

Comparison of Sexual Function and Serum Testosterone Levels in Men Opiate Addicts, under Methadone Maintenance Therapy, and Healthy Men

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Original Article

Abstract

Background: Substance abuse and consequently the use of methadone in Iran are reported at high levels. Drugs alter sexual function by affecting the organs of the body. The aim of this study was to evaluate sexual functioning and serum testosterone levels in opiate addicts, individuals receiving methadone maintenance treatment (MMT), and healthy men living in the city of Rafsanjan, Iran, in 2016.

Methods: The statistical population of this descriptive study included: A) opium-smoking men, B) individuals undergoing MMT, and C) those without any history of substance abuse. Using a formula, the sample size consisted of 70 individuals who were randomly selected from the statistical population. The study samples also completed the International Index of Erectile Function (IIEF). Moreover, the serum testosterone levels were measured using the laboratory-based Enzyme Linked Immunosorbent Assay (ELISA) diagnostic kits. The data were analyzed by SPSS software using Mann-Whitney U and Kruskal-Wallis tests with a significant level of ≤ 0.050 .

Findings: The serum testosterone levels in healthy individuals were higher than those in other two groups ($P = 0.001$). In addition, the sexual functioning indicators of men receiving MMT and opiate-smoking ones ($P = 0.001$) were lower than those of healthy individuals except for overall sexual satisfaction ($P = 0.069$).

Conclusion: Methadone and opium reduce different aspects of sexual functioning. It seems that this change was through having impacts on serum testosterone levels; however, psychological, social, and economic dimensions are suggested to be considered in this domain.

Keywords: Testosterone; Sexual dysfunctions; Methadone; Opium

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Introduction

Substance abuse is one of the major problems of today's world, which suffers from all the different categories of society. In this respect, two concepts have been inferred from the definition of dependence; psychological or behavioral dependence and physical dependence. These two types of dependence can also have loads of irreparable damage on people.¹ Among the consequences of substance abuse is the creation of neuropsychological symptoms which cannot be distinguished from prevalent mental disorders with unknown causes (such as schizophrenia and mood disorders). In other words, mental disorders and disorders related to the use of substances affecting the brain are interconnected.²

Sexual dysfunction is one of the major disorders which can be observed at different degrees and in various forms among individuals abusing drugs. This disorder can be seen in the form of erectile dysfunction, orgasmic disorder, or sexual desire disorder.³ Sexual dysfunction is always a matter of human interest and has a major impact on the quality of human life. Sexual disorders in fifth edition of the Diagnostic and Statistical Manual of Mental Disorders-5th Edition (DSM-5) consist of sexual dysfunctions, gender dysphoria, and paraphilic disorders.⁴ Sexual disorder can be common in all societies and among all races as well as both genders. Within the DSM-5, the main characteristics of sexual dysfunction have been defined as inhibiting one or more sexual stages, physiological responses, and sexual functioning including desire, arousal, orgasm, and subsidence.⁵

Sexual dysfunction is affected by physiological, psychological, and environmental factors.⁶ In this domain, drug-induced sexual dysfunction is important. Its diagnosis can be similarly confirmed since evidence obtained from taking medical history and physical examination or laboratory findings indicates that sexual dysfunctions are caused by substance abuse or withdrawal.⁷ The relationship between substance abuse and changes in sexual functioning has been investigated in various studies and their contradictory results have been published in this respect. Several studies have demonstrated that some substances in small quantities could enhance sexual functioning by reducing or

inhibiting anxiety or enhancing mood but their continued abuse could impair erection, orgasm, and even ejaculation.^{8,9} Kopetz et al. showed that use of cocaine and methamphetamine led to increase in sexual desire and sexual functioning at the beginning of their abuse, but their continuation has led to sexual dysfunctions. Moreover, they showed that those smoking cocaine had witnessed significant changes in their sexual functioning, and even their sexual pleasure had increased.¹¹ It was also observed that heroin¹¹ and cannabis⁹ use had brought about an increase in sexual pleasure in individuals. The given increase in sexual functioning was also detected at the beginning of abusing opioids or psychoactive drugs and it led to a decline in sexual desire and sexual functioning in the long term and with larger quantities.¹²

Among the multiple drug-dependence treatment methods, methadone maintenance treatment (MMT) has been of utmost importance compared to other ones. Methadone is a synthetic drug that is orally consumable and it can be replaced for addicted people. Since the duration of methadone exposure is over 24 hours, its administration by 20 to 80 g/day can keep the patient in a fixed situation.¹³ The MMT is also considered as one of the validated and recognized approaches in maintaining the state of withdrawal and no relapses after quitting the drugs.¹⁴

Sexual dysfunction including erectile dysfunction can be observed in individuals abusing drugs as well as those taking psychiatric medications such as anti-anxiety, anti-depression, anti-psychotic, anti-cholinergic medicine, as well as sedatives.⁶ In addition, the prevalence of erectile dysfunction in methadone users is reported to be more than in general population.^{15,16} The occurrence of sexual dysfunctions in individuals taking methadone is the problem discouraging them to continue this treatment and this may lead to withdrawal from the treatment and reusing the drugs.¹⁷

Some researchers believe that low testosterone level is the major cause of erectile dysfunction in drug users. This issue can be investigated from two dimensions: A) inhibited production of the gonadotropin-releasing hormone (GnRH) and reduced luteinizing hormone (LH) release from the hypophysis (the pituitary gland) resulting in lowered testosterone production, and B) increased blood prolactin levels and the effect of its negative

feedback on LH release leading to decreased testosterone production.¹⁸ Xia et al. showed negative impact of methadone on sexual functioning and consequently decline in sexual satisfaction,¹⁹ as well as the effect of the MMT on enhancing sexual functioning.^{20,21} As a result, the researchers have made attempts to explore and to better understand the relationship between substance abuse, MMT, and sexual functioning. Since testosterone plays an important role in sexual functioning, the aim of this study was comparison of sexual function and serum testosterone levels in men opiate addicts, those under MMT, and healthy men.

Methods

The statistical population in this descriptive study included all men treated with methadone who referred to MMT clinics affiliated to Rafsanjan University of Medical Sciences, Rafsanjan, Iran, in 2016 ($n = 200$), opiate-smoking individuals referring to drug rehabilitation centers affiliated to Rafsanjan University of Medical Sciences, as well as married male employees of Rafsanjan University of Medical Sciences. Considering $\alpha = 0.05$, $\beta = 20\%$, $\text{mean}_1 \pm \text{standard deviation (SD)}_1 = 36.61 \pm 23.19$, and $\text{mean}_2 \pm \text{SD}_2 = 25.93 \pm 15.20$,²² the sample size was calculated as 70 individuals that enrolled to study by convenience sampling method.

Sampling:

- A) Opium smokers referring to drug rehabilitation centers to withdraw
- B) Individuals undergoing MMT with a history of more than a year of methadone abuse
- C) Healthy men with no history of substance abuse or infliction with diseases affecting endocrine system

The required explanations of the study objectives were also given to the selected individuals and informed consent forms were obtained. The use of opium and methadone in healthy individuals was also ensured by screening through rapid urine test strips for morphine (ACON rapid test) on the basis of immunochromatography guide. All the participants also had ability to speak in Persian. People with a history of brain diseases or head injury, history of testicular trauma or testicular surgery, infertility, taking medications prescribed for changing sexual functioning, and using

psychiatric medications affecting sexual functioning were excluded from the study. As well, there were attempts to match the individuals in terms of age as much as possible. The participants also completed the International Index of Erectile Function (IIEF) in the drug rehabilitation centers or in their workplace, i.e., hospitals. Then, 5 cc of venous blood specimen was taken from one of the hand veins to measure testosterone levels. The blood sample was immediately transferred to the laboratory and centrifuged. Afterwards, the serum obtained was frozen at a temperature of $-20\text{ }^\circ\text{C}$ until the measurement time. The serum testosterone was also measured using the diagnostic Enzyme Linked Immunosorbent Assay (ELISA) kit (Diaplus, Inc., North York, Ontario, Canada). The statistical assumptions of the analysis of variance (ANOVA) were also performed. The significance level of Kolmogorov-Smirnov test (K-S test) of testosterone hormones and also different aspects of sexual functioning were significant ($P < 0.050$); therefore, the non-parametric tests of Mann-Whitney U and Kruskal-Wallis tests were used for data analysis. The significance level of the tests was considered as ≤ 0.050 . It should be noted that the IIEF is one of the appropriate research instruments to assess sexual functioning developed by Rosen et al.,²³ and validated through implementation on a group of men with sexual dysfunction. The IIEF consists of 15 items assessing erectile dysfunction of men in 5 domains of erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Based on the scores obtained from this questionnaire, the severity of dysfunctions in individuals can be divided into five groups: severe (scores 5-7), moderate (scores 8-11), moderate to mild (scores 12-16), mild (scores 17-21), and normal (scores 22-25). The Cronbach's alpha coefficients for the IIEF in the study by Rosen et al. was reported as 0.73-0.99²³ and equal to 0.94 in the present study.

Results

The mean age of the individuals receiving MMT, opiate addicts, and healthy participants was illustrated in table 1. The results of the Kruskal-Wallis test showed no difference between the groups in terms of age ($P = 0.600$) indicating the homogeneity of the groups in this study.

Table 1. Mean of age and testosterone level in 3 groups

Variable	Methadone	Opium	Healthy	P*
Age (year) (mean ± SD)	40.72 ± 8.06	42.03 ± 8.29	41.47 ± 8.78	0.600
Testosterone (ng/dl) (mean ± SD)	4.76 ± 2.03	4.94 ± 1.96	6.05 ± 2.45	0.001

*Kruskal–Wallis test, SD: Standard deviation

The results of the Mann-Whitney U test also revealed that the mean serum testosterone level in healthy individuals was significantly higher than that in men receiving MMT ($P = 0.001$) and individuals smoking opium ($P = 0.004$). There was no difference between the mean serum testosterone levels ($P = 0.496$) in individuals undergoing MMT and opiate-dependent ones (Table 2).

Table 2. Comparison of testosterone level in 3 groups

Hormone	Group	Compared with	P*
Testosterone	Methadone	Opium	0.496
		Healthy	0.001
	Opium	Healthy	0.004

*Mann Whitney U test

Moreover, the results suggested that the mean testosterone level in those taking methadone, opium abusers, and healthy people aged 25-35 years ($P = 0.616$), 36-45 years ($P = 0.373$), and 46-59 years ($P = 0.130$) did not differ significantly. Among individuals abusing methadone and opium, the mean testosterone level of those aged 36-45 years, 25-35 years, and 46-59 years was significantly higher ($P < 0.001$); however, the mean serum testosterone level in healthy participants aged 25-35 years was higher than that in other study groups ($P < 0.001$) (Table 3).

The results obtained using the Kruskal-Wallis test revealed that the mean scores of erectile function, orgasmic function, and intercourse satisfaction in healthy individuals were significantly higher than those using methadone and opium ($P < 0.001$). In this regard, the mean score for sexual needs of methadone abusers was significantly lower than that in opiate-smoking

and healthy individuals ($P < 0.001$). Furthermore, overall sexual satisfaction in individuals taking methadone, opium smokers, and healthy individuals was not significantly different ($P = 0.069$) (Table 4).

The results of the evaluation of the difference between the mean scores of the erectile function in the IIEF in terms of age were shown in table 5. The mean score of erectile function in healthy individuals in all age groups was significantly higher than that in opium smokers and methadone users ($P = 0.050$). Also, the mean score of erectile function in opiate-dependent individuals aged 25-35 years ($P = 0.003$), those taking methadone ($P = 0.001$), and healthy ones ($P = 0.011$) was significantly higher than that in men of other age groups.

Finally, the results of the Spearman correlation coefficient also showed that increased methadone ($P = 0.038$) and opium ($P = 0.440$) abuse could significantly reduce serum testosterone levels. Among those using methadone, the methadone dosage was significantly and inversely correlated with all aspects of erectile function and sexual functioning ($P = 0.050$) (Table 6).

Discussion

The results of this study showed that testosterone levels in healthy individuals were higher than those in men receiving MMT and opium smokers, which is in line with the findings of the investigations conducted by Sepehri et al.,²⁴ Mendelson et al.,²⁵ and Bawor et al.²² In this regard, Mendelson et al. showed that testosterone levels increased after methadone detoxification and then backed to normal levels.²⁵

Bliesener et al. also found that testosterone levels in individuals undergoing MMT were

Table 3. Mean of testosterone level in 3 groups based on age

Hormone	Age (year)	Methadone (mean ± SD)	Opium (mean ± SD)	Healthy (mean ± SD)	P*
Testosterone (ng/dl)	25-35	4.87 ± 1.70	5.10 ± 1.77	7.63 ± 2.77	0.616
	36-45	5.48 ± 2.21	5.88 ± 2.08	5.96 ± 1.94	0.373
	46-59	3.11 ± 0.61	3.67 ± 1.13	4.45 ± 1.65	0.130
	P	< 0.001	< 0.001	0.001	

*Kruskal–Wallis test, SD: Standard deviation

Table 4. Comparison of dimension of International Index of Erectile Function (IIEF) in 3 groups

???	Methodone (mean ± SD)	Opium (mean ± SD)	Healthy (mean ± SD)	P*
Erectile function	14.40 ± 7.80	18.51 ± 7.38	20.53 ± 7.66	< 0.001
Orgasmic function	3.19 ± 1.84	3.34 ± 1.61	5.66 ± 2.79	< 0.001
Sexual desire	3.84 ± 2.78	6.63 ± 2.76	6.40 ± 2.29	< 0.001
Intercourse satisfaction	6.52 ± 3.98	8.80 ± 3.44	10.04 ± 3.14	< 0.001
Overall satisfaction	5.94 ± 3.20	6.42 ± 2.84	7.23 ± 2.27	0.069

*Kruskal–Wallis test, SD: Standard deviation

significantly lower than those in buprenorphine users.²⁶ Likewise, Bawor et al. argued that serum testosterone levels were directly correlated with methadone dosage.²² Most studies in this respect also showed that substance abuse in various forms could reduce serum testosterone levels although such a decrease was not lower than the normal level. Moreover, Ragni et al. observed that testosterone levels in methadone abusers were normal.²⁷ Assaei et al. also demonstrated that although the mean testosterone and prolactin levels among opiate addicts were higher than those in healthy individuals, this difference was not significant.²⁸ As well, Brown et al. showed that only a small number of people abusing methadone had low testosterone levels and no

relationship was found between low testosterone levels and methadone dosage.²⁹ In this study, the normal range of testosterone on the basis of diagnostic kits used was 2-12 ng/dl and it was not lower than normal level among the study samples. From this perspective, the results of the present study are consistent with the findings of other investigations.

The results of the studies on the relationship between serum testosterone levels and methadone abuse have been inconsistent. For example, Bliesener et al. found that buprenorphine could increase serum testosterone levels in abusers rather than in healthy individuals and also could enhance sexual functioning.²⁶

Table 5. Mean scores of International Index of Erectile Function (IIEF) dimensions in 3 groups based on age

???	Age (year)	Testosterone (ng/dl) (mean ± SD)			P*
		Methodone	Opium	Healthy	
Erectile function	25-35	17.63 ± 6.99	23.67 ± 5.12	23.81 ± 6.14	< 0.001
	36-45	15.67 ± 7.00	19.07 ± 7.23	22.23 ± 6.62	< 0.001
	46-59	7.87 ± 6.85	13.96 ± 6.31	14.21 ± 7.27	0.005
	P*	< 0.001	< 0.001	< 0.001	
Orgasmic function	25-35	3.74 ± 1.79	3.72 ± 1.49	4.48 ± 2.25	0.769
	36-45	3.32 ± 1.63	3.17 ± 1.51	6.67 ± 2.68	< 0.001
	46-59	2.25 ± 2.11	3.25 ± 1.82	5.39 ± 2.71	0.002
	P*	0.107	0.717	0.015	
Sexual desire	25-35	6.21 ± 2.88	8.28 ± 1.18	7.52 ± 2.09	0.043
	36-45	3.56 ± 2.13	7.10 ± 2.69	6.43 ± 2.13	< 0.001
	46-59	1.62 ± 1.63	4.83 ± 2.76	5.10 ± 2.16	< 0.001
	P*	< 0.001	< 0.001	< 0.001	
Intercourse satisfaction	25-35	8.26 ± 3.18	10.11 ± 2.08	11.62 ± 2.82	< 0.001
	36-45	7.23 ± 3.64	8.86 ± 3.57	10.53 ± 2.34	< 0.001
	46-59	2.94 ± 3.43	7.75 ± 3.86	7.53 ± 3.20	< 0.001
	P*	< 0.001	0.105	< 0.001	
Overall satisfaction	25-35	7.68 ± 2.85	9.05 ± 0.23	7.95 ± 2.20	0.050
	36-45	6.32 ± 2.55	6.65 ± 2.81	7.73 ± 1.78	0.013
	46-59	3.06 ± 3.06	4.17 ± 2.01	5.63 ± 2.34	0.010
	P*	< 0.001	< 0.001	< 0.001	

*Kruskal–Wallis test, SD: Standard deviation

Table 6. Correlation coefficients of International Index of Erectile Function (IIEF) dimensions with serum testosterone level and dose of used drugs

Variable	Group	Testosterone	Dose
Dose	Methadone	Rho = *-0.250 P = 0.038	-
	Opium	Rho = -0.239* P = 0.044	Rho = -0.326* P = 0.006
Erectile function	Methadone	Rho = 0.200 P = 0.100	Rho = -0.326* P = 0.006
	Opium	Rho = 0.120 P = 0.317	Rho = -0.186 P = 0.121
	Healthy	Rho = -0.239* P = 0.044	-
Orgasmic function	Methadone	Rho = 0.070 P = 0.567	Rho = -0.328* P = 0.006
	Opium	Rho = -0.097 P = 0.423	Rho = -0.072 P = 0.553
	Healthy	Rho = -0.135 P = 0.266	-
Sexual desire	Methadone	Rho = 0.157 P = 0.199	Rho = -0.367* P = 0.002
	Opium	Rho = 0.153 P = 0.203	Rho = -0.131 P = 0.275
	Healthy	Rho = 0.231 P = 0.055	-
Intercourse satisfaction	Methadone	Rho = 0.274* P = 0.023	Rho = -0.288* P = 0.016
	Opium	Rho = -0.047 P = 0.698	Rho = -0.056 P = 0.644
	Healthy	Rho = 0.296* P = 0.013	-
Overall satisfaction	Methadone	Rho = 0.241* P = 0.046	Rho = -0.250* P = 0.038
	Opium	Rho = 0.163 P = 0.174	Rho = -0.140 P = 0.243
	Healthy	Rho = 0.215 P = 0.074	-

*Spearman's rho

In this regard, buprenorphine was the relative agonist of hair sensors and strong agonist of Kappa sensors in which the relative agonist of hair sensors could be attached to the hair sensor and then activated, but this activation was less than the full agonists; that is, in spite of being an opioid and having special side effects such as gait and weakened respiratory system, its maximum effect was less than complete opioid agonists such as heroine and methadone.³⁰ It seems there are different reasons for discrepancies in the results of studies. One of these factors is the regulatory mechanisms of serum testosterone levels. Accordingly, two possible mechanisms involved in decline in blood testosterone levels in

abusers of drug compounds include GnRH and LH as well as prolactin.³¹

The analysis of the findings also confirmed that erectile function, orgasmic function, and intercourse satisfaction in the group of healthy individuals were significantly higher which was in agreement with the results of the study by Ahmadvand et al.³² Tatari et al.³³ also found that 60.5 percent of individuals receiving MMT had problems with erectile function and 70.7 percent of them had difficulty in their orgasmic function. In the study by Quaglio et al. on men treated with methadone and buprenorphine, 24 percent of them reported mild to moderate sexual dysfunctions and 18 percent of these individuals

had severe sexual dysfunctions.¹² Erectile dysfunction has been introduced as a side effect of MMT which can affect overall quality of life in men and lead to a decrease in their cooperation in the course of treatment and also interfere with other known benefits of MMT.³⁴ Various studies have reported the prevalence rate of erectile dysfunction in general populations as 16-83 percent in which several factors such as age, endocrine disorders, alcohol use, smoking, and cardiovascular diseases (CVDs) can also play a role in 70-85 percent of cases.³⁵ Psychological issues may also have their own effects in this domain.³⁶ Methadone is a synthetic opiate that acts as an alternative in the treatment of drug addiction in order to reduce the damage caused by substance abuse. Although the relative risk of long-term methadone use has been demonstrated, incomplete tolerance with regard to some of its complications can bring about its own side effects.²⁰ The analysis of the results showed that there was no difference between the three study groups in terms of overall sexual satisfaction. In general, it was revealed that overall sexual satisfaction was an issue which could be influenced by various mental,³⁷ social,³⁸ personality-related,³⁹ and even economic⁴⁰ factors.

In this study, increased abuse of opium and methadone could significantly reduce serum testosterone levels, which is consistent with the findings of some researchers.^{22,41} Also, in this study, increased dosage of methadone could result in a significant reduction in various aspects of erectile function, which was not seen in opiate-dependent individuals. These findings are in agreement with the results of Babakhanian et al.⁴² and in conflict with those revealed by Saberi Zafarghandi et al.²⁰

Clinical experiences have also indicated that a major cause of medical non-compliance, discontinuation of MMT, and relapse to substance abuse is the occurrence of complications related to sexual dysfunctions. Thus, diagnosing these complications and managing the problems brought about by erectile dysfunction can help individuals adhere more to MMT, especially those undergoing MMT with higher doses or longer course of treatment.³²

Among the limitations of this study was lack of evaluating the impacts of some factors on sexual functioning such as emotional family atmosphere, cultural and economic issues, as well as sexual functioning in spouses. Use of other medications and presence of physical or mental illnesses were not also investigated. Therefore, it is suggested to consider the effects of cultural and economic factors, emotional family atmosphere, marital relationships with spouses as suitable sexual partners, and finally other medications and diseases on sexual functioning in the future studies.

Conclusion

Sexual function is reduced by the consumption of methadone or opium. This process seems to be under the influence of lower testosterone levels. However, other important factors including psychological, social, and economic ones should not be ignored.

Conflict of Interests

The Authors have no conflict of interest.

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مقایسه عملکرد جنسی و سطح سرمی تستوسترون مردان مصرف کننده تریاک، تحت درمان نگهدارنده با متادون و افراد سالم

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مقاله پژوهشی

چکیده

مقدمه: مصرف مواد مخدر و به دنبال آن، مصرف متادون در کشور ما بالاست. مواد مخدر با تأثیر بر ارگان‌های بدن، عملکرد جنسی را تغییر می‌دهد. بدین منظور، پژوهش حاضر با هدف بررسی عملکرد جنسی و سطح سرمی تستوسترون مردان مصرف کننده تریاک، تحت درمان نگهدارنده با متادون و مردان سالم در سال ۱۳۹۵ در شهر رفسنجان انجام شد.

روش‌ها: جامعه آماری این مطالعه توصیفی-مقطعی شامل مصرف کنندگان تریاک به شیوه تدخینی، افراد تحت درمان نگهدارنده با متادون و مردان بدون سابقه مصرف هرگونه مواد مخدر بود. حجم نمونه با استفاده از فرمول، ۷۰ نفر برآورد گردید که به شیوه تصادفی انتخاب شدند. نمونه‌ها شاخص بین‌المللی عملکرد نعوظ مردان (International Index of Erectile Function یا IIEF) را تکمیل نمودند. سپس سطح تستوسترون سرمی با استفاده از کیت‌های آزمایشگاهی و به روش Enzyme-linked immunosorbent assay (ELISA) اندازه‌گیری گردید. داده‌ها با استفاده از آزمون‌های غیر پارامتریک Mann-Whitney U و Kruskal-Wallis در نرم‌افزار SPSS و سطح معنی‌داری $P \leq 0/05$ مورد تجزیه و تحلیل قرار گرفت.

یافته‌ها: سطح تستوسترون افراد سالم از دو گروه دیگر بالاتر بود ($P = 0/001$). شاخص‌های عملکرد جنسی افراد تحت درمان نگهدارنده با متادون و مصرف کننده تریاک ($P < 0/001$)، به جز رضایت کلی جنسی ($P = 0/069$) از افراد سالم کمتر بود.

نتیجه‌گیری: متادون و تریاک ابعاد مختلف عملکرد جنسی را تحت تأثیر قرار می‌دهد و منجر به کاهش عملکرد جنسی می‌شود. به نظر می‌رسد که این تغییر از طریق کاهش سطح تستوسترون باشد. هرچند که جنبه‌های روانی، اجتماعی و اقتصادی آن نیز باید بررسی گردد.

واژگان کلیدی: تستوسترون، عملکرد جنسی، متادون، تریاک

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