ЧАСОПИС НА ЗДРУЖЕНИЕТО НА ФИЗИОЛОЗИ И АНТРОПОЛОЗИ НА МАКЕДОНИЈА

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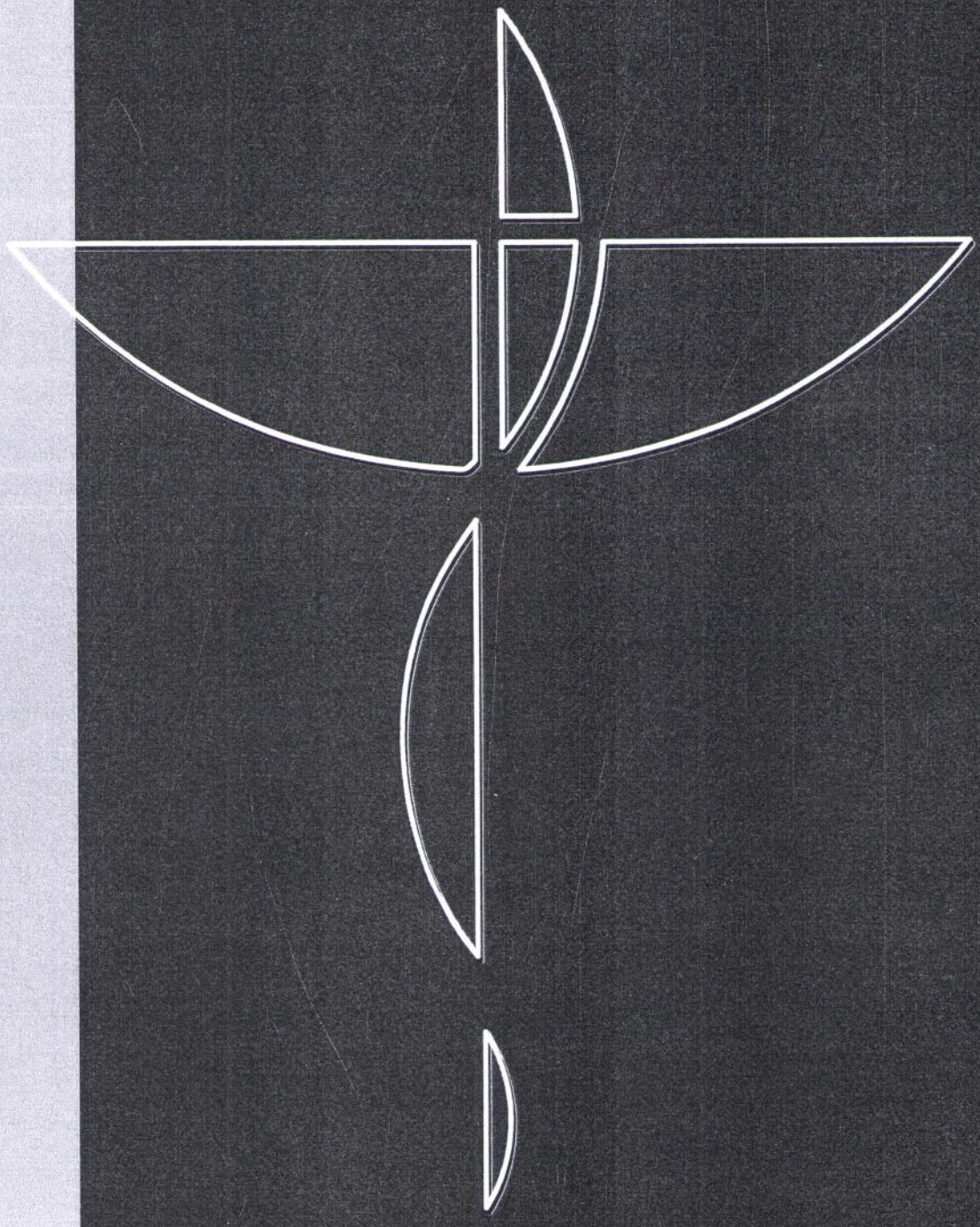

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RELATIONSHIP BETWEEN METHADONE DOSE AND SEXYAL DYSFUNCTION IN METHADONE MAINTENANCE PATIENTS

Spasovska Trajanovska A ,[1] Vujovic V ,[2] Janicevic Ivanovska D [3]

[1] *Day hospital for drug addiction, Skopje Psychiatric Hospital, Skopje, R. Macedonia*
[2] *University Psychiatric Clinic , Medical Faculty , Skopje , R. Macedonia*
[3] *University Biochemistry Clinic, Medical Faculty Skopje , R. Macedonia*

Abstract

Opioid substitution treatment is the most widespread and well-researched treatment modality for opioid dependence. Methadone is currently the most commonalty used pharmacy therapeutic agents. Sexual dysfunction has been reported as an aversive effect of opiopids including methadone therapy.. The AIM of this study was to explore the relationship between methadone dose and sexual dysfunction in patients of methadone maintenance treatment. MATERIAL AND METHODS we evaluated two groups of methadone maintenance patients. Group A consisted of 20 male heroin addicts maintained of methadone more than 3 years on oral high dose of met5hadone 80-120 mgr/day and Group B consisted of 20 male heroin addicts with lower dose of methadone maintenance therapy 10-60 mgr/day. The sexual function was assessed using Questionnaire (IIEF) with 15 items in three levels of sexual function. The differences between two examination group were determined by students t-test, The results show that patients treated with higher dose of methadone therapy had significantly higher frequency of sexual dysfunction ($p<0,05$) compared with groups of patients treated with lower dose of methadone therapy.

Key words: heroin addiction, dose of methadone therapy, sexual dysfunction

ВЛИЈАНИЕТО НА МЕТАДОНСКАТА ДОЗА ВРЗ СЕКСУАЛНАТА ДИСФУНКЦИОНАЛНОСТ КАЈ МАШКИ ПАЦИЕНТИ ПОСТЕВНИ НА МЕТАДОНСКИ ТРЕТМАН НА ОДРЖУВАЊЕ

Апстракт

Опијатниот супституционен третман е еден од најзастапените и најпроучуваните тераписки модалитети кај опијатната зависнопст. Метадонот е најчесто употребуваниот лек во супституциониот третман. Но, според одредени студии се смета дека сексуалната дисфункционалност се јавува како еден од најчестите несакани ефекти на метадонскиот третман. Целта на ова студија беше токму тоа да се согледа врската помеѓу метадонската доза и сексулната дисфункционалнлост кај пациенти постевни на метадонски третман на одржување. Материјал и методи: Беа евалуирани две групи на метадонски пациенти: првата група ја сочинуваа 20 машки пациенти поставени на високи дози на метадонска терапија од 80-120 мгр и група Б составена од 20 хероински зависници со ниски дози на метадонска терапоија од 10-60 мгр дневна доза. Сексуалната функција беше оценувана со помош на прашалник за оцена на сексуалната функционалност: Интернационален индекс на сексуалната

фунционирање составено од 15 прашања кои опфаќаат три новоа на сексуално функионирање(либидо, оргазам, ерекција). Разликите помеѓу испитуваните групи беше одредувана со студентов т-тетест. Резултати покажаа дека пациентите кои се третирани со повисоки дози на метадонска терапија имаа значајна повисока фрекефенција на сексуална дисфункционалност ($p<0.05$) во однос на група на пациенти кои се со пониски дози на метадонска терапија.

Клучни зборови: хероинска зависност, доза на метадонско одржување, сексуална дисфункционалност.

Introduction

Opioid substitution treatment (OST) is the most common and most effective modality for the treatment of opioid dependence. Currently, in Europe, over 460,000 individuals and in the U.S. over 241,000 receive opioid substitution in the form of. methadone (1). Sexual dysfunction is commonly reported side effects of opioid medications, and has been investigated in sample receiving OST ,primarily methadone maintained males. Common complaints related to sexual function, and potentially to sex hormone levels, among those on OST include decline in libido , erectile and orgasm dysfunction (2,3).
Reproductive physiology: The normal secretion of male sex hormone is mediated by pituitary hormones, primarily FSH, which is regulated by inputs from the hypothalamus (gonadotropin releasing hormone=GnRH) and gonadal tissue. GnRH in turn regulates the secretion by the pituitary of FSH in men, which in turn stimulates the production of sperm and testosterone by Leydig cells in the testes. Inhibin, secreted by Sertoli cells in the testes, provides negative feedback to both the pituitary and the hypothalamus to further regulate this feedback system in the male (4). Sexual dysfunction among men on OST appears to be related to lower-than-normal serum levels of testosterone (5).
Variety of mechanisms:

*Opioids have been show to suppress normal pituitary secretion of FSH and hypotalamus secretion of GnRH

*Interference with the usual dopaminergic mediation of prolactin secretion, leading to elevate prolactin levels, and in turn, decreased testosterone production may also cause sexual dysfunction in men on OST.

*opioids may also act directly upon testicular tissue to suppress normal testosterone production.

Studies have demonstrated higher rates of sexual dysfunction in methadone-maintained population than in the general population (7). Some studies demonstrate a dose-response relationship between methadone and sexual dysfunction or between methadone dose and serum hormone levels (8) .But some studies reported that stable long-term doses of methadone were likewise not found to have an effects on sexual dysfunction (9). Consideration of sexual dysfunction as a medication side effects is important because besides creating difficulty in intimate relationship in young people with his partners (10).

The AIM of this study was to explore the relationship between methadone dose and sexual dysfunction in male patients of methadone maintenance treatment.

Material and methods

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The present study was working in Psychiatric Hospital, Skopje, Skopje. In the study were included two groups of male heroin addicts of methadone maintenance treatment. Group A consisted of 20 male heroin addicts maintained of methadone more than 3 years on oral high dose of methadone 80-120 mgr/day and Group B consisted of 20 male heroin addicts with lower dose of methadone maintenance therapy 10-60 mgr/day. After complete description on the study, a written informed consent was obtained. The study protocol was approved by the local ethics commitment and is consistent with the Helsinki declaration. All the patients followed criteria for upload dependence and had no other significant psychiatric diagnosis, Especially patients with neuroleptic therapy were excluded from the study because nevroleptic therapy induced hyperprolactinemia. Criteria to elimination were: chronic liver of renal diseases or other chronic physical disorders, HIV diseases or active infection. All the patients were monitored with routine medical examination including blood chemistry, urinoanalisis and serology for hepatitis and HIV infection. Sexual function in males was assessed by using the questionnaire: International Index of erectile Function (IIEF) which contains 15 items. All the items are scored in 3 domains(erectile function, sexual desire and orgasmic function. Final scores can be interpreted as: severe, moderate, mild to moderate, mild and without dysfunction. The differences among examination groups were determined by using the t-test for independent samples.

Results

Table 1 show that 50 percent of heroin addicts with lower dose of methadone maintenance therapy have sexual dysfunction in tree domains: erectile function, orgasmic function and sexual desire. . But in the group of patients with oral high dose of methadone therapy none of them have normal erectile function and sexual desire; only 15 percent of them do not have orgasm dysfunction (Table 2)

Table 1 **Distribution on sexual dysfunction (percentage and number of patients in heroin addicts with lower dose of methadone maintenance therapy**

Domains of IIEF	Scored in domains				
	Severe	moderate	mild to moderate	mild	no dysfunction
Erectile function.	/	3(15%)	1(5%)	6(30%)	10(50%)
Orgasm function	/	2(10%)	2(10%)	6(30%)	10(50%)
Sexual desire	1(5%)	1(5%)	/	4(20%)	12(60%)

Table 2 **Distribution on sexual dysfunction (percentage and number of patients in heroin addicts with higher dose of methadone maintenance therapy**

Domains of IIEF	Scored in domains				
	Severe	moderate	mild to moderate	mild	no dysfunction
Erectile function	1(5%)	11(55%)	7(35%)	1(5%)	/
Orgasm function.	7(35%)	5(25%)	3(15%)	2(10%)	3(15%)
Sexual desire	9(45%)	5(25%)	3(15%)	3(15%)	/

In our study statistical analysis reported that between scores of sexual dysfunction in examination groups we got statistical significant results .The results ,show that patients treated with higher dose of methadone therapy have a statistical significances higher scores of sexual dysfunction ($p<0,05$) then group of patients with lower dose of methadone therapy.

Table 3 Statistical significant results of sexual dysfunction between examination groups

Group	erectile function	orgasm function	sexual desire
A	21, 6±5, 03	7, 94±2, 11	8, 47±2, 12
B	9,5±3,36	4,5±2,56	3,75±2,05
Students t-test	t=7,013*	t=4,641*	t=7,013*

*p<0,005

Discussion

Studies have demonstrated higher rates of sexual dysfunction in methadone maintenance population then in the general population (11). In our study results show that patients treated with higher dose of methadone therapy have higher percent of sexual dysfunction(in all patients we have sexual dysfunction) then patients treated with lower dose of methadone therapy.(in only 50% we have sexual dysfunction).This results correlate with another prospective studies which indicating that methadone influenced sex hormone levels. Willenbring et al demonstrated a maximally stimulated level of prolactin in 15 men(average daily dose of 52,7 mgr of methadone ,average duration of maintenance 18 months), providing evidence for interference by prolactin as a potential pathway leading to depressed testosterone and hence to sexual dysfunction in methadone on methadone maintenance (12). Cicero et al in their 1975 study found multiple sexual effects in 29 methadone –maintained male subject. Ejaculate volume and seminal and prostatic secretion were ,found to be 50% of those in 43 narcotic-free controls . serum testosterone levels were on average 43% of control subjects. The mean daily methadone dose in this study population was 67 mgr (7). This lead to the hypothesis that methadone may act to reduce serum testosterone levels via interference with pituitary or hypothalamic regulatory hormones.

In one of the first studies to examine particular types of sexual dysfunction in a methadone maintained sample, Tresch et al found men maintained on methadone to report reduce libido and orgasm dysfunction more frequently than controls (13). Similar to earlier studies, however, the severity of dysfunction and methadone dose were unrelated. In more recent work, Brown et al also demonstrated a link between methadone dose and orgasm dysfunction among 92 men maintained on an average of 100 mgr methadone daily. Surprisingly serum testosterone and prolactin levels were not found to be, on average, outside the normal range in spite of the relatively high daily methadone dose compared to previous study samples. Elevation prolactin was however the most common endocrinology abnormality in the sample (14). Spring et all provides some of the earliest evidence demonstrating a relationship between sexual dysfunction and methadone dose. Their study

used a validated instrument to examine sexual dysfunction in 25 men maintained on methadone for an average of 2 month. They found tan men experiencing significant sexual dysfunction were more likely to be on higher doses of methadone (15).

Mendelson also conducted some of the earliest work demonstrating a relationship between methadone dose and serum testosterone concentration. When the sample was dichotomized into groups receiving lower dose(10-60 mgr) and higher dose (80-150 mgr) methadone, the men receiving higher daily dose of methadone were found to be more likely to have abnormality low serum testosterone. As further evidence of an inverse relationship between methadone dose and serum testosterone levels in this study, reduction in methadone dose were associated with recovery of testosterone levels (16). Mendelson et all found similar results in a sample of 10 men administrated heroin in a controlled setting for 7 days and then detoxified using methadone at a starting dose for 35 mgr. Again abnormally low serum testosterone levels found during and after the period of heroin administration were found to recover to baseline after methadone detoxification (17).But the results in our study not correlate with another early study who demonstrated a dose response relationship between methadone dose and sexual dysfunction or between methadone dose and serum hormone levels. In 1974, Cushman and colleagues failed to find a main relationship between a one-time methadone dose and serum levels of LH, FSH, prolactin or testosterone in 8 male volunteers. Stable long –term doses of methadone were likewise not found to have an effects on serum, LH, FSH, prolactin or testosterone in this subject (18). Early work also indicated that if LH and FSH levels were affected by methadone, that the effects was likely mild and transient (19). In an interview study of 50 men enrolled in a methadone maintenance program, sexual dysfunction was highly prevented in the group (33%), but no relationship was found between sexual dysfunction and demographics, methadone dose or substance use history (11).Statistical analysis in our study show that we got statistical significances results between score of sexual dysfunction in examination groups. The results show that patients treated with higher doses of methadone therapy have higher score of sexual dysfunction then patients treated with low doses of methadone therapy.($p<0,05$), So the methadone dose have significantly effects on sexual function in the patients of methadone maintenance treatment. Because heroin population is young population so sexual dysfunction is most seriously problem in creating intimate relationship with his partners. So, the patients of methadone treatment attempt to solve this problem, so patients may resort to self-medication with such as stimulants, by reduced doses of prescribed medication, discontinuation of MMT or are dropping out of the treatment (21). So replacement treatment with dopamine agonist bromocriptine, bubrenorfine as a k opiate antagonist and androgens hormone maybe diminished the effects of hyperprolactinemia among the heroin addicts and methadone maintenance patients (22, 23).

Conclusion

Because the sexual dysfunction is the most frequently, in the patients on higher doses of methadone therapy patients need education of side effects of methadone therapy. In this way some conduction with sexual dysfunction may be rapidly detect and can rapidly affects with some therapeutic models. In this way will be stopped self-reduction doses of prescribed methadone therapy, dropping out of the methadone treatment or self medication with stimulants such as cocaine or amphetamine.

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