Chapter 10

Plasma Methadone Level Monitoring in Methadone Maintenance Therapy: A Personalised Methadone Therapy

Nasir Mohamad, Roslanuddin Mohd Salehuddin, Basyirah Ghazali, Nor Hidayah Abu Bakar, Nurfadhlina Musa, Muslih Abdulkarim Ibrahim, Liyana Hazwani Mohd Adnan, Ahmad Rashidi and Rusli Ismail

Additional information is available at the end of the chapter

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1. Introduction

1.1. Opioid substitution therapy

Substitution therapy for opiate abusers reduces dependencies on illicit drugs by utilizing opioid agonists that bind to opioid receptors in the brain. Apart from the physical benefits of reducing cravings and withdrawal symptoms, it also plays a role in reducing other problems associated with opioid abuse. Their longer duration of action means they do not require frequent administration and hence enables patients to carry out activities of daily living without disruption. The spread of infectious blood borne diseases is also curbed by the fact that they are usually administered orally [1].

Methadone and buprenorphine are the two most commonly prescribed and effective opioid agonists for substitution maintenance therapy in Malaysia as their oral preparation can avoid injecting behaviour among opiate users. Hence, the harm reduction promotion will be further strengthen as injecting related behaviour among opiate users are the main contributor to HIV transmission in Malaysia. Methadone Maintenance Therapy (MMT) was started in 2005 through harm reduction programme and is getting a strong foothold since then. Therefore we are seeing a lot of opioid abuser on methadone in Emergency Department with potential

overdose or withdrawal symptoms. A lot of these opiate abuser drafted into the program also frequently have whole hosts of other health problems such HIV, Hepatitis B and C or Tuberculosis which may complicate diagnosis and treatment.

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 opioid receptors at a slow pace and this creates a steady level of opioid in the blood. This characteristic avoids the "high and low" levels that generally occur with short-acting opioid administrations.

1.2. Methadone Pharmacokinetics (PK)

The efficacy of methadone is determined by the stability of methadone concentration in blood, and therefore in the action site located in the brain. Maximum concentration of methadone is reached around two to four hours after dose administration and gradually falls until the moment of next dose administration. As Methadone is extensively metabolized in the liver, its metabolic clearance is shown by the elimination rate of methadone. The clearance rate of methadone from the body was found to be 158 ml/ min and 129 ml/ min for (R)-methadone and (S)-methadone respectively. Main metabolite of methadone, which is 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine is inactive. The apparent volumes of distribution were varies with mean values 3.9 l/kg [2]. Methadone is administered single daily as in methadone maintenance treatment, the average half-life of methadone is around 24 hours. This means that at the end of the 24th hour after dose administration, the concentration of methadone should have fallen to half its peak value. Most of us would consider the increasing methadone concentration in the blood is associated with the increasing dose. However, this general rules is not necessarily expected as we can see in the patients with methadone doses as high as 70–170 mg per day, have blood concentrations similar to those of patients whose doses are as low as 25 mg per day. It is note that the blood concentrations of methadone act as an indicator of its concentration in the action sites than the dose taken. Because of this, methadone plasma concentrations measured after 24 hours have repeatedly been proposed as a parameter for the evaluation of the adequacy of treatment. The necessary level of plasma methadone concentration is found between 150 and 600 ng/ml to counter for the craving effect of opioid addicts [3]. However, plasma concentration differs in different individuals and in single person under different conditions. The determinant factor for this variability include genetic factor, physiological, pathological, and pharmacological factor. Methadone is metabolized in the body by the enzymes of P450 cytochrome system . Polymorphism in cytochrome CYP450 can affect a higher or lower level of its activity and responsible for a more rapid or a slower elimination of methadone, with a consequent shortening or lengthening of methadone's half-life and a rise or fall in its levels in plasma. Concentration of methadone in blood is influenced by various steps of absorption, plasma protein binding, metabolism and excretion processes. Interference at the level of the P450 microsomal system also can cause an induction of the methadone metabolism, with a consequent fall in its levels in plasma, or an inhibition of its metabolism, with a rise in methadone levels in plasma. Less than 200 ng/ml is associated with poor compliance and higher than 700 ng/ml is associated with toxicity, ranges from excessive sedation with small pupils, respiratory depression and fatal tachyarrhythmia such as torsade

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de pointes (TdP) [4]. Based on the methadone concentration in plasma, inter-individual and intra-individual varieties persist in response to methadone. By studying plasma concentration, probably the optimum dose of methadone can be achieved faster and minimized unwanted side effect, therefore the patient will remain in the MMT programme [5]. Other special feature of methadone is it undergoes extended reversible absorption into tissues particularly the liver and hence steady-state concentrations can be achieved after multiple administrations. Methadone is usually administered orally and as such is rapidly absorbed. There are two processes involved in metabolizing methadone, primarily in the liver namely demethylation and cyclization. The cyclization process produces 2-Ethylidene-1, 5-dimethyl-3,3-diphenylpyrrolidine (EDDP) distinct from its parent molecule. Methadone and metabolites are primarily excreted in the feces. Unmetabolized methadone excretion in the urine accounts for less than 11% of the administered dose. It is excreted unchanged and as its metabolite in the urine. The excretion of methadone is markedly enhanced by the acidification of the urine

1.3. Methadone: AUC

Major measurements in pharmacokinetic study are plasma and urine. Plasma concentration data provides an important data in PK study. The AUC (the area under curve) can be presented graphically as the area under the plasma concentration versus time curve. AUC is an important parameter in PK analysis as it often used to measure the drug exposure. AUC plays many important roles in pharmacokinetics. AUC provides a measure how much and how long a drug stays in a body. [6] In other words, AUC shows an overall amount of drug in the bloodstream after a dose administration. Studying AUC probably is the best way to understand how people handle a drug. The plasma concentration of the drug measured by AUC can be useful for clinicians or doctors to optimize the drug dosage. Each person who takes methadone has differences in the way their body handles the drug in terms of absorption, distribution, metabolism and/or elimination processes. Therefore, a patient can have a high or low methadone blood levels after taking the same dose just because of the way they handle the drug. The PK of drug also changed by certain factors. For example, the blood levels of methadone can be increased or lowered by not following the food requirements with dosing, taking antacids with the drugs, or taking certain other drugs or herbals that can cause big inhibition or induction interactions in drug metabolism. Thus, it is important to find the dose requirements out so that patients know how best to take the drugs. Finally, the level of drug concentration in the body affect how well the drug works and whether the drug might cause side-effects, particularly in a case of high drug levels. Low levels of drug also can result in poor efficacy of the methadone maintenance treatments. In case of "therapeutic drug monitoring" (TDM), a doctor may think to measure methadone blood levels as a best idea to adjust the dose. Based on the results, the doses may be adjusted and then re-check the blood levels of drug to try and get them right where they want them [7]. Much information can be obtained on drug absorption, disposition of drug molecules between blood and tissues and drug elimination by measuring the amounts or the concentrations of drugs in blood, urines or other fluids or tissues at different times after the administration. AUC is a parameter that is dependent on the drug amount that enter into the systemic circulation and on the ability that the system has to eliminate the drug (clearance). Therefore it can be used to measure the drug amount absorbed

or the efficiency of patient's physiological processes that characterize the drug elimination. Accurate estimation of the AUC can be achieved by applying "trapezoidal rule" [8]. AUC can be calculated by two PK models, which are linear PK models and non-linear PK models. Linear PK models are conducted without specifying any mathematical models (noncompartmental methods). It is helpful to use linear models as a guide in therapeutic decision making [9].

1.4. Volume of distribution (Vd)

The amount of drug in the body calculated from measurement of plasma concentration is assessed using a parameter called Volume of Distribution (Vd). The clinical importance of Vd is for computing a loading dose (eg. the first dose of a multiple dosage regimen) to reach the target therapeutic plasma concentration [10]. For example, if 1000 mg of a drug is given and the subsequent plasma concentration is 10 mg/L, that 1000 mg seems to be distributed in 100 L (dose/volume = concentration; 1000 mg/x L = 10 mg/L; therefore, x = 1000 mg/10 mg/L = 100 L). Vd is not the actual volume of the body or it's fluid compartment, but it is the distribution of a drug in the body. For the drug that is highly-bounded by a tissue, the dose that remains in the circulation is low, hence plasma concentration will be low and Vd will be high [11]. Methadone is a lipophilic drug and exhibits tissue distribution [12]. Methadone is also widely distributed to brain, kidney, gut, liver, muscle and lung with their specific plasma partition coefficients [13]. Vd of methadone is reported to be high in humans [14]. The apparent volume of distribution at steady-state (Vss) studied by other authors is much higher than actual physiological volume, indicating that methadone is predominantly tissue-bounded compared to plasma proteins binding. In opiate addicts, Vss of methadone ranged from 4.2 – 9.2 l/kg and in patient with chronic pain, the Vss is from 1.71 – 5.34 l/kg [15]. Methadone is highly bound to plasma protein by 86% and it is similar as reported in rats [16], [17]. Because of basic properties of methadone, it binds predominantly to α_1-acid glycoprotein (AAG) [18, 19]. AAG is an acute-phase serum protein that exhibits different concentration in plasma levels based on physiological or pathological conditions. In stress condition, AAG will increase and this will result in lower free fraction (*fu*) of methadone in plasma of cancer patients and opiate addicts compared in healthy volunteers [20,21]. Hence, after rapid administration of methadone, *fu* will decrease in early period and total plasma drug concentration (C_p) will increase as Vss is proportional to *fu*, but unbound plasma drug concentration (C_u) remains unchanged. A study on methadone distribution should pay attention on demographics features like weight and sex and AAG. About 33% Interindividual variability in Vss is due to sex and weight. Female exhibit higher Vss than male and this is related to weight. Meanwhile, a decrease in Vss is associated in time-dependent increase in AAG. [22]

1.5. Metabolism of methadone

Methadone is used clinically as a racemate, although R-enantiomers are responsible for the activation of opioid activity. The major pathway in methadone metabolism is *N*-demethylation to inactive 2-ethylidine-1,5- dimethyl-3,3-diphenylpyrrolidine (EDDP). This activity is mediated by cytochrome P450 CYP3A4 and CYP2B6 and somewhat by CYP2C19 in vitro which was less active [23]. In vitro, CYP2B6 is regarded as a predomi-

nant catalyst of stereo-selective methadone metabolism and may be a major determinant of methadone metabolism and disposition in vivo. In addition, CYP2B6 activity and stereo-selective metabolic interactions may confer variability in methadone disposition. CYP3A4 is the most abundant CYP form in the liver. No genetic polymorphism is observed in this enzyme. However, interindividual variability in the expression of this enzyme had been noted. CYP3A4 is inducible and this might be the reason for the induction of the methadone metabolism at the beginning of a maintenance treatment. Thus, a pattern of decrease in steady-state plasma levels of methadone is observed during maintenance treatment with racemic methadone [24]. Meanwhile, CYP2B6 gene is reported to be highly polymorphic. It is noted that CYP2B6 has a couple of variant alleles that are associated with lower expression/activity. Among of those alleles are CYP2B6*6, CYP2B6*16 and CYP2B6*18 in particular [25, 26, 27]. CYP2B6*6 is rather common in several different populations (20–30% frequency), whereas both CYP2B6*16 and CYP2B6*18 are common in Black subjects where the allele frequency is relatively high, about 7–9% [26, 27]. To a smaller extent CYP1A2 enzymes which is found in the kidney may also has influence on methadone metabolism. Knowledge from genotype analyses is importance in clinical use. It is an explanation for us to understand the therapeutic problem or a failure in question based from three major population phenotype, and these are poor metabolisers (PM), lack of functional enzyme due to defective or deleted genes, the extensive metabolizers (EM), carrying 2 functional genes; and the ultra-rapid metabolizers (UM), with more than 2 active genes encoding a certain P450 [27]. This genotyping analyses definitely will be a valuable aspect to contribute to a more efficient and safer drug therapy in the psychiatric clinic possible.

1.6. Dose of methadone

The believe that zero drug is best has similarly also led to frequent premature cessation of MMT, even though evidence suggests that maintenance therapy for at least two years is required for the maximum probability of success. Ironically the reason to discontinue MMT quite often comes from care providers working in maintenance programs. They often do not try to adequately address the reasons why patient was taking opioid was taken 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. A lot of physicians who are directly involved in MMT programs in Malaysia or indeed worldwide are quite reluctant to increase dose to a required level due to the lack of understanding of methadone Adverse Drug Reactions (ADR). Although its efficacy and safety are well documented worldwide throughout the world, the bad perception of opioid is hard to shake off. A serious side effect like hypoventilation, respiratory depression, arrhythmia and prolonged QT interval were rare and normally occurs with other concomitant drugs such as benzodiazepine [28]. Most guidelines advises gradual increase in methadone dose to achieve sufficient tolerance so that an injection of any amount of street opioid 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 80 - 100 mg per day.

Typically when these principles are followed, MMT is effective with a tolerable adverse drug reaction (ADR), and the individual and society can gains from it.

It is however unfortunate that these principles are rarely followed. Consequently, although current knowledge supports a daily dose of at least 80 mg to 100 mg to abolish further craving for opioids, a big majority, including in Malaysia, are maintained on much lower doses [5, 28-31]. To ascertain optimal dosing for MMT in clinical settings is very challenging. As explained before, higher doses (> 80mg) had been postulated to have serious adverse drug reactions (ADR) while low dose encourage defaulter and illicit drug seeking behaviour. It has been observed that physicians are too afraid to maximize methadone dosage to a required level mainly due to misconception about its side effects. This study hopes to clarify this misconception and encourage physician to optimize personalized methadone dosing. In view of the heavy burden of opioids addiction to society generally and healthcare specifically, we choose to study about methadone substitution therapy and its implementation in details. Our focus is to compare the different of ADR between high dose methadone and low dose methadone. We hope that the results from our study will be able to highlights the main side effects in different methadone groups, its safety profile and ultimately encourage a higher dose MMT regime. An increasing importance of methadone as an effective substitution therapy, as well as its potential in treating chronic pain as in outpatient settings warranted further evaluation of its safety and efficacy [32-34]. Though we are likely producing results that have already been studied, we feel it is still important as these have never been shown in our local setting. Local data such as these is extremely important in trying to convince the authorities in adopting new and bold measures to combat the drug abuse menace and the rise of HIV in Malaysia.

By determining the relationship between clinical dose of methadone and its plasma level, the methadone prescribers would probably able to determine the relationship between clinical dose of methadone with its plasma level for a better optimum dose for the best effect and response. This would further helping physician in determining and evaluate the different withdrawal effects in opioid dependant subjects with different doses of methadone. The end point measurement of this would probably keep opioid dependent patients remain in the MMT programme for a better monitoring and curbing the spread of HIV infection through the intravenous routes.

2. Methods and material

This was a comparative prospective cross sectional study, in which the sample size will be selected from MMT clinic run by government institution (HUSM Psychiatric Department) and from the authorized private MMT centre (Klinik Sahabat, Kota Bharu).

The patients selected were already enrolled into MMT programme in these clinics. During recruitment phase, we will ensure that the subjects were already receiving daily methadone therapy for 6 month, hence minimize early adverse symptoms during induction phase. During

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recruitment phase, baseline ECG from the clinics will be studied. If these pre-induction baseline ECGs shows corrected QT interval more than 450ms in male, they will be excluded from the study. This will filter out the subjects with the prolong QT interval caused by other condition such as long QT syndrome.

After recruitment the researcher will be blinded to the treatment regimes and methadone dosage. Recruited subjects then subsequently will be tested on urine drug test, electrolyte levels and questioned about concomitant drug used. If urine drug test was positive or electrolyte levels were abnormal or subjects were found to take medication that can alter Methadone level, they will be excluded from study. However they can still be included in the study during the next follow up.

Validated questionnaire will be used to grade the symptoms frequency according to the scale (0 = never, 1 = seldom, 2 = frequent). Vitals signs, pupil size measurement, and ECG will be taken using standardized equipment. Height, weight and other demographic data will be taken from patient file in the clinic. Then blood samples will be taken for plasma level measurement and genetic screening.

3. Results

3.1. Socio-demography

Forty nine subjects were enrolled into this study. All of our sample were Malay male, age between 19 – 50 years old (mean age 35.14 ± 6.66), weight ranged between 46kg to 73kg (mean weight 61.41± 6.53) and with a mean height of 167.76±5.21 cm, ranged between 154cm to 181cm, table 1. Mean value for heart rate, mean arterial pressure (MAP), respiratory rate, SPo2 and pupil size were 85 beat per min, 89.13 mmHg, 9 breath per min, 98% saturation and 3mm pupil size respectively (table 2).

Majority of patient had secondary education level (81.63%), 14.29% patients had education of high school level, and 2.04% had education level of degree. Majority of them were single (51%) while 34.7% were married and 7 or 14.3% of them were divorced.

Twenty patient or 40.8% was given less than 80mg oral methadone. Mean methadone dose was 85.51mg ± 29.85sd while mean plasma level of methadone was 235.26 (±153.27). Mean corrected QT interval was 442.49 (±20.42), table 3.

Variables (n= 49)	Minimum	Maximum	Mean	Std. Deviation
Height (cm)	154	181	167.76	5.206
Weight (kg)	46	73	61.41	6.529
Age(years)	19	50	35.14	6.658

Table 1. Descriptive statistics of height, weight and age of subjects

Variables (n = 49)	Minimum	Maximum	Mean	Std. Deviation
spo2 (%)	95	100	98.00	1.646
mean arterial pressure (mmHg)	69.33	113.33	89.92	12.363
pulse rate (/min)	62	117	85.45	14.348
respiratory rate (breath/min)	6	16	9.18	1.976
pupil size (mm)	1	3	2.61	0.571

Table 2. Descriptive statistics of vital signs of the study subjects

Variables (n = 49)	Minimum	Maximum	Mean	Std. Deviation
methadone dose (mg)	30	160	85.51	29.85
plasma methadone level (ng/ml)	26.90	708.50	235.26	153.27
QTc interval (ms)	409	500	442.49	20.42

Table 3. Descriptive Statistics of methadone dose, plasma methadone level and corrected QT interval

3.2. Methadone dose and its relationship with plasma methadone level

Methadone dosage in this study ranged between 30mg to 160mg with mean methadone dosage of 85.51±29.85mg. Mean plasma methadone was 235.56 mg (minimum 26.90mg and maximum of 708.50mg). Histogram for methadone dosage showed normal unimodal distribution curve (figure 1) which signify normal paramateric distribution. Table 4 showed the association between methadone dosage with its plasma level and other numerical variables. Using Simple Linear Regression analysis, only plasma methadone level and corrected QT interval were found to be statistically significant ($p < 0.001$ and CI didn't cross 0). However R^2 value (coefficient of determination) was only 'fair' for plasma methadone level and QTc interval (between 0.26 – 0.50). Therefore in summary, results from simple linear regression analysis had shown that there were 'fair' linear relationships between methadone dose and plasma level. For every increase in 1mg of methadone, there was an increase of 2.685 ng/ml of plasma methadone level (p<0.001, b=2.685, 95% CI 1.436, 3.934) However only 28.5% of individual can be explained by this regression model (R^2 0.285). Scatter plot (figure 2) is showing the relationship between plasma methadone and methadone dosage. Thus, relationship between Methadone dosage and Plasma Methadone can be summarised with the equation:

$$\textit{Plasma Methadone}\ (ng/ml) = 4.641 + 2.685(\textit{Methadone Dose in mg})$$

QTc interval also had a fairly significant linear regression with the methadone dose (p <0.001, b = 0.287 (95%CI 0.147, 0.426), R^2=0.267).

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Variable (n=49)	Parameter vector, b[a] (95% C I)	R^2(regression coefficient)	p value
Plasma methadone (mg)	2.685 (1.436 , 3.934)	0.285	0.001*
QTc (msec)	0.287 (0.147, 0.426)	0.267	0.001*
Pulse rate (/min)	0.17 (0.038,0.302)	0.125	0.103
Respiratory Rate (/min)	0.007 (-0.012 ,0.270)	0.013	0.439
MAP (mmHg)	0.06 (-0.153,0.09)	0.006	0.605
SpO2 (%)	-0.006 (- 0.022 , 0.01)	0.011	0.477
Pupil size (mm)	-0.004 (-0.010 , 0.001)	0.049	0.128
Height (m)	0.008 (-0.044 , 0.059)	0.002	0.765
Weight (kg)	0.032 (- 0.088 , 0.930)	0.000	0.930

a = simple linear regression

* = statistically significance

All assumptions are met in statistically significant group

Table 4. Relationship between methadone dose with plasma methadone and other numerical variables

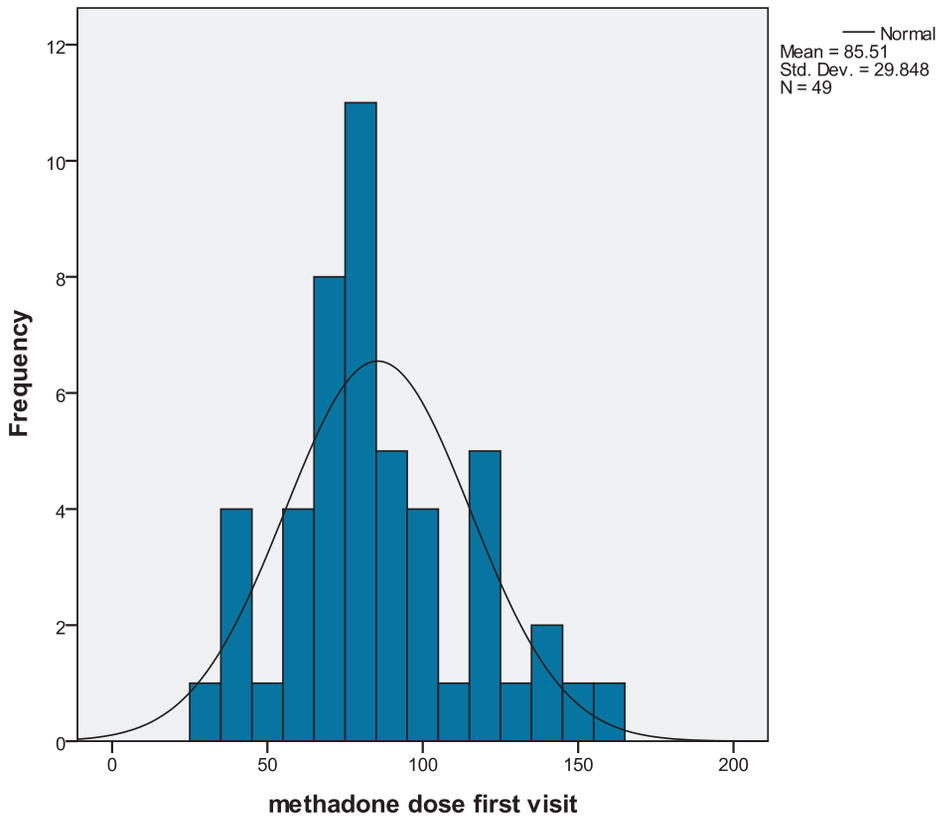

Figure 1. Histogram shows unimodal distribution of methadone dose

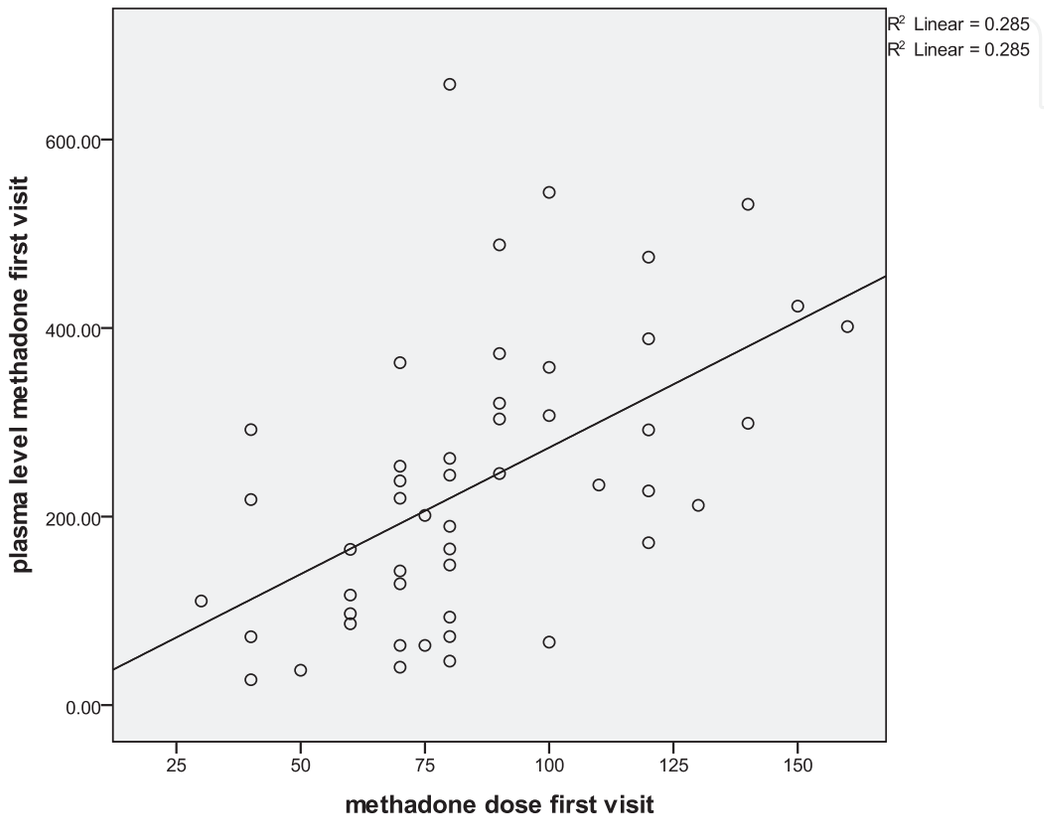

Figure 2. Scatter plot shows correlation between plasma methadone and methadone dose

3.3. Comparison of ADR between high dose methadone (≥80mg) and low dose methadone (<80mg)

Corrected QT interval was statistically significant (p = 0.025) when comparing between both methadone groups using independent-t test. Mean QTc in low dose methadone group was 434.70 (13.79) while in high dose group was 447.86 (22.64), table 5. Using Simple Linear regression, the association was fairly significant (p <0.001, b = 0.287 (95%CI 0.147, 0.426), $R^{2=}$0.267). Table 6 summarized the frequency and rate of symptoms attributed to different groups of methadone maintenance therapy (MMT). Overall, side effects with statistically significant p value (constipation, corrected QT interval, stomach upset, including nausea,

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vomiting, wind, diarrhoea, headache, lightheadedness and dizziness, chronic fatigue, sleepiness and exhaustion, drowsiness and sleepiness) showed strong positive association between methadone dose and the frequency and severity of the side effects. In other words, with increasing dose of methadone, there was high occurrence of more severe and frequent symptoms. Between the two groups of methadone, constipation and stomach upset (including nausea, vomiting, wind and diarrhea) were most significant symptoms (p = 0.001 and *p = 0.003*). Majority of subjects suffered from constipation in high dose methadone group (n = 27) albeit with minimal frequency (seldom, n = 21 out of 29).

Constitutional symptoms such as stomach upset including nausea, vomiting, wind and diarrhea were very common occurrence in patient taking methadone. Thirty seven of 49 patients in this study experienced one of these symptoms. In higher group of methadone, the situation is more pronounced (27 out of 29 patients) but less bothersome (seldom, n = 21). Using Chi square test/ Fischer exact test, problems with erection or ejaculation, was the main hormonal side effect with a *p* value of 0.005. There were 16 patients (seldom 11 and frequent 5) or more than 50% of patient from methadone ≥80mg is having problems with erection or orgasm. This was in contrast with low dose Methadone group who has only 2 patients having infrequent symptoms (10%). Headache, lightheadedness and dizziness were a common occurrence in both groups of methadone (29 out of 49 subjects). Although it was more common in high dose group (21 out of 29), it was mainly tolerable to subjects (seldom, n=21). Chronic fatigue, sleepiness and exhaustion were also common with a significant $p<0.021$. In higher methadone group (>80mg), there was at least one episodes of fatigue, sleepiness and exhaustion compared to low dose (n = 4 in low dose methadone group while n=15 in high dose group). Patient who suffered frequent symptoms also was higher in high dose group compared to low dose group with n =5 and n= 4 respectively. Nineteen out of 29 patients were suffering from drowsiness and sleepiness, with 15 of them were having infrequent episodes in high dose methadone group. Only 6 patients were having similar symptoms in low dose methadone group, with all have them having mild symptoms.

Other potential life threatening symptoms such as shallow breathing, hypoventilation, breathlessness and palpitation was not statistically significant when comparing between both methadone groups. In that respect, both methadone groups had experienced almost similar rate of symptoms.

Variables	Mean(SD) Methadone< 80mg (n= 20)	Mean (SD) Methadone≥80mg (n=29)	*p* value (95% CI)
QT_C (ms)	434.70(13.79)	447.86(22.64)	*0.025(1.73,24.60)

* statistically significant,

analysed by independent – t test

Table 5. Comparison of corrected QT interval between high dose methadone and low dose methadone

Variables	Methadone <80mg (n=20)	Methadone ≥80mg (n= 29)	*p value*
Constipation			
Never	10	2	
Seldom	10	21	*0.001[a]
Frequent	0	6	
Stomach upset, including nausea, vomiting, wind, diarrhoea			
Never	9	2	
Seldom	11	22	*0.003[a]
Frequent	0	5	
Problems with erection and ejaculation			
Never	18	13	
Seldom	2	11	*0.005[a]
Frequent	0	5	
Headache, lightheadedness, dizziness			
Never	11	8	
Seldom	7	21	*0.017[a]
Frequent	2	0	
Chronic fatigue, sleepiness and exhaustion			
Never	12	9	
Seldom	4	15	*0.021[a]
Frequent	4	5	
Drowsiness, sleepiness			
Never	14	10	
Seldom	6	15	*0.029[a]
Frequent	0	4	
Breathlessness			
Never	18	20	
Seldom	1	8	0.133[a]
Frequent	1	1	
Coughing			
Never	18	18	
Seldom	1	10	0.052[a]
Frequent	1	1	
Shallow breathing			
Never	19	20	
Seldom	1	8	0.083[a]
Frequent	0	1	
Palpitation			
Never	19	20	
Seldom	0	6	0.062[a]
Frequent	1	3	

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Variables	Methadone <80mg (n=20)	Methadone ≥80mg (n= 29)	*p value*
Dry mouth			
Never	8	25	
Seldom	1	4	0.124[a]
Frequent	1	0	
Hallucination			
Never	20	26	
Seldom	0	3	0.138[b]
Frequent	0	0	
Euphoria, elated mood			
Never	18	25	
Seldom	2	3	0.710[a]
Frequent	0	1	
Sad, depression, hopelessness			
Never	17	29	
Seldom	3	0	0.062[b]
Frequent	0	0	
Weight gain			
Never	12	10	
Seldom	7	15	0.187[a]
Frequent	1	4	
Rash			
Never	20	22	
Seldom	0	6	0.060[a]
Frequent	0	1	
Galactorrhoea	No data		
Seizure, athetosis, abnormal movement	No data		

a = Chi Square test

b = Fischer exact test

* statistically significant, p<0.05

Table 6. Comparison of ADR between high dose methadone and low dose methadone (categorical variables)

3.4. Comparison of withdrawal or mixed side effects between low dose methadone (<80mg) and high dose methadone (≥80mg)

Table 7 Illustrates a comparison of main withdrawal or mixed side effects between the two groups of methadone. Using either Chi square test or Fischer exact test, itchiness was the most significant (p =0.001) withdrawal side effect in this study. Eighteen out of 20 patients in low dose methadone had at least 1 episodes of skin itchiness, although majority of them (n = 15) was not frequent. High dose methadone group had only 8 mild skin itchiness cases and 1

frequent case. It indicates that higher dose methadone group has less withdrawal side effect including itchiness. Increase sweating had a second lowest *p* value at 0.005. Eight patients or 40% from lower methadone dose group have experienced increase sweating at some point of time, but 7 of them experienced infrequent symptoms. Only 1 patient from higher methadone group suffers from the same symptoms (3.5%).

Variables	Methadone <80mg (n=20)	Methadone ≥80mg (n=29)	*p value*
Itchiness			
Never	2	22	
Seldom	15	8	*0.001[a]
Frequent	3	1	
Increase sweating			
Never	12	28	
Seldom	7	1	*0.005[a]
Frequent	1	0	
Insomnia, lack of sleep			
Never	12	26	
Seldom	6	2	*0.033[a]
Frequent	2	0	
Flushing			
Never	11	26	
Seldom	8	3	*0.019[a]
Frequent	1	0	
Poor weight gain, anorexia			
Never	18	21	
Seldom	2	6	0.263[a]
Frequent	0	1	
Difficulty urination			
Never	20	28	
Seldom	0	1	1.000[b]
Frequent	0	0	
Aggressive, agitation			
Never	20	27	
Seldom	2	0	0.357[b]
Frequent	0	0	
Swelling of hand and feet	No data		

a = Chi Square test, b = Fisher Exact test

* statistically significant

Table 7. Comparison of main withdrawal side effects between high dose methadone and low dose methadone.

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Withdrawal patients also reported having flushing symptoms. Comparing the 2 groups of methadone, there was a significant statistical significant (p = 0.019). Nine patients having flushing symptoms in low dose group compared to 3 in high dose group.

Eight out of 20 patients were having insomnia or lack of sleep in low dose methadone group (p = 0.033). However, majority (6 out of 8) were having only infrequent symptoms. In high dose group, only 2 patients suffered from infrequent insomnia or lack of sleep (6.8%). Other variables were not statistically significant.

4. Discussion

Some centre for methadone maintenance treatment (MMT) programs prescribe inadequate daily methadone doses. Patients complain of withdrawal symptoms and continue illicit opioid use, yet practitioners are reluctant to increase doses above certain arbitrary thresholds. Plasma methadone levels (PMLs) may guide practitioners' dosing decisions, especially for those patients who have low PMLs despite higher methadone doses. To date, methadone dosing is still an issue of debate and controversy among clinicians who are involved in methadone maintenance programs. One meta analysis [35] which studied 24 articles suggest to have a goal for methadone dosing in the range of 60 to 100 mg daily However newer research suggests that doses ranging from 100 mg/d to more than 700 mg/d, with correspondingly higher PMLs, may be optimal for many patients [36-39].There does not appear to be a maximum daily dose limit when determining what is adequately "enough" methadone. In this study, there were 49 subjects taking daily methadone in the range of 30mg to 160mg. Mean methadone dosage was 85.51mg whereas methadone plasma levels ranged between 26.90 and 708.50 ng/ml with a mean of 234.24 ng/ml. Results from this study showed there was a positive, fair and significant correlation between methadone doses with its plasma level. (Pearson R = 0.36, Regression coefficient, R^2 =0.285, parameter vector b = 2.685, p = 0.001) and can be summarised into an equation:

$$\textit{Plasma methadone}\ (\textit{ng/ml}) = \mathbf{4.641} + \mathbf{2.685}\ (\textit{methadone dose in mg})$$

Thus, according to the formula, every increase in 1mg of methadone, there was an increase of 2.685 ng/ml of plasma methadone level plus a constant (b=2.685, 95% CI 1.436, 3.934, p<0.001) However only 28.5% of individual can be explained by this regression model (R^2 0.285). Result from our study is well replicated in other publication. Adelson et al. in 2007, had studied 151 MMT patient in Israel and found a significant correlation between methadone dosage and plasma level (Pearson R = 0.36, P<0.005). The study also noted a stronger correlation in patient who do not have illicit drugs [38]. Eap et al. reported on use of high methadone doses, as well as methadone levels in the plasma; they evaluated 211 MMT patients (including 31 patients who were undergoing dose reduction to stop treatment), all of whom were receiving the same methadone dose for at least 5 days. [40]

The mean methadone dose in the 211 patients was 100 ± 58 mg/day, range 5-350 mg/days, and their mean methadone level in plasma was 281 ± 169 ng/ml, range 16-976 ng/ml. They found

a significant correlation between methadone levels in plasma and methadone doses expressed as mg/kg body weight; the highest correlation was in patients with no co-medications (benzodiazepines and antidepressants) or drug abuse, and with the active enantiomer R-methadone (R = 0.65). The correlation with the racemic methadone solution was R = 0.50. However, no scatter-plot was published. Results from this study and those highlighted here shows that although the plasma methadone level was fairly correlated (R between 0.26 – 0.5), true significant linear associations is impossible. This is because the plasma level depends on the dose that the patient is actually taken, which can be subjected to cheating. It is well known that some patients may abuse methadone. High blood levels of methadone may occur for several reasons:

1. Up to 75% of the patients with high-methadone serum levels indeed were receiving high methadone doses, above 70mg/day;

2. Some patients may obtain illicitly additional methadone or other illicit drugs outside the clinic on any day;

3. Some patients, especially those who have take-home privileges, may not consume their entire doses and may have sold some of the methadone.

There are several other factors that relate to inter-subject variability among patients' serum methadone level. Specific cytochrome P-450 gene polymorphisms which Eap et al. hypothesized might produce "slow metabolizers," "rapid metabolizers," and "ultra-rapid metabolizers". Chen et al. in 2011, studies the effect CYP450 polymorphism in relation to withdrawal symptoms and side effects. In this cross sectional study, the average methadone dose was 55 mg/day among 366 methadone maintenance patients whose average steady-state plasma methadone concentrations were 193 and 142 ng/ml for R- and S-methadone enantiomers. It found out a polymorphism of the CYP3A4 is associated with opioid withdrawal symptoms (permutation, $p < 0.0097$), especially the symptom of heart rate, which was assessed as an item within 11 items of the clinical opioid withdrawal scale total score.CYP3A4 polymorphism also is associated with methadone side effects specifically the sedation side effects. The metabolism of methadone is carried out through the CYP3A4, CYP2B6, CYP2C19 and CYP2D6 isoenzymes of the CYP system in the liver [41,42]. Through the metabolic process, it produces an inactive metabolite 2-ethylidene-1, 5-dimethyl-3, 3-diphenylpyrrolidine (EDDP). It has been estimated that approximately 50% of all clinical therapeutic drugs are metabolized by CYP3A4. The subfamily of CYP3A enzymes is responsible for the other 30% of drug metabolism in adults, hence its activity and regulatory mechanism may have an impact on methadone disposition and variability [43]. Apart from polymorphism from CYP450 system, variation in acute α-glycoprotein (AAG) in plasma may play a significant role in its inter-individual variability. Methadone binds to plasma protein to a high degree of 86 percent, predominantly to acute α-glycoprotein (AAG) [44]. AAG is an acute phase protein that exhibits significant variations in its plasma levels according to the physiological and or pathological situation of the patient [45-47]. AAG levels are significantly increased in stress, leading to very low concentrations in the free fraction of methadone in cancer patients compared to healthy participants [48,49].

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Other factors that may contribute to variability include: age and sex. It has been suggested that these factors may explain about 33 percent of the inter-individual variations in steady state level [50]. From the study, females and increase in weight was found to have a positive linear relationship. However, we could not replicate the findings in our study most probably due to small sample size and "all male" subjects of our samples (for age, linear correlation, $p = 0.77$).

In summary this study has concurred with the current view (r =0.36) of fairly strong relationship between methadone dosage and plasma methadone in patient currently subscribed into MMT. The correlation is higher when the patient has a complete abstinence from illicit drug. Nevertheless only 28.5% (R^2 0.285) of correlations can be explained by the correlation equation, or in other words, the inter-variability between patient is huge. Factors such as polymorphism of cytochrome P450 system especially CYP, variation in weight and gender, unpredictable relationship between AAG and stress level and also patient factor is the main contributor for this variation. Regardless of the route of administration, opioids can produce a wide spectrum of unwanted side effects, especially during the early days of treatment when daily dose is being stabilised. Some of these are distressing but generally not dangerous such as constipation, sedation, itchiness, sweating, nausea and vomiting; whereas others are more serious and even life-threatening like respiratory depression, severe hypotension and abnormal QT interval (potentiates episodes of Torsade de Pointes (TdP). TdD is polymorphic ventricular tachycardia (VT) characterized by a gradual change in the amplitude and twisting of the QRS complexes around the isoelectric line. Often, Tdp is associated with a prolonged QT interval usually terminates spontaneously but frequently recurs and may degenerate into ventricular fibrillation. The ventricular rate can range from 150 beats per minute (bpm) to 250 bpm. The QT interval requires to be increased markedly (600 msec or greater). Therefore, a prolonged QT interval signifies a higher risk of arrhythmias especially TdP, which can deteriorates into sudden cardiac failure and sudden death. In vitro studies of levomethadyl, methadone, and buprenorphine have each demonstrated considerable blockade of the human ether-a-go-go-related–gene (*hERG*) channel activity, a property that is strongly associated with prolongation of the QT interval and the induction of torsade de pointes ventricular tachycardia (TdP) [51].

Mean and SD for corrected QT interval was 434.70(13.79) ms for low dose methadone group and 447.86(22.64) for high dose methadone group. Independent t- test showed statistically significant different between these two groups (t =2.316, mean difference = 13.16, p value = 0.025, CI = 1.73, 24.6) (table 3).

In addition, simple linear regression showed there is fair association between methadone dose and corrected QT (R=0.404, $b = 0.287$, CI = 0.147, 0.426, $R^2 = 0.267$, $p = 0.001$). Although this result proved there is an association between methadone dose and QTc, only 26.7% of the patient can be predicted by the result (R2 = 0.267) (table 2).

Results from this study are in line with dozens other findings in proving the association between methadone dose and prolongation of QTc. [52-55]. As with most QT interval prolonging drugs, the effects of methadone on cardiac repolarization are dose dependent, as evident in case reports as well as cross-sectional and prospective studies. Methadone dosages exceeding 100 mg/d have frequently been noted in published cases of torsade de pointes, and some case reports [56-58] highlight QTc interval normalization after methadone discontinua-

tion or dose reduction. Furthermore, many studies, including those of oral and intravenous methadone, demonstrate a positive correlation between doses and delayed cardiac repolarization [59-63] among both addiction treatment and pain management cohorts. In Peles and colleagues' study [61], the correlation achieved statistical significance in the subset of patients abusing cocaine, which is consistent with a synergistic effect of methadone and cocaine on hERG channel blockade. In Fanoe and colleagues' study, the QTc interval increased by 10 ms for every 50-mg increase in methadone dose, which corresponded to a higher risk for syncope (odds ratio, 1.2 [CI, 1.1 to 1.4]). Cruciani et al. found the correlation between methadone doses with QTc in "all male" subjects similar to this study. With regard to serum levels, Martell and colleagues prospectively demonstrated that the increase in QTc interval from baseline to 12 months after methadone initiation correlated with both trough and peak serum concentrations. Wedam and colleagues observed similar relationships with the methadone derivative levacetylmethadol. This creates a safety– efficacy paradox, because higher doses of methadone may reduce illicit opioid use (or diminish chronic pain) yet place patients at greater arrhythmia risk. It is important for clinicians to recognize that sudden cardiac death associated with methadone has been described at dosages as low as 29 mg/day, which suggests that arrhythmia can occur across a wide therapeutic range that includes dosages commonly used in both chronic pain and addiction treatment. This in turn suggests that methadone dosage is just one consideration with regard to limiting arrhythmia risk.

In view of the overwhelming evidence which associate methadone dose with prolonged QTc and subsequent Torsades de Pointes, a clinical guidelines in QTc interval screening in methadone therapy was proposed by Krantz et al. (2009) [64].

Respiratory depression, the hallmark of serious opioid overdose, is only seen in about 50% of patients with CNS depression and should not to be confused with [65]. It is also synonymous with drowsiness and lethargy which may confuse the observer. Methadone can reduces or eliminates the normal drive to recommence respiration or increase the rate once it diminished in the body. Overdose-induced adult respiratory distress syndrome (ARDS) has also been described for methadone toxicity [66].

Methadone overdose can follow an unpredictable course in non-tolerant patients who are at risk of death. When methadone is consumed, the effect on the breathing pattern depends on the plasma concentration of the drug. At low concentrations there is a decrease in tidal volume (normal volume of air breathed in and out), but no change in respiratory rate; at higher concentrations both tidal volume and rate are depressed [67]. Preclinical studies indicate that at very high concentrations, there may be some additional disruption to respiration as a result of NMDA (N-methyl-D-Aspartate) antagonism [68] and possible serotonergic (re-uptake inhibition) and catecholaminergic activity [69].

Generally, opioid activates the mesolimbic reward system in the midbrain. Subsequently, the system generates signals in the ventral tegmental area. As a result, dopamine neurotransmitter is released from the nucleus accumbens result in feelings of pleasure. Other areas of the brain create a lasting memory that associates these good feelings with the circumstances and environment in which they occur. These memories, called conditioned associations, often lead to the craving for drugs. Beside relieving craving and withdrawal, methadone on the other

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hand, through G-protein–coupled mechanisms also directly affect cation channel function in the postsynaptic membrane. Methadone as an agonist at both mu and delta receptors acts to increase potassium channel opening (reducing production of cAMP through inhibition of adenylate cyclase activity) and decrease the opening of voltage-operated calcium channels (inhibiting inward Ca 2+ currents). Consequent reduction in neuronal membrane excitability (depolarizing effect) exerts an inhibitory effect upon respiratory systems to diminish sensitivity to changes in O2 and CO2 outside normal concentration ranges [70]. Mu and delta receptor activity contribute in an additive way to respiratory depression. Several studies have investigated the control of respiration during chronic dosing (MMT) with the drug. Usually, while PaO_2 in blood is normal, dopamine is released inhibiting chemoreceptors in the carotid and aortic bodies. Hypoxia reduces the release of this dopamine and in doing so releases chemoreceptors, which stimulate the respiratory centre. Santiago et al. [72] found at the start (< 2 months) of MMT, ventilation was reduced and arterial blood gas altered, along with decreased sensitivity of CNS chemoreceptors to both CO_2 and hypoxia. However, after more than 8 months in MMT these indices had returned to normal except for the persistent reduction in sensitivity of the CNS receptors to hypoxia.

Durstellar et al. in 2010, had compared multiple symptoms of methadone to heroin in opioid dependence [72]. Breathing difficulties were encountered more in methadone group at 25.4% out of 63 patients compared to heroin group (11.1% out of 54 patients; $p < 0.05$).

Our samples showed similar rate in both methadone group; breathlessness (11 patient out of 49 or 22.45%, where 9 in high dose group, 2 in low dose group), shallow breathing (10 patients out of 49 or 20.41%, where 9 were in high dose group and coughing (13 out of 49 patients or 26.5%). However when comparing between low dose methadone and high dose methadone groups, none were statistically significant.

Looking at the respiratory symptoms pattern, up to 20-25% of the patient had experienced some degree of respiratory symptoms attributable to methadone or indeed other opioids. However, life threatening respiratory compromise remains rare as evidence from mortality review worldwide [73-75]. Like early research by Santiago et al. which has been stated above, Marks and Goldring [76] found hypercapnia uniformly developed in the early phases of methadone treatment persisting for up to 8 months and which was consistently associated with alteration in the central control of ventilation.

Although results from this study were comparable with previous study, more refined research with better methodology especially in detecting respiratory depression in induction phase (first 6 month) is warranted to study the dose-dependent respiratory depression.

5. Conclusion

In summary this study has concurred with the current view ($r = 0.36$) of fairly strong relationship between methadone dosage and plasma methadone in patient currently subscribed into MMT. The correlation is higher when the patient has a complete abstinence from illicit drug.

Nevertheless only 28.5% (R^2 0.285) of correlations can be explained by the correlation equation, or in other words, the inter-variability between patient is huge. Factors such as polymorphism of cytochrome P450 system especially CYP, variation in weight and gender, unpredictable relationship between AAG and stress level and also patient factor is the main contributor for this variation

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Author details

Nasir Mohamad[1,2], Roslanuddin Mohd Salehuddin[1], Basyirah Ghazali[2],
Nor Hidayah Abu Bakar[3], Nurfadhlina Musa[2], Muslih Abdulkarim Ibrahim[2],
Liyana Hazwani Mohd Adnan[3], Ahmad Rashidi[2] and Rusli Ismail[2]

1 Department of Emergency Medicine, School of Medical Sciences, Universiti Sains Malaysia, K.Kerian, Kelantan, Malaysia

2 Pharmacogenetic Research Group, Institute for Research in Molecular Medicine, Universiti Sains Malaysia, K.Kerian, Kelanta, Malaysia

3 Department of Pathology, Hospital Raja Perempuan Zainab II, Kota Bharu, Kelantan, Malaysia

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