Clients with a history of absent for more than fourteen days were recorded as non-retention to the therapy.

The independent variables in the present study were: age, sex, employment status (employed or non-employed), duration of taking drugs before enrolled in the MMT, age of started taking drugs, presence of underlying illness, type of drugs used before started treatment, urine analysis for drugs during follow up (either had a history of a positive or negative test for concurrent opioid taken during treatment) and history of being arrested and admitted to any rehabilitation centre during the registration at MMT clinics.

Meanwhile, the studied treatment factors were: method of methadone dispensing (Directly Observed Therapy (DOT) or take-home), level of methadone maintenance dose (mg/day) and completion of counselling sessions.

Statistical Analysis

Data were entered and analysed using SPSS Version 24. Descriptive statistics were used to summarise the data obtained. Numerical data were presented as mean (SD) or median (IQR) based on their normality distribution. Categorical data were presented as frequency (%). Simple and multiple logistic regression analyses (forward and backward method) were performed to determine the associated factors of non-retention among clients receiving methadone maintenance therapy. All findings were presented with crude odds ratio, adjusted odds ratio, 95% confidence interval, and p-value. The level of significance was set at a p-value of less than 0.05 for the two-tailed test.

Ethical consideration

Ethical approval was obtained from the Human Research and Ethics Committee, Universiti Sains Malaysia. The approval was also obtained from the Medical Research Ethics Committee, Ministry of Health Malaysia [No: 18-2973-44547 (IIR)].

RESULTS

A total of 155 clients were recruited and analysed. The mean (SD) age of the clients was 42.7 (6.05) years old. The majority of the clients were more than 40 years old (63. 9%) and were male (99.3%). Table I shows the sociodemographic characteristics of the clients receiving MMT in Kelantan, Malaysia.

Table II shows that DOT was the most applied method of dispensing methadone in MMT clinics (71.0%).

Table I: Sociodemographic characteristics of the clients receiving MMT in Kelantan, Malaysia (n=155)

Characteristics	Mean(SD)	n (%)
Age (years old)	42.7(6.1)	
Age started taking drugs (years)	21.2(4.7)	
Duration of taking drugs (years)	21.5(6.4)	
Quality of life		
Physical domain	57.82(12.4)	
Psychological domain	57.13(11.9)	
Social relations domain	58.81(11.7)	
Environmental domain	56.74(14.3)	
Sex		
Female		1(0.7)
Male		154(99.3)
Race		
Non-Malay		1(0.7)
Malay		154(99.3)
Employment status		
Not Employed		45(29.0)
Employed		110(71.0)
History of being arrested at a rehabilitation center		
No		31(20.0)
Yes		124(80.0)
Underlying HIV		
Yes		61(39.4)
No		94(60.6)
Underlying Tuberculosis		
Yes		22(14.2)
No		133(85.8)
Random urine for drug analysis		
Negative		100(64.5)
Positive		55(35.5)
History of taking Amphetamine-type stimulants (ATS)		
Yes		51(15.8)
No		104(84.2)

The mean (SD) level of methadone maintenance dose was 74.9 (43.13) mg/day. Only 32.3% of the clients completed all formal counselling sessions within the study period.

The proportion of non-retention among clients receiving MMT in Kelantan, Malaysia was 21.9%. Multiple logistic regression analysis using forward stepwise method analysis shows that age, no underlying HIV, and DOT method of dispensing were significantly associated with non-retention among clients receiving MMT in Kelantan, Malaysia (Table III). It was found that for every 1-year increase of age, the odds of non-retention in MMT program increased by 1.14 times (95% CI 1.04,1.25; p = 0.005) when adjusted for underlying HIV and method of dispensing methadone. Meanwhile, a client without underlying HIV has 3.0 times the odds of non-retention in MMT program (95% CI 1.27,7.10; p = 0.012) compared to those having HIV when adjusted for age and method of dispensing methadone. A client with the DOT method of dispensing methadone has 6.1 times the odds of non-retention in MMT program compared to those with the take-home method (95% CI 1.35, 27.53; p = 0.019) when adjusted for the status of underlying

Table II: Characteristics of the treatment received by the clients of MMT in Kelantan, Malaysia (n = 155)

Characteristics	Mean (SD)	n (%)
Level of maintenance dose (mg/day)	74.9(43.1)	
Method of dispensing		
Take-home		45 (29.0)
DOT		110 (71.0)
Completeness of formal counselling		
Yes		105 (67.7)
No		50 (32.3)

Table III: Factors associated with non-retention among clients receiving MMT in Kelantan, Malaysia (n=155)

Variables	Simple logistic regression		Multiple logistic regression	
	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Age	1.14 (1.05,1.24)	0.002	1.14 (1.04,1.25)	0.005
Age started taking drugs (years)	1.08 (0.98,1.18)	0.134		
Duration of taking drugs (years)	1.07 (1.00,1.13)	0.05		
Employment status				
Not Employed	Ref			
Employed	2.03 (0.92,4.50)	0.08		
History of being arrested at a rehabilitation center				
Yes	Ref			
No	5.04 (1.14,22.34)	0.033		
Underlying HIV				
Yes	Ref	0.010		
No	2.79 (1.28,6.08)		3.00 (1.27,7.10)	0.012
Underlying Tuberculosis				
Yes	Ref			
No	2.99 (1.15,7.77)	0.025		
Random urine for drug analysis				
Positive	Ref			
Negative	2.18 (1.01,4.74)	0.048		
Counselling session				
Not completed	Ref			
Completed	1.185 (0.52,2.72)	0.691		
Method of dispensing				
Take-away dose	Ref			
DOT	8.82 (2.02,38.60)	0.004	6.10 (1.35,27.52)	0.019

Forward LR method was applied
The model is reasonably fit. There is no interaction and multicollinearity problem.
Classification table is 78.1% correctly classified

tuberculosis and history of morphine use.

DISCUSSION

In the present study, the proportion of non-retention among clients receiving MMT was relatively high. This finding is in line with a study conducted in primary care clinics in Selangor and Hospital Kuala Lumpur (13) and also with another study in Dublin, Ireland (14). On the other hand, a 6-month study in Indonesia found that about 39% of their clients were not retained in the program (15). Meanwhile, in China, the range of non-retention rate among clients receiving MMT is from 27% to 70% (3, 16, 17). A higher proportion of non-retention in China compared to other countries could be due to the difference in the definition of non-retention in those previous studies. In China, the clients of MMT were classified as non-retention when they defaulted follow-up for more than seven days consecutively, but in Malaysia, it was more than 14 days continuously (12, 16). On the other hand, clients of MMT in Canada were classified as non-compliance when they defaulted taking methadone for more than 30 days consecutively (18).

A client with advanced age, not having HIV and having DOT as the method of dispensing were the predictors of non-retention in the MMT. In this study, we found that the risk of non-retention among clients receiving MMT treatment increase by the age of the clients. Each client required a different level of methadone daily dose for a long period, which makes this treatment lengthy and unpredictable. The premature mortality due to longstanding methadone intake in this study increases the risk for non-retention. As clients getting older, the dynamics of biological and physiological changes with methadone will continue. A study in Scotland found that an elderly age more 35 years old have 4.2 methadone-specific DRD-rate per 1,000 person-year at-risk irrespective of gender as compared to other types of opioid (19).

Meanwhile, in the UK, methadone-specific deaths were doubled at 35–44 years and nearly quadrupled at more than 45 years. This evidence supports the risk of methadone specific death raise accordingly with advanced age. Long term effects of daily methadone intake can influence the electrical activity of the heartbeat. Persistent high dose of methadone interacts with common medication among elderly like antidepressants, antipsychotics, antibiotics (macrolides, quinolones, azoles), antiarrhythmics, protease inhibitors and the loop diuretic furosemide are a predictor for prolonged QT interval (20). This abnormal heartbeat leads to sudden cardiac death and torsade's de pointes.

Despite the superior outcome rather than intoxication, taking methadone was found to increase the risk of getting metabolic syndrome compared to other opiate antagonists such as buprenorphine and naltrexone among the elderly. Activation of the mu-opioid receptor increases the sweet taste, thus stimulate a craving for sugary foods, which results in diet-related cardiometabolic disease such as diabetes mellitus (21, 22). A cross-sectional analysis among those who are more than 45 years old at risk of HIV men found that those receiving methadone were over six times more likely to have previously-diagnosed diabetes compared with men who were not receiving methadone (23). Regular intake of methadone was found to cause inappropriate elevation of insulin level (24). Diabetes clients on MMT will have difficulty in maintaining normal sugar levels due to the risk of hypoglycaemia. This adverse effect influences the elderly client to retain in the therapy.

There is significant progress towards scaling up treatment highly active antiretroviral therapy (HAART) among HIV patients in Malaysia (25). Around the world, the HAART coverage of opioid substitutional therapy among persons who inject drugs (PWID) was highest in South Asia. This concurrent treatment of antiretroviral treatment with different pharmacokinetics and toxicity profiles were found to be associated with improved retention and improve viral suppression. Moreover, the integrated medical and addiction treatment does not cause cross drug resistance thus provide advantages for the noncurative nature of HIV treatment (26). Enrolment on these one-stop centres will increase regular contact with health care workers towards better motivation for treatment adherence.

Furthermore, opioid use disorder with multiple comorbidities like HIV was likely to retain in MMT rather than those with no comorbidities due to health-seeking attention to become healthy (27). The client without HIV has less contact with the healthcare workers, thus reduce motivation and consistency in taking daily methadone. The DOT on methadone is also effective to increase access and retention on HAART among HIV positive opiate users by decreasing criminal activity and improved social functioning. Good overall health status will increase the retention in the MMT program (28).

Both treatments also can be a national agenda for Malaysia to strengthen healthcare services among PWID as this combination therapy to reduce viral load even though with concurrent drugs used like cocaine (29). Interestingly, retention of clients in MMT also can be a successful predictor in HAART treatment. Daily methadone ≥ 100mg/day was found to be associated with treatment adherence to HAART, and 20mg/kg increase methadone has 1.06 odd adhere to ARV treatment (30). These synergic outcomes would shed light on the way forward to reduce numerous obstacles and standardisation of protocols for care delivery among client receiving MMT.

Directly observed therapy (DOT) is the standard

method of dispensing methadone. This recommended international guideline aims to increase contact and provide good rapport between clients and health providers. The majority of them (71%) required a daily supervised dose at MMT clinics in this study. However, we found that DOT were the predictors for non-retention among the clients. Our findings are similar to another study that found increase supervision of methadone therapy reduces treatment retention (31). A systematic review to compare the effectiveness of opioid substitution therapy with the supervised method of dispensing with the take-home method was conducted in 2017 (32). They found that there is no significant difference with the treatment outcome, retention status and adverse effects between both methods, which contradicts the finding in the present study. Besides, another study found that the take-home dispensing method improves retention without increasing the risk of illicit drug use among the clients (33).

One of the reasons is prolonged strict supervision to the clients with good performance records in MMT clinics will imply a lack of trust towards them. This approach will make them less motivated to adhere to the treatment and increase the risk of non-retention as supported by one of the previous studies (32). Clients engaging in DOT are also required to come daily at a specific location and limited time per day for treatment. This restriction will affect their working performance and disturb their daily life activities. Stigma was another significant issue among clients with DOT. Daily visits to similar clinics at a particular time every day will expose them to other clients and health care workers from other disciplines. They felt disgrace and devalue with their previous immoral activities. Hence, there will be a barrier for them to visit clinics every day for the therapy (34).

Take-home MMT is a privileged method of dispensing for selective clients. It is a hallmark of the MMT contingency plan to motivate the clients to continuously retained in the program. Generally, they need to have a good track record of attendance, a negative random urine sample for drugs and a stabilised daily maintenance dose of methadone before granted for this contingency management approach for opioid addiction. Most of them are in good health status and lower history of hospital admission (35). Another study conducted in Adelson MMT Clinic in Tel Aviv found that the take-home method improves sleep quality at night, less daily sleepiness and less cognitive impairment compared to DOT (36). All of these findings suggest that take-home MMT improves adherence to MMT in Kelantan, Malaysia.

We addressed that the contingency of the take-home method will introduce selection bias as this method having a low risk of non-retention. We are highlighting that the clients with take-home doses in our populations were selected correctly, practice proper handling of methadone in a responsible manner, and absent of dangerous behaviour related to the risk of diversion and misuse of methadone at home. This finding also provides a comparative evidence to other settings which have to face challenges and obstacle handling with methadone at non-health care setting. The primary concern for take-home dose is the selling of remaining methadone at the black market, which may lead to inadequate intake of methadone and affect treatment adherence (37). The extreme potency of methadone may also cause lethal effects especially to the non-MMT clients (38).

The prevalent of co-morbid opioid and Amphetamines-like stimulant (ATS) use is higher in Kelantan state as compared to the other states in Malaysia. This could be due to its availability and the geographical location of Kelantan to Thailand. Chawarski et al. in 2012 found that 75% of heroin users reported lifetime use of ATS, and a similar trend was seen among MMT patients (39). This co-occurring opioid and ATS dependent was significantly associated with HIV infection and lowered the retention to MMT program.

The present study has a few limitations that need to be addressed. Firstly, as the study was conducted in only one state of Malaysia, it limits the generalizability of the study findings. Secondly, the clients of the study were dominated by Malays ethnicity and male, which comprised of more than 99% of the clients. This could be explained by the demography characteristics of opioid use disorder among Malaysians (40-42). Thirdly, the retrospective study design itself limits the access to the data in which it is based on the information available in the records. Also, it relies on the accuracy of the recorded data.

CONCLUSION

In conclusion, the proportion of non-retention is relatively high compared to other studies throughout the world. Future research required to scale-up evidence-based to increase retention among the elderly, which also facing challenges with progressive physical and mental health-related to aging. Our current screening and selection for take-home dose in our setting are reliable and sustainable in the future. The criteria for take-home dose can be adapted to other settings like in Southern Thailand, which culturally relevant to our population. MMT services should add more services related to co-infection among clients in MMT like Hepatitis C and tuberculosis provide new direction towards scale up health care services among opioid use disorder patients.

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