Iran J Psychiatry 2021; 16: 3: 312-319

Original Article

Comparing Sexual Function between Opioid Dependents Consuming Methadone or Opium Tincture

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Abstract

Objective: Sexual dysfunction is a side effect of methadone maintenance therapy (MMT). Opium Tincture (OT) has been used as a maintenance treatment. This study aimed to determine and compare the trend of sexual function and its related factors during treatment with both drugs.
Method: An observational study was designed to measure the blood tests including free and total testosterone, prolactin, and sex hormone-binding globulin and a battery of questionnaires, including demographics and drug use history, in 42 and 53 patients entering MMT and OT treatment before and 1 and 3 months after the treatment.
Results: Significant changes in testosterone levels were observed in the MMT but not the OT group. The difference between the two groups was not significant. Neither between nor within changes in the sexual function and premature ejaculation scores were significant (P =0.370& 0.698). Anxiety levels were significantly different (P= 0.001) within and between groups. There was a considerable difference in the trend of depression changes in the OT group, but not different in MMT group and between the two groups.
Conclusion: No difference was found between MMT and OT effects on sexual function variables. The decrease in Testosterone during the three months of MMT, was not associated with diminished sexual function. In the MMT group, anxiety levels diminished during treatment. It seems that decreased testosterone in the MMT group was compensated by improved anxiety. Gonadotropin levels may not be the sole determinant in sexual activity, and complex interaction of mood and anxiety, agonist levels, and gonadotropins are involved.

Key words: *Anxiety; Opioid Substitution Therapy; Opium; Sexual Dysfunction; Testosterone*

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Article Information:
Received Date: 2020/09/13, Revised Date: 2020/12/07, Accepted Date: 2021/02/13

Substance use and consequently methadone maintenance therapy (MMT) has been reported at high levels in Iran (1, 2). MMT has been recognized as a comprehensive and useful treatment program for opioid dependence, reducing the harms caused by drugs (3). Despite the effectiveness of the MMT program in reducing the risk of relapse, criminal and high-risk sexual behavior, and HIV transmission in patients with opioid use disorder (4), the use of methadone has been associated with several complications, such as sexual dysfunction, including reduced libido and impairments in erectile, ejaculatory, and orgasmic functions (5-7).

The meta-analytical pooled prevalence of sexual complications has been reported to be 52% in methadone users (8). One of the leading risks of premature dropout from MMT programs is the decreased quality of sexual life due to these complications (5, 9). Methadone-induced male sexual dysfunction is claimed to be attributed to an alteration in the functions of the hypothalamus-pituitary-gonadal (HPG) axis, a decrease in the production of gonadotropin-releasing hormone (GnRH), and elevated prolactin levels (10). This altered action directly or indirectly decreases the levels of sex hormones, particularly testicular testosterone secretion, which, in turn, reduces sexual desire and libido. Alterations in testosterone concentration caused by opioids may significantly impact mood, aggression, sexual drive, and stress reaction (10, 11). It has also been reported that substance abuse, in addition to its hormonal effects, has high comorbidity with mood and anxiety disorders, and maintenance treatment with methadone is supposedly associated with improved states of mood and anxiety (12, 13).

Since management of the sexual dysfunction induced by methadone has been a significant challenge for physicians (14), many studies have been conducted to find more effective treatments for these patients (4, 15). There is, in fact, a need to find alternative pharmacotherapies that are effective in the treatment of opioid dependence while causing fewer sexual complications. To respond to this need, in recent years, there has been an increased interest in using opium tincture (OT) (opium solved in alcohol and water) for treating opioid dependence in certain regions (16).

In the first clinical pilot study on the effectiveness of OT conducted at the Iranian National Center for Addiction Studies (INCAS), 63% of the patients were reported to abstain from opiates six months after the treatment initiation (17). OT is perceived as a traditional medicine for opioid detoxification and relieving opioid withdrawal symptoms in some parts of Southeast Asia (17). Regarding the assumed adverse effect of methadone on sexual performance and the widespread availability of OT prescription in the country, there might be advantages of using the latter in individuals with sexual dysfunction. Anecdotal reports from patients and service providers hint at fewer sexual side effects in OT users. This controversial superiority of the OT is commonly cited as the reason for prescribing this medicine to substance users who have erectile dysfunction and premature ejaculation (18, 19). However, this study was designed to compare the effects of methadone maintenance and OT treatment on the sexual functions and serum testosterone levels of men who used opioids.

Materials and Methods

Participants

Participants were 18 to 50 years old opioid-dependent men (based on DSM-V criteria) consuming opium for at least six months before the study (20). Regarding previous studies in this field, the sample size was adjusted to 40 for the 3-month follow-up (21). Participants were all married men who were placed in MMT or OT groups, according to the type of treatment they sought. The study was conducted in Tehran, Iran, from March to November 2019. The participants were recruited from the clients of substance abuse treatment clinics and Congress 60, an Iranian NGO active in opium-dependent treatment based on the convenience (availability) sampling method. The therapist adjusted the agonist drug's suitable dose, complying with the Iran Ministry of Health practice and safety guidelines, and the research team performed no intervention (22).

Exclusion criteria of the study were: (1) having a history of pelvic surgery; (2) consuming medications for the treatment of viral hepatitis or AIDS; (3) receiving androgen replacement therapy (ART); (4) having undergone ART therapy during the past eight weeks; (5) consumption of or positive urine tests for amphetamine-like stimuli, benzodiazepines, alcohol, and methadone; (6) using convenient therapies for drug dependence in the last three months; (7) having severe physical illnesses in history or examination, including hypertension, active infections, severe cardiovascular disease, diabetes, hyperlipidemia, and liver diseases; (8) having severe psychiatric disorders, including psychosis, suicidal ideation, severe bipolar disorder, delirium, and dementia; 9) having mental retardation and autism; (10) pelvic and testicular radiation; (11) having a history of chemotherapy; (12) current use of drugs affecting sexual function; and (13) taking drugs with antagonistic dopamine effects.

Study Variables

In this study's design, variables were measured before the treatment and 1 and 3 months after the treatment. The measured variables were age (in years), education (in years), body mass index (BMI) (kg/m2), smoking status, opium consumption and heroin use as grams per day, blood levels of testosterone (ng/mL) and free testosterone (pg/mL), the blood level of prolactin (mIU/l), sex hormone-binding globulin (SHBG) as nmol/l, anxiety and depression scores as measured by Beck anxiety and depression tests, erectile function as

the score in International Erectile Function Index Questionnaire, premature ejaculation as measured by the Index of Premature Ejaculation Questionnaire, methadone dosage as mg and opium tincture as mL reported by the consumers

Questionnaire and Lab Tests

The validated Persian versions of the following tools, measures, and questionnaires were used in this study: demographic characteristics questionnaire based on ISAP (INCAS Substance Abuse Profile) (23), drugs use history, current treatment characteristics checklist, duration of treatment, agonist dose, International Index of Erectile Function (IIEF) [Cronbach's alpha values = 0.91 and 0.73 in original and adjusted Persian versions, respectively] (24, 25); Index of Premature Ejaculation (IPE) [Cronbach's alpha values = 0.85 and 0.98 in original and adjusted Persian versions, respectively] (26, 27); Beck Depression Inventory (BDI)) [Cronbach's alpha values = 0.73 and 0.87 in the original beck and adjusted Persian versions, respectively] (28, 29), and Beck Anxiety Inventory (BAI) [Cronbach's alpha values = 0.92 and 0.92 in the original beck and adjusted Persian versions, respectively] (30, 31).

For blood levels of total and free testosterone, SHBG, and prolactin, lab tests were performed at Firoozgar hospital medical laboratory. Blood samples were taken from fasting participants before 10 AM. The SHBG assay was performed by electrochemiluminescence (ECL) and Cobas / Roche kit with a standard range of 18.3-54.1 nmol/l adjusted for the age. The DiaSorin testosterone assay kit was used to measure testosterone with a standard range of 1.20-10.19 ng/mL. The DiaSorin prolactin chemiluminescence (CL) was used to assay prolactin with a standard range of 87-392mIU/ L. Monobind kit, and the Elisa method was used to assay free testosterone in the range of 4- 30 pg/mL. Serum samples collected from patients were kept at -70 °C. The required medical laboratory tests were performed on blood charge samples free of.

The questionnaires were completed by the researcher while orally interviewing the participants. Follow-up of therapeutic interventions and coordination of research steps were done by contacting the clinics where the participants were receiving their treatment or directly contacting them by telephone .

Ethics Statement

This study's proposal was approved by the ethics committee of Tehran University of Medical Sciences (NO: 141133). Each participant signed written consent.

Statistical Analysis

SPSS software version 22 (IBMSPSS STATISTICS 22) was used to analyze the data. An independent t-test was used to compare the age and education of participants in the groups, and the Fisher exact test was used to compare body mass index. A chi-square test was used to compare cigarette smoking in the two groups. The Mann-Whitney nonparametric test was used to compare opium and heroin consumption in study groups. To analyze the trend of the variables over time, the repeated-measures analysis of variance was used. Also, the logarithm of numerical calculations was used. A $P < 0.05$ was considered statistically significant.

Results

A total of 241 clients entered the study, of whom 31 were excluded from the sample due to consuming methamphetamine, benzodiazepines, or other medications for improving sexual performance. Of the remaining clients, 111 received MMT, and 99 followed the OT treatment. In the MMT group, 75 (67.56%) and 42 (37.83%) of participants remained in the study for 1 and 3 months, respectively. For the OT treatment, the retention rates were 60 (60.60%) and 53 (53.53%), respectively. Only the data of those who passed all the three steps of the study were used for comparison.

As shown in Table 1, age, education, and BMI were compared between the study groups. The independent t-test results revealed a significant difference between the two groups in age and education variables ($P <= 0.001$). For BMI, the Fisher exact test results showed that the two groups were significantly different concerning this classification ($P = 0.007$).

There were, however, no significant differences between the two groups in terms of opium and heroin consumption before the entrance to the treatment program ($P = 0.341$ and 0.311, respectively). The chi-square test results also showed that the difference between the two groups in cigarette smoking status was not significant ($P = 0.152$).

The repeated measure ANOVA was used to examine the differences between the two groups in terms of variables measured in the three consecutive periods. The numerical values of variables and related significances for the two groups are presented in Table 2.

Table 3 presents the results of within (each group) and between-groups differences.

As can be seen, significant differences in total and free testosterone indices were observed across the three-time points ($P = <0.001$ and $P = < 0.001$, respectively) in the MMT group. No significant differences among the three-time points were found in the OT treated group ($P = 0.468$ and $P = 0.838$, respectively). However, the overall trend of changes in these two indices in all participants showed statistically significant changes ($P = 0.019$ and $P = <0.001$, respectively), the differences between the two groups were not significant ($P = 0.124$ and 0.926, respectively).

Our analysis also showed no significant difference in the prolactin index among the three-time points in methadone ($P = 0.856$) and OT ($P = 0.460$) treatment groups. The overall trend of changes in this index in all our participants was statistically significant ($P = 0.036$). Still, the difference between the two groups was not significant ($P = 0.417$).

As for SHBG, while we found significant changes ($P = 0.002$) across the three consecutive times in the MMT

group, no significant difference was observed among the three-time points in the participants treated with OT (P =0.923). There were no statistically significant changes in the overall SHBG levels across the three times (P = 0.321) or between the two groups (P = 0.784).

Analysis of the Erectile function and premature ejaculation indices showed no significant differences among the three consecutive times in the MMT group (P = 0.292 and 0.234, respectively) and OT group (P = 0.266 and 0.241, respectively). Also, no statistically significant difference was found in the overall trend of changes in these two indices in all participants (P = 0.058 and 0.104, respectively) and between the two groups (P = 0.370 and0.698, respectively).

In the next step of our analysis, we focused on depression among the participants. We found no significant differences (P = 0.173) across the three consecutive times in the MMT group. However, a significant difference across the three-time points was observed in the OT group (P = > 0.001). While the overall trend of changes in this index in all participants was statistically significant (P = > 0.001), the two groups were not significantly different in terms of depression (P =0.053).

In the final part of our analysis, we compared the two groups in terms of anxiety. The results showed significant differences among the three consecutive time points in both the methadone (P ≤ 0.001) and OT (P = 0.003) treatment groups. The overall trend of changes (P ≤ 0.001) and the difference between the two groups (P = 0.001) in all participants' anxiety levels was also significant.

Table 1. Comparing Age, Education, BMI, Use Of Cigarettes, Opium and Heroine in the Group Treated with Methadone and the Group Treated with Opium Tincture

Variable		Treated With Methadone (n = 42)	Treated With Opium Tincture (n= 53)	P-Value
Age(y) mean(SD)		35.88(7.25)	40.50(6.42)	●0.001
Education(y) mean(SD)		7.85(3.53)	10.96(3.73)	●<0.001
BMI (kg / m2) < 25 25-29.9 30 <		 21(%50) 21(%50) 0(%0)	 20(%37.7) 22(%41.5) 11(%20.8)	#0.007
Cigarettes use	YES	39(%92.9)	44(%83)	*0.152
	N0	3(%7.1)	9(%17)	
Amount of opium used(g/day) [Median(IQR)]		3(4.75)	3.50(2.75)	▪0.341
Amount of heroin used(g/day) [Median(IQR)]		1.5(1)	1(1)	▪0.311

BMI, body mass index; SD, standard deviation; g/day, grams/ day ;IQR, interquartile range
● independent t-test was done.
#The Fisher Exact test was performed.
* The chi-square test was used.
▪ The Mann-Whitney test was done.

Table 2. Comparing the Study Variables According to the Time of Measurements in Participants Treated with Opium Tincture and Methadone

Variables	OT Pretreatment	OT First Month	OT Third Month	P-Value	Methadone Pretreatment	Methadone First Month	Methadone Third Month	P-Value
SHBG (nmol/L)	76.6 (78.1)	72.5 (69.3)	61.01 (54.8)	0.923	63.07 (31.2)	69.1 (89.2)	61.7 (56.6)	0.002
IIEF	52.8 (14.7)	49.2 (18.5)	50.9 (16.7)	0.266	53.05 (14.9)	59.2 (7.2)	50.4 (22.01)	0.292
IPE	34.7 (8.1)	33.01 (7.05)	32.7 (6.9)	0.241	33.4 (7.1)	34.6 (8.1)	32.3 (9.2)	0.234
Depression	20.6 (12.5)	13.2 (11.04)	10.8 (11.2)	<0.001	24.5 (15.4)	18.1 (11.9)	19.2 (12.3)	0.173
Anxiety	7.8 (8.2)	5.01 (6.5)	4.7 (7.2)	0.003	13.9 (8.8)	9.8 (7.4)	7.6 (7.7)	<0.001

Values are presented as mean ± standard deviation
Ng/mL, Nanogram/milliliter; pgr/mL, picogram/milliliter; mIU/L, milli-international units/litre; nmol/L, nanomole/liter;
IIEF, International Index of Erectile Function; IPE, Index of Premature Ejaculation.

Table 3. Comparing the Repeated Measurements of Variables in the Two Groups

Variable	Treated With Methadone *P* Value	Treated With Opium Tincture *P* Value	*P* Value Within Group	*P* Value Between Groups
Testosterone	<0.001	0.468	0.019	0.124
Free testosterone	<0.001	0.838	<0.001	0.926
Prolactin	0.856	0.460	0.036	0.417
SHBG	0.002	0.923	0.321	0.784
IIEF	0.292	0.266	0.058	0.370
IPE	0.234	0.241	0.104	0.698
Depression	0.173	<0.001	<0.001	0.053
Anxiety	<0.001	0.003	<0.001	0.001

SHBG, Sex Hormone Binding Globulin; IIEF, International Index of Erectile Function; IPE, Index of Premature Ejaculation.

Discussion

Our data demonstrated that through 3 months of treatment with OT, no significant changes were detected in sexual function expressed through IIEF and IPE or levels of testosterone and prolactin. Changes in neither IIEF (P = 0.266) nor IPE (P = 0.241) scores were significant (Table 2). There are anecdotal reports that treatment with OT has a less unfavorable impact on sexual function and testosterone level, a claim which our data did not corroborate. Using the Arizona Sexual Experience Scale, Kheradmand, Fazeli (32) compared the mean sexual function scores of the three groups of methadone, OT, and buprenorphine treated patients at baseline and after three months of treatment. Sexual dysfunction was improved in groups after replacement therapy.

Current literature claims that MMT is usually associated with deterioration of sexual function, mostly expressed as erectile dysfunction (5, 9). It appears that deteriorating sexual function is associated with a decrease in free and total testosterone levels. Other studies have also reported hypogonadism as an essential cause of sexual dysfunction (33, 34).

This study showed that methadone maintenance for three months and at an average dose of 69.1 mg/day was not significantly associated with a deterioration of erectile function (P = 0.292). Patients' IPE scores showed no significant decline during treatment with methadone (P = 0.234).

Brown, Balousek (35) reported that the rate of sexual dysfunction in men treated with methadone was similar to that of the general population. The Zhang (36) study results, similar to those obtained in our study, showed no relationship between methadone use and sexual dysfunction. The severity of sexual dysfunction decreased with the onset of treatment. Their study was cross-sectional and retrospective and used the IIEF questionnaire. Zafarghandi, Nik (37) reported that six months of methadone treatment was associated with a significant improvement in erectile function, sexual desire, overall satisfaction, and orgasmic function. In a meta-analysis of Iranian patients, methadone therapy had no significant effect on sexual desire, erectile function, and orgasm among opium-dependent men (38).

Most previous studies have been cross-sectional and have focused only on the methadone group (39) or have compared the methadone group with control or buprenorphine user groups (11, 40). Different studies have used different questionnaires. For example, Llanes, Álvarez (9) used the PRSexDQ-SALSEX questionnaire, while Gerra and Manfredini (40) used the Arizona Sexual Experience Scale to measure sexual performance. Other examples are Hosseini, Isapour (39), and Hallinan and Byrne (34), who have used the IIEF.

Interestingly, the decrease in testosterone does not correspond to IIEF measures in our study. Clients receiving methadone had an IIEF score of 53.05 at baseline. While it temporarily increased to 59.2, it decreased to 50.4 by the third month. This shows that methadone consumption probably creates a short-lived improvement of erectile function that recedes to baseline levels with continuous use. This is despite the continued decrease in free testosterone levels. With three months of methadone use, testosterone levels significantly decreased in the MMT group ($P \leq 0.001$). While patients showed a significant decrease in testosterone, this decrease did not reduce erectile function and did not cause clinical problems. Testosterone levels shifted from 10.3 to 4.8 (pg/mL) during the three months of methadone consumption. Most of the testosterone decrease was observed in the first month of the treatment (Table 2).

Similar to our results, in the study of Zhang, Zhang (36), in which testosterone was measured by immunoradiometric assay, it was shown that plasma testosterone levels in heroin and methadone users were lower than those in the general population. However, after the initiation of the treatment, sexual functions were significantly improved in the MMT group. This shows that low testosterone levels may not be directly

related to sexual dysfunction. In Brown, Balousek (35) study, none of the sexual function subscales or overall dysfunction were associated with decreased plasma testosterone.

In previous studies, patients treated with methadone showed an increase in blood prolactin, associated with impaired sexual function (33, 40). However, in this study, prolactin levels were not significantly different in the three consecutive measurements of patients treated with methadone (P = 0.856). It is also noteworthy that the changes in prolactin levels in the two groups treated with methadone and OT were not significantly different in the three consecutive stages (P = 0.417). Therefore, the possible differences in prolactin-induced sex function indices in the scientific literature may not be relevant in this study. There was also no relationship between prolactin levels and sexual dysfunction in the study conducted by Brown, Balousek (35).

There was a significant drop in testosterone in our total samples (n = 95), while no significant change in sexual function was observed (P ≤ 0.001 and P = 0.058, respectively). Between-group comparisons also showed no significant difference in IIEF, IPE, and testosterone levels. In line with this finding, Kheradmand, Fazeli (32) reported no significant difference between their study groups. However, they did not measure psychosocial variables as well as hormones in their work .

Sexual function is a biopsychological phenomenon. Therefore, it is natural that changes in one aspect are exacerbated or compensated by others' changes. One of the psychological variables affecting sexual behavior is the mood state (40, 41). Thus, it is the interaction of variables that determines the ultimate result, and the changes in 1 single variable cannot be a good predictor of the ultimate behavior. In the present study, the interaction of the adverse effects of hormonal changes (testosterone and free testosterone) with the positive impact of changes in anxiety might have led to the stabilization of IIEF. It seems that the positive effects of OT on depression may have exacerbated the process in the group treated with OT (P ≤ 0.001).

Our findings were in line with some previous epidemiological studies that had found that psychological and behavioral factors in heroin and MMT users are associated with sexual dysfunction (34, 40). On the contrary, some other studies have suggested no relationship between sexual function and depression (36, 42).

Limitation

A critical limitation of this work was the lack of precise adjustment of the two drugs' doses. Assessing other psychosocial factors rather than anxiety and depression may be inspiring. Our findings are also limited by the differences between the groups in terms of education, age, and body mass index, all of which may affect sexual functions. Although the sample was selected from a diverse population of individuals referring to agonist maintenance treatment facilities, they might not represent substance-using individuals nationwide. Many came from stable middle-class urban backgrounds. The finding might not be applicable to clients with severe psychiatric illness or from the disadvantaged socioeconomic background. Another major limitation is the lack of randomization among patients. Clients chose their preferred mode of intervention, which might have favored some individuals with inherent differences toward either MMT or OT. A group of individuals whom we did not investigate was clients receiving buprenorphine. Studies show fewer sexual complaints in individuals receiving the medication. Such clients display a very different profile for sexual side effects. Further studies, including this sample, are highly recommended .

Future studies should consider such limitations to understand better the effect of methadone and OT on sexual functions.

Conclusion

MMT may have some adverse hormonal effects, which may, however, be compensated by its effects on mood state. It seems that it is comorbid anxiety and depression rather than testosterone and prolactin levels that have buffering effects for sexual functioning, at least in the short term. In some cases, despite the decrease in sexual hormones, due to the improvement of mood and anxiety, the overall sexual performance improves. For patients who primarily complain of sexual dysfunction, OT may be a reasonable alternative. However, more studies are required to shed light on the various aspects and mechanisms of this effect.

Acknowledgment

The authors wish to thank Ali Saleh, Dr. Shahin Akhondzadeh, and Congress 60 NGO. They also thank the participants of this study.

Conflict of Interest

None.

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