Efficacy of Tadalafilin the Treatment of Methadone Induced Sexual Dysfunction in Males with Opioid use Disorder under Methadone Maintenance therapy (MMT): Adouble-Blind, Randomized, Placebo-Controlled Clinical Trial

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Abstract

Methadone-induced sexual dysfunction (MISD) is one of the most common adverse effects of long-term use of this medication, which may affect the life quality of patients under Methadone maintenance therapy (MMT) and can decrease medication compliance and increase the risk of relapse to drug use. While there is no standard treatment for MISD, we aimed to investigate the efficacy of tadalafil, a well-known medication for the treatment of men's sexual dysfunction, in the treatment of this disorder in male opioid users under MMT. In a double-blind, randomized, and placebo-controlled clinical study, a total of 132 male married patients aged 20-60 years under MMT suffering from MISD were randomly assigned either to the intervention (taking 10 to 20mg tadalafil every 72h) or to the control (placebo) group. International Index of Erectile Function-5 (IIEF-5) and Brief Function Sexual Index (BFSI) was administered to evaluate the sexual dysfunction symptoms at the baseline, 2 weeks, and 4-weeks after the intervention. The study was registered by the Iranian registry for clinical trials (IRCT NO 20150822023705N10). The mean scores of sexual desire, erection, ejaculation, level of overall satisfaction, and the overall score of sexual function were significantly increased in the medication group compared to the control group. The interaction between time and group was significant which showed the influence of time over the treatment outcomes ($\lambda = 0.871$, $P = 0.008$, $F = 3.077$, τ^2 =

0.129). Our findings suggest that tadalafil could improve symptoms of sexual dysfunction among patients with MISD.

Keywords: tadalafil, sexual dysfunction, treatment, methadone

1- Introduction

Substance abuse and its complications are one of the most important mental health problems in today's world. Opioids, are usually used as an analgesic but have great potential for abuse. Opioid use disorder (OUD) includes misuse of prescribed opioid medications, the use of diverted opioid medications, or the use of illicit drugs. OUD is typically a chronic, relapsing illness, associated with significantly increased rates of morbidity and mortality. Among different treatment methods for OUD, methadone maintenance therapy (MMT) has received more attention (2-4). Methadone intake is effective in improving the physical and mental health of patients in addition to reducing the drug craving (5). Although the safety of methadone has been proven in its long-term use, like any other medication it has few adverse effects which may occur in patients taking this medication. Some of these side effects, such as euphoria and drowsiness, usually decrease in the first few weeks of starting treatment, but others, such as constipation, excessive sweating, and sexual dysfunction (SD), might continue after several months of treatment (6).

Methadone induced sexual dysfunction (MISD) is a common complaint among patients under MMT. However, despite its prevalence. The MISD is ahealth problem that can occur during each stage of the sexual response cycle that prevents a person or couple from experiencing sexual satisfaction.MISDcovers a wide range of symptoms such as erectile dysfunction,and ejaculation problems (in men), or vaginal spasm and sexual intercourse pain (in women) as well as sexual desire problems and response in both genders (7).The results of Tatari et alresearch (2010) on 157 male patients with Opioid use disorder (OUD) referring to MMT centers in Kermanshah, reported a prevalence rate of 60.5% for erectile dysfunction and 70.7.% for all types of SD (8).In another similar study conducted in Dagan, the prevalence rate of erectile dysfunction was reported 69% (9).Zhang, Wang, Ma, and Xu (2011) found that 90/7% of patients under MMT were dissatisfied with their current sexual function (10).In another study, some degrees of impotence was reported by 39 to 65 percent of patients received methadone(11).

Although few small clinical trials have proposed several treatment strategies for the treatment of MISD, currently no medication has been approved for this problem. Tadalafil is a specific PDE-5

inhibitor that is rapidly absorbed after oral intake and reaches its maximum plasma concentration after 2 hours. Its protein binding affinity is about 94%. It is metabolized in the liver by CYP3A4. The half-life of this medication is about 17.5 hours. Tadalafil usually uses 30 minutes before sexual activity to be more effective. As the effect of the medication on erectile dysfunction last up to 36 hours (compared to placebo), the time of consumption is important to get the optimal results (12).

Sexual function is considered an important part of human life that plays a key role in people's quality of life and health. Sexual activity and sexual intimacy among human beings are usually served at least four distinctive goals:

a) Exploring one's mating values;

b) Reproduction;

c) pair-bonding

d) Pair stabilization (13)

MISD is one of the most common adverse effects of long-term use of Methadone, which may affect the life quality of patients under MMT and can decrease medication compliance and increase the risk of relapse to drug use .

Considering the importance of this problem, we conducted the present study to investigate the efficacy of tadalafil in the treatment of MISD in male patients under MMT in Kermanshah, Iran.

- Investigation of tadalafil on men's sexual performance
- The effect of tadalafil on the sexual performance of men with methadone-induced dysfunction

2- Methods

2-1- Study design:

The study was a 4-week, randomized, double-blind, placebo-controlled clinical trial, and has been registered at the Iranian Registry of Clinical Trials (IRCT NO 20150822023705N10). The study population consisted of all people with OUD under treatment at Kermanshah MMT centers from 2018 to 2019.

The medical research and ethical committee of Kermanshah University of medical sciences, Kermanshah, Iran; approved the study (registration No.IR.KUMS.REC.1397.409 on the date August 14, 2018; grant number 97434), which was performed by the ethical principles laid down in the seventh and current edition (2013) of the Declaration of Helsinki. All participants were volunteers who signed written informed consent.

The following inclusion criteria were applied:

Married male patients were included in the study if the following criteria were met:

1. The age from 20 to 60 years. 2. Had at least elementary education 3. Suffering from SD. 4.Under MMT. 5. Suffering from MISD based on clinical interview according to the Diagnostic and Statistical Manual of Mental Disorders Criteria (DSM-V) which was approved by a psychiatrist.

The following points were the exclusion criteria :

1-Not meeting the inclusion criteria as described above.

2-The patient did withdraw from the study

3-The concurrent use of any stimulants or other substances except methadone (based on urine test)

4-Any medication intake that affects the patient's sexual activity.

5-Suffering from chronic or severe physical illnesses (such as liver disease, kidney failure, hypertension, diabetes, etc…)

6-Suffering from endocrine disorders (prolactin, sexual, and thyroid hormones according to laboratory findings assessed before enrolling at the study).

7-Any sensitivity to tadalafil medicine and its derivatives.

The treatment regimen remained unaltered throughout the present study, and those who have recently had significant changes in their medical condition or intake new medication during the study were excluded from the research. Informed written consent was obtained from all eligible volunteers.

Of the 266 patients who were screened, 154 were randomly assigned either to the intervention or to the placebo group. Randomization occurred as follows: 77 blue (medication) and 77 red (placebo) chips were put in a ballot box and stirred; patients draw a chip and were then assigned to the respective study condition. Neither patients nor the hospital staff responsible for the randomization was aware of the patient's group assignment. Further, all staffs, involved in the study were unaware of the patient's assignments. The study responsible person was not involved in performing the study.

3- Medication:

22subjects were excluded because they discontinued to use of the medication or placebo regularly, and finally 132 subjects (66 patients in each group) were analyzed. The first group received placebo tablets every 72h (containing lactose powder, 5% gelatin solution, and Avesil), and the patients in the second group were treated with tadalafil 10mg every 72h for the first 2 weeks and then 20mg for the second 2-weeks of the treatment course. Tadalafil and placebo were placed in similar and completely identical

packages in terms of shape, size, color, and smell that had been numbered. The clinician asked the patients to use the tablets every 72 hours, 30 minutes before the time of their sexual intercourse. There were no significant differences between the two groups with respect to age, addiction history, methadone dosage, and other demographic variables (see Table 1).

The drug was prepared and made by the authors of the article. In order to check the compliance of the drug, people who did not have any problems with drug use, sensitivity, or side effects were selected and included in the research, and people who had problems with drug use were excluded from the statistical population.

.Medicines were first given for a period of two weeks as a single dose of 5 half tablets of 10 ml After the evaluation, if there was no response, the dose of 10 ml was given again for 15 days, the evaluation was repeated and finally, the maximum dose of 20 was performed. Medicines were given together every two weeks. Sex was free. In this research, drug interaction was controlled.

3-1- Instruments:

International Index of Erectile Function (IIEF-5): The severity of erectile disorder was assessed using IIEF-5, with 5 questions rated on a 5-point Likert scale. The scope of the questionnaire was classified into 4 levels according to grades: severe (5-7), middle (8-11) mild to the middle (16-12), and mild (21-17) (14).

Brief Function Sexual Index (BFSI): This questionnaire contains 11 questions that measure 5 aspects of sexual function: sexual desire, erection, ejaculation, perceptions of sexual function issues in each of these dominates, and overall satisfaction each item is rated on a 5-point scale. O'Leary et al. (15) examined the psychometric features of the BSFI on data obtained from men in a general medical clinic and men who complained of sexual disorder. Internal consistency coefficients for Cronbach's alpha ranged from 0.62-0.95. The test and retest showed an intra-class correlation coefficient of 0.79-0.90 for different domains for a 1-week interval.

3-2-Statistical analysis

The results of the evaluation of the symptoms of SD, (Sexual desire, erection, ejaculation, perception of sexual function issues in each of these areas, overall satisfaction, and the overall score of sexual function with erectile disorder score) were assessed by administration of BFSI and IIEF-5, at three stages: at the baseline, after two, and four weeks of intervention. All referrals were subjected to clinical interviews at each visit (every two weeks) in addition to completing the questionnaires. Demographic

data were collected and the two groups were evaluated for sexual dysfunction by completing sexual function indexes at the beginning of the study. The Chi-square test and Fisher exact test were used to survey the homogeneity of demographic characteristics in two groups. Also, the existence of confounding variables between SD and demographic characteristics was examined by Spearman's correlation coefficient. The level of pairwise correlation between sexual desire, erectile function, ejaculation, overall satisfaction, total sexual function, and perception of sexual function in each of these domains was calculated using Pearson's correlation coefficient .

The process of averages changing was evaluated using Multiple Dimensional Variance Analysis with Duplicate Sizes (GLMRM) with time (start studying, end of the second week, end of the fourth week), studied groups (group treated with tadalafil and placebo consumer group), one time for the dependent variables (sexual desire, erectile function, ejaculation, perceptions of, overall satisfaction, total sexual function score, and sexual function in each of these domains), and the second time for the dependent variable of erectile function. In both models of duplicate measurements according to the results of the sphericityMoshli test, the analysis of variance of duplicate sizes was performed using modified results of Epsilon Greenhouse-Gieser values with adjusted degrees of freedom. The effect sizes were expressed in analytical models by using the partial eta of the squared coefficient (η2). Follow-up analyzes were also performed by Bonferroni simultaneous comparisons to adjust the significance level in multiple and simultaneous comparisons. Linear graphs were also used to graphically represent the process of changing the average of these concepts during the follow-up period of the study.

The nominal alpha level was set at 0.05; post hoc analyses were performed with Bonferroni-holm correction p-value for multiple testing. All analyses were performed using SPSS-15 statistical software.

4- Results

In this study, 66 subjects in the treatment group and 66 subjects in the placebo group (control group) completed three evaluation stages the beginning of the study, the end of the second, and fourth week. (See Fig. 1).

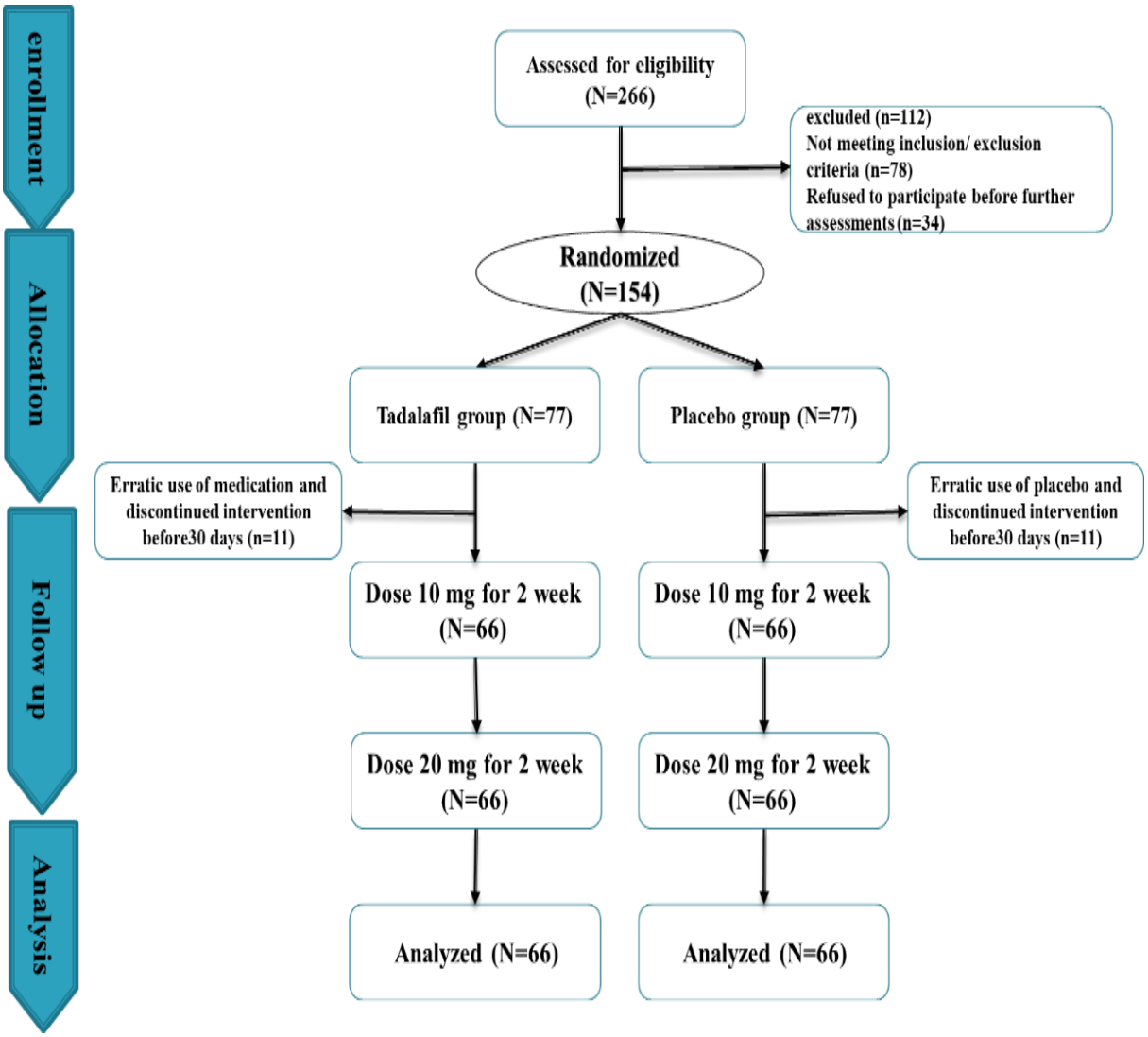

Figure 1. CONSORT diagram showing the flow of participants through each stage

The mean age of subjects in the intervention and control groups was 40.4± 9.29 and 41.2 ±9.34 years respectively, and t-test results showed no statistically significant difference between the two groups (t(0.025, 130) = 0.476, p-value=0.635). Family history of addiction was positive in 40.9% of the subjects in both groups and most of them were opioid users. Also, patients in both groups reported that they started substance use at the age of 19-28 years. 65.2% of the subjects in the two groups reported no substance use except opioids and opioids before went under MMT. The majority of individuals in both groups had several short-term withdrawal periods as well as frequent relapses according to their medical reports .

There was no statistically significant difference between the two groups regarding the age distribution level of education, occupation, economic status, the first age of substance use, history of relapse, history of addiction, and history of psychiatric illness in the family (all P-values> 0.05) (Table 1). Patients' demographic findings are summarized in table1.

Table 1.characteristics of participants based on intervention and control group

Variable	Levels	Total N (%)	Studied groups n(%)		p-value
			Placebo N =66	Tadalafil N =66	
Age group (years)	25-35	39(29.5)	17(25.8)	22(33.3)	0.447
	36-45	57(43.2)	32(48.5)	25(37.9)	
	> 45	36(27.3)	17(25.8)	19(28.8)	
Educational level	<High school	80(60.6)	43(65.2)	37(56.1)	0.187
	>high school	52(39.4)	23(34.8)	29(43.9)	
Occupation	Employed	110(83.3)	57(86.4)	53(80.3)	0.242
	unemployed	22(16.7)	9(13.6)	13(19.7)	
Socio economic status	High	17(12.9)	11(16.7)	6(9.1)	0.319
	Middle	48(36.4)	25(37.9)	23(34.8)	
	Low	67(50.8)	30(45.5)	37(56.1)	
The first age of substance use	< 18	31(23.5)	13(19.7)	18(27.3)	0.589
	19-28	74(56.1)	39(59.1)	35(53.0)	
	> 28	27(20.5)	14(21.2)	13(19.7)	
The first type of substance	Opium	127(96.2)	64(97.0)	63(95.5)	0.604
	Stimulant	4(3.0)	2(3.0)	2(3.0)	
	Multiple substance	1(0.8)	0(0.0)	1(1.5)	
History of other substance use	Yes	46(34.8)	22(33.3)	24(36.4)	0.428
	No	86(65.2)	44(66.7)	42(63.6)	
History of substance quit	Yes	90(68.2)	45(68.2)	45(68.2)	0.574
	No	42(31.8)	21(31.8)	21(31.8)	
Years of methadone	1-5 year	82(62.1)	42(63.6)	40(60.6)	0.429

substitution	> 5year	50(37.9)	24(36.4)	26(39.4)	
Methadone dosage (mg)	0-10	122(92.4)	62(93.9)	60(49.2)	0.362
	11-12	5(3.8)	3(4.5)	2(3.0)	
	> 20	5(3.8)	1(1.5)	4(6.1)	
Family history of addiction	Yes	54(40.9)	30(45.5)	24(36.4)	0.188
	No	78(59.1)	36(54.5)	42(63.6)	
Type of substance used in the family	opium	36(66.7)	17(56.7)	19(79.2)	0.186
	stimulant	1(1.9)	1(3.3)	0(0.0)	
	Multiple substance	17(31.5)	12(40.0)	5(20.8)	
Total		132(100.0)	66 (100.0)	66(100.0)	

Also, the Spearman correlation coefficient of demographic factors and self-reports was not significant between the two groups. (all P-values > 0.096 and all rs<| 0.23 |) which means that none of the demographic factors and self-reported records played a confounding role in the study (t (0.025, 130) =0.476, P-values =0.635.(

The average score of the five aspects of sexual dysfunctions in the baseline for tadalafil and placebo groups was not statistically significant but the difference between tadalafil and placebo in dose 10mg and 20 mg for five aspects of sexual dysfunctions were significant. There was a strong relationship between increasing the dose of tadalafil and reducing SD. So, BFSI in the tadalafil group increased from 15.92 to 30.12 (near twice the increase) from baseline to the dose of 20mg, whereas for the placebo group it was from 15.96 to 17.72. In general, tadalafilconsumption had a significant effect on the overall satisfaction, Assessment Problem, and the score of erectile disorder (IIEF) rather than on other sexual functions (figure 2).

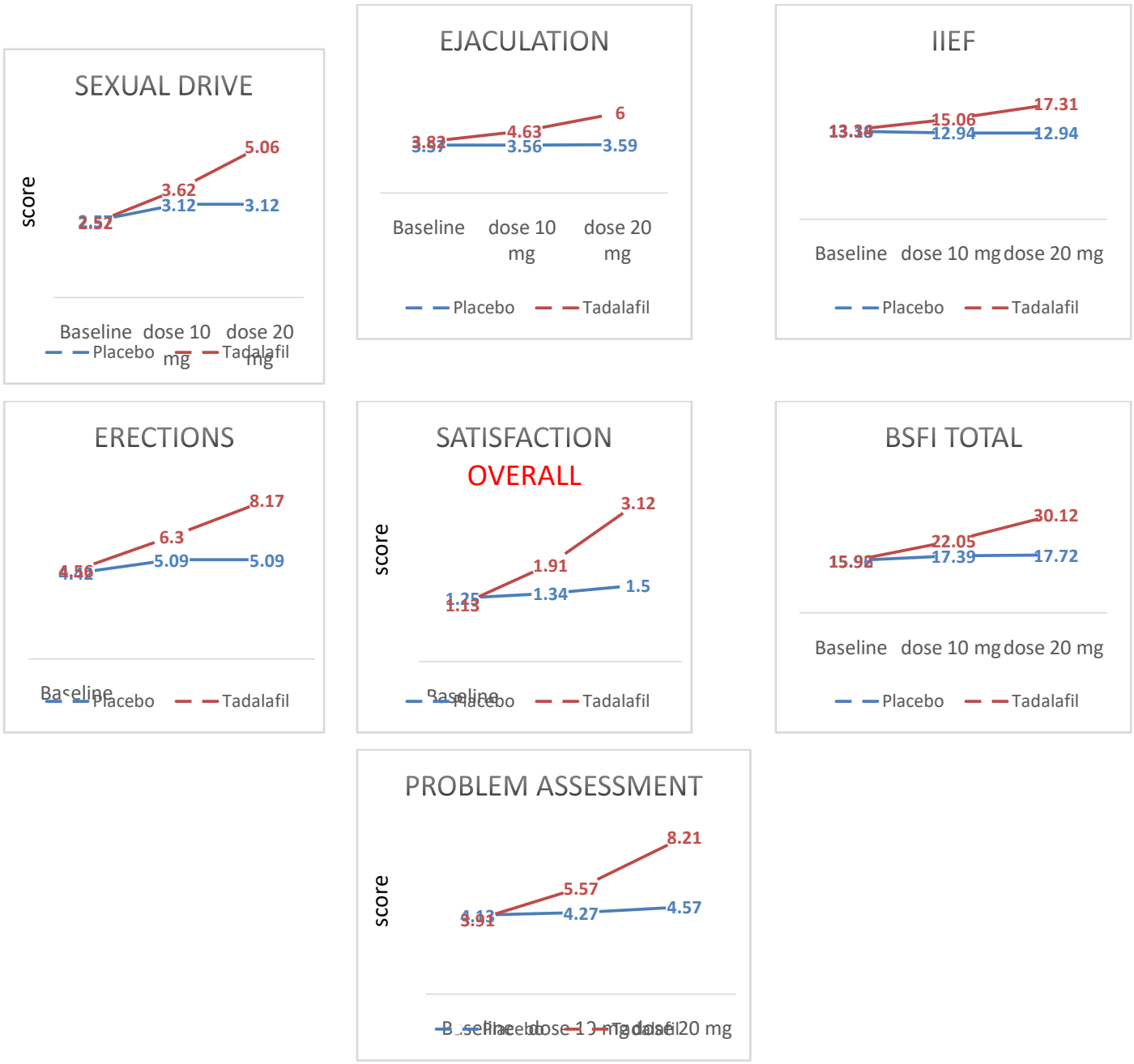

Figure 2: the aspects of sexual function erections, ejaculation, Assessment Problem, and overall satisfaction. Sexual drive, the overall score of sexual function (BSFI Total), and (IIEF) in baseline dose 10mg and dose 20 mg in the control and intervention group.

Linear and second-order contrasts between different evaluations showed that for all concepts studied, the dose-effect is significant (P s<0.05). Also, the linear effect of the does * group, along with the secondary effect of the does * group for the concepts of sexual drive and BSFI total, is significant (all

Ps <0.05). The results of multiple comparisons, along with adjusting Bonferroni for p-values, showed that the rate of improvement increased from the end of the second week to the end of the fourth week of the study. The mean of the improvement values generated in all sex concepts studied, among the three-time points evaluated, in the tadalafil group compared to the placebo group, showed that the trend of changes in the rate of recovery for all sexual concepts during the follow-up period of the study in the tadalafil group compared to the placebo group is increasing and observed (Table 2).

Table 2: Overview of the inferential statistics for the factors time (baseline, dose 10 mg, dose 20 mg) and group (tadalafil versus placebo) with sexual function as the dependent variable

Degrees of freedom		**dose (2,260) F[η2] (EF)**	**Group (1,130) F[η2] (EF)**	**dose × Group (2,260) F[η2] (EF)**	**Greenhouse Geisser Epsilon**
BFSI	**Sexual Drive**	79.04** [0.38] (L)	10.28** [0.073] (M)	30.15** [0.19] (L)	0.917
	Erections	57.09** [0.31] (L)	13.007** [0.09] (M)	35.13** [0.21] (L)	0.890
	Ejaculation	29.71** [0.19] (L)	12.47** [0.09] (M)	28.71** [0.18] (L)	0.977
	AssessmentProblem	41.85** [0.24] (L)	8.94** [0.06] (M)	28.49** [0.18] (L)	0.868
	SatisfactionOverall	61.98** [0.32] (L)	16.07** [0.11] (M)	37.90** [0.23] (L)	0.894
	BSFI Total	86.21** [0.40] (L)	13.29** [0.09] (M)	54.39** [0.30] (L)	0.877
IIEF	**IIEF**	17.14** [0.12] (M)	10.03** [0.72] (L)	21.24** [0.14] (L)	0.920

Notes: * = *P*<0.05; ** = *P*<0.01. "W4> W2, Bl" indicates that all values at week 4 were statistically higher than the values at week 2 and baseline. "T> Pl at W4" indicates that at week 4, values of the tadalafil group were statistically higher than the values of the placebo group. **Abbreviations:** EF, effect size; S, small effect size; M, medium effect size; L, large effect size; W4,

week 4; W2, week 2; Bl, baseline; T, tadalafil; Pl, placebo.**Effect sizes:** They are indicated with the partial eta squared (η^2), with $0.059 \geq \eta^2 \geq 0.01$ indicating small (S), $0.139 \geq \eta^2 \geq 0.06$ indicating medium (M), and $\eta^2 \geq 0.14$ indicating large (L) effect sizes.

5- Discussion

MISD is a common complaint among people with OUD under MMT (16). This medication complication could affect patients' quality of life significantly and may result in medication non-compliance and drug use relapse. One explanation is that methadone, like all opioids, affects the funnel-shaped part of the brain and the pituitary glands. As a result, prolactin levels may increase, which reduces the release of gonadotropin-releasing hormone, leading to a lower regulation of sex hormones such as testosterone (17.(

The present study is a 4-week randomized double-blind clinical trial with placebo control which was performed in men with OUD under MMT. Our results showed that Tadalafil was effective in improving sexual function, including erection, ejaculation, sexual desire, perception of SD as well as overall sexual satisfaction.

Data analysis revealed that the trend of changes in the mean scores of sexual function and related areas at the beginning of the study, the end of the second week, and the fourth week of the study had an increasing trend in the tadalafil group compared to the placebo group. Also, it was found that the effect of time, and group interaction was significant in the model (0.871=λ ،P=0.008 ،3.077=F،τ^2=0.129) which means the effect of the medication on MISD was increased over time.

The study results also revealed that a dosage of 20 mg/72h of tadalafil had greater effects on all aspects of sexual dysfunction including sexual desire, erection, ejaculation, and especially overall satisfaction compared to 10 mg/72h.

Although the effectiveness of tadalafil in the improvement of male sexual function was reported in several previous studies, to our knowledge this is the first study that investigates the effect of this medication on MISD.

Tadalafil is a PDE5-specific inhibitor whose mechanism of action increases smooth muscle relaxation and improves erection resulting in increased blood flow by preventing the destruction of cGMP by the enzyme phosphodiesterase, it increases cGMP levels and inhibits cGMP accumulation in smooth muscle by inhibiting this enzyme (18). Tadalafil is a vasodilator; this means that by dilating the blood vessels, it works to improve blood flow, thus increasing blood flow to the penis. Tadalafil works by inhibiting the action of a chemical in the body called type 5 phosphodiesterase. As a result, the blood

vessels dilate and after sexual arousal, blood flow to the penis improves. On the other hand, one of the unique features of tadalafil is its long half-life of 17.5 hours, which makes it a distinctive, effective, and appropriate treatment (19.(

In 2016 in a meta-analysis, Brook et al. studied the effectiveness of tadalafil in men with erectile disorder by using the International Erection Function Index in baseline and reported that tadalafil had improved erectile function in all groups, except for the group who received a daily low dose (5 mg) of tadalafil (20.(

Also, Gold Fisher et al. (21) reported that tadalafil compared to placebo had a significant effect in reducing the symptoms of erectile dysfunction, and was more effective in men with higher testosterone. Yang et al. (22) investigated the effect of combination therapy (edible tadalafil with low dose and vasodilator) in the treatment of men's erectile dysfunction. The results showed that edible tadalafil, along with low-dose vasodilators, led to a better clinical response than high-dose vasodilators.

However, the results of a study by Lacano et al. (23) who evaluated the effect of the new natural composition "tradamixina" against the administration of 5 mg per day tadalafil in people with decreased sexual desire and erectile dysfunction revealed that the total IIEF scores increased more after treatment in the tradamixina group, compared to tadalafil group, but the quality of sex life had improved in both groups.

In a small open trial Tatari et al (24) reported the efficacy of trazodone, an antidepressant, in the treatment of MISD. Also, Farnia et al (25,26) evaluated the efficacy of two herbal remedies in two different studies for the treatment of MISD. In one of them, they tried to assess the effect of ginseng among patients with MISD in a double-blind, randomized and placebo-controlled study and reported that in the intervention and control groups the sexual function was improved over time but more in patients under treatment with ginseng. In another study, they administered Rosa Damascena oil in a double-blind, randomized, and placebo-controlled trial and showed that this herbal extract improved sexual function and testosterone levels among males with MISD .

However considering the high prevalence of MISD among patients under MMT and its effects on patient's mental and sexual health, more investigations are necessary to manage this important medication side effect. According to the present study, tadalafil might be considered an effective treatment for SD in men with MISD. Also as we diagnosed several cases with thyroid, prolactin, and testosterone abnormalities during the early screening process of the patients enrolled in the study, we recommend assessing the hormonal function of patients with MISD before prescription of any

medication. We suggest well-controlled future studies with a larger sample size to evaluate the efficacy of tadalafil and other sexual enhancers to find better strategies for the treatment of MISD. Also researches to find treatment for females with MISD is warranted.

6- Limitations and strengths:

Our study has several limitations. Firstly we relied on patients' "self-rating"; this might be considered a limitation because self-reporting tools may can lead to bias. Secondly, our study sample size was rather small and participants were selected from a limited population of a city in the west of Iran. Finally, due to the private nature of the sexual assessment form, patients without education did not include in the study. Consequently, the overgeneralization of our study results should be with appropriate caution. However, considering the scarcity of evidence in this field we believe that the present findings merit publication .

The strengths of the present study include the use of laboratory testing to exclude patients with SD due to other etiologies and performing psychiatric interview besides the self-rating tools in every phase of the study assessments.

7- Conclusion

Evidence from this double-blind, randomized, and placebo-controlled study showed that tadalafil is effective to improve different areas of sexual function in men with methadone-induced sexual dysfunction.

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