

# Methadone Maintenance Therapy (MMT) in Malaysia: An observational clinical study

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## RESEARCH

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## ABSTRACT

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### Background

Methadone is widely used to treat opiate addiction, in particular heroin. Proper administration via drug optimisation is the only way to achieve net clinical outcomes.

### Aims

This is an observational cross-sectional study, sought to observe the clinical response to a methadone maintenance therapy (MMT) program.

### Methods

**Setting:** Four treatment clinics in Kuala Lumpur, Malaysia.

**Patients and methods:** One-hundred and twenty-two methadone patients. Their demographic characteristics, medical history, methadone doses, duration in the program, and compliance rates were recorded.

**Main outcome measures:** The opiate withdrawal scale was used to assess the severity of withdrawal symptoms.

### Results

The mean methadone dose was 50mg (range, 20–160mg). The minimum recorded duration in the MMT program was

three months, the maximum was 40 months, and the mean was seven months. 90 per cent of the patients were addicted to multiple substances; of those, 70 per cent were addicted to three or more substances. Many patients reported cravings and seeking behaviours while on methadone.

### Conclusion

Gradual increments in methadone doses are relatively safe, but patients should be monitored daily. Doses should be increased to control withdrawal symptoms. Despite optimal dosing, cravings and drug-seeking behaviours may not be controlled in some patients, and an alternative to methadone may be an option.

### Key Words

Methadone, psychological dependence, detoxification, hypertension

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### What this study adds:

#### 1. What is known about this subject?

Methadone has been a good choice for opiate addiction with a reasonable safety profile especially in low doses. High doses may control addiction in a better way, with higher incidence of cardiac events.

#### 2. What new information is offered in this study?

Although many patients have been optimized on methadone, seeking and craving might not disappear in full. Thus, this could be a sign for methadone failure, regardless of the positive control of withdrawal symptoms.

#### 3. What are the implications for research, policy, or practice?

Monitoring seeking and craving alongside other withdrawal symptoms is very crucial in methadone therapy. Investigating the plasma level once the patient is therapeutic is judicious. Once seeking is evident, change to another alternative.

## Background

Addiction and substance abuse are a worldwide problem, and Malaysia is no exception. Opiate addiction is expected to affect nearly 1.3 per cent of adults in Malaysia.<sup>1</sup> In addition to aggressive criminal activities, HIV risk may reach as much as 15 per cent in people who inject drugs.<sup>2</sup> Thus, the establishment of methadone maintenance therapy (MMT) was an essential step in controlling opiate use and reducing HIV transmission.<sup>3,4</sup>

MMT has been widely used in Malaysia to treat opiate addiction and reduce its associated risks.<sup>5–7</sup> MMT helps to reduce the severity of withdrawal symptoms and gradually eliminate physical and psychological dependence.<sup>8</sup> Numerous countries have also been using this approach successfully, including the USA, the UK, Canada, Switzerland, the Netherlands, Germany, Italy, Australia, New Zealand, Bangladesh, Thailand and many others worldwide. The majority of those consider MMT a part of their national health program.<sup>9,10</sup>

At MMT clinics, addiction to opiates must be established clinically and historically, and the list of substances to which a patient is addicted must be enumerated as well. Once confirmed, the starting MMT dose depends on the type of program and the purity of heroin in that area. Overdosing on methadone can be fatal, while a too-low dose may lead to opiate withdrawal.<sup>5,8,11–13</sup> Accordingly, the initial dose should range between 10–30mg. If the patient's tolerance to opiates is very high, 25–40mg would be an appropriate dose; low dosing should be used if the tolerance is unknown. Patients should be kept under surveillance for 2–4 hours, in case a dose increase is warranted. After that, patients should be seen daily during the first week to re-assess the dosing scheme. Dosing can be increased by 5–10mg, but not by more than 20mg weekly. For long-term detoxification, the net dose can reach 60–120mg by the same incremental fashion.<sup>1,14,15</sup> It has been reported that low doses (40mg) are equivalent to high doses (80mg) with regard to opiate abstinence symptoms and cravings.<sup>16–18</sup>

The MMT in Malaysia is run in the form of out-patient clinics and counselling, either in general practice clinics or hospitals. Patients are supervised on a daily basis for several months before being prescribed take-home methadone doses. Without evidence of compliance, patients are not allowed to take any doses back to their homes.<sup>11–13</sup> Advocates of the harm reduction approach of methadone recognise that full abstinence may not be reached in every case, but the approach aims instead to improve the health and social life of the addicts while on treatment, and to

prevent the transmission of HIV and other dangerous infectious diseases.<sup>16,19–21</sup>

## Aims

We sought to observe the clinical benefits of the MMT program, which may help to reduce the severity of withdrawal symptoms and help patients to overcome opiate addiction.

## Method

This study had an observational cross-sectional design, and was approved by the ethics committee of Malaya University Hospital. Patients were invited to participate in this study in four clinics in Kuala Lumpur. The patients were heroin addicts who had been visiting the clinics daily for MMT for at least three months. Upon accepting, compliance to therapy was assessed based on the number of missed treatment days.<sup>22</sup> Given the nature of the program, this method is simple to use and well-validated:

Compliance % = (missed days for this month/30) × 100

If compliance exceeded 80 per cent, patients were eligible to participate. Patients were excluded if they were:

1. Not stable on methadone.
2. Less than 80 per cent compliant.
3. Not willing to sign the written informed consent form.

If compliance exceeded 80 per cent, the study was explained to the patients, who were required to read the information sheet carefully and free to ask questions. Upon understanding and accepting the policy and procedure, they all were required to sign informed consent forms. Their demographic information and relevant medical and substance abuse history were recorded. Subjective and objective measurements for the Clinical Opiate Withdrawal Scale (COWS) and the Objective Opiate Withdrawal Scale (OOWS) were recorded as well.<sup>23,24</sup> Due to the nature of the program, the names of the patients and clinics were kept confidential.

All descriptive data were summarised in Excel® (Microsoft Corporation, Redmond, WA, USA). Minitab® version 17 (Minitab Inc., State College, PA, USA) was used to analyse the data and generate all statistical calculations. The level of significance ( $\alpha$ ) was set at 0.05. The data were all checked for normality before appropriate statistical tests were selected. Spearman's rho was used for correlation and ANOVA for dose comparison among the clinics.

## Results

### Demographics

Table 1 displays the means of subjects' demographic characteristics. The vast majority of our subjects were male (120); there were only two female subjects in the study. The majority were Malay (90 per cent), followed by six per cent Chinese, three per cent Indian and one per cent Pakistani. The maximum reported dose was 160mg, and the maximum MMT duration was 40 months. Both high values were reported for one patient only. The minimum reported dose was 20mg, and the minimum duration was three months. The median methadone dose was 50mg, and the median for duration was 7 months. All subjects continued MMT after the completion of the study. The most commonly abused substances were amphetamines, amphetamine-type stimulants (ATS), and Ganja (Figure 1).

Table 2 displays the medical conditions reported by the patients in this study. Three patients had hypertension, although only one of them was actively treated with amlodipine. Four patients had asthma, and all were treated for acute situations with Ventolin® and corticosteroid inhalers. Two patients were diagnosed with depression and were prescribed the psychotropics lorazepam, fluvoxamine, haloperidol and benzhexol. A few others reported current use of the antibiotics Bactrim® and Augmentin® and the pain reliever paracetamol. Eight patients took multivitamins, five took protein supplements, three used herbal remedies and one reported taking calcium supplements.

### Opiate abstinence symptoms

The most reported symptoms were yawning, sweating, tearing, restless sleep, muscle twitching, flushes, irritability, anorexia, insomnia, restlessness, low-grade fever, abdominal cramps, diarrhoea, weight loss and general weakness. The opiate abstinence scores were computed accordingly. Figures 2-4 show a clear variability between the four clinics. Subjects in clinic 4 had the highest craving rates (Figure 2). Drug-seeking behaviours were highest in clinic 3 (Figure 3). In contrast, a large number of subjects presented with no COWS in clinics 1 and 2 (Figure 4).

ANOVA calculations revealed a significant difference in mean dosing between the four clinics: 60, 90, 72 and 40mg ( $p=0.0001$ ). Dosing in clinic 1 differed least from the mean for all clinics. The mean for clinic 2 (90mg) was the highest. In terms of the COWS, no significant difference was found between the clinics ( $p=0.38$ ). A moderate correlation was found between the size of the dose and the compliance (Spearman's  $r=0.6$ ). However, only a weak negative

correlation was detected between the dose and the opiate abstinence score (Spearman's  $r=-0.1$ ). Likewise, only a weak negative correlation was detected between compliance and the opiate abstinence score (Spearman's  $r=-0.1$ ).

## Discussion

This study described the clinical benefits of a cohort at the MMT program in Malaysia. The demographics and types of substances used are all similar to what has been described by the National Anti-Drugs Agency (AADK, [www.adk.gov.my](http://www.adk.gov.my)).

The primary objective of MMT is to eliminate withdrawal symptoms. It has been reported in the literature that methadone doses of 80–120mg can relieve narcotic cravings, suppress the opiate abstinence syndrome for 24–36 hours, block the effects of administered heroin, and help develop tolerance to euphoria. The exact dose would depend mainly on clinical endpoints.<sup>26,27</sup> Increasing the methadone dose gradually helps to avert any potential fatal adverse events and to ameliorate the withdrawal symptoms. Nonetheless, the complexities involved in methadone dosing can lead to either overdosing or withdrawal symptoms.<sup>6,7</sup>

Very high doses, however, must be used cautiously. MMT's medical safety has been monitored since 1964, and it is considered a safe and non-toxic therapy with only a few transient, treatable adverse effects.<sup>5,28</sup> Serious adverse events are rarely reported in MMT programs. However, mortality from overdosing has been reported numerous times.<sup>29,30</sup> Therefore, MMT inclusion criteria are very strict in many countries, and include a consideration of factors such as age, supervision, addiction history, compliance and strict follow-up. Several risk factors have been suggested to increase methadone mortality, including overdosing, lack of compliance, benzodiazepine and antipsychotics use, alcohol abuse, heart failure and mood disorders.<sup>31</sup> Our study and other Malaysian studies reported no serious adverse drug reactions in subjects if the recruitment and dose optimisation processes were carefully designed.<sup>3,4,6,7</sup>

Most of our subjects seemed clinically stable and satisfied with doses of 50–70mg. Some of them, however, presented with some withdrawal symptoms, which may warrant higher doses for better management. The symptoms reported varied among the clinics and patients. Control of cravings and seeking behaviours cannot be achieved in all patients; changing from methadone to another alternative could be a good strategy if problems persist.<sup>29</sup> The most common symptoms among our patients were heroin

seeking, heroin craving, anxiety, yawning, restless sleep, flushes, irritability, insomnia, restlessness, low-grade fever, abdominal cramps, diarrhoea and general weakness. For the most part, these symptoms are an integral part of opiate withdrawal. Therefore, dosing can be increased by 5–10mg, but by no more than 20mg weekly. For long-term detoxification, the net dose can reach 60–120mg by the same incremental scale.<sup>14,15</sup> Heroin craving and seeking behaviours among long-term MMT patients has been reported numerous times.<sup>17,18,32,33</sup> A relationship between methadone levels and craving patterns has been found only for subjects who were in the therapeutic range of methadone. In contrast, when methadone doses were sub- or supra-therapeutic, no relationship was identified and patterns were inconsistent.<sup>14,17</sup> Unfortunately, we could find no recent studies on this phenomenon, and this study did not investigate methadone plasma levels. A large percentage of our patients reported no withdrawal symptoms overall, indicating a full abstinence. This study found that the percentage of cravings and seeking behaviours reported were lower with a higher-dose regimen. Further, we reported a very weak negative correlation between dose and the opiate abstinence score, and a very weak negative correlation between compliance and the opiate abstinence score.

Psychosocial and psychotherapeutic risks are independent risk factors for the success of the treatment.<sup>33–35</sup> Moreover, the number of substances to which a patient is addicted may contribute to the cumulative impact. Numerous recent studies have shown a strong inverse correlation between the number of illicit substances and the size of the required MMT dose. Furthermore, when the dosage was titrated to clear the subjective and objective measures of withdrawal symptoms, not according to any ceiling, the number of illicit substances was reduced drastically.<sup>36</sup> This study, however, did not find any significant difference between the number of illicit substances and dosing. In addition, frequent use of amphetamine derivatives may be an indicator of sub-optimal therapy.<sup>37</sup>

This study is small in nature and patients were not followed up frequently. Thus, a larger study is required to assess the net clinical benefits with multiple follow up design.

## Conclusion

Methadone seems to be a good choice for many patients to overcome opiate addiction. Close monitoring and gradual dose increments are recommended. Reducing cravings and drug-seeking behaviours should be the primary targets, and controlling them may not always be achieved with

methadone. Patients treated with inadequate methadone doses may complement the methadone with illicit substances, masking the actual need for higher methadone doses.

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**PEER REVIEW**

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**CONFLICTS OF INTEREST**

The authors declare that they have no competing interests.

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**ETHICS COMMITTEE APPROVAL**

University Malaya Medical Center (Ref. 685.58).

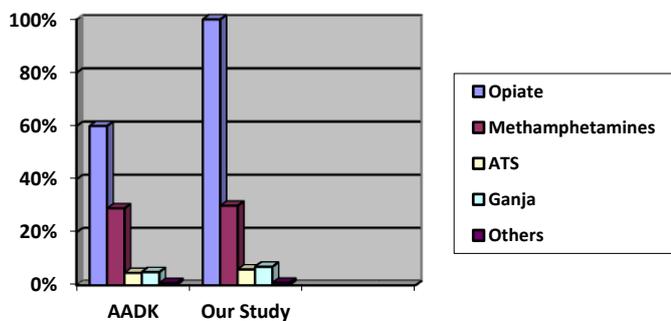
**Table 1: Means of subjects' demographic characteristics**

Characteristic	Mean (SD)
Compliance (%)	90 (10)
Dose (mg)	50 (20)
Duration (months)	11 (7)
Age (years)	38 (8)
Body Mass Index	22 (6)

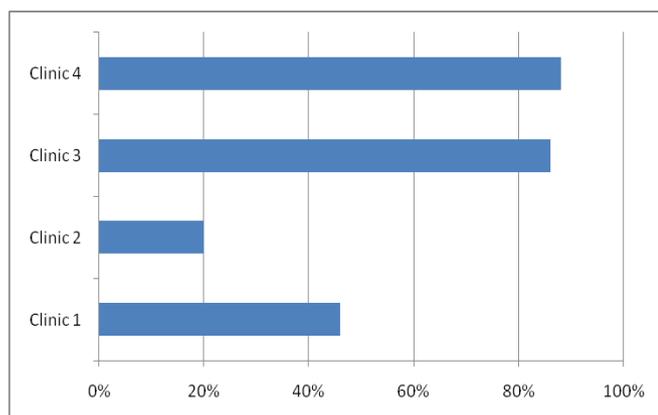
**Table 2: Baseline medical history and medication information**

Disease or disorder	Number of patients	Number of patients receiving active therapy
Hepatitis C	3	1
Hepatitis B	8	1
HIV	5	2
Co-infection: Hepatitis C and HIV	1	2
Hypertension	3	1
Asthma	4	4
Depression	1	3
Asthma and depression	1	1

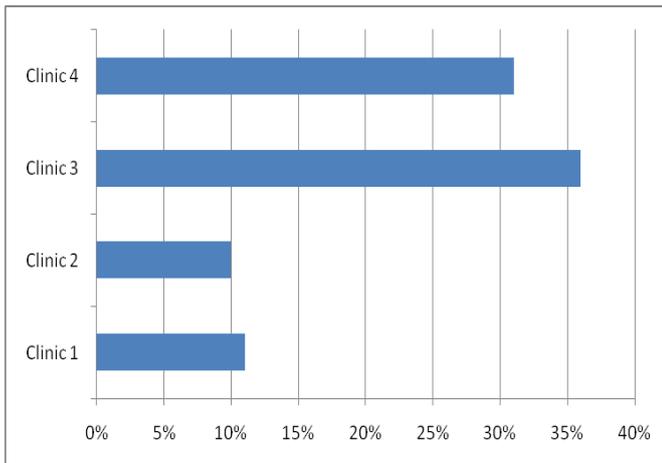
**Figure 1: Most commonly abused substances**



**Figure 2: Percentage of subjects experiencing drug cravings**



**Figure 3: Percentage of subjects displaying drug-seeking behaviours**



**Figure 4: Percentage of subjects reporting no withdrawal symptoms**

