EFFECT OF METHADONE ON CHRONIC ILLNESSES AND BEHAVIORS AMONG PEOPLE WITH OPIOID USE DISORDER (OUD) RECEIVING METHADONE MAINTENANCE TREATMENT (MMT) AT PONTIAN PRIMARY HEALTHCARE CLINICS

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by

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LIST OF SYMBOLS

x

T_{max}	Plasma Concentration of methadone
pKa	Number of the PLS or PCA component
φ	Effect of size

LIST OF ABBREVIATIONS

ADR   Adverse Drug Reaction

ACD   Anemia of Chronic Disease

AIDS   Acquired Immune Deficiency Syndrome

ALP   Alkaline Phospahtase

ALT   Alaline Aminotransferase

ATS   Amphetamine-type stimulant

COPD   Chronic Obstructive Pulmonary Disease

CVD   Cardiovascular Disease

CP450   Cytochrome P450

DOT   Direct Observe Therapy

DM   Diabetes Mellitus

FBS   Fasting Blood Sugar

HPT   Hypertension

HBV   Hepatitis B

HCV   Hepatitis C

HIV   Human Immunodeficiency Virus

IDU   Injected Drug User

MMT   Methadone Maintenance Treatment

MHA   Ministry of Home Affair

MOH   Ministry of Health

MOR   Mu-Opioid Receptor

NADA   National Anti-Drug Agency

NIDDM   Noninsulin-Dependent Diabetes Mellitus

OUD   Opioid User Disorder

SPUB   Sistem Pengambilan Ubat Bersepadu

TB   Tuberculosis

WHO   World Health Organization

LIST OF APPENDICES

KESAN METHADONE TERHADAP PENYAKIT KRONIK DAN TINGKAHLAKU DALAM KALANGAN ORANG YANG MEMPUNYAI MASALAH PENGUNAAN OPIOD YANG MENERIMA RAWATAN TERAPI GANTIAN METHADONE DI KLINIK KESIHATAN DAERAH PONTIAN

ABSTRAK

Rawatan metadon yang berpanjangan boleh mempengaruhi status kesihatan pesakit seperti menghidap penyakit kronik; diabetes, hipertensi, kardiovaskular, dan morbidity serta mempengaruhi fungsi hati menyebabkan penurunan kualiti hidup pesakit. Selain itu, keberkesanan MMT juga berdasarkan tingkah laku pengguna opiod dalam penggunaan dadah terlarang semasa rawatan methadon. Tujuan kajian ini adalah untuk mengetahui kesan metadon terhadap penyakit kronik dan tingkah laku di kalangan pengguna opiod bagi penjagaan kesihatan primer khusus untuk menentukan prevalensi penyakit kronik dan morbiditi, kematian serta tingkah laku di kalangan pengguna opioid terhadap pengambilan ubat terlarang. Kajian ini terbahagi kepada dua bahagian yang dijalankan dari bulan September 2018 sehingga September 2019. Bahagian pertama adalah kajian retrospektif bagi menentukan kadar kematian pada pengguna opiod dengan mengambil data dari rekod perubatan dan rekod pesakit dari tahun 2007 sehingga 2019. Manakala, bahagian kedua adalah kajian prospektif untuk menilai tingkah laku pengguna opiod dalam pengambilan dadah terlarang semasa rawatan terapi metadon dengan menggunakan soal selidik. Kajian fasa kedua ini menggunakan persampelan rawak. Seramai 164 pengguna opiod telah ditemuduga untuk fasa kedua ini. Kedua-dua data yang dikumpulkan dari bahagian satu dan dua dianalisa melalui SPSS. Bahagian pertama: sejumlah 380 pengguna opiod mendaftar MMT di daerah Pontian, majoriti adalah HIV negatif (n =

309, 81.3%), positif HIV (n = 65, 17.1%) dan tidak diketahui (n = 6, 1.6%). Majoriti adalah HCV (n = 234, 61.6%), status jelas (n = 101, 26.6%) dan HBV (n = 45, 11.8%). Prevalensi pengguna opiod pada penyakit kronik: diabetes (6.6%), hipertensi (5.5%), Dislipidaemia (4.5%), penyakit jantung Iskemia (1.3%), penyakit pernafasan (1.6%) dan penyakit bersama (2.9%). Manakal, penyakit berjangkit: HIV (16.1%), Hepatitis (71.3%), HIV dan Hepatitis (1.3%), tuberkulosis (0.5%), hepatitis dan tuberkulosis (5.5%) dan HIV, Hepatitis dan tuberkulosis (14.5%). Analisis semua kematian berlaku 12 tahun dengan kadar kematian 98/1000 (25.8%). Bahagian kedua: 164 pengguna opiod (lelaki, n = 161: 98.2%) (wanita, n = 3: 1.8%) ditemuramah dengan pendapatan median rm 1000.00. Skor min tingkah laku peribadi [78.6%: 23.6 (5.7)], tingkah laku kegiatan [85.4%: 20.5 (4.1)], tingkah laku emosi [80.3%: 24.1 (5.5)] dan tingkah laku penggunaan dadah haram [78.6%: 33 (12.2)]. Metadon mempengaruhi fizikal dan psikologi pada status kesihatan pengguna opiod semasa MMT. Kesimpulannya, prevalensi penyakit kronik dan penyakit berjangkit di kalangan orang yang mempunyai masalah penggunaan opiod membantu untuk menjalani saringan kesihatan melalui intervensi klinikal dan pemeriksaan awal untuk mengurangkan risiko terkena penyakit ini. Selain itu, hasil tingkah laku menunjukkan rawatan metadon membantu orang yang mempunyai masalah penggunaan opiod dengan menunjukkan tingkah laku yang baik semasa menerima metadon serta mengurangkan risiko mengambil ubat terlarang, membina watak dan tingkah laku diri, meningkatkan dan menguatkan emosi di kalangan orang yang mempunyai masalah opiod.

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ABSTRACT

The prolonged methadone treatment may affect the patient's health status, such as developing chronic illness, diabetes, hypertension, cardiovascular events, co-morbidities, and affecting liver functions lead to decrease patient quality of life. Besides, the effectiveness of MMT is also based on the behavior of OUD to quit taking the illicit drug. This study aims to determine the effect of methadone towards chronic illness and behavior among OUD in primary healthcare precisely to assess the prevalence of chronic disease and co-morbidities, survival and mortality rate, and also the behavior among OUD on the acquisition of illicit drug. It is two-part of study that was conducted from September 2018 to September 2019; part one is a retrospective study to determine the prevalence, and mortality rate on OUD by retrieving data from the medical record and file patient record from 2007 until 2019. While part two is a prospective study to evaluate OUD behavior on the acquisition of illicit drugs during MMT by using a validated questionnaire. For part two, 164 people with OUD were recruited for interviewed through random sampling. Both data collected from parts one and two were entered into SPPS. In part one, a total of 380 OUDs enrolled MMT at Pontian district, minority were HIV positive (n=65, 17.1%) and unknown (n=6, 1.6%). Majority were HCV (n=234, 61.6%), clear status (n=101, 26.6%) and

HBV (n=45, 11.8%). Prevalence OUDs on chronic illness: diabetes (6.6%), hypertension (5.5%), Dyslipidaemia (4.5%), Ischaemic heart disease (1.3%), respiratory disease (1.6%) and underlying co-morbidities (2.9%). Prevalence on infectious disease: HIV (16.1%), Hepatitis (71.3%), HIV and Hepatitis (1.3%), tuberculosis (0.5%), hepatitis and tuberculosis (5.5%) and HIV, Hepatitis and tuberculosis (14.5%). An analysis of all death occurred 12 years with mortality rate 98/1000 (25.8%). In part two, 164 OUDs (male, n=161:98.2%) (female, n=3:1.8%) were interviewed with median income rm 1000.00. Mean score personal behavior [78.6%: 23.6 (5.7)], conduct behavior [85.4%: 20.5(4.1)], emotional behavior [80.3%: 24.1(5.5)] and illicit drug use [78.6%: 33(12.2)]. In conclusion, the prevalence of chronic illness and infectious disease among people with OUDs helps healthcare providers undergone clinical intervention and early screening in order to reduce the risk of developing the disease. While, as a behavior outcome, methadone treatment helps people with OUD as they perceive to have good behaviour during receiving methadone which reduce risk taking illicit drugs, develop personal character and self-conduct, enhance and strengthen emotional among people with OUDs.

CHAPTER 1

INTRODUCTION

1.1. Background

Opioid abuse leading worldwide death. There are significantly increase in rates of opioid abuse and risk of its addiction. This risk of addiction includes medical, psychiatric comorbidity, infection, use of polysubstance and criminal behaviour. (Bawor., 2014) The increasing pattern of opioid abuse and illicit substance use will approximately double from 2.8 million which is annual average in 2002 to 2006 to 5.7 million in the year 2020. (Han, Gfroerer, Colliver, & Penne, 2009)

Addiction is featured as inability to remain abstain, craving towards illicit drugs, impairment in behavioural control and dysfunctional emotional response. Addiction disease involve cycles of relapse and remission. If no treatment or engagement method, it will progressively result in disability and premature death (Waller, 2014)

Treatment of addiction to opioid tends to be more effective when is identified earlier. There is variety of treatment replacing opioid available for opioid use disorder (OUD). Individualised treatments depending on the patient needs. However, methadone and buprenorphine shown effectiveness to reduce opioid intake and improve behaviour. Besides, there is non-pharmacological approaches such as behavioural therapy method is used for treating OUDs. When these therapies are used in conjunction patient treatment outcome become superior. (Waller, 2014)

1.2.   Definitions

1.2.1   Substance Abuse

According to World Drug Report 2018 stated World Health Organization define "Substance Abuse" as the harmful or hazardous use of psychoactive substance which include illicit drugs and alcohol. (Smith & Smith, 2018)

The most common types of substance use abuse:

A. Alcohol consumption: heavy alcohol consumption contributed to the possibility of a severe health problem such as damage to the brain and liver, heart disease, and hypertension. It may cause health problems linked to symptoms of withdrawal and intoxication. (Senbanjo, Wolff, & Marshall, 2007)

B. The excessive misuse of stimulants such as amphetamine, methamphetamine and cocaine resulted in increased alertness, shortness of breath, increased heart rate and blood pressure, seizures, heart failure and death. (Martin, 2019)

C. Opioid (Heroin and Morphine): A drug that contains opium-derived active compounds.

D. Hallucinogen (Ecstasy, Phencyclidine, Lysergic acid diethylamide) is a substance that distorts the perception of reality and causes hallucination.

E. Tobacco is a leafy plant that contains an active compound of nicotine. Nicotine overuse by smoking cigarettes, cigars, and pipes may cause serious health problems such as coronary heart disease, chronic obstructive pulmonary disease (COPD) and cancer danger. (Icick, 2018)

American Psychiatric Association (2013) define substance abuse as use of substance (opioid, alcohol, hallucinogen) a maladaptive pattern of substance use manifest by recurrent and significant and adverse consequences related to repeated use of substances, including repeated failure to fulfil major role obligations, repeated use in situation in which it is physically hazardous, multiple legal problems and recurrent social and interpersonal problems.

American Social Health Association (1972) define substance abuse as use of illegal substance which can altering individual mood outside supervision of medical practitioner that harmful to the individual and community.

Van Bilsen, 1986 define drug misuse as the use of the drug (opioid, alcohol, hallucinogenic) a maladaptive pattern of substance usage presents chronic and serious and detrimental effects due to frequent use of drugs, including frequent failure to perform significant duties, repeated use in physically dangerous circumstances, numerous legal issues and persistent social and social issues.

Van Bilsen, 1986 defines drug abuse as the use of an illegal substance that can alter individual mood outside the supervision of a medical practitioner that is harmful to the individual and the community.

1.2.2 Drug Addiction

Addiction comes from the Latin verb, which is *addicere* means to attach a person to one thing or another. Although drug addiction is a loss of control over drug use, even in the face of adverse physical, personal or serious social consequences. (Novick & Kreek, 2008)

National Institute on Drug Abuse (NIDA) defines addiction as a relapse disorder due to continually compulsive drug seeking despite harmful effects on the function of the body and brain. The American Psychiatric Association (1994) defines drug addiction as a chronic relapsing disease characterized by (a) compulsion to seek and take the drug, (b) loss of control in reducing intake, and (c) emergence of negative emotional conditions (dysphoria, anxiety, and irritability).

1.2.3 Behavioral Addiction

Behavior defines the action or reaction of something (things or substance) which, under certain circumstances, is associated with themselves or their environment. The intake of illegal substance use may have an effect on brain function, reflecting particular behaviour. This cause of decreased control of brain activity has led to behavioral dependence. Behavioral addiction is defined as an intense desire to repeat any action that has a pleasing effect, or is regarded to improve well-being, or is capable of relieving some emotional problems, despite the awareness that such a move may have a negative effect on a person or their community. (Zhang, Chow, 2013) Characteristics of behavioral addiction are the failure to resist the urge, drive or desire to act that is harmful to the person or others and often accompanied by the emotional feelings of "tension and excitement before committing the act" and "pleasure, gratification, or relief at the time of committing the act" (Zhang,2013).

1.3   Opiates

Opiates are natural opium poppy alkaloids (*Papaver somniferum L.*) such as heroin, morphine, and codeine. The term is associated with an opioid. In regards, opioid is a naturally occurring substance derived from opioids.

The most common illicit drugs-based opiate:

a.   Morphine is a chemical compound retrieved from opium or straw. Morphine is absorbed rapidly by subcutaneous and intramuscular injections. In relation, morphine has a faster distribution, metabolism, excretion and well absorbed in the intestinal system. (Klimas, 2019)

b.   Heroin (diamorphine or diacetylmorphine) is sub-synthetic, extracted from morphine. Heroin has two forms of water-soluble diacetylmorphine base and water-insoluble diacetylmorphine base. By comparing the pharmacokinetics of morphine, heroin is fat-soluble and enters the blood-brain barrier more rapidly, approximately 15-20 seconds and nearly seventy per cent absorbed into the brain. (Tegeder,1999)

1.3.1   Drug Addiction and Associated Risk Factors

Numerous people are susceptible to the risk factors of drug addiction in the prolonged use of illegal drugs and alcohol. Some of them may progress and develop a serious habit. Childhood trauma events (post-trauma or child abuse), mental illnesses and chronic pain and stressors are the most important risk factors for drug addiction. (Zhuang, 2012)

There are risk factors associated with addiction:

1. Biological predisposition is characterized by genetic inheritance, mental illness and sexuality. Substance abuse is fifty percent dependent on genes passing through one generation to another. It really does, even so, mean that every family who has an addict in their close relatives will develop one. Individuals who experience mental illnesses such as bipolar and depression are prone to developing an illicit drug addiction. Women are much more likely to have chronic pain complaints. People who use pain medications for non-medical reasons either originate them primarily from friends and family or receive a medication from their healthcare professional.(Evans, 2015)

2. Brain reacts that change the feelings and physicality of someone who is more susceptible to substance use. Illegal drugs contain a substance or active ingredient that may alter the function of the brain. A few other people are taking it to improve the overall feelings and state of mind. Other people are taking illicit drugs to strengthen stamina and physical in sport activities. However, this may significantly raise the risk of an individual developing a drug addiction. In addition, when people use drugs for a prolonged period of time, they can cause brain changes's in the chemical process and circuit, which can impact our personal judgement, decision-making, consciousness, and capacity to learn. (Liao, 2014)

3. Psychological factors, such as personality characteristics, stress, and mental health. People suffering from mental illness, depression, and stress may use illicit drugs or behavior as a coping strategy. This condition helps people to continue to use illicit drugs and later to relapse into drug use, even after successful treatment for addiction. (Icick, 2018).

4. Environmental exposure, such as exposure to substance use or dependence in the family or among peers, physical or sexual abuse, and exposure to popular culture references that encourage. Tasty and healthy home environments during childhood are crucial if the risk of addiction is to be reduced later. In addition, influences between friends and peers across a person's life can have a major impact about whether or not they use drugs. (Skinner, 2014)

5. Starting with nicotine, alcohol or any other illegal drug use at an early age. The more quickly a person takes substance first, and they will develop a drug addiction.

The risk factors associated with an addiction among people with OUD are physiological factors, environmental exposure and exposure to illegal substance at an early age are prominent risk among Malaysian illicit drug users. (Chawarski, 2006)

1.4 Epidemiological Opioid Abuse

1.4.1 Global Data on Opioid Abuse

Estimation in 2016, approximately 275 million people (range 204 million to 346 million) corresponding to 5.6 percent (field 4.2 to 7.1 percent) or around 1 of every 18 people of the worldwide population aged 15-64 had used an illicit drug. People tend to abuse illegal substances such as opioids, cannabis, cocaine, or amphetamine-type stimulant (ATS). (Ireland, 2013).

There is an increment in the use of marijuana globally in 2016 with 192.2 million past-year users, which estimate 3.9 percent of the world population aged 15-64 years. While opioid is the most drug abuse and harmful substance associated with adverse health impact. Approximately 34.3 million past year users of opioids in 2016, which corresponding to 0.7 percent of the world population aged 15-64 years. (Ireland, 2013).

People who injected drug (PWID) in 2016 is approximately 10.6 million (range 8.3 million to 14.7 million) corresponding to 0.22 percent (field 0.17 to 0.30 percent) of the world population aged 15-64 years. PWID are exposed to negative health-related aspects due to unsafe injecting techniques. These led to the transmission of blood-borne diseases such as HIV, hepatitis B (HBV) and hepatitis C (HCV). (Martin, 2019)

The prevalence of HIV among PWID in South West Asia and Eastern and Southern Eastern Europe is the highest, respectively, 2.4 and 1.9 times the world average. Moreover, an estimated 53 percent of PWID living with HIV in 2016 (662,000 people) situated in just three countries: Pakistan, China, and the Russian Federation. HCV infection is a high prevalence among PWID. The prevalence of HCV among PWID corresponding to 91 percent of the estimated world number of PWID. (Zhang, 2013)

Women have a higher risk of spreading HCV infection. A study conducted among 1868 PWID in the United States, Canada, Netherlands, and Australia estimated that women who inject drugs have a 38 percent higher risk of contracting HCV than their male counterparts. The significant risk is associated with differences in access to prevention services and genetic factors. While the prevalence of HBV among PWID is 7.5 percent, corresponding to 0.8 million PWID are living with HBV. (Grella, Anglin, & Annon, 1996).

World Health Organization (WHO, 2018) estimates 167,750 death attributes to substance abuse, and it remains high worldwide for the past 15 years from an estimated 105,000 deaths in 2000. This death is the consequence of taking illegal drug overdose but indirectly due to health issues such as HIV, HBV, and HCV.(Smith, 2018)
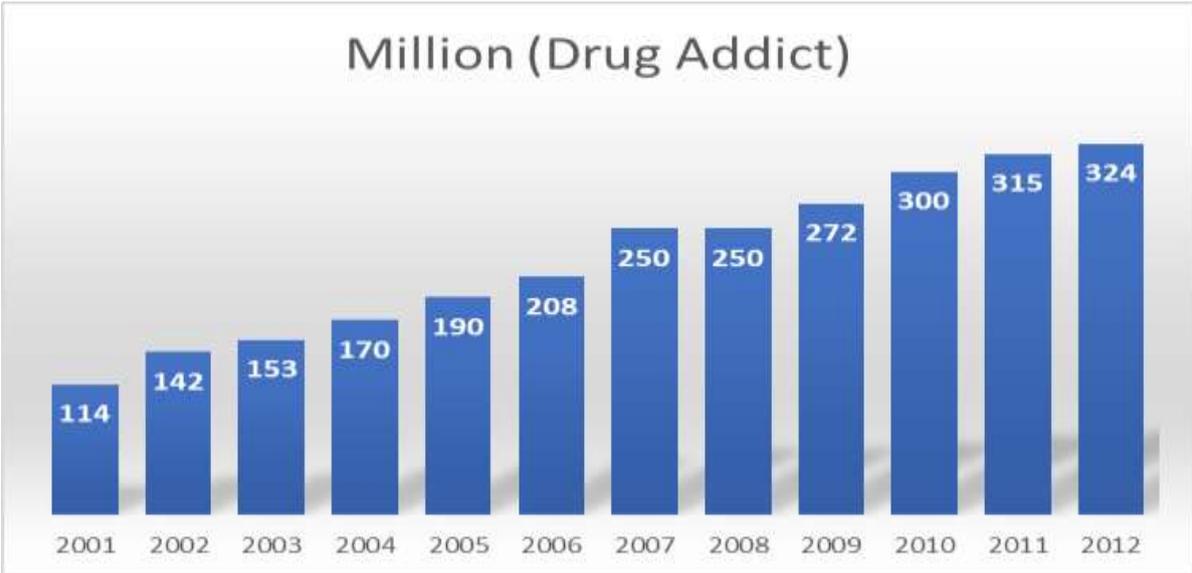
Figure 1.1. The increasing pattern of drug addict worldwide

Source: World Drug Report (Smith, 2018)

Percentage	2017 African	2018 African	2017 America	2018 America	2017 Southeast Asia	2018 Southeast Asia	2017 European	2018 European	2017 Eastern	2018 Eastern	2017 Western Pasific	2018 Western Pasific
Percentage	8	10	20	23	15	18	16	23	9.9	13	23	20
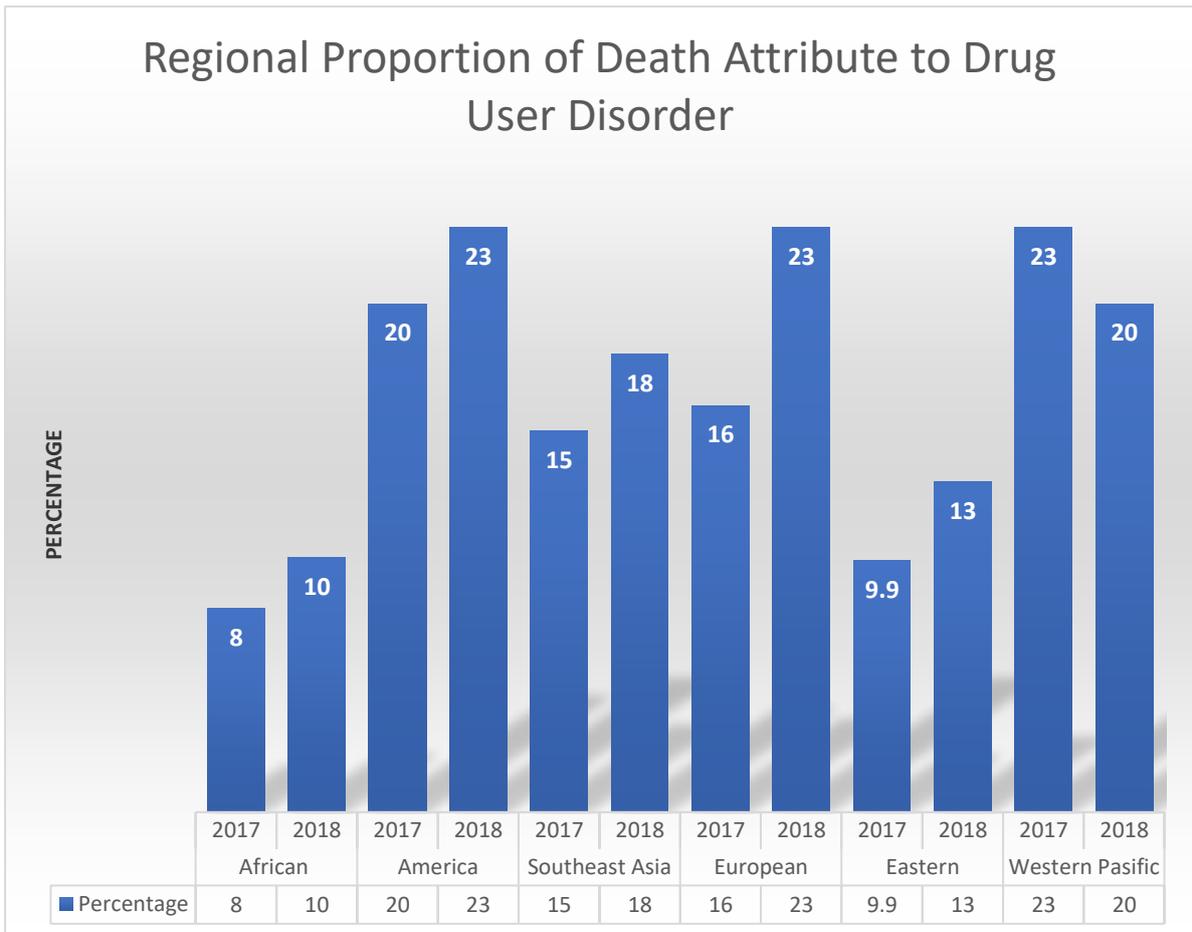
Figure 1.2. Global health estimates opiate use disorder comparing by region

Source: World Drug Report (Smith, 2018)

1.4.2   Malaysian Data on Opioid Abuse

Malaysia has the fastest developing and expanding economies in the South East Asia region, with a population of 32.05 million, which represented multiple ethnic groups that living together in the country. Opioid abuse is the main problem and burden in Malaysia, showing the pattern of opioid abuse increasing per year, with approximately half of the Malaysian prison having taken to various drug-related offenses. Many studies regarding drug opioid and addiction were carried out in Malaysia. (NADA, 2020).

The Malaysian government is taking this as a severe public health issue by implementing numerous programs and activities to advocate, curtailing drug distribution, and enhancing treatment program. National Anti-Drug Agency (NADA) creates a rehabilitation program that offers an open-concept approach to facilitate drug addicts with the opportunity to receive treatment voluntarily at local community service. The most drug types that commonly misused by a Malaysian drug addict in 2013 are opiates (75.07%) as the highest-ranked substance, followed by methamphetamine (13.58%), cannabis (8.82%), amphetamine-type substance (ATS) pills (2.23%) and psychoactive pills (0.22%). (NADA, 2020)

The NADA showed an increase in the total number of newly detected drug addicts and relapse cases who formerly recognized and received treatment in the past five years from 2013 to 2017, which from total number 20,887 to 25,922 in both cases. In 2016, Malaysia spent more than 200 million of government expenditure for rehabilitating drug addicts at Serenti Center. (NADA, 2020).

Table 1.1. Distribution of drug addicts per year cases in Malaysia from 2013 to 2017

Case/Year	2013	2014	2015	2016	2017
New	13, 481	13,605	20,289	22,923	18,440
Relapse	7,406	8,172	6,379	7,921	7,482
Total	20,887	21,777	26,668	30,844	25,922

Source: Malaysian National Anti-Drug Agency Report 2013-2017

The Ministry of Home Affair (MHA) reported Pahang state is the highest drug addict throughout nationwide 16, 918 drug addicts followed by Kelantan state 16,150 drug addicts, Terengganu state 10,576 drug addicts and Perlis state 2,123 in the year 2019.

While for this study is conducted at Johore state of Malaysia. Johore is located on the southern Malaysia peninsula. Johore has land borders among Malaysia states such as Malacca and Negeri Sembilan at Northwest and north borders with the state of Pahang. The 2015 Malaysian Census reported the population of Johor at 3,553,600, which the second-highest population in Malaysia. Out of the Johore population are 1,893,100 (53.3%) are Malay, 1,075,100 (30.3%) are Chinese, 230,700 (6.5%) are Indian and another 16,900 (1.7%) identified as bumiputra. (NADA, 2020)

NADA (2020) reported increasing trends of drug users in Johore state from 2013 to 2017 from 1,841 to 2,108 drug users. In 2018, 13,003 drug addicts or 0.003 percent of its population of 3,553,600 million in Johore state.

1.5 Pharmacotherapy and treatment procedures of opioid abuse

The selection of pharmacotherapy and treatment procedures depend on the clinical features and preference of the patient that perceived treatment. The patient should be treated in the least restrictive setting, which proves to be safe and effective.

There are many approaches to pharmacotherapy and treatment procedures of drug abuse. There are five modalities in which most treatment of opioid-related abuse disorder occurs, such as in the ward or inpatient hospital setting, health care outpatient setting, self-help program, therapeutic communities, and opioid treatment programs. (Gillani, 2009).

There are some recommended and approaches to treatment for opioid-related disorders. Methadone is a synthetic opioid agonist that produces effects in the same way as morphine and heroin and another opioid. When methadone client takes methadone, the act is to relieve withdrawal symptom and opioid craving. Besides, at a maintenance dose, methadone does not induce a euphoric effect on the methadone client. Most methadone clients, who at the beginning of the treatment, may experience few side effects, withdrawal, or intoxicated symptoms. (Gillani, 2009)

Besides, if an overdose of opioids occurs, in severe cases, such a life-threatening emergency should be treated with an opioid antagonist (e.g., naloxone) to reverse overdose effects. While, if withdrawal symptom of opioid occur can be managed replacement pharmacotherapy such as opioid agonist (e.g., methadone, buprenorphine), an opioid antagonist (e.g., naltrexone) or nonopioid (e.g., clonidine). (Gillani, 2009).

1.5.1   Diagnostic approach and drug testing on the opioid abuser

Diagnostic procedure and drug testing on opioid abusers vary depending on the class of substance or drug being tested and the type of specimen being collected. Test specimens such as hair, urine, oral fluid (saliva), or sweat can be tested for drug screening. Drug screening to identify drugs or substance such as opioid, amphetamine, benzodiazepine, marijuana and phencyclidine (PCP)

Table 1.2. Diagnostic approach and drug testing on the opioid abuser

Source: Gillani (2009)

Types of diagnostic testing use	Detection	Advantages	Limitation
Urine	urine strip: 2-5 minutes, laboratory urine test: 1 to 5 days	1. Easiest and flexible to determine drug	1. The specimen may be adulterer, diluted and substituted
		2. Not expensive and affordable to buy urine strip	2. Urine test sometimes viewed as embarrassing or invasive
		3. Reliable results	3. Limited to specific drug and detection rate
			4. Biological hazard specimen handling and shipping to the lab
Saliva or oral fluids	10 to 24 hours and may up for two days	1.Minimal risk of tampering	1. Less efficient than another testing
		2.The sample obtained during supervision	2. Drug and metabolites of the drug do not remain saliva or oral fluid as compared to urine
		3. The specimen can be collected easily	
		4.Can detect alcohol use	
		5. Reflects recent drug use	
		6. Less susceptible to contamination or substitution	
Blood	5 to 2 hours depending on the case	1. Variety drug can be tested	1. The short period, many illicit drugs metabolize quickly
		2. Reliable results	
Hair	Depend on the length of the hair as a specimen, so 11/2-inch specimen shows a 3-month history. The collector usually takes	1. Less risk of substitution or adulteration	1. The test traditionally limited to basic five drug panel
		2. Longer detection range	2. More expensive
		3. More excellent stability (not quickly deteriorated)	
		4. Convenient shipping and storage (do not require refrigerated)	

	100gm (100-200 strands) cut close to the scalp	5. Collection procedure does not consider embarrassing or invasive	
		6. Detect alcohol/cocaine combination use	
Sweat patch	The patch cannot detect even low levels of drugs 2-5 hours after last use	1. Longer detection range	1. Passive exposure to drugs may contaminate patch and effect results
		2. Variable removal date (generally 1 to 7 days)	2. People with skin problems such as excessive hair, abrasions, and eruptions cannot wear the patch

Types of illicit drug and detection time in urine also vary depending on the mechanism of pharmacokinetic properties and body metabolism. There are many types of illicit drug in the market and each differ from each other. People with OUDs tend to abuse several illicit drugs during receiving methadone treatment. Thus, it's important to differentiate types of illicit drug use during MMT.

Table 1.3. Types of illicit drug and detection time in urine

Source: Gillani (2009)

Drug	Class	Street Name	Prescription Brand Name Examples	Detection Time in Urine
Amphetamines	Stimulant	speed	Dexedrine, Benzedrine	Up to 2 days
Barbiturates	depressants / sedatives / hypnotics	downers, barbs, reds	Amytal, Fiorinal, Nembutal, Donna	short-acting: 2 days long-acting: 1-3 weeks (based on half-life)
Benzodiazepine	depressants/sedatives/hypnotics	bennies	Valium, Ativan, Xanax, Serax	therapeutic dose: 3 days chronic use: 4-6 weeks or longer
Cocaine (benzoylecgonine metabolite)	Stimulant	coke, crack, rock cocaine	Not available	Up to 4 days
Codeine	Analgesic / Opiate	N/A	Not available	Two days
Ethyl alcohol, ethanol	depressants / sedatives / hypnotics	alcohol, liquor, beer, wine	Not available	urine: 2 to 12 hours serum/plasma: 1 to 12 hours
Heroin	Analgesic / Opiate	smack, tar, chasing the tiger	Not available	Two days
Marijuana, Cannabinoids	Hallucinogen	pot, dope, weed, hash, hemp	Marinol, Cesamet	Single-use: 2 to 7 days Prolonged, chronic use: 1 to 2 months or longer
Methadone	Analgesic / Opiate	fizzies	Dolophine	Three days
Methamphetamine	Stimulant	speed, ice, crystal, crank	Desosyn, Methedrine	Up to 2 days

Methaqualone	depressants / sedatives / hypnotics	ludes, disco bisquits, 714, lemmons	Quaalude (off U.S. market)	Up to 14 days
MDMA (methylenedioxymeth amphetamine)	Stimulant	ecstacy, XTC, ADAM, lover's speed	Not available	Up to 2 days
Morphine	Analgesic / Opiate	N/A	Duramorph, Roxanol	Two days
Phencyclidine	Hallucinogen	PCP, angel dust	Not available	8-14 days, but up to 30 days in chronic users
Propoxyphene	Analgesic / Opiate	Not available	Darvocet, Darvon (all form of propoxyphene withdrawn from U.S. market in November 2010)	

1.5.2 Methadone Maintenance Treatment (MMT)

Methadone was the first synthesis in 1938 by Max Bocmuhl and Gustav Erhart during world war 2 to replace morphine. During that time, the trade name of methadone is dophine taken after the first name of Hitler. This drug was used by German soldiers during the war period to treat pain but with a weak acceptance cause by its side effects. The chemical name of methadone is (6-dimethylamine-4,4-diphenyl-3heptanone) (Shah & Diwan, 2010).

MMT has been introduced since 1960 and has proved efficacious in the replacement of opioids. Besides, it prevents OUDs on MMT spreading infectious diseases associated with the use of needle sharing, for example, human immune deficiency virus (HIV) and hepatitis virus (HBV and HCV). The high rates of drug use through needle sharing, they exposed higher risk of tumor malignant, cancerous, diabetes, and another chronic illness disease.

MMT has been established in Malaysia in 2005. This therapy is one of the strategies of the Ministry of Health (MOH) as a harm reduction program to reduce bloodborne diseases such as HIV and Hepatitis among drug users. This program reduces the spread of blood-borne diseases by years to date. (Aziz, 2018).

1.5.2(a)Management

The key aim of MMT management is to suppress the withdrawal of opioids and help to stop the use of illicit drugs. In methadone maintenance treatment for opioid dependence, the induction dose of methadone is 20-30 mg, with an increase of 5 to 10 mg every other day as tolerated by the patient. The usual dose of methadone given in MMT ranges from 30-100 mg. A higher treatment range of 80 to 100 mg per day is more effective than a moderate dose range of 40 to 50 mg per day in reducing the use of illicit opioid. (Rhoades 1998;Caplehorn, 1993).

Table 1.4. References induction dose worldwide according to methadone dose range

Source: Clinical Guidelines of Methadone Maintenance Treatment

Induction dose	
Methadone dose range	**Country (reference)**
The initial treatment for induction 20mg to 30mg without waiting lab result	Malaysia (KKM, 2016)
Initial dose 20-40mg, based on estimated tolerance and documented drug use three days prior	Australia (Humeniuk, 2002)
Initial treatment 15-30mg during the first three days	Canada (Health Canada, 2001)
Initial dose 20 -30mg, more than 30mg on the first day only in patients with tolerance threshold know to be quite high	Italy (Marremmani, 2002)
Initial dose 10-20mg if opioid tolerance is low or uncertain, while 25-40mg if opioid tolerance is high	Europe (Verster, 2000)
Initial dose does not exceed 30mg to 40 mg on the first day	USA (Federal register, 2001)
Initial dose 10-20mg if opioid tolerance is low or uncertain, while, 25-40mg if opioid tolerance established	U.K. (Strang, 1999)

1.5.2(b)Adverse effect or side effects

The most common side effect of methadone are:

a) Abdominal cramps

b) Difficulty passing urine

c) Loss of appetite, nausea, and vomiting

d) Libido

e) Rashes and itching

f) Aching muscle and joints

g) Sedation

h) Sweating

Table 1.5. Sign and symptom of withdrawal and intoxicated from methadone

Sign and symptom of withdrawal and intoxicated	
Intoxicated sign and symptom	Pinpoint pupils, hypotension, bradycardia, respiratory depression (overdose), depressed mental status, flushing, sedation (nodding off, drowsy), Hypoventilation, Pulmonary edema, unsteady gait, slurred speech, feeling intoxicated, coma
Withdrawal symptom	anxious, drug craving, depression, irritability, aching muscle/joints, anorexia, nausea, body cramps, restlessness, the desire for drugs
Withdrawal Symptom	Substance use, diarrhea, vomiting, lacrimation, rhinorrhoea, yawning, sneezing, fever, tachycardia, muscle tremors/twitching, diaphoresis, mydriasis (dilated pupils)

1.5.2(c)Pharmacokinetic of Methadone

Methadone is a pure, agonist, mu-opioid receptor (MOR). MOR is an opioid receptor that activates when the agonist, such as morphine and heroin, binds to the active site of MOR. Activation of MOR causes a number of effects, such as sedation, euphoria, itching, decreased bowel and blood pressure. (Shah, 2010).

Methadone is a liposoluble basic drug with a pKa of 9.2, which compose of a racemic mixture of two stereoisomers; L-methadone and D-methadone. L-methadone is the active pharmacological isomer, and D-methadone retains particular pharmacological activity such as the antitussive activity. (Ferrari, 2004) Methadone is administered via oral, first-pass effect and detectable in the plasma about 30 minutes after taken. The methadone bioavailability varies from 41-76 to 85-95 percent. (Ferrari, 2004; Garrido, 1999) The time needed to reach the plasma concentration (Tmax) from one to six-hour, with average values of 2.5 to 4.4 hours. (Ferrari, 2004).

Over time, methadone plasma concentrations follow a bi-exponential curve, with a rapid α phase corresponding to the transfer of the drug from the central compartment to the tissue compartment and the start of elimination and a slow β-phase corresponding to elimination. (Ferrari, 2004; Garrido, 1999).

Methadone has a relatively steady-state plasma concentration following a repeated daily administration. Methadone commonly administered orally, and 90 percent is absorbed in the gut. Methadone is metabolized by the liver enzymes CP450 and eliminated mostly in the urine and faces (Mattick, 2009).

The large volume of distribution of methadone indicates that there is a large, dynamically balanced tissue compartment with a small central compartment. This result of a short-term decrease in methadone blood levels is usually not associated with clinically evident withdrawal symptoms during maintenance. (Ferrari., 2004; Garrido & Trocóniz, 1999; Li, Kantelip, Gerritsen-Van Schieveen, 2008).

The plasma half-life of the β elimination phase varies little in the same patient, even if the dose of methadone in the patient is increased or decreased, from 22 to 25 hours, since there are significant differences between individuals. The body clearance of methadone varies between individuals, ranging from 0.96 to 6.1 ml / min / kg. These may affect the pharmacokinetics of methadone among people with OUDs. (Li., 2008; Ferrari, 2004).

Elimination of methadone and its metabolites is subject to hepatic metabolism and renal excretion. Due to its basic (pKa = 9.2) and lipophilic properties, changes in the pH of the urinary tract is very crucial. Urinary pH is greater than 6; renal clearance represents only 4 per cent of total drug elimination. Although Ph is below 6, unchanged methadone excreted by the renal route may increase to 30 % of the total administered dose. Another study reported a 27 per cent decrease in the estimation of inter-individual variability in methadone clearance when urine pH was incorporated into the model as covariate. (Li, 2008). As regard to its hepatic elimination, mean estimates of 3.1 and 1.5 ml/min/kg for clearance among OUDs (Garrido, 1999).

1.6   Statement of the problem

In MMT, long-term patients may progress towards developing chronic illnesses and comorbidities such as diabetes, cardiovascular disease, dyslipidemia, asthma and chronic obstructive pulmonary disease. These may be due to the side effect of methadone and the physical component made up of concentrated sugar. (Cullen, 2009). There are limited studies regarding chronic illness and comorbidities among people with OUD who are receive methadone treatment especially in Malaysia.

In addition, there are people with OUD with poorer physical health who are more likely to have chronic illnesses and co-morbidities. In addition, the older age of people with OUD in MMT has a higher risk factor for developing chronic disease and comorbidity in the future. (O'Toole, 2014)

Besides, the behavior among people with OUD is essential for successful treatment in MMT. MMT approach toward people with OUD may promote positive behaviours that will prevent them from taking illicit drug in future. People with OUD receiving methadone not just only were treated with methadone, but with other psychological intervention to enhance their self-motivation, promote individual character and improve social-being with their community.

However, there is limited of studies regarding behavior of these people with OUD during receiving methadone. The issues of behavior among people with OUD during receiving methadone are (a) personal behavior on how themselves control good character towards others, (b) conduct behaviour on how conduct themselves from surroundings, (c) emotional behaviour on how perceive their emotion and feeling and (d) illicit drug use on how handling themselves from taking illicit drug.

Therefore, the outcome from this study are helpful and essential during the intervention and may prevent any unwanted chronic illness in the future. Thus, this research will focus on the prevalence and incidence of chronic illness and multimorbidity among drug users on methadone. Moreover, there are OUD's with poorer physical health were more likely to have chronic illnesses and comorbidities. Besides, the older age of OUD's in MMT has a greater risk factor in developing chronic illness and comorbidities in the future. (O'Toole, 2014).

1.7   Rationale of the study

This study will be focusing on seeing the prevalence of developing chronic illness and infectious diseases among drug users on methadone treatment. This study may provide helpful information to physicians and pharmacists during monitoring patients and to perform an intervention on methadone dose adjustment and management of sign and symptom withdrawal and intoxication effect. Moreover, this study helps health care providers to understand chronic diseases and infectious diseases that can affect people with OUD during receiving methadone treatment.

1.8   Study objectives

1.8.1   General aims of the study

To determine the effect of methadone towards chronic illness and behavior among people with OUD in MMT at primary healthcare at Pontian District

1.8.2   Specific objectives

1) To determine the prevalence of chronic illness and comorbidities and chronic infectious disease in the MMT program

2) To determine the mortality rate during MMT among people with OUD during methadone treatment

3) To evaluate the behaviors among people with OUD receiving methadone.