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Clinical Correlates of Erectile Dysfunction among Male Patients on Methadone Maintenance Therapy (MMT) in Kuala Lumpur

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ABSTRACT

Introduction: Sexual dysfunction is common but not often assessed in the routine clinical care among males on opiate substitute treatment. **Objective:** To determine the association between clinical variables and erectile dysfunction (ED) among men on methadone maintenance therapy (MMT). **Methods:** A cross-sectional study involving 108 participants who attended the Drug Clinic, Hospital Kuala Lumpur. The instruments used include the Structured Clinical Interview for DSM-IV Axis-I Disorder (SCID-I), Beck Depression Inventory (BDI) and International Index of Erectile Function-15 (IIEF-15). **Results:** Concurrent heroin abuse was significantly associated with presence of ED (p=0.024). Treatment factors including methadone dose and duration of methadone treatment were not significantly associated with ED. **Conclusion:** Education on sexual dysfunction as a potential adverse effect and its association with illicit heroin use should be considered in the doctor-patient consultation to encourage treatment adherence and abstinence from heroin.

Keywords: Erectile Dysfunction, Methadone Maintenance Therapy

INTRODUCTION

Erectile dysfunction (ED) is a common but often neglected side effect of opiate substitute treatment. Yet, it is highly clinically relevant as it may interfere with therapeutic compliance to MMT [1, 2]. MMT, an effective treatment option in the management of heroin addiction was started in Malaysia in 2005 as part of harm reduction strategies.

The role of methadone in causing ED is still inconclusive. Age, medical, psychological, lifestyles factors as well as drugs and medications have been implicated in the etiology of ED, which impacts negatively on self-esteem, quality of life and interpersonal relationship [3-5]. Several studies demonstrated that ED is common among both heroin users and people in treatment for heroin addiction. Two physiological mechanisms thought to be responsible for the reported ED among opioid users are: 1) the inhibition of the production of gonadotropin-releasing hormone which decreases the release of the luteinizing hormone (LH) hence reduces the testosterone production 2) the stimulation of hyperprolactinaemia, which produces negative feedback on the release of LH and consequently lowers testosterone production [6].

The relationship of methadone to sexual functioning is a complex interaction of physical, pharmacological, psychological and socio-cultural variables. Medical co-morbidities such as diabetes, hypertension and hypercholesterolemia are established risk factors of ED in general [7]. However, among methadone patients, many studies did not find significant association between medical co-morbidities and ED [8, 9]. Some excluded subjects with chronic medical illnesses as it might become a cofounding factor [10]. Psychological factors especially depression is also commonly associated with ED but its relationship remains unclear. [9, 11, 12]. Brown and Halliman [9, 11] used Beck Depression Inventory (BDI) to measure the presence of depression in methadone patients and reported significant association with ED while another study did not find this to be significantly associated with ED either in methadone or buprenorphine group [8].

Two main treatment factors associated with ED in MMT are its dosage and duration of treatment. Positive effects of MMT are strongly associated with higher daily methadone dose and longer duration in treatment [13-15]. Earlier studies showed an inverse relationship between methadone dosage and plasma testosterone during methadone detoxification [16]. This suggested higher dosage of methadone correlated with decreased sexual desire and performance. Meanwhile

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patients on low dose methadone had testosterone levels which were not significantly different from normal adult male controls [17].

More recent studies which used validated sexual function questionnaire like International Index of Erectile Function (IIEF-15) reported no significant association between ED and methadone dose [9, 10, 18] or plasma testosterone [11]. This latter finding argues against the effect of endocrine component to ED in the methadone maintenance population.

Many studies were inconclusive regarding the association between duration of MMT and testosterone level, due to the limited number of subjects and the use of non-validated sexual questionnaire [17, 19]. More current studies did not report significant correlation between duration of MMT and ED [11, 18].

There are few local studies that focus on the problems that opiate addicts face but none has examined the sexual issues in patients receiving opiate-subsitute treatment. [20] Jesjeet SG, Hatim S, Hussain H found that heroin addicts treated for at least 4 months with methadone could eventually lead to abstinence from heroin, decrease high risk behaviors and crime, and improves work performance and relationship with the carers. Locally, many studies found a high prevalence of depressive symptoms and disorders among opioid dependents which could also contribute to problems of ED [21, 22].

To the authors' knowledge, this is the first local study on ED among men on MMT in Malaysia. This study aimed to examine the clinical factors associated with erectile function among men on MMT. Understanding these factors is important to tailor the medication to suit a patient's treatment needs that better ensures a successful therapy.

METHODS

Study background and design

This is a cross-sectional study conducted at the Drug Clinic of Hospital Kuala Lumpur (HKL) between 1st October 2008 and 30th December 2008. The clinic operates seven days a week i.e. all day from Monday to Friday while on Saturday, Sunday and Public Holiday, it is open only in the morning. The patients who came daily to the Drug Clinic as MMT had to be under Direct Observed Treatment (DOT) were not allowed to take away doses for the first 4 to 6 weeks except during weekends, under strict family/guardian supervision.

During the study period, a total of 265 patients attended the clinic on a daily basis. All of the patients were screened for inclusion and exclusion criteria. Inclusion criteria were subjects who 1) were male 2) fulfilled the diagnosis of opioid dependence based on [23] 3) were at least more than two months on treatment with maintenance dose of methadone (as the period of 2 months or more on MMT is necessary to qualify for maintenance therapy) 4) aged between 18 and 65 years old 5) were in stable heterosexual relationship for the past six months 6) were able to read and understand the national language (Bahasa Malaysia) or English and 7) consented to the study. Having stable heterosexual relationship was defined as "having a person you consider an intimate and primary sexual partner" in the last six months. Respondents were excluded if they were in withdrawal or intoxication.

Instruments

Demographic and clinical data

The demographic variables included the name, age, race, marital status, educational level, employment status, type of occupation, age of the partner and monthly family income. Their co-morbid medical history, history of other substance use in the last one month, duration and dosage of methadone were also included in this questionnaire.

Structured Clinical Interview for DSM-IV Axis I disorders (SCID-I)

SCID-I [24] was used in this study to confirm the diagnosis of Heroin Dependence according to DSM IV Axis I diagnosis. It is a semi structured interviewer-rated questionnaire and has seven diagnostic modules: mood, psychotic, substance abuse, anxiety, somatoform, eating and adjustment disorder.

Beck Depression Inventory (BDI)

The Beck Depression Inventory (BDI), developed by Aaron T. Beck in 1961, is a self-administered measure of the severity of depression. In this study, BDI 21 items version that was translated to Bahasa Malaysia and has internal reliability coefficient (Cronbach Alpha) of 0.956 was used. It contains 13 cognitive-affective items (mood, pessimism, sense of failure, self dissatisfaction, guilt, punishment, self dislike, self accusation, suicidal ideas, crying, irritability, social withdrawal and body image) and 8 somatic-performance items (work difficulties, insomnia, fatigue, appetite, weight loss, bodily preoccupation and loss of libido). In this study, the scoring for general population was used whereby subject scoring 21 or above represent depression.

The BDI scale was translated to Bahasa Malaysia and back translated independently by two groups. Trainee psychiatrists were the translator in the first group and second group consisted of a trainee family medicine specialist and a final year medical student. The two sets of translation and back-translation were than compared by a team

consisting of a Senior Consultant Psychiatrist, a trainee psychiatrist and a trainee clinical psychology. A pretest was conducted and it showed internal reliability coefficient (Cronbach Alpha) was 0.956.

International Index of Erectile Function (IIEF-15)

IIEF-15, developed by Raymond C. Rosen in 1996 is the most widely used, multi-dimensional self-report instrument for the evaluation of male sexual function [2, 25, 26]. It has 15 items, divided into five domains of sexual dysfunction: erectile function (6 items), orgasmic function (2 items), sexual desire (2 items), intercourse satisfaction (3 items) and overall satisfaction (2 items).

In this study, the Malay version of the IIEF-15 was used which is a reliable and a valid instrument with the internal consistency for the five domains (Cronbach's alpha) of 0.74 and higher with test-retest correlation of coefficient and intraclass correlation of coefficient for 15 items and five domains were high (ICC = 0.59 and above) [27].

Data Collection

Subjects who fulfilled the inclusion criteria were invited to participate in this study. The researcher explained about the study to the subjects and written consents were obtained if they agreed to participate. They were assured of their anonymity and the confidentiality of the data obtained.

In a day, about six to seven patients were interviewed individually in a room at the clinic to ensure privacy. SCID-I was administered to confirm the diagnosis of heroin dependence. Subsequently, the subjects were asked to complete the sociodemographic form, IIEF-15 and BDI. Altogether, the participant took about 25 to 30 minutes to complete the questionnaires.

Statistical analysis

The data were analyzed using the Statistical Package for Social Science (SPSS) version 12. The ED domain of IIEF-15 score dependent variable was categorized as present or absent of ED. Chi-square and independent t-test were used to examine the association between the clinical data and ED. The p value for statistical analysis was set at 0.05 for level of significance.

RESULTS

Of the 265 patients who attended Drug Clinic of HKL for the MMT, 11 of them were females and 254 were males. From the 254 male patients, only 135 were in stable heterosexual relationship. However 23 patients did not consent while 4 patients did not complete the IIEF-15 or BDI questionnaires. The overall response rate was 80% with the final total of 108 respondents recruited for the study.

The sociodemographic of the respondents are shown in Table 1.

Table 1. Sociodemographic characteristics of the patients

Variable	Characteristics	N	%	Mean (SD)
Age (year)	21 – 30	9	8.3	44.6 (±9.198)
	31-40	23	21.3	
	41-50	48	44.4	
	>51	28	25.9	
Ethnicity	Malay	82	75.9	
	Chinese	11	10.2	
	Indian	14	13	
	Others	1	0.9	
Marital status	Married	85	78.7	
	Single	23	21.3	
Employment	Present	94	87	
	Absent	14	13	
Family income (RM/month)	> 2000	65	60.2	
	500-2000	30	27.8	
	< 500	13	12	

Continuation
Table 1. Sociodemographic characteristics of the patients

Variable	Characteristics	N	%	Mean (SD)
Education level	Primary	19	17.6	
	Lower secondary	41	38	
	Upper secondary	38	35.2	
	STPM/Diploma	10	9.2	

Clinical Factors and ED

Table 2 shows that concurrent heroin abuse is the only significant clinical variable associated with ED (x2= 5.099, p=0.024). No significant associations were found between ED and depression, co-morbid medical illness including hepatitis C, hepatitis B, bronchial asthma and hypertension as well as concurrent abuse of other substances among patients on MMT in HKL.

Table 2. Clinical Variables of Patients with Erectile Dysfunction among patients on MMT in HKL

Clinical variables	N	Erectile Dysfunction		Chi-Square	p-value	OR (95% Confidence interval)
		Present	Absent			
Depressive symptoms						
Present	48	35(72.9%)	13(27.1%)	0.775	0.379	1.450(0.633-3.320)
Absent	60	39(65.0%)	21(35.0%)			
Co-morbid medical illness						
Present	46	33(71.8%)	13(28.2%)	0.304	0.582	1.273(0.539-3.00)
Absent	62	41(66.3%)	21(33.7%)			
Hepatitis C						
Yes	34	24(70.5%)	10(29.5%)	0.601	0.438	1.50(0.536-4.190)
No	74	50(67.5%)	24(32.5%)			
Hepatitis B						
Yes	18	8(44.4%)	10(55.6%)	2.638	0.104*	0.331(0.083-1.323)
No	90	66(89.2%)	24(20.8%)			
Bronchial Asthma						
Yes	9	9(100.0%)	0(0.0%)	3.059	0.080*	1.523(1.321-1.756)
No	99	65(65.7%)	34(34.3%)			
Hypertension						
Yes	4	4(100.0%)	0(0.0%)	0.694	0.405*	1.480(1.290-1.690)
No	104	70(67.3%)	34(32.7%)			
Concurrent substance abuse						
Heroin abuse						
Yes	49	39(79.6%)	10(20.4%)	5.099	0.024	2.674(1.123-6.367)
No	59	35(59.3%)	24(40.7%)			
Alcohol						
Yes	16	10(62.5%)	6(37.5%)	0.315	0.574	0.729(0.241-2.200)
No	92	64(69.6%)	28(30.4%)			

Continuation
Table 2. Clinical Variables of Patients with Erectile Dysfunction among patients on MMT in HKL

Clinical variables	N	Erectile Dysfunction		Chi-Square	p-value	OR (95% Confidence interval)
		Present	Absent			
Smoking						
Yes	101	69(68.3%)	32(31.7%)	0.000	1.00*	0.863(0.159-4.686)
No	7	5(71.4%)	2(28.6%)			
Cannabis						
Yes	12	7(58.3%)	5(41.7%)	0.227	0.63*	0.606(0.178-2.068)
No	96	67(69.8%)	29(30.2%)			
Amphetamine						
Yes	9	5(55.6%)	4(44.4%)	0.250	0.62*	0.543(0.136-2.167)
No	99	69(69.7%)	30(30.3%)			
Benzodiazepine						
Yes	3	1(33.3%)	2(66.7%)	0.491	0.484	0.219(0.019-2.505)
No	105	73(69.5%)	32(30.5%)			

* Yates correction

Dose and Duration of methadone therapy and ED

The mean duration on methadone maintenance therapy was 24.26 (s.d + 6.99) months with the range of four months to thirty-six months. The mean methadone dosage was 62.41 (s.d + 17.51) mg and the range was 30 mg to 150 mg. There is no significant difference between dose and duration of methadone treatment between respondents with and without erectile dysfunction as shown in table 3.

Table 3. Comparison of dose and duration of methadone therapy and ED

Variables	Erectile Dysfunction		Mean difference (95% CI)	t statistic	P value
	Present (n=74) Mean (sd)	Absent (n=34) Mean (sd)			
Methadone dose	62.50(17.06)	61.36(18.34)	1.503(-6.934-7.522)	0.409	0.936
Methadone duration	24.36(6.33)	24.03(8.35)	0.42(-5.798-6.435)	0.685	0.735

DISCUSSION

Factors contributing to ED are important considerations in the administration of MMT in any treatment setting to ensure good compliance and best outcome. In this study, we found that concurrent use of heroin is the only clinical variable that was significantly associated with ED. Patients who also took heroin while on MMT were 2.6 times more likely to have ED than those without (OR=2.67, 95% CI = 1.12-6.37). The effect of heroin, an illicit opiate on ED may be explained physiologically.

Smith [28] observed that as the patient became a chronic daily user of heroin and the heroin drug cycle escalated, the patient would experience both ejaculatory and erectile dysfunction. Mendelson [17] reported that high dose opiate use might decrease sexual performance by a corresponding decrease in testosterone level from the testes via peripheral mechanism. In this study, we did not measure the plasma levels of pituitary or gonadal hormones. Nevertheless, it can be postulated that the concurrent use of heroin in methadone therapy increases the opiate levels (in addition to methadone) albeit in variable potency in view of its illicit nature. This worsens the underlying opiate-induced hypogonadism by way of reduced plasma testosterone as consistently demonstrated by many studies [9, 29, 30].

In this study, other substance used including smoking and alcohol were not significantly associated with ED. The

majority of the respondents smoked cigarettes (n=101; 93.5%) but did not drink alcohol (n=92; 85.2%). Of those who smoked cigarettes, 68.3% had ED while 62.5% of alcohol drinkers had ED. While smoking has been inconsistently associated with ED [31-33], its association with other risk factors of ED like hypertension is well established [3]. Cross-sectional studies of alcohol and ED have yielded conflicting results, with some reporting a lower prevalence of ED among moderate drinkers [32, 34], a greater risk among heavy drinkers [3, 35], or a lack of association [36]. In population based follow-up study of MMAS cohort, neither smoking nor heavy drinking status showed association of with ED [31].

In this study, a very small number of non-smokers and alcohol drinkers among respondents as well as insufficient characterisation of substance use such as number of cigarette smoked/alcohol units per day, smoking status (ex-smoker, current smoker or never smoked), etc. could have contributed to the non-significance of the finding.

Interestingly though, neither higher dose of methadone nor duration of treatment were significantly associated with ED in this study. While this finding is in contrast with older study findings [16, 37], it supports the results of current studies [9, 18]. This might be attributed to improved methodology particularly in terms of relatively large sample size and use of validated questionnaire on ED. In this study, the mean daily dose of methadone prescribed was 62.41mg (range: 30-150 mg) and the mean duration of MMT was 24.26 months (range: 4-36 months). Based on methadone treatment guidelines [38], most patients require methadone in the range between 60 and 150mg or higher. By comparison, the dose used in MMT in HKL was low. This could explain the non-significance association of methadone dose to ED in our patients. Our study finding notably implied that the current practise in the dosing and duration of MMT in HKL had no significant adverse effect on the patients' erectile functions. These results also implied that alteration of methadone dosing or discontinuation of methadone would not be expected to improve erectile function.

The most frequent substance-induced medical illness among heroin addiction was Hepatitis C, Hepatitis B and human immunodeficiency virus (HIV). Of the respondents treated with methadone, 22% were Hepatitis C virus seropositive, 8% Hepatitis B virus seropositive and 1.8% was HIV seropositive. Our finding was similar to other methadone and buprenorphine studies which found no significant associations between substance-induced medical illness and ED [9, 30, 37].

Emotional disorder like depression and anxiety were found to be prominent in this group of patients [39, 40]. A substantial 44.4% of the respondents had depression here which is comparable with previous local studies [21, 22].

The causal relationship between erectile ED and depression is probably bidirectional, i.e. ED may be a consequence of depression and depression may follow ED [18, 41]. Data regarding depression and ED are inconsistent. The presence of depressive symptoms was not significantly associated with ED in this study consistent with findings from Niclaas B, Susanne A, *et al* [30] and Brown R, Balousek S, Mandt M, Fleming M [11]. On the other hand, Spring [12] who found patients on MMT with lower Derogatis Sexual Functioning Inventory (DSFI) score had higher level of depression and anxiety on the Hamilton scale concluded that the sexual dysfunction might be due to the psychiatric problems rather than to the opiates. Halliman [9] also reported that depression was found to be associated with global sexual dysfunction and with erectile dysfunction in groups of patient either receiving methadone or buprenorphine. Though not significant here, it is notable that higher percentage of respondents with depressive symptoms had ED compared to those without. Probably, a more accurate finding would be obtained using structured interview instrument and clinical evaluation compared to the self-rated questionnaire used in this study which runs the risk of underestimation.

In contrast to previous studies [33, 42, 43], medical co-morbidities such as diabetes, hypertension, coronary artery disease and hypercholesterolaemia among the respondents were not significantly associated with ED in this study. Here, only very few respondents admitted to having any medical disorders (refer table 2). The data on medical co-morbidities were obtained by subjects' self-report, which might not reflect the true number of respondents with medical illnesses. Further biological investigation in this group could possibly identify those with medical co-morbidities.

CONCLUSION AND CLINICAL IMPLICATIONS

Since sexual dysfunction is common in men receiving opioid replacement therapy, discussion on potential sexual side effects should be included in the consultation between doctor and patient to promote better treatment adherence and longer retention period. Evaluation for ED should also be carried out in routine assessment of patients on methadone.

The clinical profile of patients with ED did not differ significantly from the group without ED except for the concurrent heroin use. Patients should be educated about this potential adverse association to discourage illicit heroin use while they are on MMT hence ensuring better success in achieving the treatment goal.

Although lack of endocrinology evaluation, it is reasonable to assume from the above finding that ED in these patients are not the direct result of methadone use itself, but rather a combination of biopsychosocial factors. ED, (with the exception of trauma or surgical aetiology), was found to be mediated through endothelial dysfunction seen in cardiovascular disease [7, 33]. It is therefore deemed useful for clinicians to view ED as a clinical marker for early

detection of possible underlying vascular diseases like hypertension, diabetes and coronary artery disease at an early stage. Consequently, the implication is clear that men with ED and other cardiovascular risk factors (e.g. obesity, smoking) should also be counselled in lifestyle modification.

ACKNOWLEDGEMENT AND ETHICAL CONSIDERATION

This research project was approved by the Research and Ethics Committee, Faculty of Medicine, Universiti Kebangsaan Malaysia. The permission to carry out this study was obtained from Hospital Director of General Hospital Kuala Lumpur. The purpose of the study was explained to the participants, and written informed consent was obtained from them.

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