

Relationship between Dose and Retention of Methadone Maintenance Therapy to Drug Dependence Patients in Primary Health Care

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ABSTRACT

Methadone Maintenance Therapy is one of the substitution therapies needed as a harm reduction approach to reduce the harm of drug abuse. This study aims to determine the relationship between dose and retention in drug-dependent patients on the methadone maintenance therapy (MMT) program at Kramat Jati District Health Center in 2009-2018. This type of research is cross-sectional using secondary data from medical records which are then analyzed for their meaning. This study involved 136 patients who met the inclusion criteria. The results of statistical analysis showed that the average initial dose received by patients was 27.65 mg (range 10-40 mg), and after 2 weeks of therapy, the average dose received by patients was 51.6 mg (range 22.5-85 mg). The mean of the smallest and largest maintenance doses received by patients was 30.9 mg (range 0.25-115 mg) and 84.39 mg (range 15-140 mg), meanwhile the average maintenance dose received by patients was 62.36 mg (range 7.77-126.92 mg). This study shows that the retention value of 1 year or more reaches 64.71%. The 2-week maintenance dose ($P=0.005$), the smallest maintenance dose ($P=0.000$), the mean maintenance dose ($P=0.004$), and a history of missed doses ($P=0.000$) were significantly associated with retention. From the results of this study, it can be concluded that the more optimal the maintenance dose received by the patient, the greater the patient's retention in undergoing methadone maintenance therapy, conversely, the smaller the frequency of missed doses, the better the patient's retention in undergoing methadone maintenance therapy.

Keywords: *Methadone Dosage; Retention; Methadone Maintenance Therapy*

INTRODUCTION

Drug abuse is one of the causes of the high mortality rate in Indonesia. According to National Narcotics Board (2016), the mortality rate for heroin users that is in the range of 1-2% per year is due to overdose, illness due to drug use, and death due to violence. Heroin users generally experience bacterial infections that cause skin abscesses, endocarditis, lung infections especially tuberculosis, and virus infections that cause hepatitis C, as well as Acquired Immunodeficiency Syndrome (AIDS).¹

This requires proper handling, especially for opiate narcotic abuse. The treatment for opiate dependency can be carried out based on two types of interventions, namely pharmacological and psychosocial interventions that aim to reduce or stop opiate use, prevent the dangers of opiate use, and improve the quality of health and social functioning of the patients.¹ One of the types of opiate dependence therapy that uses

pharmacological and psychosocial interventions is methadone maintenance therapy. Methadone maintenance therapy is one of the substitution therapies needed as a harm reduction approach.²

The administration of an effective dose of methadone maintenance therapy will be achieved when the patient begins to receive therapy at a dose of 60-120 mg per day which is generally achieved within \pm 2-6 weeks of the first therapy.² The dose is said to be optimal if it can overcome opiate withdrawal symptoms, can block the euphoria of using heroin, and eliminate heroin craving without causing sedation or other side effects.³

One measure of the effectiveness of the management of methadone maintenance therapy (MMT) is the length of time the patient is in the therapy program (retention). The longer the patient is in the therapy program, the better the methadone therapy will be obtained. Various studies have shown an increase in patient outcomes at retention times

of 1 year or more. Patients who undergo therapy for more than 1 year receive better benefits from methadone therapy than patients who attend therapy for less than 1 year. The longer the patient is in the therapy program, the patient will avoid crime and heroin use and prevent withdrawal symptoms.⁴ Information regarding the relationship between variations in methadone dose and therapeutic retention is needed to determine how much the dose given to a patient affects the amount of retention and whether a larger dose of methadone will result in longer retention.²

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METHODOLOGY

This research was a cross-sectional study of secondary data in the form of medical records received by methadone maintenance patients at Kramat Jati District Health Center who had just undergone therapy in the 2009-2018. The data were collected retrospectively and collected as a population. The samples in this study were all patients with the methadone maintenance therapy program who first received therapy in 2009 who met the inclusion criteria and were observed from the start of therapy until 31 December 2018. Patients who met the inclusion criteria were patients with opiate addicts who received methadone maintenance therapy for the first time in Kramat Jati Subdistrict Health Center since 2009 - 2018 and patients who had been in therapy for more than 6 weeks (42 days). The sampling method was done by purposive sampling. The research data used was a data collection sheet that included the patient's name, gender, age, education, marital status, occupation, medications that had been used by the patient, history of therapy, history of missed doses, complaints of withdrawal, and side effects of

the patient, and drugs consumed by the patients concurrent and interacting with methadone, patient therapeutic status, initial dose, 2 week dose, smallest maintenance dose, largest maintenance dose, and average patient maintenance dose and length of patient on methadone maintenance therapy (retention). Retention is the length of time the patient is in therapy, calculated from the first day the patient received methadone until he was discharged from therapy or until the end of the data collection limit. The focus of this study was on the dose and retention given to opiate-dependent patients receiving methadone maintenance therapy. The effectiveness of methadone maintenance therapy was measured based on the longer the patient was in therapy, the better the therapy was obtained. The parameters observed were the initial dose, 2 weeks therapy dose, the smallest maintenance dose, the largest maintenance dose, and the average maintenance dose as independent variables, and therapy retention as the dependent variable. The relationship between the various doses and the retention of methadone maintenance therapy was further analyzed. The research data were analyzed statistically with descriptive analysis and correlation analysis. The relationship between variables was analyzed using cross-tabulation analysis. A two-way correlation test was carried out with $P < 0.05$ considered significant.

RESULTS AND DISCUSSION

Patients Characteristics

The results showed that 126 patients who were doing methadone maintenance therapy were male (92.65%), most of whom were 25-35 years old and married. These patients had education from elementary to tertiary education, and in MMT, most of the patients had high school education, with work status of 68.38 having a job. All samples had used opiates before starting methadone therapy, most of them had a history of smoking as many as 132 patients (97.06%), consuming alcohol as much as 118 patients (86.76%), using marijuana as many as 112 patients (82.35%), using methamphetamine as

Table I. Patients Characteristics

Patients Characteristics	Total	%
Gender		
Male	126	92.7
Female	10	7.3
Age		
18-24	12	8.8
25-35	87	64.0
>35	37	27.2
Marital Status		
Not Married	34	25.0
Married	92	67.6
Divorced	10	7.4
Education		
Elementary School	3	2.2
Junior High School	16	11.8
Senior High School	78	57.4
Tertiary Education	39	28.7
Occupation		
Employed	93	68.4
Unemployed	43	31.6
History of addictive substance use		
Opiates	136	100.0
Nicotine	132	97.1
Alcohol	118	86.8
Marijuana	112	82.4
Methamphetamine	89	65.4
Benzodiazepines	86	63.2
Cocaine	42	30.9
Hallucin	16	11.8
Inhalation	6	4.4
Urine test data		
Morphine	65	47.8
Benzodiazepines	48	35.3
Marijuana	8	5.9
Methamphetamine	3	2.2
Not using addictive substance	12	8.8

many as 89 patients (65.44%), using benzodiazepines as many as 86 patients (63.24%), using cocaine as many as 42 patients (30.88%), using hallucin as many as 16 patients (11.76%), and using inhaled substances as many as 6 patients (4.41%).

Based on patient urine test data when they were about to start treatment, 65 patients (47.79%) were detected still using morphine, 49 patients (35.29%) used benzodiazepines, 8

patients (5.88%) used marijuana, and 3 patients (2.21%) used meth. Only 12 patients (8.83%) were not detected using these substances. Details of sample characteristics can be seen in Table I.

Initial Dose

The majority of patients (85.29%) received an initial dose of 20-30 mg, ranging within the guidelines for methadone

maintenance therapy. In general, the initial dose of methadone can be divided into three categories, namely opiate dependence with low or uncertain neuroadaptation at a dose of 15-20 mg, moderate-high neuroadaptation starting with a dose of 25-30 mg, and high neuroadaptation of 25-30 mg. Although assessed to have a high opiate tolerance, the initial dose should not exceed 40 mg. Opiate dependence that is assessed as not or likely to have not developed neuroadaptation can be given an initial dose of 20 mg or less.⁵

Administration of the initial dose observed the principle of safety, considering the highest mortality in methadone maintenance therapy occurs in the first days of therapy.⁶ This is related to the slower metabolism of methadone in patients who have recently received therapy compared to patients who have reached steady-state levels. In addition, the incomplete cross-tolerance of methadone and other opiates means that patients new to methadone maintenance therapy have a lower tolerance for methadone than they should, and hence the initial dose may be considered too high. This difference explains the tendency for fatal toxicity occurring in patients at the start of the therapy and not for patients who have reached a steady state.⁷

We found 12 and 5 patients who received initial doses of 35 mg and 40 mg, respectively, and none of the patients received more than 40 mg. Initial doses in this range should only be given if it is certain that the patient is before opiate dependence, or if the withdrawal symptoms appear to be severe. The initial dose of 40 mg was given when the administration of the 30 mg dose did not show an adequate reduction in withdrawal complaints within 24 hours after administration.⁸

The initial dose of methadone should not exceed 40 mg and there is an increased risk of overdosing at initial doses above 30 mg. The principle of safety for the induction period is based on increasing the dose until the patient

is observed at peak methadone levels, or at least 3–8 hours after administration.²

2 Weeks Dose Therapy

Most of the patients (58.09%) received a dose of methadone in the first 2 weeks of therapy of 41-59 mg, and 38.24% of patients received a dose of ≥ 60 mg. In patients who continued taking heroin or other opiates, increasing the methadone dose is an effective approach to reduce heroin use. Increasing the dose after the first week is safe, should be done gradually, considering that it takes up to seven days to reach a new stable state after increasing the dose. Increasing the dose should be done every 3–5 days.²

In this study, it was found that 5 patients received 2-week methadone doses < 30 mg. These patients received the dose after going through the dose titration process until the optimal dose was achieved. The 5 patients felt comfortable with a dose of 20-30 mg and did not feel any complaints about withdrawal. In addition, the first 2 weeks of therapy were not intended to achieve the optimal dose, and further dose adjustments could be made once the patient had stabilized.²

Smallest maintenance dose

The smallest average methadone maintenance dose in this study was 0.25 mg with a range of 0.25-115 mg. Patients only received a dose of 0.25 mg in the maintenance phase because they had completed treatment therapy, and the level of opiate dependence was as small as possible. As many as 24 patients (17.65%) missed the dose for 3 consecutive days so that the dose had to be reduced by half to prevent an overdose due to concerns about reduced tolerance to methadone. These patients would gradually increase their dosage until they reached the optimal dose.⁹

It was found that 1 patient in the maintenance phase (more than 6 weeks) had received a methadone dose of more than 100 mg, these patients complained of withdrawal and, according to therapy guidelines, the dose was increased by 5-10 mg every 3–5 days until

Table II. Methadone Dosage Overview

	Initial Dose (mg)	2 Weeks Dose (mg)	Smallest maintenance dose (mg)	Highest maintenance dose (mg)	Average maintenance dose (mg)
Smallest dose	10	22.5	0.25	15	7.77
Highest dose	40	85	115	140	126.92
Average	27.65	51.6	30.9	84.39	62.36

the optimal dose was reached. Increasing the dose of methadone in patients who are still using heroin is considered an effective means to stop heroin use.⁹

Highest maintenance dose

The highest maintenance dose, on average, was 84.39 mg with a range of 15-140 mg. Patients who received the highest dose of 15 mg were patients who, from the beginning of the maintenance phase to the end of the study limit, felt comfortable and did not experience withdrawal complaints with that dose. The patient initially complained of vomiting and was unwilling to increase his dose. There were several possibilities that occurred in these patients related to the pharmacokinetics of methadone. The bioavailability of methadone ranges from 80% while the variation between subjects is 36-100%, so that patients who have high bioavailability, at relatively small doses, can achieve a therapeutic effect.⁸

It was found that 45 patient in the maintenance phase (more than 6 weeks) had received a methadone dose of more than 100 mg, these patients complained of withdrawal and, according to therapy guidelines, the dose was increased by 5-10 mg every 3-5 days until the optimal dose was reached. The highest dose received by the patient during the maintenance phase was 140 mg. This is possible if the patient is still using opiates while undergoing therapy. Increasing the dose of methadone in patients who are still using heroin is considered an effective means to stop heroin use.¹⁰

Average Maintenance Dose

The average methadone maintenance dose in this study was 62.36 mg with a range of dose 7.77-126.92 mg. The maintenance dose value is included in the effective maintenance dose range in methadone maintenance therapy, which is in the range of 60-120 mg per day.² High maintenance doses (> 60 mg per day) are essentially given to prevent withdrawal symptoms, induce adequate cross-tolerance of heroin to prevent intoxication, and prevent craving for heroin.¹¹ Therefore, it takes a relatively larger dose of methadone to achieve a range of therapeutic effects. A relatively smaller dose of methadone (30 – 60 mg) is effective in suppressing withdrawal symptoms; however, a larger dose is required to have a cross-tolerant effect on the effects of heroin.¹⁰ Patients receiving relatively lower doses (<60 mg) will experience incomplete cross-tolerance effects of euphoria and heroin-strengthening effects. In this study, the description of the methadone maintenance dose is as shown in Table II.

Retention

The effectiveness of methadone maintenance therapy can be seen based on the longer the patient in therapy, the better the therapy obtained. Retention is the length of time the patient in therapy, calculated from the first day the patient received methadone until he was discharged from therapy or until the end of the data collection limit.¹²

The mean retention time of the patients was 769.63 days which was in the range of 53–2,478 days. Of the total 136 patients, 89 patients

Table III. Overview of Patient Termination Methadone Dosage

	Initial Dose (mg)	2 Weeks Dose (mg)	Smallest maintenance dose (mg)	Highest maintenance dose (mg)	Average maintenance dose (mg)	Retention (days)
Smallest dose	10	22.5	0.25	15	7.77	180
Highest dose	40	70	7.5	115	90.46	2,478
Average dat	26.94	49.08	2.76	72.2	42.09	947.43

(65.44%) stayed on therapy for 1 year or more, and 47 patients (34.56%) were on therapy for less than 1 year. The study sample that fit into the inclusion criteria was 136 patients (46.74%), who had started treatment from 2009-2018 from a total population of 291 patients. This sample consisted of 51 patients (37.5%) who completed therapy, 36 patients (26.47%) did not complete therapy, 33 patients (24.26%) moved places or therapy programs, 12 patients (8.82%) died while undergoing therapy, and 4 patients (2.94%) were still registered as active patients at the MMT at Puskesmas Kramat Jati District.

Various studies have shown an increase in patient outcomes at retention times of 1 year or more. Patients who undergo therapy for more than 1 year receive better benefits from methadone therapy than patients who attend therapy for less than 1 year. The longer the patient is in the therapy program, the patient will avoid crime and heroin use and prevent withdrawal symptoms.⁴ Retention in therapy has been associated with increased social productivity, reduced crime rates, and mortality rates. The percentage of patients who were working, continuing school, or working in the household, increased the patient's therapeutic retention.⁴

In patients with methadone maintenance therapy, opiate receptor occupation will occur continuously. This is a factor that helps maintaining stability so that methadone maintenance patients have normal behavior and stop using heroin. In this case, methadone is not a "substitute" for heroin because methadone has very different pharmacokinetic properties with different effects. Occupation of μ opiate receptors by

methadone is stable and persistent, in contrast to repeated and excessive "peak" conditions followed by excessive "trough" conditions due to heroin.¹³

In this study, it was found that 51 patients (37.5%) had completed therapy (termination). From the 51 patients, the data obtained is as shown in Table III.

The smallest maintenance dose on the data set was the last dose the patient received at the completion of therapy. On average, the patient completed the therapy with a dose of 7.5 mg, and the smallest dose was 0.25 mg.

The average maintenance dose obtained by terminated patients was 90.46 mg. The maintenance dose value is included in the effective maintenance dose range in methadone maintenance therapy, which is in the range of 60-120 mg per day.²

The shortest retention achieved by terminated patients was 180 days. This can be achieved if the patient initially wants to target methadone therapy to finish quickly for there is something to be achieved. This is usually supported by the patient's desire to quit drugs and have a better life. In addition, the patient's physiological and psychological factors, as well as the support of family or closest people, also support the success of MMT.¹⁴

Missed doses of more than 3-4 consecutive days also cause the patient to terminate quickly. Patients who have missed a dose of 3-4 consecutive days will receive half the dose of the patient's last dose of therapy. Patients who experience a missed dose of more than 3-4 days but remain in therapy are probably because the process of increasing the dose is sufficient, therefore the optimal dose is achieved in a relatively fast time so that it does

Table IV. Cross-tabulation of the Relation between Dosage Measurement and Retention

Dose	Retention				Sig
	< 1 years		>1 years		
	Total	%	Total	%	
Initial dose < 30 mg	21	44.68	42	47.19	0.926
Initial dose ≥ 30 mg	26	55.32	47	52.81	
2 Weeks Dose Therapy < 40 mg	2	4.26	3	3.37	0.005
2 Weeks Dose Therapy 41-59 mg	20	42.55	59	66.29	
2 Weeks Dose Therapy ≥ 60 mg	25	53.19	27	30.34	
Smallest maintenance dose < 60 mg	24	51.06	82	92.13	0.000
Smallest maintenance dose ≥ 60 mg	23	48.84	7	7.87	
Highest maintenance dose < 100mg	32	68.09	59	66.29	0.712
Highest maintenance dose < 100 mg	15	31.91	30	33.71	
Average maintenance dose < 60 mg	15	31.91	48	53.93	0.004
Average maintenance dose ≥ 60 mg	32	68.09	41	46.07	

* Chi Square statistical test, P = 95%

not cause withdrawal symptoms associated with relapse of heroin use. Moreover, the reasons for missed doses as well as the patient's motivation to stay on therapy need to be further explored.¹⁵

The achieved terminated patients was 2,478 days. This may occur because the patient feels comfortable at the optimal dose received during therapy. The optimal dose for each patient is different, not necessarily the largest dose that can be received by the patient but the dose that can make the patient feel comfortable in therapy and can reduce or eliminate symptoms of withdrawal and violence as well as the desire to return to using illegal drugs.¹⁶

The Relation Between Initial Dose, Dose After 2 Weeks, Smallest Maintenance Dose, Largest Maintenance Dose, and Average Maintenance Dose with Retention

The results of the study related to the relation between dose measurement and retention, can be seen in Table IV, which shows the 2-week maintenance dose, the smallest maintenance dose, and the average maintenance dose was significantly associated with retention, namely, respectively (P=0.005; P=0.000; P = 0.004).

The relation between the 2-week dose, the smallest maintenance dose, and the average maintenance dose (P=0.005; P=0.000; P=0.004) illustrates that the more optimal the maintenance dose received by the patient, the higher the retention rate. The closest relation is between the optimal maintenance dose (60-100 mg) and retention.¹⁷Higher doses provide better therapeutic outcomes against retention than lower doses.⁴Cross tolerance to heroin increases along with increasing doses and inhibits the euphoric effect. Methadone doses of 60 mg or more are adequate to achieve tolerance levels in the majority of individuals. The relation between average maintenance dose and retention shows the most significant relationship compared to other dose measures. The closest relation is between the optimal maintenance dose Average and retention.¹⁷Patients receiving a dose of 80 mg/day were twice as likely to remain on therapy. The use of maintenance doses > 60 mg per day is intended to achieve three things: prevent withdrawal symptoms, induce adequate cross-tolerance and prevent intoxication, and prevent heroin craving.⁴

At a dose of 2 weeks of therapy, patients with a dose of 2 weeks of 41-59 mg were on therapy ≥ 1 year of 66.29%, this amount was

Table V. Cross-tabulation of Relation between Age, Therapy History, Missed Dose History, and Drug Interactions with Retention

Dose	Retention				Sig
	< 1 years		>1 years		
	Total	%	Total	%	
Gender					
Male	44	93.6	82	92.1	0.69
Female	3	6.4	7	7.9	
Age					
18-24 years	2	4.3	10	11.2	0.08
25-34 years	35	74.4	52	58.5	
≥ 35 years	10	21.3	27	30.3	
Marital Status					
Not Married	9	19.1	25	28.1	0.39
Married	33	70.2	59	66.3	
Divorced	5	10.7	5	5.6	
Education					
Elementary School	1	2.1	2	2.2	0.78
Junior High School	4	8.6	12	13.5	
Senior High School	27	57.4	51	57.3	
Tertiary Education	15	31.9	24	27.0	
History of therapy					
Without history of therapy	30	63.8	54	60.7	0.77
With history of therapy	17	36.2	35	39.3	
History of missed dose					
Without history of missed dose	22	46.8	71	79.8	0.00
Missed dose 1-2 days	19	40.4	9	10.1	
Missed dose 3-4 days	9	19.2	15	16.9	
Drug interaction					
Without drug interaction	18	38.3	20	22.5	1.00
With drug interaction	29	61.7	69	77.5	

* There is a significant difference P=95%

greater than patients with a dose of > 60 mg (30.34%). Retention was consistent with dose after 2 weeks.¹⁸

Relationship among Gender, Age, Marital Status, Education, History of Therapy, History of Missed Doses, and Drug Interactions with Retention

The analysis results in Table V, show that missed dose and retention showed a positive and significant relationship (P=0.000). Among patients who were in therapy > 1 year, a total of 71 patients (79.78%) had no history of missed doses, 15 patients (15.78%) experienced a missed dose of 3-4 days, and 9

patients (9.47%) experienced a missed dose of 1-2 days. This shows that the smaller the missed dose experienced by the patient or no missed dose during therapy, the better the retention of therapy received by the patient.

There were various reasons for patients experiencing missed doses and these were not explored in this study. By examining the reasons for patients having missed doses, the understanding of the effect of missed doses on retention will be more complete. In addition, motivational factors also need to be considered, patients who experience missed doses but with high motivation to stay on

therapy are certainly different from patients who experience missed doses but lack motivation in therapy.¹⁷

Patients with a missed dose of 3 days or more will receive half the dose of methadone before the missed dose, gradually increasing the dose until it reaches the optimal dose. Patients who experience a missed dose of more than 3-4 days but remain in therapy are probably because the process of increasing the dose is sufficient, therefore the optimal dose is achieved in a relatively fast time so that it does not cause withdrawal symptoms associated with relapse of heroin use. Moreover, the reasons for missed doses as well as the patient's motivation to stay on therapy need to be further explored.

In this study, there are drug interactions, namely the use of benzodiazepines and alprazolam together with methadone. Low to moderate doses of benzodiazepines was still possible but it is necessary to be aware of increased drowsiness and reduced psychomotor performance. Concomitant use of high doses of benzodiazepines is a risk factor for sudden death in patients receiving methadone therapy. Concomitant use of benzodiazepines and methadone may increase the effects of sedation and respiratory depression, and possibly increase the effects of opiates.¹⁹The use of ciprofloxacin together with methadone causes inhibition of CYP1A2 and CYP3A4 activity by ciprofloxacin, this results in inhibited methadone metabolism and can cause sedation.¹⁹Caution should be paid to patients taking ciprofloxacin and methadone together, especially if there are other factors such as smoking or the use of drugs that are enzyme inhibitors. In the use of fluconazole or ketoconazole (azole group) which are known to interact with methadone which is mediated by inhibiting the activity of cytochrome P450 isoenzymes CYP3A4, the methadone clearance is reduced.¹⁹Close monitoring of the increased effects of methadone is recommended. The use of methadone together with H2 blockers inhibits the activity of liver enzymes associated with N-demethylation of

methadone, reduces the metabolism of methadone so that it accumulates as a result of which there is an excessive respiratory depressant effect, as well as reported decreased liver function, especially in elderly patients.¹⁹This study did not find a clinical effect due to drug interactions with methadone because there was no such record in the medical records. At least, based on the literature, there is information on drug interactions that occur, as well as the type and frequency of drug use that interacts with methadone.

CONCLUSION

The 2-week maintenance dose, the smallest maintenance dose, and the average maintenance dose were significantly associated with retention, namely $P=0.005$; $P=0.000$; $P=0.004$, which means that the more optimal the dose, the better the patient's retention in the methadone maintenance program. Based on the demographic data, only ones with the history of missed doses had a significant relation with retention ($P=0.000$), meaning that the smaller the missed dose experienced by the patient or no missed dose during therapy, the better the patient's retention in methadone maintenance therapy.

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