A CLINICAL AND PHARMACOGENETIC INVESTIGATION OF METHADONE MAINTENANCE THERAPY (MMT) IN OPIATE DEPENDENT INDIVIDUALS.

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by

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LIST OF ABBREVIATIONS

AIDS	Acquired immune deficiency syndrome
ARV	Anti retroviral treatment
AUC	Area under curve
CYP2B6	Cytochrome P450 family 2 subfamily B polypeptide 6
CYP3A4	Cytochrome P450 family 3 subfamily B polypeptide 4
ELISA	Enzyme-Linked Immunosorbent Assay
HAART	Highly Active Anti-Retroviral Treatment
HIV	Human Immunodeficiency Virus
HRP	Horseradish peroxidise
INFORMM	Institute for Research in Molecular Medicine
MMT	Methadone Maintenance Therapy
NSEP	Needle Syringe Exchange Program
OOW	Objective Opioid Withdrawal Score
OPRM1	Mu opioid receptor variant 1
PCR	Polymerase Chain Reaction
PTSQ	Pittsburgh Total Sleep Quality Score
SAHABAT	Persatuan Perantaraan Pesakit-Pesakit Kelantan
SOW	Subjective Opioid Withdrawal Score
TMB	Tetramethylbenzidine

LIST OF DEFINITION

Group of Dose

- **Low Dose** Dose of methadone of 80 mg or less (Krantz *et al*, 2004)
- **High dose** Dose of methadone of 80 mg or less (Krantz *et al*, 2004)

Retention The patient has to attend the therapy for at least fifteen days in a month (Ministry of Health, 2005)

SATU PENYIASATAN KLINIKAL DAN FARMAKOGENETIK TERHADAP RAWATAN PENGEKALAN METADON (MMT) DI KALANGAN INDIVIDU PENGGUNA OPIAT

ABSTRAK

Sehingga kini terdapat banyak penemuan yang telah merevolusikan bidang perubatan. Metadon telah merevolusikan pengurusan pengguna opiate. Melalui MMT, kebanyakan pesakit memberikan respon yang baik dan menunjukkan peningkatan dari segi taraf kesihatan. Walaubagaimanapun, sifat farmakologinya yang kompleks dan pemikiran "*opiophobia"*telah membataskan kegunaannya. Di kalangan "opiophobics" ini, penggunaan ubatan Cina telah menarik perhatian mereka untuk menggunakannya sebagai rawatan alternatif. Kami telah melakukan kajian klinikal dan makmal terhadap faktor-faktor yang terlibat dalam meramal kejayaan program MMT, sebagai satu langkah untuk membaik pulih rawatan dengan metadon dan untuk membantu kami merangka satu panduan untuk mengoptimakan MMT. Kami juga mengkaji kesan herba Cina, BioLitrin ke atas pesakit yang telah distabilkan dengan MMT bagi menilai peranannya sebagai tambahan kepada MMT.

Bahan dan Kaedah

Kajian klinikal ini telah menerima kelulusan etika daripada Pusat Perubatan Universiti Malaya di Kuala Lumpur dan Universiti Sains Malaysia di Kelantan. Kajian ini melibatkan dua komponen iaitu kajian klinikal dan kajian makmal farmakogenetik. Kajian klinikal melibatkan 2 fasa.

Dalam kajian klinikal fasa 1, pesakit MMT yang hadir ke Klinik Khafiz di Semenyih dan Klinik SAHABAT di Kota Bharu yang telah memberikan persetujuan dan memenuhi kriteria kajian kami telah dijemput untuk menyertai kajian ini. Mereka telah mengambil metadon secara harian berdasarkan panduan yang disediakan oleh Kementerian Kesihatan Malaysia. Parameter-parameter klinikal dan makmal pula dipantau berdasarkan protokol kajian kami. Di sepanjang tempoh kajian tersebut, mereka telah melalui rawatan susulan selama 12 bulan. Kepelbagaian genetik pada lokus-lokus gen *CYP2B6*, reseptor opiat-μ, dan *CYP3A4 telah* dikenalpasti dengan mengekstrakkan DNA daripada subjek-subjek menggunakan kit mini QIAgen DNA. Bagi *CYP3A4*, kaedah *nested allele* Polimerasi Tindak Balas Berantai (PCR) yang spesifik telah diaplikasikan untuk mengesan jenis dan frekuensi-frekuensi alel yang berikut: *CYP3A4*1B, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*7, CYP3A4*8, CYP3A4*9, CYP3A4*10, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*14, CYP3A4*15, CYP3A4*16.* Manakala bagi alel *CYP2B6* (*CYP2B6*2* dan *CYP2B6*9)* dan *OPRM1* (G31A, G691C dan A118G) pula, kaedahnya adalah dengan menggunakan Kit "*Personalized Medicine for Methadone"* yang telah dicipta di Institut Penyelidikan Perubatan Molekul (INFORMM). Kit ini juga telah digunakan untuk mengenalpasti plasma metadon. DNA daripada kawalan normal yang terdiri daripada orang Melayu, Cina dan India juga telah dikenalpasti untuk kepelbagaian genetik pada lokus-lokus seperti di atas.

Dalam kajian klinikal fasa II, seramai 40 orang pesakit yang telah memberikan persetujuan dan memenuhi kriteria kajian kami telah menyertainya. Setiap daripada mereka pada permulaannya menerima sama ada dua kapsul yang mengandungi 200 mg

BioLitrin diambil 2 kali sehari atau dua kapsul mengandungi ”*placebo”* bersama-sama dengan metadon pada dos yang tetap sebanyak 40 mg selama 4 minggu berturut-turut. Darah juga diambil untuk mengesan paras plasma metadon dan kualiti tidur serta skor tarikan opiat diukur dan dibandingkan. Selepas ”*wash-out period*” selama dua minggu, penukaran telah dilakukan, di mana pesakit-pesakit yang telah menerima Biolitrin pada permulaannya kini telah diberikan ”*placebo*”, manakala pesakit-pesakit yang dahulunya menerima ”*placebo*” kini menerima Biolitrin.

Keputusan

Seratus dua puluh lapan orang pesakit telah menyertai fasa I kajian klinikal. Seterusnya 40 orang pesakit dikaji di dalam fasa II Secara umumnya, kadar kekal *(retention rate)* pada 12 bulan adalah 54.69% dengan 58 pesakit telah hilang semasa rawatan susulan. Daripada mereka yang masih “kekal”, 80% daripadanya telah menerima dos sebanyak 80 mg atau lebih sehari. Tiada di antara mereka yang berada dalam kumpulan dos 0 – 39 mg sehari. Kadar kekal untuk kumpulan dos 40 – 79 mg sehari pula adalah sebanyak 20%. Perbezaan di antara kumpulan dos-dos ini dari segi kadar kekal dan injeksi semula mencapai statistik yang signifikan, (masing-masing adalah $p<0.001$, $p<0.001$). Purata dos harian pula ialah 57.2 mg (SD ± 22.7) dan berada dalm lingkungan 20 to 160 mg sehari, iaitu perbezaan sebanyak lapan kali ganda. Purata kepekatan plasma metadon berkenaan pula adalah 281.3 ng/ml (SD ± 567.9) dan berada dalam lingkungan 0 to 4634 ng/ml. Di antara pesakit yang menerima dos harian tetap metadon pada 40 mg, plasma metadonnya adalah berbagai dari 14 ng/ml ke 331 ng/ml, iaitu perbezaan sebanyak 23 kali ganda. Dalam kajian klinikal fasa II, purata SOW adalah 32 (SD ± 10.4) dan dalam

lingkungan 11 ke 51. Purata OOW pula adalah 8.2 (SD ± 1.5). Pada lokus *CYP2B6,* 7% adalah heterozigus *CYP2B6*1A / CYP2B6*2* (64 C/T). Pada G15631T pula, 51.3% adalah homozigus *CYP2B6*1A* (15631 G/G), 39.1% adalah heterozigus *CYP2B6*1A / CYP2B6*9 (*15631 G/T) dan 9.6% adalah homozigus mutasi *CYP2B6*9.* Frekuensi-frekuensi bagi *CYP2B6*2* dan *CYP2B6*9* masing-masing adalah 3.5 dan 29.1. Daripada 17 alel yang telah diuji untuk gen reseptor opiat-μ, frekuensi pada alel-alel G31A, G691C dan A118G masing-masing adalah 3.9, 20.9 dan 56.1. Sejumlah besar pesakit adalah pembawa alel *CYP2B6* iaitu alel yang boleh memberikan petunjuk tentang metabolism metadon yang rendah. Selain itu, sejumlah besar pesakit yang lain juga adalah pembawa alel reseptor opiat-μ mutasi, yang mana boleh memberikan ramalan mengenai kesan opiat yang kurang baik. Subjek kawalan kesemuanya membawa gen "*wild type".* Alel mutasi pada *CYP3A4*1B* pula telah dijumpai dalam 2.17% subjek-subjek pengguna opiat.

Pada kajian klinikal fasa II, plasma metadon adalah lebih rendah daripada sasaran 400 ng/ml dalam kebanyakan keadaan dalam kebanyakan pesakit. Tiada kepekatan plasma metadon yang diperolehi melebihi 700 ng/ml, di mana ia boleh dianggap sebagai had atas untuk plasma metadon. Purata SOW dalam pesakit yang menerima hanya metadon sahaja adalah 32 dan dalam pesakit yang menerima gabunngan metadon dan BioLitrin puratanya adalah 3.5, iaitu perbezaan sebanyak sepuluh kali ganda. Purata OOW dalam "*placebo"* adalah 8.2 dan semasa mengambil BioLitrin adalah 0.7, iaitu perbezaan sebanyak lebih daripada sepuluh kali ganda. Semasa mengambil BioLitrin pesakit mengalami kurang tarikan berbanding semasa "*placebo"* dan ini mencapai perbezaan statistik yang signifikan.

Kesimpulan

Walaupun metadon ada potensi untuk merevolusikan perawatan penggunaan opiat, sifat farmakologinya yang kompleks dan pemikiran ”*opiophobia*” yang meluas telah membataskan keberkesanannya. Kami menggunakan kit diagnosa yang telah dicipta di INFORMM untuk mengesan kepelbagaian *CYP2B6* dan reseptor opiat-μ dan juga untuk mengukur plasma metadon. Selain daripada mencari kaedah untuk mengesan variasi *CYP3A4* , kami juga mentakrifkan kepelbagaian genetik *CYP3A4* . Kami juga telah menyiasat rawatan yang menggabungkan metadon dan BioLitrin. Dos-dos harian metadon,paras metadon dalam plasma, kadar kekal dan injeksi semula adalah pelbagai. Walaubagaimanapun, maklumat diperolehi mengenai kepelbagaian pada lokus-lokus *CYP2B6*, reseptor opiat-μ dan *CYP3A4* yang diperolehi daripada kajian ini adalah tidak mencukupi untuk merekacipta rejimen dos metadon. Ramalan yang paling bagus ke atas keberkesanan MMT boleh dilakukan dengan mengambil dos harian yang melebihi 80 mg. Dalam kebanyakan pesakit, plasma metadonnya adalah tidak berguna tetapi di dalam sesetengah kes tertentu, plasma metadon boleh digunakan untuk perawatan dalam kes kegagalan terapeutik. BioLitrin boleh bertindak secara sinergistik bersama metadon. Ia membantutkan tarikan dan meningkatkan kualiti tidur. Seterusnya, kajian susulan diperlukan untuk menggabungkan BioLitrin dan metadon terutamanya untuk kegunaan jangka masa panjang. Kajian yang lebih besar juga diperlukan untuk mengenalpasti lebih banyak kegunaan kit ”*Personalised Medicine for Methadone”* dalam pengurusan rutin MMT.

Kata Kunci: MMT, kekal, variasi kepekatan plasma metadon, Biolitrin, kualiti tidur, skor tarikan opiat, farmakogenetik, *CYP2B6, OPRM1* dan *CYP3A4*.

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ABSTRACT

Over time, many discoveries revolutionized medicine. Methadone has revolutionized the management of opiate dependence. With MMT, most patients respond well and their health improves. Its complex pharmacology and "opiophobia" however impede its full usefulness. Among the "opiophobics", alternative therapies with, as an example, Chinese medicines, are frequently sought and advocated. We performed a laboratory and clinical study with the objective of investigating factors that predict successful MMT program, in an effort to improve therapy with methadone and to help us develop guidelines on the optimization of MMT. We also studied the effect of a Chinese herb, BioLitrin in patients maintained on MMT to evaluate its role as an adjunct to MMT.

Materials and Methods:

The study received ethical approvals from University Malaya Medical Centre in Kuala Lumpur and Universiti Sains Malaysia in Kelantan. The study consisted of both Clinical and Pharmacogenetic laboratory components. The clinical studies involved 2 phases.

In phase I clinical study, MMT patients attending Klinik Dr Khafidz in Semenyih and Klinik SAHABAT in Kota Bharu who consented and met our study criteria participated in the study. They took their daily methadone according to guidelines of the Malaysian Ministry of Health. Laboratory and clinical parameters were monitored based on our

study protocols. They were followed up for 12 months of study period. The genetic polymorphisms at the *CYP2B6,* μ-opioid receptor and *CYP3A4* gene loci were determined from subjects' DNA extracted using QIAgen DNA mini kit. For *CYP3A4* a nested allele specific PCR was applied to detect the types and frequencies of the following allele: C*YP3A4*1B, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*7, CYP3A4*8, CYP3A4*9, CYP3A4*10, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*14, CYP3A4*15* and *CYP3A4*16.* For the allele of *CYP2B6 (CYP2B6*2* and *CYP2B6*9),* and *OPRM1 (G31A, G691C* and *A118G)* the Personalized Medicine for Methadone Kit developed at Institute for Research in Molecular Medicine (INFORMM) was used. This kit was also used to determine plasma methadone. DNA from Malay, Chinese and Indian normal controls were also determined for genetic polymorphisms at the above loci.

In phase II, 40 patients who met our study criteria and who consented participated. Each initially received either 2 capsules containing 200 mg BioLitrin twice a day or two capsules containing placebo together with a fixed dose of methadone, 40 mg daily for 4 consecutives weeks. Blood for plasma methadone level was obtained and sleep quality and opiate withdrawal scores were measured and compared. After a two-week wash out period, a switch over was done with the patients initially receiving BioLitrin now given placebo and patient initially given placebo now given BioLitrin.

Results:

One hundred and twenty eight patients were enrolled in Phase I. A further 40 patients were studied Phase II. Overall retention rate at the 12-month was 54.69% with 58 patients lost to follow up. Of the "retained" patients, 80% were receiving 80 mg or more per day. None was found in the 0 – 39 mg per day dose group. Retention rate for the 40 – 79 mg per day dose group was 20%. The differences between the dose groups in terms of retention rates and re-injection reached statistical significance ($p<0.001$, $p<0.001$ respectively). Daily dose averaged 57.2 mg (SD ± 22.7) and ranged from 20 to 160 mg per day, an 8-fold difference. The corresponding plasma methadone concentration averaged 281.3 ng/ml (SD ± 567.9) and ranged from 0 to 4634 ng/ml. Plasma methadone among patients at fixed 40 mg daily methadone dose varied from 14 ng/ml to 331 ng/ml, a 23-fold difference. In phase II clinical study, SOW averaged 32 (SD 10.4) and ranged from 11 to 51. OOW averaged 8.2 (SD ±1.5). At the *CYP2B6* locus, 7% were heterozygous *CYP2B6*1A / CYP2B6*2* (64 C/T). For G15631T, 51.3% were homozygous *CYP2B6*1A (*15631 G/G), 39.1% heterozygous *CYP2B6*1A / CYP2B6*9* (15631 G/T) and 9.6% homozygous mutant *CYP2B6*9.* The frequencies for *CYP2B6*2* and *CYP2B6*9* were 3.5 and 29.1. Of the 17 alleles tested for μ-opioid receptor gene, the frequencies for the following G31A, G691C, and A118G alleles were 3.9, 20.9, and 56.1, respectively. A significant proportion of the patients carried *CYP2B6* alleles that predicted reduced methadone metabolism. Similarly a significant proportion carried μ- receptor mutants that predicted poor opiate effect. Control subjects all carried

the wild-type gene. Mutant *CYP3A4*1B* allele on the other hand was found in 2.17% of opiate-dependent subjects.

In phase II plasma methadone were lower than the desired 400 ng/ml in most instances in most patients. None of the plasma methadone concentrations obtained was above 700 ng/ml, a suggested upper limit for plasma methadone. SOW in methadone alone patients averaged 32 and in methadone with BioLitrin patients averaged 3.5, a 10-fold difference. OOW during placebo averaged 8.2 and during BioLitrin 0.7, a more than 10-fold difference. During BioLitrin, patients suffered much less withdrawal compared to during placebo and this difference reached statistical significance.

Conclusion

Although methadone has the potential to revolutionize the management of opiate dependence, its complex pharmacology and a generalized "opiophobia" impede its effectiveness. We used a diagnostic kit developed at INFORMM to detect *CYP2B6* and μ-opiate receptor polymorphisms and to measure plasma methadone. Coupled with a method for the detection of *CYP3A4* variants, we also defined the genetic polymorphisms of *CYP3A4*. We also investigated combined methadone and BioLitrin therapy. Daily methadone doses, resulting plasma methadone and retention and re-injecting rates varied. Information on the genetic polymorphisms at the *CYP2B6*, μ-opiate receptor and *CYP3A4* loci from this study was not sufficient to design methadone dosage regimens. Best prediction for MMT effectiveness was provided by a daily dose in excess of more than 80 mg. In the average patient, plasma methadone was not useful but in selected

patients, plasma methadone can be used to manage therapeutic failures. BioLitrin acted synergistically with methadone. It inhibits withdrawal and improved sleep quality. Further work is needed with BioLitrin with MMT, especially on its long term usefulness. Larger studies are also needed to better define the usefulness of the Personalized Medicine for Methadone kit in the routine management of MMT.

Keywords: MMT, retention, re-injecting, variable concentration of plasma methadone level, BioLitrin, Sleeping quality, Opiate Withdrawal Score, Pharmacogenetic, *CYP2B6, OPRM1* and *CYP3A4.*

CHAPTER ONE

INTRODUCTION

1.1 An Overview of the drug situation in Malaysia

The proximity of Malaysia to the "Golden Triangle" makes Malaysia especially vulnerable to drug use problems and Malaysia has been grappling with the issues for decades now. As it is elsewhere, drug problem in Malaysia is not just a social and health problem. It has transgressed into multiple sectors; health, economic, social-justice and indeed it is threatening the very fabric of the society especially as it is now known as the driver for the growing HIV epidemic in the country.

In Malaysia, traditionally, the illicit drug of choice is opiate-based drugs (heroin and morphine) and marijuana. Although the Government has vowed to make Malaysia "drug-free" by 2015, in the past decade, annually the government identified more than 35,000 drug dependent cases in the country (on the average, 55% relapse cases) but this number seemed to have reduced in the past few years to about 25,000 cases reported annually. (National Anti Drug Institution Report, 2008).

1.1.1 Opiate Distribution in Malaysia

There are three main areas (triangle) that supplies drugs throughout the world. There are the Emerald Triangle which includes Columbia-Mexico-Peru, mainly distributing into the

USA and Canada; the Golden Crescent which includes Afghanistan-Iran-Pakistan and mainly distributing into Europe, Asia, Africa and the USA and the Golden Triangle which includes Myanmar-Laos-Thailand, mainly distributing into South East Asia, other parts of Asia, Australia and Africa.

In Malaysia, the most commonly abused opiate is Heroin, followed by morphine, codeine and cannabiss. The supply of heroin is mainly from the Golden triangle. The majority of users are concentrated in West Malaysia but lately, opiate abuse started to establish itself in East Malaysia.

In 2008, there were 4,974 recorded heroin users, 3,640 morphine users and 70 codeine users. Most of them (67.91%) were at their fertile and productive age (age of 20-39 year-old), followed by 28.22% between the ages of 40-59 year-old and 3.87% aged less than 19 year-old (National Anti Drug Institution Report, 2008). Reasons given for why they were involved with drugs were: influenced by friends (55.0%), for excitement and stimulant (22.1%), out of curiosity (14.7%), depression (6%), as pain killer (0.6%) and incidental (1.6%). Educational level does not seem to influence the potential for drug abuse. On study done in 2008 found that most users (96%) belonged to those with education at the SPM (Sijil Pelajaran Malaysia and below) level (National Anti Drug Institution Report, 2008).

1.1.2 Evolution of National Anti Drug Policy

Government drug policy has changed over time to suit culture, norms, environment and of late, prevailing evidence. It evolved from the pre-independence to 1980 approach which saw the Dangerous Drug Act (1952) enacted based on the perceived correlation between drug use and criminal activities. Drug addiction was also then looked at as a social problem which required treatment, rehabilitation and care under the purview of the Social Welfare Department. In 1983, the drug epidemic escalated drastically and drug addiction was declared as a security problem. The Drug Dependants (T &R) Act 1983 was passed by Parliament to focus on mandatory drug treatment with the setting up of the Drug Treatment and Rehabilitation Department. A mandatory drug treatment in Pusat Serenti using the "tough and rugged" philosophy with a combination of health, psychosocial, occupational, religious and civic approaches was attempted and private drug treatment facilities were registered. (National Anti Drug Institution Report, 2008).

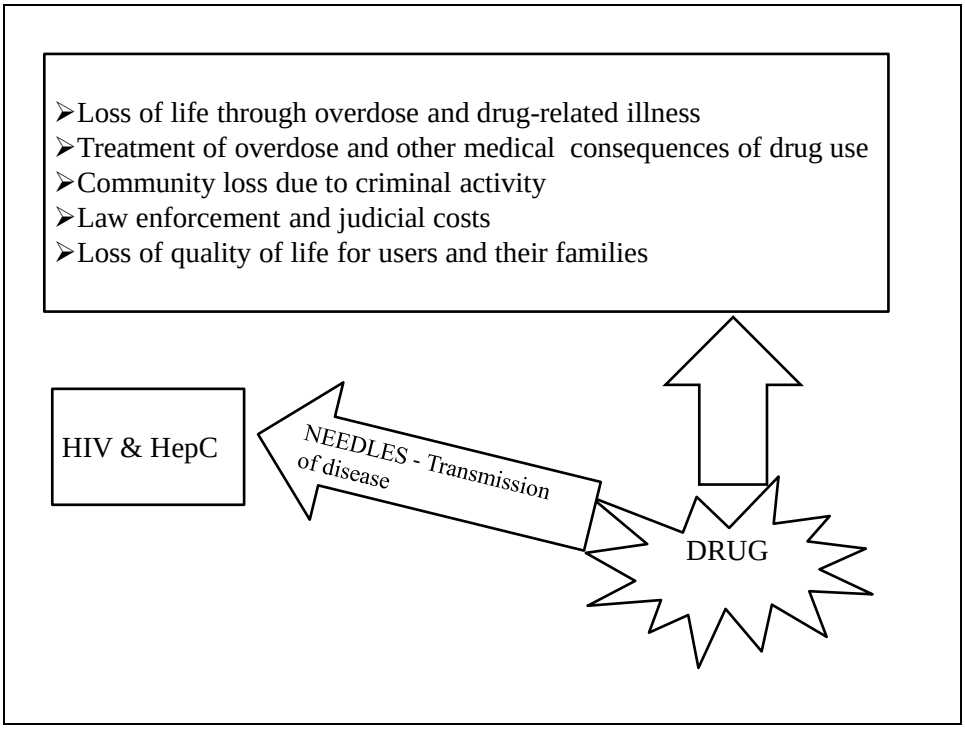

Figure 1.1: The many harms of drug use disorder

Beginning in 2000, the focus was to embrace the term drug dependant, and to be aware that there is drug misuse and abuse, and its relationship to criminal activities. Drug addiction was also redefined as a disease that must be treated as a chronic recurring disease, to keep up with current knowledge. In 2004, the NADA Act 2004 was approved to provide for continuity of rehabilitation and after care in the community. In terms of the overall approach to the drug problem, three approaches have been advocated. They are supply reduction meant to eliminate the supply of drugs into the country by sharing information/intelligence, regional and international collaboration targeted at drugs and crimes, demand reduction to focus on treatment and rehabilitation (abstinence-based) in treatment institutions and community-based programmes, primary prevention with community involvement, and relapse prevention and subsequently in 2005, harm

reduction programme was implemented. Harm reduction is an intermediate goal in the treatment drug dependence. Harm reduction is a way of dealing with behavior that damages the health of the person involved and of their community. Harm reduction tries to improve individual and community health. Drug use won't disappear but its harmful effects can be reduced. Harm reduction should be a goal for service organizations and governments. Some drugs are safer than others. Some ways of using drugs are less harmful than others. Drug users can best reduce the harm of their own drug use. With harm reduction, the initial goals of the treatment of opiate dependence can be summarized as follows: reducing the use of illicit drugs; reducing the risk of infectious disease; improving physical and psychological health; reducing criminal behaviour; reintegration in the labour and educational process; and improving social functioning, all without necessarily ceasing drug use. There are many components of harm reduction and programs may vary from place to place. They include outreach activities to provide risk reduction information, to educate on and provide condoms, bleach and clean needles, to provide referrals to treatment programs including primary health care' to provide HIV testing and counseling, treatment of HIV/AIDS and shelter and food. It involves teaching drug users about the risks of different drugs and how they are used and providing information on using drugs more safely, and reducing the harm of overdoses. In more advanced centre, it provides methadone as a substitute for heroin and medications to counteract a drug overdose. Education and referral to drug treatment opportunities are also provided and some programs permit drug users to exchange used syringes, or buy new syringes. Outreach services are also provided in areas where drug sales occur so that it will bring it to the core of the problem. At SAHABAT, harm reduction involves the

needle-syringe exchange programme (NSEP) and methadone mantainance therapy. Harm reduction involves the needle-syringe exchange programme (NSEP) and methadone mantainance therapy (MMT) to substitute opiate with methadone.

1.2 Intravenous Illicit Opioid Injection, HIV/AIDS and Blood Borne-Infections in Malaysia

Opioid dependence and injecting drug use is a serious problem world-wide. It has been estimated that close to 15 million people world-wide are opioids user, with some 10 million using heroin. This is a staggering 0.2 % of the world's total population. As the global epidemic of heroin use continues, it adds an increasing burden, driving the AIDS epidemic in Malaysia and other parts of Asia, with consequent additional health, economics and social problems.

The primary modes of transmission of HIV have changed little over the years: unprotected intercourse, unprotected penetrative sex between men, injection-drug use, unsafe injections and blood transfusions, and transmission from mother to child during pregnancy, labor and delivery, or breast-feeding. Direct blood contact, such as the sharing of drug-injection equipment, is a particularly efficient means of transmitting the virus. In parts of China, India, Thailand, Vietnam and Malaysia, the epidemic is being driven primarily by injection-drug use. It is projected that the number of people infected with HIV in the Asia Pacific region will increase to thirty million by 2010 with Malaysia having the distinction of being a country with the fastest growing HIV epidemic in the

region. Asia appears set to take over from Africa as the global epicentre of the AIDS epidemic. This poses threats to our already struggling economy, our stability and even our national security as more people succumb to the disease, lose their jobs and become poorer. The sharing of injecting equipment is an efficient means of not only HIV transmission. It is also now the dominant means of transmission of hepatitis C. Hepatitis C results in a chronic carrier status for the virus. Some 10 to 15% of carriers later develop serious liver disease. The morbidity is substantial and will further add to our burden.

HIV was first reported in Malaysia in 1986 with 3 cases. It has since exponentially grown peaking in 2002 when the number recorded was 51256 with six thousand deaths. It is predicted that in 2015, there will be 300000 people with HIV in the country, based on the current trend. Studies have however also suggested that cases of HIV are grossly under reported with estimates saying that for every reported case, there were 3-4 that go unreported. Thus, if we assume that for every reported HIV case in Malaysia, there are 3 others unreported, in 2015, 1 million Malaysian will be people living with HIV/AIDS (PLWHA). Almost 80% of PLWHA are Malays. Thus, in terms of the Malay population that makes up about 50% of the current Malaysian population 1.2% of Malays now are PLWHA and this will rise to 6% in 2015. The impact of this on the demography of the Malaysian population can be staggering because these PLHA will die prematurely thus reducing the relative proportion of the Malays in the Malaysian population. More than two thirds of the 60,000 Malaysian PLWHA's are injecting drug users and almost one in five injecting drug users in Malaysia is already infected with HIV. (National Anti Drug Institution Report, 2008).

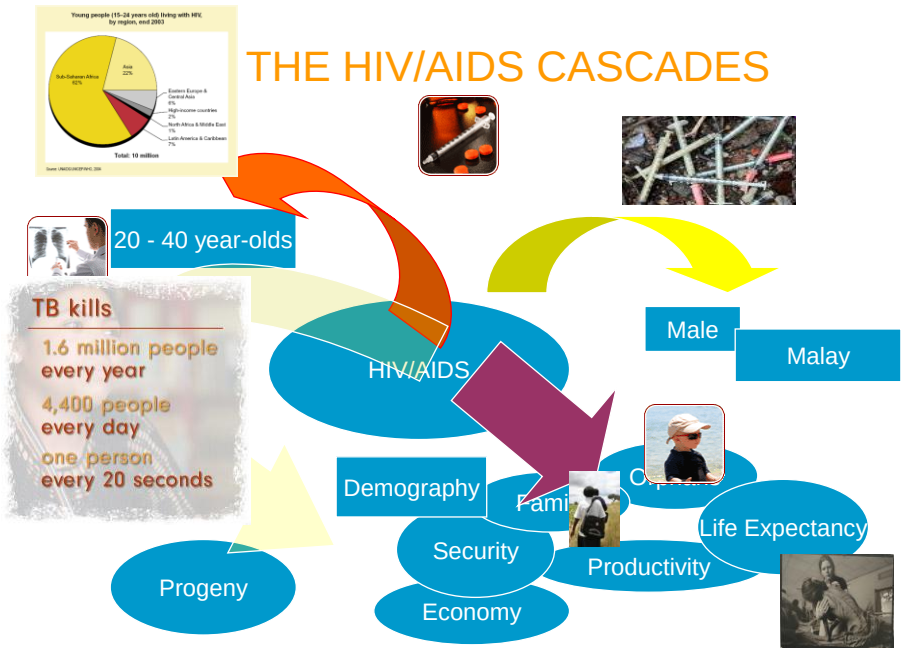

Figure 1.2: Consequences of HIV/AIDS in Malaysia

In many circumstances illicit opiate use and criminal behaviour are also linked. Users commit crime to obtain money to maintain their habits and some commit crime under the influence of drugs. There is also an overlap between factors associated with the development of criminal behaviour, and factors associated with the initiation of illicit drug use. The drug using communities are also frequently "closed" and "fringed" communities with their own sub-cultures. They are frequently in the fringes of main-stream societies with added social stigmas and discrimination that will add to the problems of criminality and social break down.

In Malaysia and in most countries, drug use problems are treated as a criminal/law enforcement issue with zero tolerance to drugs. Thus, in Malaysia, the approach to illicit drug use is primarily aimed at abstinence. A lot of emphasis is put on "rehabilitation", either voluntary or otherwise. Drug users are regularly rounded up by the authorities and some are sent for "rehabilitations" at the AADK-run rehabilitation centres (Pusat Serenti). This strategy is aimed at inducing abstinence in drug users through cold turkey and social-behavioral approaches, generally by non-medical personnel. Many countries have attempted this but generally the success rate is only about 10%, an experience shared by Malaysia. In 2002, 14163 were incarcerated at the 28 rehabilitation centers run by AADK and this represented only about 6% of the estimated number of drug users then. Thus apart from the high failure rate, this effort can only reach a small percentage of the drug users in the country although the money spent is tremendous. (National Anti Drug Institution Report, 2008). This surely is not a very cost-effective approach. The complication is, when drug users undergo treatment, the community expects them to achieve a drug-free lifestyle. It is therefore not surprising that many of the approaches taken are aimed at achieving a drug-free lifestyle, a delusion. While abstinence is an important long-term goal, to put it as the only goal reflects our poor understanding of the complexities of drug dependence. Drug dependence is a complex disease. The combination of physical, biological, psychological and social dimensions makes drug dependence a complex condition. For drug dependence to be successfully overcome, all these dimensions must be addressed at. For many of them, this may entail substantial physical, biological, psychological and lifestyle adjustments – a process that usually requires a long time. We cannot treat addiction today as we used to treat mental illness,

leprosy and tuberculosis in the olden days. The stigma faced by addicts today is probably no different from those faced by patients suffering from these illnesses before.

There is no single effective treatment for the management of heroin dependence. Nevertheless, current evidence indicates that a broad range of treatment options are available that can substantially impact on the course of opiate dependence and its consequences. Drug substitution treatment (DST) is an example. DST has been extensively investigated with hundreds of randomised clinical studies done. These studies consistently reported benefits for those in treatment. (National Instittutes of Health. 1997) For instance, there is overwhelming evidence that methadone maintenance is safe, effectively improves health outcomes, reduces crime and enhances social functioning while lowering the risk of HIV transmission.

There is therefore a need to develop a broad range of community based treatment responses to manage heroin dependence in Malaysia. The rapid spread of HIV amongst injecting drug users in Malaysia further underscores the imperative to organise a comprehensive treatment approach. However, people in Malaysia may wish to see evidence from research undertaken in the local context.

1.3 How methadone Maintenance Treatment (MMT) works

Methadone was developed by German scientists in the late 1930s. It was approved by the U.S Food and Drug Administration (FDA) in 1947 as a painkiller, and by 1950 oral methadone also was used to treat the painful symptoms of persons withdrawing from heroin (Payte, 1991; Rettig and Yarmolonsky, 1995; Joseph *et al*, 2000).

In 1964, Dole's husband and wife team discovered that continous daily doses of oral methadone were beneficial, allowing otherwise debilitated opioid addicts to function more normally (Dole, 1988; Joseph and Appel, 1993; Kreek, 1993; Payte and Khuri, 1993; National Instittutes of Health, 1997; Payte *et al*, 2003; Stine *et al*, 2003). An adequate maintenance dose of methadone does not make the patient feel "high' or drowsy, so the patient can generally carry on a normal life. Daily drug seeking to feed a habit ceases.

Methadone can be taken once daily by mouth without the use of injection needles and this limits exposure to blood-borne-viruses (BBV) like hepatitis C and B and HIV. Its gradual, long-lasting effects eliminate drug hunger or craving. There is also little change in tolerance to methadone over time, so it does not take more of the drug to achieve the same results as it would be with short acting opiates like heroin and morphine. The euphoria-blocking effects of methadone cause undesirable effect to illicit opioid users and this will encourage them to stop taking their illicit opiates. If used properly, methadone is generally safe and non-toxic with minimal side effect (Dole, 1988; Joseph

and Appel, 1993; Kreek, 1993; Payte and Khuri, 1993; National Instittutes of Health, 1997; Payte *et al*, 2003; Stine *et al*, 2003).

Methadone mantainance therapy (MMT) is generally considered as corrective therapy, rather than as a "cure" for opioid addiction, and it had no or only limited efficacy in treating dependence on other substances of abuse (Joseph *et al*, 2000). This is the contentious point taken by methadone detractors. They object to methadone because they claim that methadone will replace one addiction to another although experts have never claimed that methadone is to cure opiate addiction. However, taken in optimal doses, methadone can correct the compulsive use of heroin and other opiates by addicts (Dole, 1988). Furthermore, oral methadone has a demonstrated favorable safety profile when properly prescribed and used. Although it can sometimes cause cardiac arrhythmias, no other serious adverse reactions or organ damage have been specifically associated with continued methadone use extending more than 20 years in some patients. Minor side effects, such as constipation or excess sweating, may appear during the early days of treatment and are easily managed. Indeed, women stabilized on methadone generally have healthier pregnancies compared to current opiate users and their newborns also do not suffer lasting adverse consequences (Payte *et al*, 2003; Stine *et al*, 2003). Furthermore, methadone at appropriate doses does not hinder a patient's intellectual capacities or abilities to perform tasks (Gordon, 1994).

For therapeutic success, adequate methadone dosing is critical. Dole's original research discovered that 80 to 120 milligrams of methadone per day, on average, was an effective dose. Dozens of studies since then have demonstrated that dosing in that range resulted in superior treatment outcomes, such as better retention of patients in treatment and less illicit drug use (Payte and Khuri, 1993; Nadelman and Mc Neely, 1996; Stine *et al*, 2003). Patients maintained on inadequately low doses are much more likely to use illicit opioids and respond poorly to therapy (Gordon, 1994). On the other hand, for a variety reasons such as, pharmacologic variability at the enzyme and receptor levels, high tolerance to opioids, physical condition, mental status, concurrent medications, or prior use of high-purity heroin, some patients require much higher daily methadone doses for treatment success, sometimes exceeding 200 mg/day or more (Leavitt, 2003; Payte *et al*, 2003; Stine *et al*, 2003).

Remaining in treatment for an adequate period of time is critical for treatment effectiveness. The appropriate duration for an individual depends on their problems and needs, but research indicates that for most drug users, the threshold of significant improvement is reached only after about three months in treatment, with further gains as treatment is continued. Because people often leave treatment prematurely, and premature departure is associated with high rates of relapse to drug use, programmes need strategies to engage and keep patients in treatment.

In general the impact of treatment should be viewed in terms of its capacity to:

- improve the quality and quantity of life of the individuals who come into treatment;
- improve the quality of life of their family;
- reduce criminal justice expenditure through diversion away from prison;
- reduce health and welfare costs;
- reduce the costs incurred by victims of crime; and
- Improve the social environment.

In summary, MMT adds importantly to our ability to deal with the ever increasing menace of illicit drug use. Methadone is a long-acting drug. It occupies the opiate receptors at a slow pace and this creates a steady level of opiate in the blood. This characteristic avoids the "high and low" levels that generally occur with short-acting opiate administrations. The resulting constant tolerance threshold, stabililises the patient's deranged homeostatic mechanism, caused by opiate use, the deranged cognitive and motor function is also stabilised, and normalcy is maintained. Furthermore, as MMT is taken orally once daily, it also eliminates the cycle associated with frequent injections and the complications associated with this practice, such as the transmission of BBV. Most guidelines advises gradual increase in methadone dose and this results in a gradual increase in the tolerance threshold enabling patient to develop a tolerance threshold sufficiently high that an injection of any amount of street opiate will not be able to produce euphoria, thus eliminating the reward for injecting drugs. A high dose of methadone is usually required to achieve this effect and it averages 100 mg per day. The

stability so provided by MMT can serve as a platform for other treatment modalities and rehabilitative process can begin. When these principles are followed, MMT is effective, and the individual and society gains. It is however unfortunate that these principles are rarely followed. Thus, although it the body of knowledge supports a daily dose of at least 80 mg to 100 mg to abolish further craving for opiates, a big majority, including in Malaysia, are maintained on much lower doses. The believe that zero drug is best has similarly also led to frequent premature ceasation of MMT although evidence suggests that maintenance therapy for at least two years is required for the maximum probability of success. Ironically the encouragement to discontinue MMT quite often comes from care providers working in maintenance programs. Most caregivers often also do not try to adequately address the reasons why opiate was taken by the patient in the first place or the existence of coexisting psychiatric illnesses. This frequently results in increasing anxiety among patients that may explain their needs for other mood-altering drugs, such as the benzodiazepines.

1.4 MMT Criticisms, Concerns and Regulation

Methadone is a much maligned drug, both by physicians as well as the lay public. The reason for such a negative attitude is less than clear except for the fact that drug addiction has always been stigmatized and many views and believes that the only meaningful treatment of addiction is total abstinence. Arguably we can attribute the negative views of the lay public is due to their ignorance and inability to truly understand addictive behaviours. This however cannot be true with the physicians and other care givers as

literature, both scientific and lay, abounds that espouses the reasons and advantages of methadone. Their mistrust for methadone can even be looked as sinful as they betray the trust accorded to them by both the Government and the patients. Their ignoring of the basic principles will jeopardize all the gains that can potentially accrue from MMT.

Physicians acting in this manner cannot hide behind their ignorance of pharmacologic principles. Their contention for not wanting to prescribe mood altering drugs too freely cannot also be supported as other similar medications such as the benzodiazepines are often freely prescribed by them and they too can produce severe psychologic and physiologic dependence. Methadone, if at all is only minimally associated with adverse, physiologic effects and it is a drug probably with the least side effects of any drug in a physician's pharmacologic armamentarium, when used appropriately.

Through the years, MMT has attracted some negative attitudes and actions by critics. A segment of public opinion has opposed the use of methadone for treating opioid addition and political initiatives have even been enacted or proposed to thwart access to MMT (Ehlers, 1999; PRNewswire, 1999). Some even support the closing down MMT programs or instituting such strict regulations to make it difficult for people on methadone maintenance to hold jobs. Their contention is that persons on methadone are noncompliant and may sell their methadone, and may continue to use heroin. However, compliance rates for methadone maintenance are no less than those seen with other chronic disorders, such as diabetes, asthma, or hypertension. Indeed, they are much greater as the methadone is taken under direct supervision in most programs. Those who

sell their medication are few compared to those who function well when MMT is appropriately provided.

Many people still perceive opioid dependence as a self-controllable "bad habit" and dismiss MMT as an effective, addictive-narcotic substitution therapy (Rettig and Yarmolonsky, 1995; National Institutes of Health, 1997) despite most authorities recognising that methadone is not merely a substitute for illicit opioids, and that MMT does not simply replace one addiction with another (U.S. General Accounting Office, 1990; Zweben and Payte, 1990; Ehlers, 1999; ONDCP, 1999; Payte *et al*, 2003; Center for Substance Abuse Treatment, 2004; Krantz and Mehler, 2004). Although methadone can cause physical dependence, its steady and long-term action in the brain contrasts sharply with the disruptive cycle of "highs" and "lows" produced by short-acting opioids that lead to addictive behaviors (Kreek, 1993; Nadelman and Mc Neely, 1996; McCaffrey, 1999; Payte *et al*, 2003;). Methadone substitutes a stable existence for one of compulsive drug seeking and taking, criminal behavior, chronic unemployment and high-risk sexual and drug-use behaviors (ONDCP, 1999).

As alluded, for MMT to give the best benefits, adequate doses are required. Unfortunately, especially during the early days of MMT there were rapid clinic expansion of the MMT programs in the face of deceased funding (Kreek, 1993; D' Aunno and Pollack, 2002) and this unwittingly led to the use of low doses with the consequent poor results that in turn fed into the already sceptical public. Surveys have observed that a majority of U.S. MMT clinics once provided average methadone doses far below the 80

mg/day recommended minimum (D' Aunno and Pollack, 2002). There have been some improvements. Many programs now achieve average doses of 80 mg/day or more although many more patients still receive inadequate doses (D' Aunno and Pollack, 2002; Leavitt, 2003) with the consequent poor response, just as would any individuals prescribed insufficient drug therapy for any chronic medical disorder (D' Aunno and Pollack, 2002; Stine *et al*, 2003) and such failures will be viewed negatively by the detractors.

Malaysia is not spared the negative sentiments about MMT. Measures have however been taken to improve MMT in Malaysia at the primary care levels by the Governmental and non governmental (NGOs) agencies notably the Ministry of Health and the Malaysian AIDS Council and its partner organisations. The strategies include strengthening community organizations which often are weak and highly reliant on small numbers of dedicated individuals (many of whom volunteer their labour). Professionals in collaboration with policy makers and other stakeholder are also meeting to standardise the strategies such as in education, in needle syringe exchange programme, in MMT and in anti retroviral treatment (ARV).

Preventive programmes for most at- risk populations are now widely implemented through community based and other civil society organizations. Nevertheless, many still have to struggle to secure adequate resources to do their work, to obtain adequate and sustainable funding and to increase human resources. Information and preparation time often prevent many volunteers from participating in national processes although their

counsel are now frequently sought. Supporting and strengthening such consultation will auger well for our efforts at continous improvement to our HIV response.

As alluded, the expectation of the society as regards treatment of drug addiction is for the dug users to cease taking drugs. MMT is viewed as replacing one addiction for another. Thus stigma and discrimination remain troublesome and many drug users find it very difficult to reintrgrate themselves into the society. This may actually impact on the user's views themselves as regards MMT. Continued discussions are carried out to minimise such negative views.

1.5 Regulations and Accreditation Promote "Best Practices"

In the U.S, MMT has been a tightly controlled medical specialty.with methadone itself being a highly regulated drug (Nadelman and Mc Neely, 1996; National Instittutes of Health, 1997). Revised Federal regulations however emphasized improved patient care and increased healthcare Practitioner discretion in meeting patients' needs; particularly allowing more liberal methadone dosing and permitting qualified patients to take home doses for self-administration (CFR, 2001). However, state and local regulations may be more stringent. Thus, as a component of the regulations, MMT programs must successfully complete accreditation process similar to that required of much larger healthcare organizations. Best-practice guidelines and standards have been developed, reflecting the latest evidence promoting excellence in the treatment of opioid addiction.

Results to date indicate that MMT program accreditation has been successful in improving patient care, safety, and treatment outcomes (Krantz and Mehler, 2004).

A similar approach has been taken in Malaysia with MMT and methadone being highly regulated. Not all doctors in Malaysia are authorized to prescribe methadone and even then, caps are put on the maximum number of patients a given doctor can have on his MMT program. Given the underlying sceptism people have on MMT, these stringent regulations and capping make access to methadone somewhat problematic to the average drug user. Continued efforts have to be made to change this mindset, to get MMT to be more freely available with the understanding that its primary goal is harm reduction rather then the reduction in opiate addiction.

1.6 Pharmacogenetic of Methadone.: An Overview

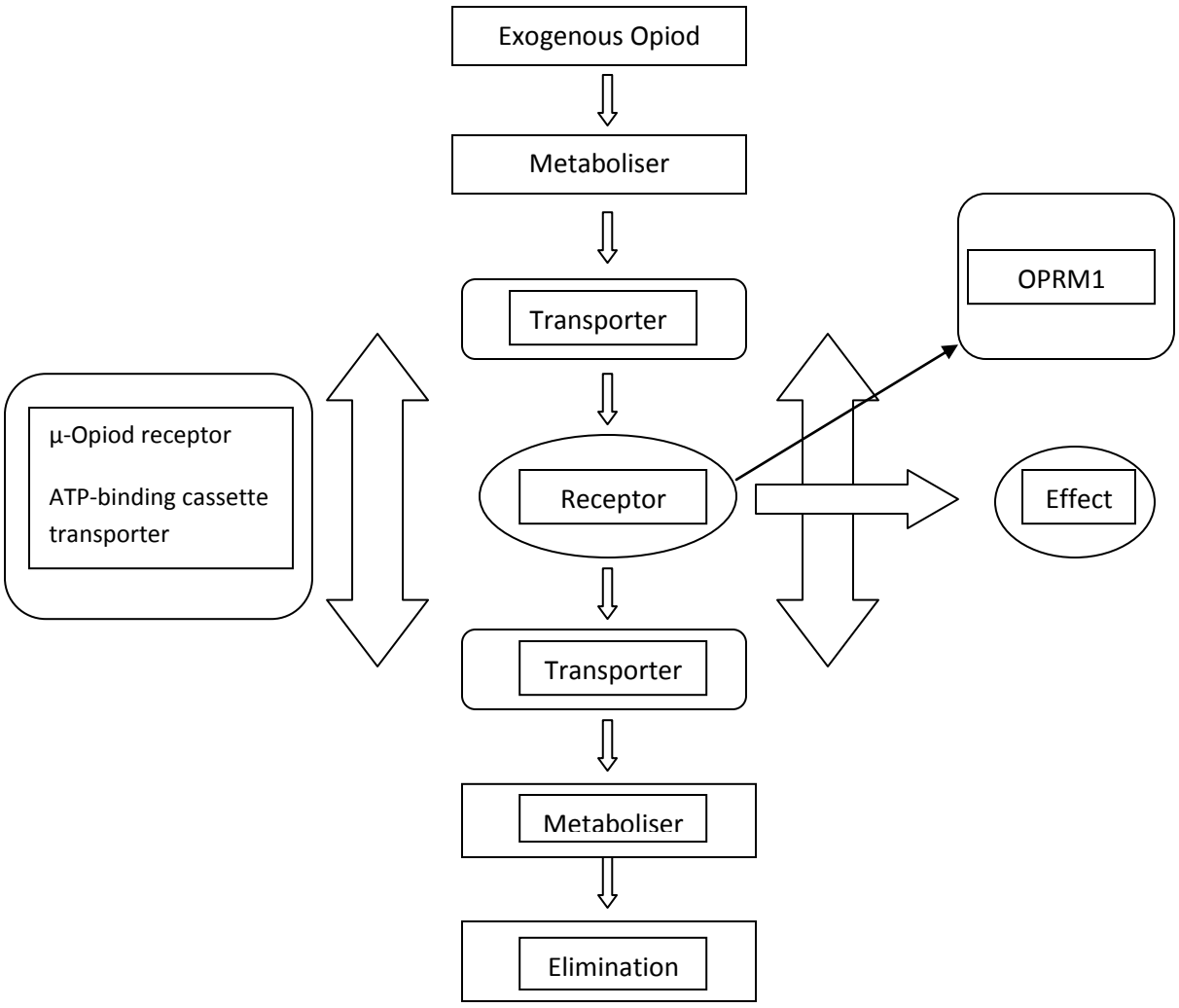

Figure 1.3: An overview of drug fate inside body

Methadone is a synthetic opioid, used mainly as an analgesic, and a replacement for opiate in MMT. It was developed in Germany in 1937. Methadone acts on the opioid receptors and produces many of the same effects of morphine and heroin, the drugs it is replacing. In the treatment of opioid dependence, methadone has cross-tolerance with other opioids including heroin and morphine and a long duration of effect. Higher doses of methadone can block the euphoric effects of heroin, morphine, and similar drugs. As a result, properly dosed methadone patients can reduce or stop altogether their use of these substances.

Methadone is a misunderstood drug and ignorance about it is commonplace. Even professionals, physicians and pharmacists who are supposed to be the "guardians" of MMT receive very little training about the very medication that they are responsible for. To compound the issue, addiction is mostly viewed not as a disease and its care is frequently relegated to the lay public, at least until very recently. In Malaysia, addiction has solely been under the charge of AADK, an agency that has mainly adopted a criminal approach to addiction. This has recently changed in Malaysia. Addiction is now recognized as a medical illness, under the purview of the medical professionals. Nevertheless, many in the medical profession only have a rudimentary understanding of addiction. Most physicians, pharmacists and nurses receive very little training about addiction and much less regarding methadone. Thus, generally, both medical and other care givers have very limited knowledge about addiction and much less about methadone. They have generally been taught to approach addiction as a character disorder and administer methadone as a substitute.

Methadone has variable pharmacology. It binds to the μ-opioid receptor, the NMDA ionotropic glutamate receptor to exert its effects. Its metabolism is mediated by several enzymes including CYP3A4, CYP2B6 and CYP2D6, enzymes that are polymorphic and hence exhibit great variability. It is mainly administred through the oral route and adverse effects include hypoventilation, constipation and miosis, in addition to tolerance, dependence and withdrawal difficulties.

As a full μ-opioid agonist, methadone exhibits all the opiate-like effects. Furthermore, its binding to the glutamatergic NMDA (N-methyl-D-aspartate) receptor makes it a receptor antagonist against glutamate which is the primary excitatory neurotransmitter in the CNS. NMDA receptors modulate long term excitation and memory formation and NMDA antagonists such as dextromethorphan (DXM), ketamine, tiletamine and ibogainehave been studied for their role in decreasing the development of tolerance to opioids and as possible for eliminating addiction/tolerance/withdrawal. It action on the NMDA has been proposed as a mechanism by which methadone decreases craving for opioids (Xiao *et al*, 2001).

Methadone is a lipophilic drug and requires biotransformation for elimination. It has a slow metabolism and is longer lasting than morphine-based drugs. Typically its elimination half-life ranges from 15 to 60 hours with a mean of around 22 hours. Due to the polymorphic nature of its metabolism, its metabolism rates vary greatly between individuals, up to a factor of 100. This variability is apparently due to genetic variability in the production of the associated enzymes CYP3A4, CYP2B6 and CYP2D6. Several

studies have been conducted to explain the intra-as well as inter-individual variability in methadone's pharmacokinetic and clinical response. Typically, methadone is a substrate for several CYP 450 enzymes as well as P-glycoprotein (PGP). Many Single Nucleotide Polymorphisms (SNPs) have been reported to contribute to its variability. Furthermore, as it binds to μ-receptors, SNPs in *OPRM* gene that encodes for these receptors may contribute to the clinical response in MMT patients. Thus, SNPs in *OPRM* gene, *CYP* gene and *ABCB1 (MDR1)* gene may contribute to determine the clinical outcomes of the MMT (Lötsch *et al*, 2009).

1.7 Role of Cytochrome P450 in Methadone metabolisms

Methadone is available in most countries as a racemic mixture of (R) and (S) enantiomers, though most of the clinical effect is from (R) methadone. Methadone metabolism is mediated by several CYP 450 enzymes leading to the inactive 2ethylidene-1,5-dimethyl-3,3diphenylpyrrolidine (EDDP) via N-demethylation pathway (Sullivan *et al*, 1973). It has been found that *CYP3A4, CYP2B6, CYP2D6, CYP1A2, CYP2C8, CYP2C9,* and *CYP2C19* all have either major or minor involvement in methadone metabolism (Lanz and Thormann, 1996; Eap *et al*, 2001; Wang and DeVane, 2003; Eap *et al*, 2004; Gerber *et al*, 2004; Totah *et al*, 2007; Totah *et al*, 2008). This complexity has led to a great and unpredictable intra-individual as well as inter-individual variability causing a misleading interpretation for/of the pharmacokinetic data. Recently, it has been demonstrated that *CYP3A4* and *CYP2B6* are the main influential contributors to methadone's metabolism. *CYP2B6* shows stereoselectivity towards (S)-enantiomer,

whereas *CYP2C19* shows stereoselectivity towards (R)enantiomer. *CYP3A4* shows no stereoselectivity towards either (Gerber *et al*, 2004; Kharasch *et al*, 2004).

Initial studies have shown that *CYP3A4* is the major contributor for the metabolism of methadone. Accordingly, drugs that induce or inhibit *CYP3A4* are considered interacting drugs. *CYP3A4* activity is measured by the midazolam phenotyping test. It was shown that higher doses are required when high activity is evident (Shinderman *et al*, 2003). Unfortunately, it was shown that midazolam lacks the adequacy of specificity and sensitivity for *CYP3A4*. Furthermore, *CYP3A4* activities were similar in patients receiving doses lower than 200 mg. The difference rose in patients for whom dosing was greater than 200 mg daily. Further, the expression of *CYP3A4* is highly varied among individuals, indicating that these patients might have a higher clearance rate or more expressed enzymes rather than being rapid metabolizers. Moreover, *CYP3A5* may constitute as much as 50 % of the total hepatic content of *CYP3A* in people who express it. This enzyme plays no role in the metabolism of methadone (Crettol *et al*, 2006). As a result, it has been suggested that *CYP3A4* plays minimal role which significantly varies in terms of intra- as well as inter-individual basis.

Most in-vivo studies have suggested a minor contribution of *CYP2D6* in methadone metabolism (Wang and DeVane, 2003). *CYP2D6* inhibitors, however, have shown relatively significant drug-drug interactions with methadone, and these include such as paroxetine, fluoxetine and fluroxamine (Eap *et al*, 1997; Iribarne *et al*, 1998; Begré *et al*, 2002). In a study, patients were divided into: *CYP2D6* poor metabolizers (PM), extensive