PREVALENCE AND ASSOCIATED FACTORS OF OPIOID RELAPSE AMONG METHADONE MAINTENANCE THERAPY PATIENTS IN JOHOR BAHRU GOVERNMENT HEALTH CLINICS, MALAYSIA

By

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Thesis Submitted to the School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the degree of Master of Science

June 2021

FPSK (m) 2021 46

Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for the degree of Master of Science

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The increasing number of opioid user and opioid overdose worldwide was quite concerning. The increment trend of annual opioid seizures reported from 2017 with 603kg to 1441kg in 2018 reflecting increase opioid use among Malaysian. National Anti-Drug Agency (NADA) reported an increasing pattern of relapse cases from 23.9% in 2015 to 30.8% of cases in 2018. As opioid relapse after detoxification was reported as one of the risk factors for opioid overdose, exploring factor contributed to relapse was crucial in reducing relapse related problem. Moreover, government have spent quite a lot for drug addiction and methadone program in Malaysia. Failing in detoxification program may impose a financial burden on the government for dealing with the drug misuse problem as well as reducing the objective of methadone treatment. This study aims to determine the prevalence of opioid relapse and the relationship of various contributing factors with opioid relapse among patients registered under the Methadone Maintenance Therapy (MMT) program in Johor Bahru Health District.

A cross-sectional study was performed among patients who reached dose stabilization (eight weeks at a constant dose of methadone), comparing between relapse and non-relapse group, involving 159 patients registered under Methadone Maintenance Therapy (MMT) Program in Health District Johor Bahru. The contributing factors studied were socio-demographic characteristics, MMT history, comorbidity, crime history, cognitive and interpersonal factors, and social-environment influence. Face to face interview based on a structured questionnaire was done. Multiple logistic regression was used to determine the predictors. A significant level was set at alpha less than 5%.

The response rate was 86.9% with the majority of them were Malay, male, and Muslim. The prevalence of opioid relapse was 11.9%. Respondents with no polydrug user history (only took heroin) were more likely to have an opioid relapse as compared to polydrug users (AOR= 3.701, 95% CI= 1.182, 11.587, p=0.025). With regards to relapse risk assessment, respondents who 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) were about 6 times have a higher risk of having opioid relapse as compared to respondents who classified as having low relapse risk. Respondents with higher cognitive and behavioral problemsolving response scores were less likely to have an opioid relapse (AOR= 0.949, 95% CI=0.909, 0.991, p=0.008).

This study revealed that one in a tenth of MMT patients reported having an opioid relapse. Non-polydrug users and higher relapse risk were positively associated with opioid relapse while patients with higher cognitive and behavioral problem solving response scores were negatively associated with opioid relapse. Efforts should be made by the policy makers and program planers to advocate relapse-free among MMT patients, taking into consideration the significant predictors. This could help spearhead the program to be, parallel with the main aim targeted by the Ministry of Health for Methadone Maintenance Therapy in Malaysia.

Keywords: relapse, opioid, methadone, methadone maintenance therapy, dose stabilization

Abstrak tesis yang dikemukakan kepada Senat Universiti Putra Malaysia sebagai memenuhi keperluan untuk ijazah Sarjana Sains

MENGENALPASTI PENENTUAN RELAPS OPIOD DI KALANGAN PESAKIT YANG BERDAFTAR DI BAWAH RAWATAN TERAPI GANTIAN METHADONE DI PEJABAT KESIHATAN DAERAH JOHOR BAHRU, MALAYSIA DAN FAKTOR PENYEBABNYA

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Peningkatan bilangan pengguna opioid dan overdos opioid di seluruh dunia cukup membimbangkan. Trend peningkatan penyitaan opioid tahunan yang dilaporkan dari 2017 dengan 603kg hingga 1441kg pada tahun 2018 menunjukkan peningkatan penggunaan opioid di Malaysia. Agensi Anti Dadah Kebangsaan (AADK) melaporkan peningkatan pola kes relaps dari 23.9% pada tahun 2015 kepada 30.8% kes pada tahun 2018. Memandangkan relaps opioid merupakan satu faktor risiko overdos opioid, mengenalpasti faktor penyumbang relaps sangat penting dalam mengurangkan masalah berkaitan relaps. Lebih-lebih lagi, kerajaan telah membelanjakan banyak perbelanjaan untuk program penagihan dadah dan metadon di Malaysia. Kegagalan dalam program detoksifikasi dapat membebankan pemerintah untuk menangani masalah penyalahgunaan dadah serta mengurangkan objektif rawatan metadon. Kajian ini bertujuan untuk menentukan prevalen relaps opioid dan hubungan pelbagai faktor penyumbang dengan relapse opioid di kalangan pesakit yang berdaftar di bawah program RawatanTerapi Gantian Methadone (MMT) di Pejabat Kesihatan Daerah Johor Bahru.

Satu kajian keratan rentas dilakukan di kalangan pesakmembuat perbandingan antara kumpulan relaps dan bukan relaps, yang melibatkan 159 pesakit yang didaftarkan di bawah MMT Pejabat Kesihatan Daerah Johor Bahru. Faktor penyumbang yang dikaji adalah ciri sosio-demografi, sejarah MMT, komorbiditi, sejarah jenayah, faktor kognitif dan interpersonal dan pengaruh persekitaran sosial. Temu ramah bersemuka berdasarkan soal selidik berstruktur telah dilakukan. Regresi logistik berganda digunakan untuk menentukan peramal relaps. Tahap signifikan ditetapkan adalah alpha kurang dari 5%.

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Kadar sambutan pesakit adalah 86.9% dengan majoriti daripadanya adalah Melayu, lelaki, dan Muslim. Prevalen relaps opioid adalah 11.9%. Responden yang tidak mempunyai sejarah penggunaan lebih dari satu jenis dadah (hanya mengambil heroin) lebih cenderung mengalami relaps opioid berbanding pengguna mengambil lebih dari satu jenis dadah (AOR=3.701, 95% CI= 1.182, 11.587, p= 0.025). Bagi penilaian risiko relaps, responden yang diklasifikasikan mempunyai risiko relaps sederhana (AOR=5.869, 95% CI=1.524, 22.595, p= 0.010) dan risiko relaps tinggi (AOR= 5.952, 95% CI=1.000, 35.445, p= 0,050) mempunyai 6 kali lebih tinggi risiko mengalami relaps opioid berbanding dengan responden yang diklasifikasikan mempunyai risiko relaps rendah. Responden dengan skor tindak balas penyelesaian masalah kognitif dan tingkah laku yang lebih tinggi cenderung tidak mengalami relaps opioid (AOR=0.949, 95% CI=0.909, 0.991, p=0.008).

Kajian ini menunjukkan bahawa satu dari sepuluh pesakit MMT dilaporkan mengalami relaps opioid. Pesakit tanpa sejarah pengambilan lebih dari satu jenis dadah dan mempunyai risiko relaps yang lebih tinggi secara positif berkaitdengan relaps opioid sementara pesakit dengan skor tindak balas penyelesaian masalah kognitif dan tingkah laku yang lebih tinggi berkait secara negatif dengan relaps opioid. Usaha harus dibuat oleh pembuat dasar dan perancang program untuk menjayakan bebas relaps di kalangan pesakit MMT, dengan mempertimbangkan peramal yang signifikan. Hal ini boleh membantu menjayakan program ini, selari dengan tujuan utama yang disasarkan oleh Kementerian Kesihatan untuk Rawatan Terapi Gantian Methadone di Malaysia.

Kata kunci: relaps, opioid, methadone, Rawatan Terapi Gantian Methadone, kestabilan dos.

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ACKNOWLEDGEMENTS

This thesis was submitted to the Senate of Universiti Putra Malaysia and has been accepted as fulfilment of the requirement for the degree of Master of Science. The members of the Supervisory Committee were as follows:

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LIST OF ABBREVIATIONS

AMO	Assistant Medical Officer
ARCQ	Adolescent Relapse Coping Questionnaire
HIV	Human Immunodeficiency Virus
IVDU	intravenous drug user
KK	primary health clinic
MMT	Methadone Maintenance Therapy
NADA	National Anti-Drug Agency
PSS-Fa	Perceived Social Support from Family
PSS-Fr	Perceived Social Support from Friends
UPM	Universiti Putra Malaysia

CHAPTER 1

INTRODUCTION

1.1   Background

Drug abuse was a well-known growing problem in Malaysia. From a bigger perspective, illicit drug use and relapse problems after detoxification remain a major problem in managing drug abuse worldwide (Liu et al., 2018). In drug abuse problems, opioid use disorder continues to be a significant public health problem around the world. Clinically, opioid use disorder was characterized as physical dependence on opioids and as evidenced by tolerance and physical symptoms towards opioid addiction including the effect of drug cravings, depression, anxiety, and inability to control the use of opioids (Hu et al., 2019). Opioid addiction, with an estimated prevalence of 16.5 million in 2013 worldwide carries economical interference in society due to unemployment, crime as well as family disruption, not to mention the increase in blood-borne infection transmissions such as Human Immunodeficiency Virus (HIV) and Hepatitis C (Nurulhuda et al., 2016).

The statistic in 2016 reported it was estimated around 400 000 to 800 000 drug users in Malaysia, with 234 000 heroine abusers (Nurulhuda et al., 2016). National Anti-Drug Agency (NADA) statistic in 2018 showed the most commonly abused drug is methamphetamine which indicating 62%, followed by opiates (30%), amphetamine-based stimulants (4.4%) cannabis (4.3%), and others (NADA, 2018). Opioid addiction is a complicated disorder which many factors were found to be the leading factor towards initiation of use, addiction, and relapse (Chalana et al., 2016). Opioid addiction induces long-lasting alteration in the central nervous system resulting long term physical dependence that causes an aversive withdrawal symptom due to tolerance effect (Liu et al., 2018).

United Nations Office on Drugs and Crime (UNODC) had estimated the prevalence of opioid demand in Malaysia for 2018 was the highest compared to other substances with 1.16%. The increment trend of annual opioid seizures reported by UNODC in Malaysia from 2017 with 603kg to 1441kg in 2018 was quite worrying. (UNODC, 2018). WHO reported the number of opioid overdosesincreased in several countries, in part due to the increased use of opioids in prescription and illicit drug markets (WHO, 2020). A study done in Malaysia among 460 opioid users, 20% reported non-fatal overdose (Bazazi et al., 2015). Reconsumption of opioids after detoxification was reported as one of the risk factors for opioid overdose (WHO, 2020).

Acknowledging the importance of counteracting drug abuse and relapse, the Malaysian government has implemented several programsto curtail drug distribution and improve detoxification programs. Indeed, the government has built repos with various agencies to work together in impeding drug use, parallel to the mission of enhancing Malaysia

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and Malaysian society free of drug threats as per aimed by National Drug Policy 2017 (National Drug Policy, 2017).

Methadone Maintenance Therapy (MMT) has been known as the most widely use and extensively explored treatment for opioid addiction. MMT act as replacement therapy rather than cure and was proved effective in reducing the frequency of opioid use, reduce mortality, reduce the risk of blood borne infection transmission, improve employment prospect and reduce the frequency of criminal behavior. In Malaysia, MMT services had been introduced in 2005 and nowadays being expanded to jail, rehabilitation centers, as well as private centers mainly to optimize the benefit of this treatment. The opioid detoxification program, particularly with medication, play important role in preventing relapse and increasing working ability for addicted individuals, thus they can have longer periods of abstinence (Wang et al., 2019).

Relapse can be defined as an act of taking illicit substances after following a detoxification program (Firdaus et al., 2019). The growing additional crisis among addicted individuals can contribute to relapse. Relapsed addicts are commonly confused and overreact due to loss of ability to think clearly, unable to control the feeling and emotions, the difficulty in remembering things, and easily infuriated (Liu et al., 2018). NADA classifies patients who register again in NADA program after completing the program before as relapse.

However, the treatment remains controversial as relapse to opioid use following cessation of agonist maintenance treatment is a common incident among MMT patients (Hu et al., 2019). Furthermore, this relapse issue has already been counted as the fourth objective of MMT in Malaysia (Methadone Standard Operating Prosedur, 2016). The risk of relapse is heightened as a result of terrible withdrawal symptoms experience with craving feeling, as well as neurobiological changes in the central nervous system due to repeated opioid abuse (Wang et al., 2019). Interpersonal factors were 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 factor of relapse (Chalana et al., 2017, Muhammad Ashraf et al., 2020, Kabisa et al., 2021). Unhealthy mental status such as depression, anxiety also one of the risk factors for increasing drug craving for opioids and relapse (Chalana et al., 2017, Muhammad Ashraf et al., 2020, Kabisa et al., 2021). Relapse cases are also affected by social environment influence such as family conflict, poor family support, and peer influence (Kabisa et al., 2021, Kadam et al., 2017).

1.2   Problem statements

It has been known for many years that addictive disorders tend to run a chronic relapsing course. Relapse is a central problem in the treatment of addictive behavior, and a specific problem in the out-patient treatment of opiate withdrawal syndrome.

The prevalence of relapse varies in different MMT centers which involving jails, rehabilitation centers, government health facilities as well as a private facilities. Statistics provide by NADA Malaysia shows among 24972 cases registered in 2018, 30.1% was relapsed case. Study done in Malaysia found out that among 225 patients, 46.2% of them misuse after taking opioid substitution therapy from private clinics (Mahmood Nazar and Muhamad Dzahir, 2007). A recent study done at a methadone center at a government hospital found that 36.5% of patients relapse after 6 after joining the MMT program (Firdaus et al., 2019). Globally relapse among those who underwent detoxification programs ranging from 20% to 80% (Kabisa et al., 2021, Moradinazar et al., 2019, Chalana et al., 2017; Naji et al., 2016, Termorshuizen et al., 2005). This various relapse phenomenon differs in a different type of treatment center probably due to different detoxification treatment procedures, patients' criteria before recruitment of the program as well as many other environmental and social factors.

Relapse is common phenomenon happened in detoxification program which comes from multiple factors which originating from individual patient characteristic, the drug and environment reinforce (Kadam et al., 2017). The predictor of opioid relapse was heavier opioid use before the treatment, got a history of higher index crime, failure to comply to the treatment and lower coping skill; which all those factors carries a substantial mortality risk due to accidental overdose, especially for IVDU (Kadam et al., 2017; Naji et al., 2016; Liu et al., 2018). NADA reported that the majority of the case registered (70%) were in the socially and economically most productive age group (20-39 years) and almost 98% of the addicts who occupied these rehabilitation centers were male (NADA, 2018).

Illicit drug use can harm users both physically and mentally and reducing their ability to work (Fadzlon et al., 2014). Froma bigger point of view, it will reduce human resources in the Malaysian industry and affecting economic growth (Fadzlon et al., 2014). In dealing with the drug-related problem, the government has spent so much in low enforcement, health care, drug and HIV intervention, rehabilitation, and justice (Fadzlon et al., 2014). It also ties up a chunk of law enforcement resources. The battle against drug addiction has been an expensive project. It would cost the government about RM3000 per month for each drug addict and a staggering RM300 million annually for its rehabilitation programs (Mohammad Hussain and Mustafa Ali, 2011). Money that could be spent on improving life for a family was wasted because one of them is a drug addict. The family of a substance abuser may be living on the poverty line while this individual wastes a small fortune feeding their habit. The demand for these illegal substances feeds the criminal underworld.

Opioid relapse might increase the risk of HIV, Hepatitis B, and Hepatitis C transmission. Methadone is taken orally while heroin is often injected, which can lead to HIV, Hepatitis B, and Hepatitis C transmission if needles and syringes are shared (Clinical Guidelines for Withdrawal Management, 2009). The increment trend of opioid overdose worldwide was quite concerning (WHO, 2020). Moreover, the annual opioid seizure reported by UNODC in Malaysia from 2017 with 603kg to 1441kg in 2018 reflecting the increment in illicit opioid usage among Malaysia (UNODC, 2018). Concomitant use of illicit opioids in combination with MMT stands as the largest risk factor for increasing the incidence of abnormal cardiac conductivity, respiratory

depression, overdose, and death (Naji et al., 2016). Reconsumption of opioids after detoxification was reported as one of the risk factors for opioid overdose (WHO, 2020). It is reasonable that treatment should be tailored toward lowering the risk of continued opioid abuse (relapse of opioid drug user) during treatment, to improve treatment outcomes, as well as reduce the risk of detrimental side effects associated with concomitant use of illicit opioids during MMT (Naji et al., 2016).

In the Ministry of Health, many types of research elaborating on review of MMT as a whole but lacking at accessing relapse rate in Malaysia. By evaluating the current relapse status in Malaysia particularly in detoxification centers, many factors contributing to relapse can be identified, and remedial action can be taken to decrease relapse incidents in Malaysia as well as reaching the main objective of the detoxification program.

1.3   Significance of study

Drug abuse is a complex issue and has been a serious public health problem in Malaysia. The high relapse rate which has been consistently over 50% for the past decades has been worrying also. This study enables us to determine the associating factors and predictors of drug relapse among patients taking methadone as a detoxification treatment. The data gathered in this study will also be used as baseline information to plan a management program for the target population for the next intervention program to reduce relapse among patients taking methadone. In advance, any researcher who focused on survival rate also can take the prevalence of relapse in this study as an advantage.

1.4   Research Questions

What is the prevalence of opioid relapse and the contributing factors of opioid relapse among patients registered under the Methadone Maintenance Therapy (MMT) program in Johor Bahru Health District?

1.5   Objectives

1.5.1   General Objectives

The general objective is to determine the prevalence of opioid relapse and factors associated with opioid relapse among patients registered under the Methadone Maintenance Therapy (MMT) program in Johor Bahru Health District.

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1.5.2 Specific Objectives

a. To describe the prevalence of relapse among patients registered under the Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

b. To describe the proportion of factors contributing to relapse among patients registered under the Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.
   i. Socio-demographic characteristic
   ii. MMT history
   iii. Comorbidity
   iv. Crime history
   v. Cognitive and interpersonal factors
   vi. Social-environment influence

c. To determine the association between opioid relapse among patients registered under Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District with:
   i. Socio-demographic characteristic
   ii. MMT history
   iii. Comorbidity
   iv. Crime history
   v. Cognitive and interpersonal factors
   vi. Social-environment influence

d. To determine the predictor of relapse among patients registered under the Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

1.6 Hypotheses

a. There is an association between opioid relapse and socio-demographic characteristics (age, race, gender, religion, marital status, education level, employment status, and income) among patients registered under Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

b. There is an association between opioid relapse and MMT history (age begin to the misused drug, duration of misusing the drug, type of misuse drug taken, polydrug user, history of intravenous drug user (IVDU), family history of substance abuse, duration of MMT, current methadone dose, duration of current methadone dose, methadone adherence) among patient registered under Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

c. There is an association between opioid relapse and comorbidity (type of disease, comorbidity treatment, medication adherence) among patients registered under the Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

d. There is an association between opioid relapse and crime history (history of imprisonment, history of rehabilitation) among patients registered under the Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

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e. There is an association between opioid relapse and cognitive and interpersonal factors (relapse coping response, cognitive and behavioral problem solving response, self-critical thinking response, and abstinence focused coping response) among patients registered under Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

f. There is an association between opioid relapse and social-environment influence (social functioning, friends support, family support) among patients registered under Methadone Maintenance Therapy (MMT) Program in Johor Bahru Health District.

1.7   Definition of terms

a.   Relapse
Relapse is defined as the patients returned to even a single usage opioid (heroin or morphine) after methadone dose stabilization (Termorshuizen et al., 2005).

b.   Opioid
'Opioid' is refers to any substance, natural or synthetic, that binds to specific opioid receptors in the brain (Azadfard et al., 2021). Synthetic and exogenous opioids (i.e., morphine, heroin, Oxycontin, etc.) act on the same receptors as these endorphins and thus have substantial potential for abuse (Weinshenker and Schroeder, 2007).

c.   Methadone
Methadone is a synthetic opioid agonist, a fat-soluble drug that is rapidly absorbed after oral administration (Kreek, 2000). The half-life approximately 15 hours; after repeated dosing, the half-life extends to approximately 24 hours (Clinical Guidelines for Withdrawal Management, 2009).

d.   Methadone Maintenance Therapy
A corrective therapy works as an opioid replacement, rather than as a "cure" for opioid addiction (Joseph et al., 2000). The government had introduced this program in 2005 and is currently being expanded to the prison and private sector to widen the efficacy of this replacement therapy to reduce drug addiction in Malaysia.

e.   Dose stabilization
Early dose stabilization was defined as a period of eight weeks at a constant dose of methadone (Scavone et al., 2013). In this study, the patient considered reachinga stabilization dose after eight weeks of a constant dose of methadone.

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