ORIGINAL ARTICLE

Prediction of Relapse Among Individuals Undergoing Methadone Maintenance Therapy in Johor Bahru Health District

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ABSTRACT

Introduction: Increase in the number of opioids seized in the recent year may indicate increased opioid use in Malaysia. In counteracting opioid abuse, Methadone Maintenance Therapy (MMT) was introduced in Malaysia but relapse following MMT has become an important issue. This study aimed to determine the prevalence and patient factors that served as predictors of opioid relapse among MMT patients. **Method:** A cross-sectional study involving 159 MMT patients who have reached dose stabilization (eight weeks at a constant dose of methadone) was conducted in Johor Bahru Health District. The dependent variable was opioid relapse, while the independent variables include socio-demographic characteristics, MMT history, crime history, cognitive and interpersonal factors, and social-environment influence. Face-to-face interviews using structured questionnaires and secondary data collection using data collection sheets were done. Multiple logistic regression was used to determine the predictors. Significant level set at alpha less than 5%. **Result:** The response rate was 86.9% with majority of them were Malay, male, and Muslim. The prevalence of opioid relapse was 11.9%. Those who were non-polydrug users (AOR=3.701, 95%CI=1.182, 11.587, p=0.025), classified as having moderate (AOR=5.869, 95%CI=1.524, 22.595, p=0.010) and high (AOR=5.952, 95%CI=1.000, 35.445, p=0.050) relapse risk response after given hypothetical situation whether respondent been offered drug or not, were more likely to have relapsed. Respondents with higher cognitive and behavioral problem-solving response scores were less likely to have relapsed (AOR=0.949, 95%CI=0.909, 0.991, p=0.008). **Conclusion:** About 1 in 5 MMT clients had relapsed after they reach dose stabilization. The predictors of opioid relapse were non-polydrug users, having moderate to high relapse risk, and cognitive and behavioral problem-solving responses.
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INTRODUCTION

Opioid use disorder continues to be a significant public health problem around the world. Opioid addiction is a chronic relapsing condition with multiple complex consequences (1). Opioids can be divided into natural opioids (morphine, codeine, and thebaine), semi-synthetic opioids (heroin, hydromorphone, hydrocodone, and oxycodone), and fully synthetic opioids (fentanyl, pethidine, levorphanol, methadone, tramadol, and dextropropoxyphene) (2).In Malaysia, it is estimated that the prevalence of opioid demand for 2018was the highest compared to other substances (3). According to United Nations Office on Drugs and Crime (UNODC), there was an increasing trend of annual opioids seized in Malaysia from 603kg in 2017 to 1441kg in 2018 which may indicate an increase in opioid use among Malaysians (3). In addition, available data in 2016 reported an estimated 400 000 to 800 000 drug users in Malaysia, with 234 000 of them being heroin abusers (4). The increased use of opioids in prescription and illicit drug markets also inflicts an increase in opioid overdose as reported by WHO in several countries (2). Acknowledging the problem of opioid overdose, a study done in Malaysia among 460 opioid users in 2010 revealed that there was a large, previously undocumented burden of non-fatal overdose among opioid user in Malaysia and suggested that this issue need to be highlighted and require further intervention to reduce the risk of opioid overdose and prevent fatal overdose (5). Relapse into taking opioids at the previous usual amount after detoxification was one of the risk factors for opioid overdose due to the lost tolerance effect (2).

Methadone is one type of opioid that has been used legally as medication-assisted treatment for the purpose

of decreasing illicit opioid use, overcoming opioid addiction, and decreasing associated risk behavior. In detoxification therapy using methadone, the initial period of methadone dose stabilization is the most vulnerable moment to relapse due to the effect of low to moderate grade of withdrawal symptoms and associated stress during dose titration (6). Early dose stabilization is a period of eight weeks at a constant dose of methadone (6).In this study, the patient is considered to have reached a stabilization dose after eight weeks of a constant dose of methadone. Relapse is termed as the worsening of a clinical condition that had previously improved. In opioid rehabilitation programs, opioid relapse is the act of taking illicit opioids again after a period of abstinence due to various interventions (7). Lapse and relapse are used interchangeably. Lapse is single unplanned use of drugs or alcohol while relapse is thought to happen after the recovery plan achieved its goal (8,9). Both lapse and relapse can be dangerous as reexposure to drugs or alcohol might cause overdose as their bodies can no longer handle the high dose of the drugs (8,9). This study defines opioid relapse as the patients returning to even a single usage of opioids (heroin or morphine) after methadone dose stabilization (6,7).

Methadone Maintenance Therapy (MMT) was introduced as part of the National Harm Reduction Program in Malaysia in 2005 and has shown a positive impact in decreasing the frequency of opioid use, mortality, the risk of blood borne infection transmission, as well as elevating employment prospects and alleviate crime (10).MMT in Malaysia has been expanded to government and private facilities and it consists of the induction phase, titration phase, and maintenance phase (11). During the induction phase, the starting dose of methadone ranges from 20mg to 30mg and can be titrated up at least after three days until the patient reach dose stabilization (11). In general, the maintenance dose ranging from 60mg to 80mg depends on patients' response; however, no maximum dose has been set (9). Throughout the treatment, urinalysis is done randomly to ensure patients are not taking illicit substances, and personal or group counseling is given to provide good support for the patient throughout this rehabilitation journey (11). The government has built a good rapport with various agencies to work together in impeding drug use; parallel to the mission of enhancing Malaysia and making Malaysian society free of drug threats as outlined in the national Drug Policy 2017 (12). However, several studies were done in Malaysia reported the concurrent use of opioid among MMT patients still happened and further action need to be addressed to make sure this program reach optimum outcome (7,13). In fact, concurrent use of illicit opioids with methadone triggers drug-drug interaction and becomes the risk factor in increasing the incidence of abnormal cardiac conductivity, overdose, and death (14,15,16). Since those who entered the MMT program aim to improve their life compared with during using period and improve other aspects of their life in terms of social functioning and employment status, abstaining from illicit opioid use during this detoxification program is very important. Furthermore, this relapse issue has already been included as the fourth objective of MMT program in Malaysia (11). Many factors are contributing to relapse, including clinical factors, patient factors, and program factors (13,17,18).

Statistics provided by National Anti-Drug Agency (NADA) Malaysia shows that among 24972 cases registered in 2018, 30.1% was relapsed case. A study done in Malaysia found that among 225 patients, 46.2% of them reverted to misuse after taking opioid substitution therapy from private clinics (19). A recent study conducted at a government hospital methadone center found that 36.5% of patients relapse 6 months after joining the MMT program (9). Globally, relapse among those who underwent detoxification programs ranges from 20% to 80% (1,13,16,20,21).

There are many clinical and patient factors that contribute to relapse. A few socio-demographic characteristics have been reported as being associated with relapse including patients' age (16,22,23), education level (9,22,24) employment status (17,22,24,25) and household income (17,24,26). A few studies reported shorter durations of methadone enrollment (15,27,28), poor methadone adherence (24,29), and longer duration of heroin use (30) as having a higher risk of relapse. History of multiple illicit drugs usage (22,28) and history of intravenous drug use (IVDU) have also been reported as factors associated with opioid relapse (13,21,31). Another factor associated with opioid relapse is having a history of imprisonment (1,28). Those with a family history of substance abuse show a higher risk of relapse. Interpersonal factors such as unstable mood state, psychological stress, lack of willpower, frustration, poor anger management, boredom, and lack of assertiveness were reported as the common risk factors of relapse (1,13). Unhealthy mental status such as depression, anxiety are also risk factors for increasing drug craving for opioids and relapse (1,13). Relapse cases are also affected by social environment influence such as family conflict, poor family support, and peer influence (13,17). Despite those clinical and patient factors, there were a few program factors reported had contributed to relapse which was urinalysis procedure, methadone take-home privileges, and methadone clinic operation hours (18).

Relapse can be a reason for failure of the methadone program and can impact the economic sector due to possible increases in crime and medical care costs (9). Despite reducing opioid addiction, the MMT program also aims towards lowering the risk of opioid relapse during treatment, improving treatment outcomes, as well as to reduce the risk of adverse side effects due to concurrent use of illicit opioids and methadone. The objective of this study was to determine the prevalence of opioid

relapse and evaluate key clinical and sociodemographic characteristics that serve as predictors of opioid relapse among MMT patients. Variables assessed were socio-demographic characteristics, MMT history, crime history, cognitive and interpersonal factors, and social-environment influence. The data gathered in this study could be used as baseline information to plan an intervention program to reduce relapse among patients taking methadone.

MATERIALS AND METHODS

Study design study population

This was a cross-sectional study among MMT patients who have reached dose stabilization (eight weeks of a constant dose of methadone). This study was conducted in Johor Bahru. According to NADA statistics in 2018, Johor was the second-highest of high-risk regions of drug abuse in Malaysia, and one of a region in Johor Bahru was classified as the red zone region (12). Thus, Johor Bahru Health District was selected as the study location in this study. There were 13 MMT centers in Johor Bahru Health District. The total number of active patients in all 13 centers was 316. Patients who already completed 8 weeks stabilization period were included in this study while those who were prescribed opioid medication while on MMT were excluded. The sample size was calculated using two proportion formula; assuming 47.2 % of patients with doses of methadone more than 80mg have relapsed and 33.6% of patients who are unemployed have relapsed (16), the sample size calculated was 176. Considering 20% attrition, the final sample size estimated was 211.

Data collection

Data collection was done from September 2020 to October 2020. Prior to data collection, all respondents signed the informed consent form. To collect the data for this study, a face-to-face interview based on structured questionnaires was applied with questions about socio-demographic characteristics, cognitive and interpersonal factors, social-environment influence, and methadone adherence. Data collection sheet was filled based on the patient's MMT files to collect urinalysis results, MMT history, and crime history.

Study instrument

This study used a questionnaire that was filled by researchers during face-to-face interviews with respondents. The dependent variable was opioid relapse among respondents. Proof of opioid relapse has been obtained through the result of urinalysis that was recorded in the MMT file using data collection sheet. Those who have at least one positive urinalysis for opioid after reaching dose stabilization were classified as 'yes' while those who have negative urinalysis for opioid were classified as 'no'.

The independent variables were socio-demographic characteristics (age, race, gender, religion, marital status, education level, employment status, monthly household income), MMT history (age began to misuse the drug, duration of misusing the drug, type of drug taken, polydrug user history of IVDU, family history of substance abuse, duration of MMT, current methadone dose, duration of current methadone dose, methadone adherence), crime history (history of imprisonment, history of rehabilitation), cognitive and interpersonal factor (relapse coping response, cognitive and behavioral problem-solving response, self-critical thinking response, abstinence focused coping response) and social-environment influence (social functioning, friends support, family support).

The validity and reliability of most of the questionnaires had been validated in the previous research. However, the entire questionnaire was pretested for this study. A pilot study was done among 20 patients from KK Pekan Nanas MMT center in Pontian District who have the same criteria as respondents in August 2020 to assess the reliability of the questionnaire.

Family history was adapted from Opioid Treatment Index (11). Methadone adherence status consists of 4items and was adapted from Maryam Khazaee et al. (2017) (32) with the test-retest internal consistency of 1.00. Those items were worded as follows: miss dose in one week; got dose adjustment due to miss dose; complete adherence for the last 30 days; and reason of non-adherence. The highest score was 3 while the lowest score was 0. Patients were classified as having poor adherence if the score was 0-1 and good adherence if the score was 2-3.

Cognitive and interpersonal factors were assessed using relapse coping questionnaire. The relapse coping questionnaire consists of two domains and was adopted from Adolescent Relapse Coping Questionnaire (ARCQ) (33), a self-report measure to evaluate substance abuser coping skills. The questionnaire introduces a hypothetical situation "You arrive at a friend's house in the evening. There are a few other people; everyone is sitting around talking, drinking, and using drugs. When you sit down, you are offered drugs and something to drink." The questionnaire consisted of two domains: The first domain consists of 6 items with test-retest internal value of 0.988 used to assess appraisal and how respondents respond to this hypothetical situation. This domain assesses appraisal and how he/she responds to this hypothetical situation by 10 points scale in six items. Question 1 assesses whether respondents had been in this situation or not which consists of 4 Likert points named as; never (1), once or twice (2), three to five times (3), and more than 5 times (4). Question 2 to 6 were used to illustrate respondents' responses to this hypothetical situation and were classified into 3 groups. For scores 1 to 3, respondents are classified as having low relapse risk response (recoded as 1); for scores 4 to 7, respondents

are classified as having moderate relapse risk response (recoded as 2); and for scores 8 to 10, respondents are classified as having high relapse risk response (recoded as 3) (34). The second domain evaluates the relapse coping strategies in seven points with 28 items with the test-retest internal consistency of 0.926 used to evaluate the relapse coping strategies. This domain consists of cognitive and behavioral problem-solving response (12 items), self-critical thinking response (7 items) and abstinence focused coping response (9 items) which are answered on 7 points Likert scale ranging from rated between "1-definitely would not do or think" to "7-definitely would do or think".

Respondent's social functioning contains a few questions concerning the social aspect of the patient's life adapted from the Opioid Treatment Index (11) with the test-retest internal consistency of 0.943. It consists of 11 questions ranked with 5 Likert points from 0 to 4.

Friends and family support were subdomains of social environment influence. Perceived Social Support from Friends (PSS-Fr) was used to access friend support. Friends were defined as anyone who did not fit into the categorized of sex partner, neighbor, and professional contact (35). Friends can be anyone from the same circle of old friends who use drugs or a new circle of friends. This questionnaire consists of 20 items and is adapted from Perceived Social Support Questionaire (35) with the test-retest internal consistency of 0.926. PSS-Fr consists of 2 sections. Section 1 (14 items) is rated using5 Likert scales; never (0), rarely (1), sometimes (2), often (3), and very often (4). Section 2 (6 items) reversely rated into 5 Likert scales; very often (0), often (1), sometimes (2), rarely (3), and never (4).

Perceived Social Support from Family (PSS-Fa) relates to family support. This questionnaire consists of 20 items and is adapted from Perceived Social Support Questionaire (35) with the test-retest internal consistency of 0.920. PSS-Fa consists of 2 sections. Section 1 (15 items) is rated using5 Likert scales; never (0), rarely (1), sometimes (2), often (3), and very often (4). Section 2 (5 items) reversely rated into 5 Likert scales; very often (0), often (1), sometimes (2), rarely (3), and never (4).

A data collection sheet was used in this study to obtain patients MMT history (type of drug abuse, age began to misuse drugs, duration of misusing drugs, duration of misusing heroin, duration of MMT, current methadone dose, duration of current methadone dose, polydrug user, IVDU); urinalysis result (opioid, cannabis, amphetamine, methamphetamine and benzodiazepine); and crime history (history of imprisonment and history of rehabilitation). The data collection sheet was filled based on patients' MMT records.

Statistical analysis

Data from the subjects were analyzed using Statistical Package for Social Science (SPSS) version 25 software. All variables have been analyzed using simple logistic regression. The dependent variable was the incidence of relapse among MMT patients which has been classified into yes and no. The association between each independent variable with dependent variable was analyzed. Those with p-values less than 0.05 indicating a significant association with the dependent variable were included in the final model of multiple logistic regression. The model was built to determine the predictors of opioid relapse. The results are presented as odds ratio (OR) with 95% confidence intervals for each variable investigated that had statistical significancep<0.05.

Ethical clearance

Prior to conducting the study, ethical approval was obtained from Medical Research Ethics Committee (NMRR-20-168-52511 (IIR)), Ministry of Health Malaysia. Permission letter to use facilities was sought from Health District Johor Bahru. Respondents were ensured that their anonymity was maintained throughout the study to ensure that this research was carried out ethically and that respondents are not at risk. They were informed that they can withdraw from the study at any time.

RESULTS

Distribution of respondents

Out of 316 active patients recorded, only 183 patients reached dose stabilization. The 183 patients who reach dose stabilization were recruited for this study. Of the 183 patients eligible for inclusion in this study, 159 (86.9%) consented and agreed to participate. Of these respondents, 98.1% were male, Malay (83.6%), and Muslim (84.9%). The prevalence of opioid relapse among methadone patients was 11.9%. Table I shows the socio-demographic characteristics of the respondents.

The median ± IQR for the age when respondents began to misuse drugs and durations of misusing drugs was 22 years ± 7 and 16 years ± 14 respectively. All respondents have history of heroin abuse. The proportion of respondents with history of polydrug use was 73.6%, history of IVDU was 73.6%, and family history of substance abuse was 22%. The median ± IQR for durations of MMT, current methadone dose, and duration of current methadone dose were 7 years ± 5, 55 mg ± 45, and 16 months ± 18 respectively.

Methadone adherence consists of 3 questions. The highest score was 3 while the lowest score was 0. Patients were classified as having poor adherence if the score was 0-1 and good adherence if the score was 2-3. Majority of respondents have good methadone adherence (91.8%). The highest reason for non-adherence was busy with working schedules (11.9%) followed by forgetfulness (2.5%), having illnesses (1.3%), and long-distance from home (0.6%).

Table I: Socio-demographic characteristics of the respondents (N=159)

Characteristics of sample	Mean ± SD	f	%
Age	48.13 ± 9.468		
Race			
Malay		133	83.6
Non-Malay		26	16.4
Gender			
Male		156	98.1
Female		3	1.9
Religion			
Muslim		135	84.9
Non-Muslim		24	15.1
Marital Status			
Single		54	34.0
Married		75	47.2
Divorced or widowed		30	18.8
Education level			
No formal education		4	2.5
Primary		29	18.2
Secondary		111	69.8
Tertiary		15	9.4
Employment			
Unemployed		53	33.4
Temporarily Employed		12	7.5
Permanently Employed		94	59.1
Household Income			
RM 0 – RM 500		47	29.6
RM 501 – RM 1500		56	35.2
RM 1501 – RM 2500		45	28.3
RM 2501 – RM 3500		8	5.0
>RM 3501		3	1.9

Respondents' crime histories consist of history of imprisonment and history of rehabilitation. Data was collected using data collection sheets. Out of 159 respondents, 55.3% have a history of imprisonment while 41.5% have a history of rehabilitation.

More than half (63.5%) of respondents claim to have never been offered drugs or alcohol while 23.3% of them had been offered once to twice, 10.1% three to five times and 3.1% had been in this situation more than five times.

The highest relapse risk response was 15 and the lowest was 5. The prevalence of respondents with low relapse risk, moderate relapse risk, and high relapse risk were 64.8%, 24.5%, and 10.7% respectively. Table II illustrates the distribution of cognitive and behavioral problem-solving responses, self-critical thinking responses, and abstinence-focused coping responses.

Table II: Median of cognitive and behavioral problem solving response, self-critical thinking response and abstinence focused coping response (N=159)

Characteristics of sample	Lowest score	Highest score	Median ± IQR
Cognitive and behavioural problem solving score	18	139	66.00 ± 9.00
Self-critical score	7	47	25.00 ± 9.00
Abstinence focused coping score	12	63	42.00 ±12.00

Respondent's social functioning highest score was 25 and the lowest score was 0. The median score ± IQR was 9.00 ± 11.00. PSS-Fr assessed friend support. The highest score was 80 and the lowest score was 6. The median score ± IQR was 28.00 ± 35.00. PSS-Fa assessed family support. The highest score was 80 and the lowest score was 0. The median score ± IQR was 65.00 ± 31.00.

Predictors of Opioid Relapse

Table III shows the first model of predictors of opioid relapse. Polydrug users (p= 0.040), having a family history of substance abuse (p= 0.030), been offered drug before (p= 0.005), relapse coping response classification (p <0.001), cognitive and behavioral problem solving response (p <0.001), abstinence focused coping response (p <0.001), and perceived social support-family (p= 0.005) has p-value of below 0.05. Thus, those variables proceeded to the final model of predictors of opioid relapse.

The initial model with (Block 0) with only the constant was able to correctly classify cases with 88.0% accuracy, however, the final model with significant predictors variable included increased this accuracy to 90.5%. The Omnibus test of the model coefficient was statistically significant (X2 (6)= 30.819, p <0.001). The model was able to explain between 17.7% (Cox and Snell R square) and 46.5% (Nagelkerke R square) of variability in opioid relapse. The result for the Hosmer and Lemeshow test (X2 (6)= 4.346, p= 0.825) shows that model has a good fit (good fit: p-value more than 0.05).

Table IV demonstrates the final model of predictors of opioid relapse. Respondents with no polydrug user history (only took heroin) were reported to be more likely to have opioids relapse as compared to polydrug users (AOR= 3.701, 95% CI= 1.182, 11.587, p= 0.025). Respondents who were classified as having moderate relapse risk (AOR= 5.869, 95% CI= 1.524, 22.595, p= 0.010) and high relapse risk (AOR= 5.952, 95% CI= 1.000, 35.445, p= 0.050) have about 6 times higher risk of having opioid relapse as compared to respondents who are classified as having low relapse risk. Respondents with higher cognitive and behavioral problem-solving response score are less likely to have opioids relapse (AOR= 0.949, 95% CI= 0.909, 0.991, p= 0.008).

DISCUSSION

This study explored the prevalence and predictors of opioid relapse among MMT patients in Johor Bahru Health District. Majority of them were male, Malay, and Muslim.

The findings of this study reported that about one in five

Table III: Simple logistic regression showing the first model of predictors of opioid relapse (N=159)

Variables	B	SE	Wald	AOR	95% Confidence Interval		p-value
					Upper	Lower	
Age	0.009	0.026	0.127	1.009	0.960	1.061	0.721
Race							
Malay	-0.705	0.572	1.518	0.494	0.161	1.517	0.218
Non-Malay	Ref						
Gender							
Male	19.227	23205. 445	0.000	22404 4012.0	0.000	.	0.999
Female	Ref						
Religion							
Muslim	-0.822	0.576	2.032	0.440	0.142	1.631	0.154
Non-Muslim	Ref						
Marital Status							
Single	Ref						0.137
Married	-0.920	0.601	2.193	0.411	0.127	1.333	0.139
Divorced or widowed	0.363	0.596	0.371	1.438	0.447	4.622	0.543
Education level							
No formal education	Ref						0.935
Primary	-0.734	1.274	0.332	0.480	0.040	5.831	0.565
Secondary	-1.012	1.194	0.717	0.364	0.035	3.779	0.364
Tertiary	-0.773	1.382	0.313	0.462	0.031	6.929	0.576
Employment status							
Unemployed	Ref						0.454
Temporarily Employed	-0.045	0.857	0.003	0.959	0.178	5.125	0.958
Permanently Employed	-0.811	0.521	2.427	0.444	0.160	1.233	0.444
Others	-19.639	40192. 970	0.000	0.000	0.000	.	1.000
Household Income							
RM 0 – RM 500	Ref						0.900
RM 501 – RM 1500	-0.536	0.581	0.852	0.585	0.187	1.826	0.356
RM 1501 – RM 2500	-0.495	0.613	0.653	0.609	0.183	2.026	0.419
RM 2501 – RM 3500	-19.619	14210. 361	0.000	0.000	0.000	.	0.999
> RM 3501	-19.619	23205. 422	0.000	0.000	0.000	.	0.999
Age began to misuse drug (year)	0.010	0.040	0.056	1.010	0.933	1.093	0.813
Duration of misusing drug (year)	-0.010	0.026	0.158	0.990	0.941	1.041	0.692
Duration of misusing heroin (year)	0.000	0.026	0.000	1.000	0.949	1.052	0.986
Duration of MMT (year)	0.080	0.046	2.979	1.083	0.989	1.187	0.084
Current methadone dose (mg)	-0.002	0.005	0.101	0.998	0.988	1.009	0.751
Duration of current methadone dose (month)	0.011	0.008	1.951	1.011	0.996	1.027	0.163
Polydrug user							
Yes	Ref						
No	1.022	0.498	4.208	2.780	1.047	7.384	0.040 *
History of IVDU							
Yes	1.048	0.775	1.829	2.851	0.625	13.017	0.176
No	Ref						
Family history of substance abuse							
Yes	1.113	0.512	4.733	3.044	1.117	8.297	0.030 *
No	Ref						
Methadone adherence							
Good	Ref						
Poor	-0.322	0.811	0.158	0.725	0.148	3.552	0.691
History of imprisonment							
Yes	1.050	0.793	1.752	2.857	0.604	13.519	0.186
No	Ref						
History of rehabilitation							
Yes	-0.241	0.587	0.169	0.786	0.249	5.482	0.681
No	Ref						
Relapse coping response (been offered with drug)							
Never	Ref						0.005 *
Once or twice	0.343	0.645	0.283	1.409	0.398	4.989	0.595
Three to five times	2.202	0.624	12.440	9.042	2.660	30.735	<0.001 *
More than five times	-18.750	17974. 843	0.000	0.000	0.000	.	0.999
Relapse coping response classification							
Low relapse risk	Ref						< 0.001 *
Moderate relapse risk	1.854	0.646	8.238	6.387	1.801	22.657	0.004 *
High relapse risk	2.852	0.709	16.175	17.325	4.315	69.557	< 0.001 *
Cognitive and behavioral problem solving response score	-0.076	0.018	17.552	0.927	0.895	0.961	< 0.001 *
Self-critical thinking response score	0.039	0.029	1.750	1.040	0.981	1.102	0.186
Abstinence focused coping response score	-0.091	0.025	13.872	0.913	0.870	0.958	< 0.001 *
Social functioning score	0.049	0.034	2.068	1.051	0.982	1.124	0.150
Perceived social support-friend score	-0.028	0.015	3.602	0.973	0.945	1.001	0.058
Perceived social support- family score	-0.028	0.010	8.015	0.972	0.954	0.991	0.005

Note: [a] Simple Logistic Regression, *significant at p-value <0.05

Table IV: Multiple logistic regression showing final model of predictors of opioid relapse (N=159)

Variables	B	SE	Wald	AOR	95% Confidence Interval		p-value
					Upper	Lower	
Poly drug user							
Yes	Ref						
No	1.309	0.582	5.050	3.701	1.182	11.587	0.025 *
Relapse risk							
Low relapse risk	Ref						0.029 *
Moderate relapse risk	1.770	0.688	6.619	5.869	1.524	22.595	0.010 *
High relapse risk	1.784	0.910	3.840	5.952	1.000	35.445	0.050 *
Cognitive and behavioural problem solving response	-0.052	0.022	5.529	0.949	0.909	0.991	0.019 *

Note: *significant at p value <0.05

respondents who reach methadone dose stabilization have opioid relapse. This prevalence in this study was quite low as compared to a study done among 225 methadone patients in private settings in Malaysia in 2007 (19). This variation in findings was because, during those periods, detoxification programs in private settings were less regulated and monitored compared to government setting which was highly controlled and regulated with a collaborative effort between MOH, NADA, and the Anti-Narcotic division of the Royal Malaysian Police Force, thus detoxification program showed a better outcome in government settings (19). However, a study done in China has quite similar characteristics with this study reporting quite similar prevalence (36). The most reasonable explanation was because this study focuses on opioid relapse and only selects those who reach dose stabilization. Dose stabilization is a period of reaching the maintenance phase after undergoing dose titration (11). Patients who reach dose stabilization were less vulnerable to relapse as the effect of low to moderate grade opioid withdrawal that usually happens during dose titration was less (6).

Several other studies suggested that employment status (17,22,24,21) and household income (17,24,26) were among the best indicators for relapse among methadone users. However, this study reported employment status and household income were not associated with opioid relapse. These findings were contrary to our expectations and do not support the notion that unstable socioeconomic status was a risk factor of opioid relapse. However, the findings that showed unemployed respondents and those with lower household income have the highest proportion of relapse was parallel with other study explanations (17,22,24,25,26). Thus it can be explained that there might be a correlation between employment status and household income with opioid relapse. This study was conducted during Covid 19 pandemic. Department of Statistic Malaysia (DOSM) reported void 19 pandemic causing decreases in income for B40 and M40 households (37). Some of respondents' employment status and household income were also affected. The difference in employment status and household income distribution between before pandemic and during pandemic might be the reason for this non-significant finding.

Numerous studies reported friends support as having a strong relationship with relapse (13,38). Contrary to those findings, this study reported no significant association between friends' support with opioid relapse. Good friends and social support were found to be protective factors against having relapses and one of the best indicators for abstinence from treatment. The significant relationship between friend support with opioid relapse can be explored further as the p-value is just borderline between significant and not. A bigger sample size might help in establishing more concrete findings.

In this study, the first model for predictors of opioid relapse showed that polydrug users, having a family history of substance abuse, been offered drugs before, relapse coping response classification, cognitive and behavioral problem-solving response, abstinence focused coping response, and perceived social support-family have a significant association with opioid relapse. Those variables then proceeded to the final model of predictors of opioid relapse. The final model demonstrates that non-polydrug users, those who are classified as having moderate and high relapse risk response after given hypothetical situation whether respondent been offered drug or not, were more likely to have relapses.

According to the analysis via multiple logistic regression, respondents with no polydrug use history (only took heroin) were more likely to have an opioid relapse as compared to polydrug users. The correlation was supported by a study done in Malaysia (25). A study done among patients who underwent an opioid detoxification program in Bangladesh reported those with history of heroin use have more than 3 times higher risk of relapse (39). A cohort study done in Amsterdam reported those with history of intense use of heroin prior to the detoxification program have a significant association with opioid relapse (21). However; studies done in Rwanda and the United States reported a reversed relationship where those with polydrug use were more likely to have relapse (13,28). The one possible explanation was high and repeated heroin use alters the physical structure and physiology of the brain, creating long-term imbalances in neuronal and hormonal systems that are not easily reversed (40). Other drugs cause an elevation in dopamine level to some extent, providing rewarding effect to patients (40). Heroin produces a high degree of tolerance and physical dependence thus resulting in a

high risk of relapse (40).

Respondents were given a questionnaire that introduces a hypothetical situation "You arrive at a friend's house in the evening. There are a few other people; everyone is sitting around talking, drinking, and using drugs. When you sit down, you are offered drugs and something to drink." Data investigating appraisal and how respondents respond to this hypothetical situation reveals that those who were classified as having moderate and high relapse risk response after being given this hypothetical situation, have a 6 times higher risk of having opioid relapse. The result is in line with studies done United States, Malaysia, and China that confirm that substance relapse is likely to be contingent on the level of relapse risk among patients (25,30,41).

In this study, respondents with higher cognitive and behavioral problem-solving response scores were less likely to have an opioid relapse. Similarly, a few other studies exploring quite a similar variable as cognitive and behavioral problem-solving response showed significant association with relapse (42,43). There is evidence that cognitive and behavioral problem-solving response helps individuals to recognize difficult situations, avoid them at the right time and apply effective coping mechanisms (42,43). Many instruments have been used to monitor relapse coping responses. Generally good cognitive and interpersonal control are good predictors in avoiding relapse (23,25,44,45).

This study has some limitations. First, owing to the cross-sectional nature of data, the causal relationship between relapse and exposure cannot be determined because both are examined at the same time. Besides that, interview bias can occur due to human error as the interviewer judges a candidate not only on their skills and competencies but on the interviewer's expectation and opinion hence making the interview less objective. Another limitation that needs to be highlighted is there is no effort made to verify whether the patient's stable dose is actually the optimum dose to overcome the craving. Some patients persist at low doses sufficient to get rid of withdrawal symptoms only. Many patients hide the truth as just want to be at low dose just sufficient to control withdrawal symptoms but not to alleviate craving. Some still would like to experience the joy of taking heroin and prefer to be at methadone dose that 'not fully blocked opiate receptor '. Patients with lower doses were more prone to take opioid during detoxification treatment. Despite these limitations, this study provides clear evidence of predictors and clinical and patient factors associated with opioid relapse among methadone patients.

CONCLUSION

This study shows the prevalence of opioid relapse among MMT patients was 11.9%. History of polydrug use, moderate to high relapse risk, and cognitive and behavioral problem-solving response were found to be predictors for opioid relapse. In this research, non-polydrug users and having moderate to high relapse risk have a higher risk of having opioid relapse. Respondents with higher cognitive and behavioral problem-solving response scores were less likely to have opioid relapses. As interpersonal factors pose major findings in this study, few remedial actions focusing on interpersonal factors can be done. The predictors obtained from this study could provide important input for future studies in constructing new interventions or strengthening current interventions such as psychosocial intervention to advocate relapse-free outcomes among methadone patients, parallel with the aim targeted by the Ministry of Health for MMT in Malaysia.

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