THERAPEUTIC DRUG MONITORING IN METHADONE MAINTENANCE THERAPY (MMT): AN EVALUATION OF GENETIC FACTORS INFLUENCING CLINICAL OUTCOMES AND SERUM CONCENTRATIONS OF METHADONE

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by

NOR ILYANI BINTI MOHAMED NAZAR

Thesis submitted in fulfilment of the requirements

for the degree of

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NOR ILYANI BT. MOHAMED NAZAR	**THERAPEUTIC DRUG MONITORING IN METHADONE MAINTENANCE THERAPY (MMT): AN EVALUATION OF GENETIC FACTORS INFLUENCING CLINICAL OUTCOMES AND SERUM CONCENTRATIONS OF METHADONE**	**2013**	**PhD**

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AADK	- *Agensi Anti Dadah Kebangsaan* (National Anti Drug Agency)
AIDS	- Acquired Immunodeficiency Syndromes
BTOM	- Brief Treatment Outcome Measure
CDC	- Centre for Diesease Control
CI	- Confidence Interval
C_{trough}	- Trough serum methadone concentration
CV	- Coefficient of variation
DIC	- Drug Intervention Community
DME	- Drug metabolizing enzyme
DNA	- Deoxyribonucleic acid
DOT	- Directly observed therapy
DPM	- Deputy Prime Minister
EDDP	- 2-Ethylidene- 1,5-Dimethyl-3,3-Diphenylpyrrolidine
ELISA	- Enzyme- Linked Immunosorbent assay
GC-MS	- Gas chromatography mass spectrometry
HAART	- Highly active anti retroviral therapy
HIV	- Human Immunodeficiency Virus
IDU	- Intravenous drug use
IDUs	- Intravenous drug users
IIUM	- International Islamic University Malaysia
IM	- Intra muscular
INFORMM	- Institute for Research in Molecular Medicine

IV	- Intravenous
MAC	- Malaysian AIDS Council
MMT	- Methadone Maintenance therapy
MOH	- Ministry of Health
MTBE	- tert-butyl-methyl-ether
NDARC	- National Drug and Alcohol Research Centre
NIDA	- National Institute on Drug Abuse
NSB	- Non specific binding
NSEP	- Needle syringe exchange program
OD	- Optical density
OST	- Opiates substitution therapy
OTI	- Opiates treatment index
PCR	- Polymerase chain reaction
PFS	-Psychological Functionaing Scale
PLWHA	- People living with HIV AIDS
PWUD	- People who use drug
QC	- Quality control
SD	- Standard deviation
SDS	- Severity of Dependence scale
SFS	-Sociology functioning scale
SMC	-Serum methadone concentration
SNPs	- Single nucleotide polymorphisme
SOWS	- Subjective Opiates Withdrawal Scores
TA	-Take away

TMB	- 3,3’,5,5’-tetramethylbenzidine
UNODC	- United Nation Office for Drug and Crime
USM	- Universiti Sains Malaysia
VD	- Volume of Distribution
WHO	- World Health Organization
WPRO	- Western Pacific Region Office

PEMANTAUAN TERAPEUTIK UBAT DALAM TERAPI GANTIAN METHADONE (TGM) : SUATU PENILAIAN TERHADAP FAKTOR GENETIK YANG MEMPENGARUHI KEBERKESANAN KLINIKAL DAN KEPEKATAN METHADONE DARAH (SERUM)

ABSTRAK

Pengenalan: Terapi Gantian Methadone (TGM) telah digunakan secara meluas dan berfungsi untuk mengelakkan berlakunya gejala penarikan dalam kalangan penyalahguna dadah jenis opiat. Ia merupakan salah satu daripada kaedah pendekatan "pengurangan kemudaratan" *(harm reduction)* bagi menurunkan kadar penularan jangkitan melalui darah dalam komuniti terutamanya HIV AIDS yang boleh membawa maut. Walau bagaimanapun, proses penentuan dos yang optimum bagi setiap pesakit adalah sukar dan mencabar kerana ia menunjukkan kepelbagaian aktiviti farmakologi yang tinggi dalam individu yang berbeza. Kajian ini menghuraikan hubungkait di antara kepekatan methadone darah *(C_{trough})* dengan dos harian pesakit dan keberkesanan yang dikehendaki iaitu keterukkan gejala penarikan dan ujian pengesahan air kencing bagi pengambilan dadah terlarang. Hubungan antara pelbagai haplotaip gen CYP2B6 dengan kepekatan methadone darah dan variasi polimorfisme nukleotida tunggal OPRM1 (A118G) dengan tahap keberkesanan klinikal yang diukur juga dikaji.

Kaedah: Seramai 115 orang pesakit melepasi ujian saringan dan menandatangani borang persetujuan menyertai kajian. Sampel darah diambil bagi tujuan penentuan genotaip CYP2B6 dan OPRM1 (sekali) dan untuk penentuan kepekatan methadone darah (setiap kali proses pengambilan data). Kepekatan methadone darah ditentukan

melalui kaedah ELISA dan penentuan genotaip ditentukan menggunakan kaedah PCR. Analisis statistik yang bersesuaian diaplikasi sewajarnya.

Keputusan: Dos methadone didapati mempunyai hubungkait yang sederhana dan positif dengan tahap kepekatan methadone darah ($r=0.4$, $p<0.001$), dengan hanya sekitar 20% perubahan yang berlaku dalam kepekatan methadone darah dapat dikaitkan dengan perubahan yang berlaku pada dos ($r^2=0.16$-0.19, $p<0.05$) walaupun setelah mengambil kira faktor-faktor persekitaran pesakit yang mungkin akan mempengaruhi kedua-dua pembolehubah tersebut. Walau bagaimanapun, kepekatan methadone darah menunjukkan hubungkait yang lemah dengan keterukkan gejala penarikan atau pengambilan dadah terlarang. Manakala dos pula, tiada menunjukkan sebarang hubungkait dengan kedua-dua keberkesanan klinikal tersebut. Kajian terhadap gen CYP2B6 mendapati pesakit dengan variasi CYP2B6*6 mempunyai min kepekatan methadone darah terubahsuai *(log* C_{trough}*/dose)* yang lebih tinggi berbanding pesakit dengan haplotype CYP2B6*1 *(wildtype).* Kajian terhadap gen OPRM1 pada lokus 118 seterusnya menunjukkan pesakit dengan variasi GG didapati tidak menggunakan dadah terlarang pada tahap kepekatan methadone yang rendah iaitu di bawah paras 250ng/ml berbanding pesakit dengan genotaip AA (*wildtype)* ($p<0.05$).

Kesimpulan: Gen CYP2B6 dan OPRM1 dengan polimorfisme nukleotida tunggal pada lokus 118 mungkin berupaya menghuraikan sebahagian variasi kepekatan methadone darah dan keberkesanan klinikal. Namun, aplikasinya dalam pendekatan pemantauan terapeutik ubat (methadone) bagi tujuan pengindividualan dos methadone berasaskan keberkesanan klinikal didapati adalah tidak sesuai.

THERAPEUTIC DRUG MONITORING IN METHADONE MAINTENANCE THERAPY (MMT): AN EVALUATION OF GENETIC FACTORS INFLUENCING CLINICAL OUTCOMES AND SERUM CONCENTRATIONS OF METHADONE

ABSTRACT

Introduction: Methadone maintenance therapy (MMT) has been widely used to prevent withdrawal symptoms among opiate use disorder patients. It is one of the harm reduction approaches in order to reduce the spread of fatally blood borne diseases in the community especially HIV AIDS. However, determining the optimal dose in patients is somehow difficult and challenging as it shows wide inter-individual variability of pharmacological activity. This study correlates the trough serum methadone concentrations (C_{trough}) at steady state with the methadone dose and the clinical outcomes namely severity of withdrawal symptoms and urinalysis for other illicit drugs. The relationship between various CYP2B6 haplotypes with the C_{trough} and OPRM1 (A118G) single nucleotide polymorphisms (SNPs) with the clinical outcomes measures were also studied.

Methodology: One hundred and fifteen (115) patients participated in the study after screening and signing the informed consent form. Blood samples were collected for genotype determination (once) and C_{trough} determination (each data collection point). The methadone serum concentrations were analyzed by using ELISA (methadone ELISA kit) method and genotyping of CYP2B6 and OPRM1 (A118G) were determined by using validated PCR method. Statistical analysis was applied appropriately.

Results: Methadone dose was found to have moderate and positive correlation with the C_{trough} ($r=0.4$, $p<0.001$) with only about 20% of changes in C_{trough} can be explained by the changes in dose ($r^2=0.16$-0.19, $p<0.05$) even after considering possible patients characteristics which may influence the two variables. Nevertheless, Ctrough have shown poor correlation with severity of withdrawal symptoms or urinalysis for other illicit drugs. Dose on the other hand did not show any correlation with both of the clinical outcomes measured. Study on CYP2B6 gene shows those patients with CYP2B6*6 variants have significantly higher mean of corrected trough serum concentrations (log Ctrough/dose) compared to the wildtype (CYP2B6*1). Further study on the OPRM1 (A118G) gene further shows those patients with homozygous variants (GG) did not involved in illicit drug use at lower methadone concentration of less than 250ng/ml compared to the wildtype (AA) ($p<0.05$)

Conclusion: CYP2B6 and OPRM1 gene with A118G SNPs may able to explain some of the variability in C_{trough} and clinical outcomes measured in MMT. However, those genes may not be of value in therapeutic drug monitoring for the purpose of personalizing the dose of methadone as based on the clinical outcome measures.

CHAPTER 1
INTRODUCTION & LITERATURE REVIEW

1.1 Background

"Opioid addiction is a curse wrapped-in a gift", a perfect phrase from an opioid user which directly describes the rewarding and at the same time, the slow bringing forth of its addictive mechanisms, enclosing patients in a tunnel-like trap with nowhere to escape (Tasman *et al*., 2008). Popularly regarded a social or personal affliction, in the 1960s, opiate addiction was redefined a medical disease (Kreek, 1993; Kuehn, 2005). In the 1990's Dr Alan Leshner, a former director of the National Institute for Drug Abuse (NIDA) described opioid use disorder as an illness of the brain with suffers exhibiting untoward behavioural manifestations (Kreek, 1993). Understanding the pathophysiology and the treatment intervention of opioid use disorder was not traditionally of a priority. However, when studies consistently revealed the nestled relationship between intravenous drugs use (IDU) and the spread of human immunodeficiency virus (HIV) (D'Aquila & Williams 1987; Mascola *et al*., 1989; Schrager *et al*., 1991; Des Jarlais *et al*., 2003) it could no longer be ignored. In 2004, a study in 130 countries put the number of intravenous drugs users (IDUs) worldwide at approximately 13.2 million with 78% in developing and transitional countries. Prevalence of acquired immunodeficiency syndrome (AIDS) in these populations was estimated to be at least 20%. The virus spread mainly through the sharing of contaminated needles and other injection equipment but spread also occur through sexual intercourse, homosexual activity and mother to child transmission (Aceijas *et al*., 2004).

In 2009-2010, a worldwide study estimated that, worldwide, there were 15.9 million (11.0-21.2 million) IDUs and the highest percentage occurred in China, in the United States and in the Russian Federation. The average global prevalence of HIV/AIDS among IDUs was then estimated at 17.9%, with around 1 in 5 IDUs being HIV positive. Even though the global trend listed cannabis as the most widely used illicit drug, in Asia, opiates (nearly three quarters were heroin users) and other opioids were the most commonly used drugs implying a high proportion of IDU among drug users in the region (UNODC, 2011). In Malaysia, heroin has been the major drug of abuse contributing to approximately 84.0% to the overall drug-use burden (Scorzelli, 1988).

From their figures, in some countries, apart from it being the predominant role in transmitting the virus, injecting drug use also played a vital role in transmitting the virus to non-needle users. More transmission occurred from IDU compared to those from mother to foetus with a similar HIV prevalence observed among IDUs and non IDUs. IDUs probably transmitted HIV to their spouses through unsafe sex, thus their importance in HIV spread in people not using drugs. Thus, what probably started as a concentrated epidemic among IDUs has now showing evidence of generalization in the population (Strathdee & Stockman, 2010). In Malaysia and other countries in South East Asia, IDU is the major contributor to the HIV epidemic (Strathdee & Stockman, 2010). Parallel transmission of other blood-borne infections among IDUs adds a further complication with the added disease burdens of other fatal and contagious diseases like hepatitis B, C, and endocarditis (Chawarski *et al.,* 2006; UNODC, 2011).

In Malaysia, due to its proximity to the "Golden Triangle" drug use disorder became very prominent and dated back to the 1960's. Recreational use of opiates in Malaysia and elsewhere peaked during the era of the "hippies" in the 1970's (Kamaruddin, 2002). The numbers has since rapidly increased and in response, the Malaysian Government announced a war against drug use in 1983, similar to the approach in the US, probably then assuming Americans as having the most effective policy. Three acts-the Drug Dependants (Treatment and Rehabilitation) Act 1983- the Dangerous Drugs (Special Preventive Measures) Act 1985 and the Dangerous Drugs (Forfeiture of Property) Act 1988 were legislated to curb the spread (Kamaruddin, 2002).

The approach to drug use in Malaysia has been criminal as exemplified from its declaration of total war against its use. Malaysia has also displayed "zero-tolerance" to drug use and users and traffickers are generally treated similarly using its tough draconian drug laws, first introduced in 1983. In the main, drug use is considered a psychological/social problem that is self-inflicted (Rusdi, 2008). Thus, apart from criminalizing users, tremendous efforts are made at the "rehabilitation" of users and traffickers alike. In 1987, rehabilitation centres were built at great cost under the supervision of the Ministry of Home Affairs. Traffickers and users were then bundled into these and given the *"cold turkey*" treatment. They would usually remain there for up to two years, leading a regimented life of "rehabilitation" with the *cold turkey*, educational counselling, religious related teachings and preaches, as well as life skills enhancement programs bundled in. Pharmacological interventions were shunned although refractory subjects were given opioid antagonists such as naltrexone or naloxone to prevent craving (Mazlan *et al*., 2006).

After this period of “rehabilitation”, “rehabilitated” users would be discharged back to the society, almost with zero follow up. Not surprisingly, many would return for “repeat rehabilitations”, some up to ten times. The number steadily increased and between the years 1983 to 1988, it ranged from 44.3 - 60.7%. This was despite reports of a decrement in the number of new users in 1988. Thus the continued use of the approach was questioned (Scorzelli, 1992; Rusdi, 2008). Other interventions taken by the Government included awareness programs, education and media campaign for the prevention of drug use, specifically targeting the young population and other vulnerable groups (Wah *et al.,* 1996). Such remained the chosen policy until HIV became pandemic.

The way drug use disorder was seen has changed little over time, not until HIV came into being. The world saw its “first” HIV infection in 1981 (Centre for Disease Control and Prevention, 2001) not too long before it grew to be a rapidly growing pandemic. HIV is blood-borne. How HIV is transmitted has changed little over time and includes penetrative sex (homo- or hetero-), mother-to-fetal transmission and blood transfusion from infected donors. The sharing of injection equipment among injecting drug users is however a very efficient means of HIV transmission. There occurs a direct transfer of blood between individuals who share needles and other injection paraphernalia. A close association between injecting drug users (IDUs) and the HIV pandemic then began to emerge as exemplified in a study in a drug use community in New York in 1987 where 50% of the community became infected two years after the virus entered the community (Des Jarlais & Friedman 1989). When HIV entered the drug use community, its spread became explosive.

HIV first entered Malaysia in 1986. Soon after, its transmission became almost uncontrollable, peaking in 2003 with almost 24 new cases per 1000 population per year (AIDS/STI Section, Ministry of Health, Malaysia, 2012). Fueled by drug use, Malaysia's pandemic quickly became the fastest growing epidemic in the Asia Pacific region. HIV control is the only failed WHO millennium goal for Malaysia (United Nations Country Team, 2010). According to the regional office of WHO Western Pacific Region in 2011, the proportion of people living with HIV/AIDS (PLWHA) in Malaysia was estimated at 0.3% of the overall population (69,000 out of 25,347,000). From those, 73.7% occurred among people who used drugs (PWUD), specifically IDU, due to their sharing of injecting equipment (WHO WPRO, 2011). More alarmingly, what started as a concentrated epidemic among IDU, the epidemic is now showing evidence of a generalized spread. Thus although women make up a very small portion of drug users in Malaysia, the proportion of them infected with the virus has increased to an alarming 100-fold in ten years. Despite of all the numbers and all the evidence, little changed in Malaysia as regards drug use. Drug users continued to be marginalized and put into prisons and rehabilitation centres, further feeding the epidemic where the prison and centres became places of concentrated epidemics that would eventually spread to the population. In February 2003, a group of activists forming the working group for harm reduction at the Malaysian AIDS Council (MAC) that was convened by Professor Adeeba Kamarudzaman, an HIV-physician at Universiti Malaya succeeded in presenting a case to the committee headed by the then Deputy Prime Minister (DPM), YAB Dato Sri Najib. Nevertheless and very unfortunately, the policy change that was approved at this meeting with the DPM did not actually roll out until 2006.

In the year, the country saw its first needle syringe exchange programme (NSEP) and opioid substitution therapy (OST) with methadone maintenance therapy (MMT) program coupled with outreach programs primarily targeting the high risk groups that included the drug use community (WHO WPRO, 2011). This actually occurred only after the MMT program tabled and approved in the Parliament in October 2005. As espoused by Dato' Seri Najib, the primary responsibility for the program including its monitoring shifted to the Ministry of Health through the National Advisory Committee on AIDS and the Technical Committee on AIDS with the role of National Anti-drug Agency (AADK- *Agensi Anti-dadah Kebangsaan*) then relegated to being the secretariat. Soon after, promising results were seen (Ministry of Health (MOH) Malaysia, 2005).

1.2 Methadone maintenance therapy (MMT).

The use of methadone hydrochloride as maintenance therapy in opioid use disorder was initially proposed by Professor Vincent P. Dole and the late Professor Marie E. Nyswander in 1965. In their now famous study, MMT was shown to prevent and relieve opiate craving while blocking its euphoric effects (Dole & Nyswander, 1965). The take up of MMT however remained low because of critics and stigmas (Ausubel, 1966). Although the modality is now accepted in most of the world, MMT remains stigmatized and even now, more than 40 years after, methadone remains a widely studied drug (Kuehn, 2005).

His success with MMT prompted Dole to advance a new theory for opiate addiction, the opiate deficiency syndrome. Thus MMT was more a corrective rather than curative type of therapy, a normalising therapy. MMT normalizes the somatic, neurological as well as endocrinological dysfunction associated with prolonged opiate use. There is almost an immediate positive outcome seen with MMT where the patients exhibit a quick shift in their topic of interest that usually is centred on their next opiate dose such as from the time and context of their next opioid dose to more normal, leisurely topics and behaviours (Dole, 1988). Methadone also exerts a longer period of action which ultimately reduces fluctuations in serum concentrations, making it more convenient for both the patients and their physicians. Methadone is stored in the tissues and released slowly once there was a reduction in the serum level giving it a buffering characteristic. It has in fact been suggested that blood methadone be optimally maintained between 150-600ng/ml to ensure its efficacy (Dole & Kreek, 1973).

Several characteristics make methadone especially suitable for maintenance therapy (Kreek, 1993). Methadone exhibits an excellent oral bioavailability that ranges between 80-90%. The drug also exhibits a long half-life allowing for a once daily dosing that can fit well into the patients' daily life. Patients will be able to lead a normal lifestyle and maintain productivity, without the deliberating craving. Another important criterion of methadone is its slow onset of action, which prevents the fluctuations of drug concentrations in the blood and brain, preventing withdrawal symptoms. This allows for a steady state "perfusion" of the drug at its site of action on the specific opioid receptors and other sites involved. (Kreek, 1993).

Although MMT is now generally accepted in most countries, practices vary. In countries like the USA and Malaysia, a "high-threshold" approach is taken where stringent guidelines and protocols dictate how MMT is to be implemented. As an example, under such an approach, a person can only be prescribed methadone if there is family support and patients can be expelled from the program if they breach the stringent program rules. These occur despite agreements that MMT is an essential component in managing the ongoing world-wide HIV epidemics.

Thus**,** in the United States of America (USA) where its National Institute for Drug Abuse (NIDA) recognizes MMT as the main strategy to overcome the HIV/AIDS pandemics (NIDA, 2005), methadone is prescribed in its oral-form only and under close monitoring according to strict guidelines and protocols (Legislative Council Secretariat US., 1996). Such is regrettable as, it is known that even interim methadone clinics did show positive effects on the use of illicit drugs and HIV related risks behaviour even without the full and comprehensive methadone treatment in official programs. (Stanley,1991).

In Canada, although MMT is adopted, they subscribe to the high-threshold approach with their comprehensive but stringent guidelines (New Brunswick Addiction Services, 2009).

In countries like the United Kingdom (UK) and the Netherland on the other hand, a "low threshold" approach is adopted where there is a generally less stringent controls. The comfort and convenience are also given due considerations. As an example, patients could choose to take one of the several formulations of methadone available in the market according to their needs (daily illicit injectors, had poorer psychological and physical health at entry) (Ford & Whitehead, 1996; Strang *et al.,* 2000). Formulations included tablets, syrups or liquids and even intravenous routes where it has been shown to result in similar success rates in sub-populations of poorly responding patients given maximal doses of methadone.

Unlike their counterparts in high-threshold programs who have to comply to the many stringent rules, low-treshold regular/returning patients can have their prescription filled at the community pharmacies, saving them long waits at the clinics to see their doctors. They were also not required to be closely supervised as in the directly observed therapy (DOT) of the high-threshold patients (Gossop *et al.,* 2001). The low-threshold is also adopted in Australia although political expediencies sometimes override good science. The MMT program in Australia has been very successful and together with their extensive NSEP coverage, it is regarded as the most effective approach in reversing their growing epidemic. Australia now has over 25,000 people on MMT and this has been touted as a successes story in policy decisions (Mc Arthur, 1999).

HIV knows no borders. Even the socialist/communist countries with their strict laws could not prevent the attacks of HIV. Thus in China for instance, where the actual numbers of PLWHA is anybody's guess, HIV is also a major threat. Fortunately though, China boasts of probably having the most extensive program coverage with the highest number of MMT clinics that first begun in 2004 with 8 pilot methadone clinics (Liu Z. *et al*., 2006). Indeed, looking at their progress now, it is almost unbelievable that the Chinese came to learn from Malaysia when they were embarking on the program, and look at them now (Ismail, 2004), although there are concern about patients' aftercare, unsatisfactory participation levels in training programmes for volunteers (Yin *et al.*, 2010). In Malaysia, according to the current practice guideline (MOH Malaysia, 2005) on initiating the dosage of methadone, upon enrolment, patients were subjected to 2 phases of MMT; 1) Induction and 2) Maintenance phase. During induction phase, the dose is gradually increased until withdrawal ceases and the clinical response is satisfactory. A good history is vital as it gives information on previous methadone intake. It has also being recommended that patients should not be commenced with methadone in the case of no evidence of physical dependence in order to prevent the incidence of methadone intoxication. Generally physicians normally start treatment with a 20 - 40 mg daily dose of methadone, to be taken usually in the morning. During the initial week or two, dosage increments were kept relatively low, typically 5 mg/increments every 3 days as clinically indicated. Patients are followed up closely, every day or every other day during the first several weeks, for efficacy as well as toxicity. Fresh urine samples were also obtained to screen for abstinence. Up to a month is required before a steady-state is reached after which there would be less fluctuation in blood methadone**.**

The guidelines call for strict monitoring of the patients and during the maintenance phase, they would be reviewed every month and their urine tested randomly for illicit drugs. Outcomes were measured using several instruments; the WHO-BREF Quality of Life, Opiate Treatment Index (OTI) with urine tests for illicit drugs (methamphetamine, amphetamines, ketamine, tetrahydrocannabinoids and the benzodiazepines that included midazolam and alprazolam). Apart from the MMT, supportive therapy was also given in an effort to enhance the success rate of therapy (Brooner & Kidorf, 2002).

Patients would be given counselling with either the pharmacists and/or designated counsellors and they were also monitored for toxicity. Of note are some characteristics of the patients that may also impact on their therapy. Generally these patients have greater illicit drugs exposure, higher rates of psychiatric diagnoses and other medical conditions, high rates of unemployment together with low psychosocial status. Furthermore, peer pressure associated with the drug culture in the community may make it difficult for the patients lead a drug-free life, even legally (Brooner & Kidorf, 2002).

1.3 Pharmacology

Methadone is a synthetic drug with a full μ-opioid receptor agonistic property. It is classified as opioid analgesics / opioids (Micromedex online database). Clinically, methadone has been used in the chronic treatment of moderate to severe pain and also in the management of opiates dependence (Fredheim *et al.,* 2002 ; Eap *et al.,* 2002) which is our focus in this study.

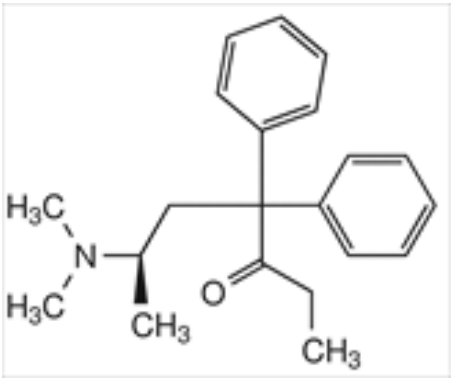

Figure 1.1: Chemical structure of methadone
(Source : Martindale. Complete Drug Reference)

Isolated methadone is liposoluble and basic with pKa of 9.2 that also gives it buffering properties as seen during its initial discovery (Dole & Kreek, 1973 ; Garrido & Troconiz, 1999). Oral bioavailability is highly variable and reported to range from 41% - 95 % (Meresaar *et al.,* 1981; Ferrari *et al.,* 2004) with large inter-subjects variation. At doses between 10-60 mg, oral bioavailability of its tablet lies between 70-80% (Eap *et al.,* 2002) and this contributes to inter-subject variability which is important for the determining of the initial and maintenance doses.

Methadone plasma concentrations over time follow a bi-exponential curve, with a rapid α-phase (the transfer of the drug from the central compartment to the tissue compartment and to the beginning of elimination) and a slow β-phase that corresponds to elimination (Ferrari *et al*., 2004). As it has a rapid α-phase, the kinetics of oral methadone at steady state has been described as following a single compartment model (Wolff *et al*., 1993). The $t1/2_{\alpha}$ (α-phase) shows marked inter-individual variability, and ranges from 1.9 to 4.2 hours (H), with an average value of 2.95 ± 0.9 H (Meresaar *et al.,*1981). The $t1/2_{\beta}$ of elimination (β-phase) varies even more, from 8.5 to 47 H (Nilsson *et al*., 1982[a]; Wolff *et al.,* 1991). It is widely accepted that the population half life of methadone was between 24 ± 13 H (Eap *et al.*, 2002).

Methadone is prescribed as a racemic mixture of two stereoisomers. Apart from other pharmacological effects, (*R*)-methadone is responsible for analgesia but (*S*)-methadone, while retaining some of the effects like the antitussive activity (Ferrari, 2004) is responsible for some of the methadone toxicity, namely cardiac arrythmias. Several formulations are available; solution (syrup-based), tablet and injectable for intravenous (IV) or intramuscular (IM) injection. Absorption from tablets and syrup appear comparable (Meresaar *et al.,* 1981). It is expected that there will be no significant difference between oral formulations in terms of their pharmacokinetics profile (Eap *et al.*, 2002)

After oral administration, onset of action is variable but typically it occurs after about two hours. Its duration of action, again, although variable, it is typically between 2-10 hours after the dose (Dale *et al.,* 2002) and so is the time to peak concentration that

varies between 2-4 hours (Inturrisi & Verebely, 1972 (b); Verebely & Kutt., 1975). Enterohepatic recirculation of methadone is probably responsible for the second peak which occurs approximately 4 hours after its administration (Eap *et al.,* 2002). Methadone can be detected in the blood within 15–45 minutes after an oral administration (Wolff *et al.,* 1993; Inturrisi *et al.,* 1972; Ferrari *et al.,* 2004).

Methadone is highly bound to plasma proteins, including to albumin, γ-globulins, lipoproteins and the most prominent one is α1-acid glycoprotein (Foster et al., 2004; Eap et al., 2002). Protein binding is about 71-89% (Olsen, 1973) that varies depending on serum protein concentration (Horns *et al.,* 1975). As an example, acute phase protein, α1-acid glycoprotein will increase during pathological conditions such as cancer and long term opioid exposure. This explains a lower free fraction of methadone in cancer patients than in control subjects. Eap *et al.* reported that methadone free fraction have shown 3-6 fold in variability depending on patients' conditions (Eap e*t al.,* 2002).

Due to its high lipid solubility, methadone rapidly attains high tissue concentrations in the kidneys, spleen, liver and lungs and a smaller amount goes into the brain (Blinick *et al*., 1974) almost simultaneously (Ferrari *et al*., 2004). Methadone also readily crosses the placenta. However, the exposure of breast-fed infants to methadone consumed by their mothers is minimal. Women on MMT should therefore not be discouraged from breast feeding because of this (Wojnar-Horton *et al.,* 1997). In general, its volume of distribution (VD) is about 1-8L/kg (Micromedex online database). It has been found that oral clearance and VD of racemic methadone were not influenced by body weight over the 44-110kg range, even when allometrically scaled (Foster *et al.,* 2004).

Methadone is extensively metabolized and mainly in the liver. Small amounts undergo gut metabolism mediated by intestinal CYP3A4. The main metabolite of methadone (2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EDDP) is inactive and it is formed by *N*-demethylation with a subsequent spontaneous cyclization (Ferrari *et al.,* 2004). Other than methadone and EDDP, eight other metabolites have been identified in the urine, and three metabolites in the faeces (Eap *et al.,* 2002).

Subsequent to the biotransformation, methadone is eliminated in the kidneys as well as the faeces. In a study conducted with four subjects given radio-labelled methadone, two of the subjects excreted the major part of the radioactivity in the urine with the other two eliminating the radioactivity in both urine and faeces (Eap et al., 2002). The rate of renal clearance was approximately 2.9-15.6 ml/min (Inturrisi & Verebely, 1972(a)). Methadone and EDDP together account for 17–57% of a given dose, 15–60% during the first 24 hours (20% as an unmodified drug, and 13% as 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; EDDP).

Faecal elimination accounts for 20–40% of the total elimination. Overall faecal elimination accounts for about 25% of total elimination during the first 24 hours, and 52% during the first 96 hours (58% as methadone and 42% as metabolites). Urinary elimination of unmodified methadone is pH-dependent and is increased by urine acidification. When urinary pH is less than 6, the amount of excreted methadone is three to eight-times greater than at pH higher than 6 (Ferrari *et al.,* 2004).

The elimination of methadone is mostly due to a metabolic clearance. The limited amounts of circulating drug that undergoes glomerular filtration are partially reabsorbed by the kidney tubules, and this re-absorption is also pH-dependent. In one study, a 3-fold higher renal clearance was calculated in a group of patients with a 24-hour urine pH of 6.1 as compared to another group with a 24-hour urine pH of 6.6 (Foster *et al.,* 2004).

1.4 Clinical Use

The treatment of drug use disorder prevents HIV/AIDS (Sorensen & Copeland, 2000) and clinical trials have shown its effectiveness especially in terms of reducing HIV seroprevalence and transmission of other blood-borne viruses. Two decades of study in the Bronx in New York on MMT has shown that methadone was effective as a protective measure in cutting down the number of HIV infection (Hartel & Schoenbaum, 1998). Positive outcomes included a reduction of illicit drug use which in itself will reduce HIV AIDS risks due to reduction injecting frequencies (Bloor *et al.,* 2008; Marsden *et al.,* 2009) and a reduction in needle sharing which again protects against HIV/AIDS.

MMT is a life-long commitment. The longer the patients receive MMT the better the outcome and this has been used by detractors who saw MMT simply as replacing one dependency with another (Gossop *et al.,* 2003). A longitudinal prospective cohort study showed a long term continuous improvement in the quality of life of patients on long durations that ranged from 3 to 12 months and this has also supported long term use of the treatment (Maremmani *et al.,* 2007[b]).

The benefits are maintained in patients with psychiatric co-morbidity who also showed improvements including longer treatment retention, reduction of illicit drug use and reduction in HIV-related risks behaviour (Pani *et al.,* 1997). Similarly, providing methadone in incarcerated settings are also effective but the therapy has to be continued post-release (Kinlock *et al.,* 2009).

Gossop *et al.* has undertaken a big study called the National Treatment Outcome Research Study (NTORS). The majority of patients in the study demonstrated improvements in each domain measuring illicit drug use, criminal behaviour, withdrawal symptoms, HIV AIDS risk behaviour, health status and overall socioeconomic position as well as quality of life (Gossop *et al*., 2000). A similar study conducted in Malaysia produced similar trends of success with improvements in the quality of life in patients undergoing MMT. Retention rate was 63.6% after 2 years and significant improvements were documented in terms of physical and psychological health, socio-economic status and existence of supportive environment ($p<0.001$) (Musa *et al.,* 2011).

Take home privileges may encourage retention as it reduces the burden and stress of patients having to attend daily methadone clinics. The rule which prohibits the take-home doses has a negative consequence (Pani *et al.,* 1996). Take-home doses among highly motivational and stable patients even increased patients' incomes when compared patients who have to comply to rigid daily scheduled observed therapy (King *et al.,* 2002).

In general, the case for the effectiveness of MMT has been strongly made. MMT is of proven benefits in decreasing the following: relapse; number of days using illicit opioids; usage of opioid and cocaine after release from prison; criminal activity; injection and HIV transmission activity. MMT also increased employment rate; proven cost effective; improved retention rates in HIV care; improved the use and effectiveness of highly active anti retroviral therapy (HAART) (Altice *et al*., 2010).

On the flip side, several studies failed to demonstrate the effectiveness of MMT in specific populations as measured by degree of drop outs, dose deviation, violation of rules and regulation under methadone programs, death due to overdose, suicide which has been confirmed by autopsy as well as transfers to centres which serve heroin. These occurred mainly with patients who continued taking illicit heroin despite being under MMT (Mino *et al.*, 1998). In European countries, the continuous use of cocaine and alcohol continue to threaten the success of MMT (Maremmani *et al.*, 2007[a]). Cocaine use during treatment has been shown to be detrimental to treatment retention and promoted heroin relapse (Hartel & Schoenbaum, 1995) and alcohol dependence frequently occurred as co-dependence (Hillebrand *et al.*, 2001).

Used safely in millions over the years, MMT is relatively safe. Nevertheless it has been associated with some very serious adverse effects, the most serious of which is probably the precipitation of QTc-prolongation. The prolongation can herald the occurrence of potentially fatal arrhythmias including torsade des pointes (Justo, 2006; Anchersen *et al.*, 2009; Mayet *et al.*, 2010).

Respiratory distress and neuropsychology impairment can also occur. These may occur after prolonged use of methadone and has led to the sudden discontinuity of treatment and treatment failures. Nevertheless, despite these, MMT has been shown to be consistently superior to other approaches that include drug-free forced abstinence (Prosser *et al*., 2006).

Poor adherence indicates a failure to achieve the goal of therapy and among others, it has been associated with unsupervised methadone prescribing and consumption (Haskew *et al.,* 2008). Poor adherence is however contentious. Some authors suggested measuring EDDP as a means to assess compliance (Larson & Richards, 2009).

Many factors contribute to the failure of methadone treatment and effectiveness. Among others, as has been shown in many studies, failure to use sufficiently high methadone doses has been reported to importantly contribute to treatment failures (Capplehorn *et al*., 1993; Mino *et al*., 1998; Leavitt *et al*., 2003). Indeed using an optimal dose is the key to successful MMT. However determining an optimal dose is a major challenge (Hiltunen *et al.,* 1999; Trafton *et al.,* 2006). Many studies have in fact showed that low doses caused treatment failures. It is our objective in this study to determine factors that can contribute to treatment failures and further optimize the dosing regimen.

1.5 Dose Optimization

Methadone has a complex disposition mediated by polymorphic enzymes, transporters and receptors. The consequent pharmacokinetic variability makes similar doses not yielding similar plasma concentrations or clinical effects in different subjects. Its long half-life and wide inter-patient variability in its clearance also make methadone use difficult to optimize. These variability may be further altered by drug interactions.

Patients on MMT frequently receive treatment with other drugs due to the frequent comorbidity. Common are the use of psychotropic drugs, antibiotics, anticonvulsants and antiretroviral drugs and these can cause pharmacokinetic interactions. The consequent pharmacokinetic drug–drug interactions with methadone can reduce the concentrations and the effects of methadone with the consequent withdrawal and increased risks of relapse. Justified or otherwise, due to fears of high doses and the occurrence of toxicity, many physicians use relatively low doses of methadone in MMT. The use of low doses threatens to derail successful MMT programs.

As a surrogate for effectiveness, Dole and Nyswander have long proposed the use of therapeutic drug monitoring for MMT and they recommended that blood concentration be maintained around 150-600 ng/ml for effectiveness (Dole & Kreek., 1973).

1.5.1 High dose yields better outcome

"Higher is better". That generally holds through with methadone maintenance dose to ensure retention in programs, up to a limit. As an example, it was found that a dose of 50 mg/day was associated with higher retention rates compared to lower doses (Farre M. *et al*., 2002). Similarly, patients maintained on 60 mg/day or higher had better treatment outcomes and indeed, doses exceeding 100 mg/day have been used safely and effectively in long-term maintenance treatments (Maxwell & Shinderman, 2002).

The odds of patients maintained on 40 mg were 2.2 times more likely to be back on heroin use compared to those maintained on 80 mg daily (Caplehorn *et al.,* 1993).

A study by Hartel *et al.* further concluded that the use of high methadone doses is important to promote heroin abstinence. They found that heroin use during the 3 months prior to study interviews was highest among (1) patients maintained on less than 70 mg/day (adjusted odds ratio [OR] = 2.1, 95% confidence interval [CI] = 1.3, 3.4) and (2) patients who used cocaine during treatment (adjusted OR = 5.9, 95% CI = 3.8, 9.1). They further reported that these were independent of treatment duration, treatment compliance, alcohol use, and socioeconomic factors. Cocaine users were more likely than non-users to use heroin at all methadone dosage levels (Hartel *et al.,* 1995).

Similarly, yet another study reported that patients on higher doses (more than 70mg/day) had a better prognostic outcome in terms of retention rates and illicit opioid use, even though the authors also reported a similar role for other factors that included the quality of interpersonal relationships, stable income and low withdrawal scores that yielded a better prognostic outcome (Gerra *et al.,* 2003). Similar observations were also reported in other studies that included those by Ball & Rose, (1991); Maremanni *et al.,* (1994); Mohamad *et al*., (2010).

On the contrary, several studies failed to find a clear association between positive treatment outcomes and high doses. In Canada for instance, both higher and lower dosage protocols have been clinically implemented with parallel end results in different populations. Older and more motivated patients were given the low dose (40 mg) whereas higher doses (100 mg) were given to less motivated and more chronic users (Williams *et al*., 1971).

In an earlier study (Craig, 1980) where a dose of 30 mg daily was used, it was reported that patients remained on treatment for 6 to 12 months and scored higher in terms of outcomes, such as reduced illicit heroin consumption, reduced arrest due to criminality and full-time employment compared to the dropouts (Craig, 1980) even at this low dose. Other studies reported continuing use of illicit drugs and cravings despite high methadone dosage (deVos *et al.,* 1995). In yet another study by Blaney & Craig (1999), reported lack of significant difference in any of the outcome variables attributable to methadone doses (Blaney & Craig 1999).

Based on the above, it has been suggested that the dosage of methadone should be individualized instead of relying solely on the study population. Mino *et al., (*1998) proposed the use of individualized doses in concert with psychosocial support to increase success rates of MMT. They suggested that flexibility in methadone doses will lead to improved retentions as compared to rigid and population-based doses. However, it has been suggested that patients who have responded well to doses less than 30 mg should have no reason to increase their doses (Mino *et al.,* 1998) but there may be a case for stopping MMT altogether in the patients because it is conceivable that the patient does not require MMT at all.

Methadone dose increase and abstinence reinforcement have been reported to decrease urine positive tests during treatment. However, it is probably best to give doses to individual patients' needs (Preston *et al.*, 2000). Alas, evidence may not translate to practice and many physicians continue to prescribe low doses, probably for psychological reason (Loimer & Schmidt, 1992). In Malaysia average dose is less than 40 mg per day but we recently showed that even in Malaysia, a daily dose of 80 mg was superior to lower daily doses (Mohamad *et al.*, 2010).

1.5.2 Methadone concentrations and TDM for methadone

As with many other drugs with low therapeutic indices, therapeutic drug monitoring (TDM) with use of plasma methadone may help in dose optimization for MMT to improve outcomes. A therapeutic range of 300 - 400 ng/ml racemic methadone has been proposed (Torens *et al.,* 1998). Wolff *et al.,* (1991) have indeed proposed a dosage nomogram for improved application of MMT. They found a good correlation between dose and serum methadone concentration with an r of 0.89. They then proposed that plasma methadone increased by 0.263 mg/L for every milligram of methadone consumed per kilogram of body weight (Wolff *et al*., 1991).

Generally though, clinical practice can probably not now benefit from TDM due to a lack of suitable analytical methods. General application needs to await for an analytical method that, not only it is sensitive and specific but are also easy to perform by non-experts. Currently methadone concentrations can only be determined using relatively sophisticated equipments and published methods include gas or liquid chromatography and immunoassay. (Wolff *et al.*, 1992; Schmidt *et al.*, 1993; Kell & Techman, 1996).

Bell *et al.* in the 1990's, suggested that the continued use of illicit drugs despite MMT were due to the patient's desire to seek "desired" effects of methadone. It had nothing to do with either the drug dose or concentration. Their patients with lower serum concentration seemed to similarly have adequate methadone doses as did their patients with higher concentration. (Bell *et al*., 1990).