IOSR Journal of Nursing and Health Science (IOSR-JNHS)
e-ISSN: 2320–1959.p- ISSN: 2320–1940 Volume 10, Issue 6 Ser. I (Nov. – Dec. 2021), PP 48-54
www.iosrjournals.org

Evaluation of Gonad Function in Men Undergoing Methadone Treatment

Hypothalamus-Pituitary-Gonad axis and erectile function in patients on Methadone Maintenance Treatment (MMT)

S. Petrov[1], M. Orbetzova[1], F. Lotti[4], D. Byodzhiev[3], T. Deneva[2]
[1.] *Endocrinology Department, Medical University Plovdiv, Bulgaria, 15A V. Aprilov bul., 4002 Plovdiv, Bulgaria.*
[2.] *Medical University Plovdiv, Bulgaria, 15A V. Aprilov bul., 4002 Plovdiv, Bulgaria.*
[3.] *Plovdiv University "Paisii Hilendarski".*
[4.] *Sexual Medicine and Andrology Unit, Department of Experimental and Clinical Biomedical Sciences, University of Florence, Florence, Italy.*
Corresponding author: Sava Petrov, 15A V. Aprilov bul., 4002 Plovdiv, Bulgaria.

Abstract
Background: *Although the suppressive effect of methadone on testosterone levels is widely studied, detailed influence on hypothalamus-pituitary axis (HPA) and erectile function (EF) together has been poorly investigated.*
Aim: *To assess the effect of methadone maintenance treatment (MMT) on the HPA and EF.*
Methods: 119 patients from 18 to 40 years of age on chronic MMT were investigated in a cross-sectional study. As controls were used clinically healthy people from the same age and ethnicity without a history of drug abuse, psychiatric and somatic diseases which served as a control group. All patients and controls underwent clinical, biochemical, hormonal and erectile assessment. On the focus of investigation is assessment of hypothalamus-pituitary-gonad axis, androgen status and erectile function of patient undergoing chronic treatment with methadone.
Outcomes: *Clinical, biochemical, hormonal and erectile function assessment of patients undergoing chronic MMT.*
Results: *In the investigated opioid-dependent patients an androgen-deficient status was found with diminished levels of DHEA-S (222.33±101.03 µg /dL vs. 500.14±69.82 µg /dL in controls, p<0.001) and testosterone (3.99±1.97 ng/ml vs. 5.11±1.56 ng/ml in controls, p=0.02). Patients also demonstrated significantly lower results in all components of International Index of Erectile Function (IIEF) survey when compared to controls. Conducted patients in this study were on scale of mild erectile dysfunction. No significantly differences were found in the measurements of carbohydrate and lipid metabolism. Patients and controls are matched by age and Body Mass Index (BMI).*
Conclusions: *Chronic MMT is associated with androgen deficiency state with low levels of testosterone and DHEA-S and mild erectile dysfunction.*
Key Words*: Methadone Maintenance Treatment; Hypogonadism; Erectile Dysfunction; Heroin abuse.*

Date of Submission: 06-11-2021 Date of Acceptance: 23-11-2021

I. Introduction

The chronic use of oral opioids, including methadone, is associated with hypogonadotropic hypogonadism in 89% of men[1-5,] In heroin addicts the levels of testosterone and active fraction of testosterone are significantly low with elevated levels of sex-hormone binding globulin[6]. erectile dysfunction, decreased libido and infertility Heroin addiction and methadone maintenance treatment (MMT) subjects show higher rates of sexual dysfunction (SD) in comparison to the healthy controls[7-9]. SD rates have ranged 34-85% for heroin addicts[8] and 14-81% for MMT[10, 11]. On the other hand, opioid antagonists, such as naltrexone, can ameliorate erectile function and hypogonadism-related symptoms without influencing T and LH levels probably acting on central opioid pathways involved in erectile activity[12]. SD in patients treated with naltrexone can raise up to 90%[13].

As it is related to fertility a study of Ragni et al. shows that semen analyses from all of the heroin addicts and from the dual heroin- methadone users were abnormal, whereas only 10 out of 22 (45%) of the

methadone takers were pathological. In all cases asthenospermia was one of the abnormalities (100%). Twenty- four per cent also showed teratospermia and hypospermia and 17% showed oligozoospermia. Such seminal pathology, especially of forward motility, even in combination with normal hormone levels, might be an early indication of heroin toxicity to the male reproductive tract[14].

Opioids have also a suppressive effect on adrenal androgen production, including DHEA and DHEA-S, which are T precursors[15].

The chronic use of opioids has also direct negative effect on the male gonads [16]. Testicular opioids seem to be "messenger"-molecules with morphine-like structure which directly suppress production of testosterone. Chronic abuse with alcohol leads to increase of β-endorphins which is associated with negative influence on testicular function

The most used opioid agonist for maintenance treatment of heroin-addicted patients is methadone [17]. It is a synthetic, long-acting mu-receptor agonist for per oral intake. The chronic use of methadone leads to psychic and physic addiction [18].

Methadone maintenance treatment (MMT) is associated with high prevalence of erectile dysfunction [19], as derived by studies using validated instruments such as International Index of Erectile Functions. However, the mechanisms implicated in MMT-related ED are not well understood.

The aim of this study was to try to evaluate the influence of MMT on hypothalamic-pituitary-gonadal (HPG) axis and erectile function.

II. Materials And Methods

A cross-sectional, observational, case-control study was conducted in Bulgarian men undergoing chronic methadone maintenance treatment (MMT). The study included a consecutive series of 119 men (mean age 31.63 ± 4.133 years) on MMT, attending outpatient clinics for patients with dependency to heroin which is labelled as a patient group (group 1). In this cross-sectional study a total of five outpatient clinics for opioid dependency took part. These clinics conduct Methadone maintenance treatment of more than 1000 opioid-dependent patients in four regional cities in Bulgaria – Sofia, Plovdiv, Pazardjik, Stara Zagora, were included in the study.

The study meets the standards and criteria for science and ethics and has been approved by the Scientific Ethics Committee of the Research Council of the Medical University of Plovdiv with protocol No 3 / 26.06.2014.

Inclusion Criteria:

- Personally, signed patient's informed consent;
- Patients undergoing chronic MMT, defined ad lasting for at least six months in maintenance treatment phase;
- Age between 20 and 40; A narrow-age window is used because of physiological variations in HHG axis occurring in age before 20 and after 40.
- Negative urine tests for heroin and marijuana;

Exclusion Criteria:

- Patients with a history of chronic endocrine disease, including diabetes mellitus, thyroid diseases, adrenal, gonadal disturbance, prolactinoma, metabolic syndrome.
- Intake of hormonal preparations or medications affecting hormonal status, carbohydrate and/or lipid metabolism up to 3 months before the beginning of the study, including androgens, levothyroxine, metformin, dopamine agonists;
- Cessation of methadone maintenance treatment (MMT) in the last six months;
- Positive urine tests for heroin and marijuana.

As a control group (group 2) we evaluated 22 age- and BMI-matched (mean age 30.18 ± 1.468 years) healthy men without a history of any endocrine disease, infertility, erectile dysfunction, concomitant diseases, use of any medications, illicit drugs.

Biological material was taken in the morning (between 8:00 and 10:00 a.m.). The standard requirements for taking biological material with 30-minutes rest immediately prior to the study were followed.

Conditions for taking, processing and storing blood samples, as well as choosing biological material, were complaint with the manufacturer's requirements and the recommendations of several authors to overcome the variation factors and standardization of the pre-analytical stage.

The study meets scientific and ethical standards and criteria and was approved by the Scientific Ethics Committee of the Medical Research Council at the Medical University Plovdiv with № 3/26.06.2014 г.

Biochemical evaluation with hormonal and metabolic assays

Blood samples were drawn in the morning, after an overnight fast for determination of luteinizing hormone (LH), follicle-stimulating hormone (FSH), total testosterone (TT), prolactin (PRL), dehydroepiandrosterone sulfate (DHEA-S), insulin by chemiluminescent immunochemical assay (CLIA, Beckman Coulter, Inc., USA), Inhibin B by enzyme-linked immunosorbent assay (ELISA Beckman Coulter, Inc., USA), blood glucose by the glucose oxidase method (Beckman Coulter Cat. № OSR6121); and total cholesterol, high-density lipoprotein cholesterol and triglycerides by an automated enzymatic colorimetric method (CHOD-PAP, Beckman Coulter Cat. № SR6116). The homeostatic model assessment for insulin resistance (HOMA-IR) score was evaluated as (fasting glucose (mmol / l) x fasting insulin (μIU / mL)) / 22.5.

Evaluation of erectile function

Erectile function was evaluated in both groups using the International Index of Erectile function (IIEF) survey in its Bulgarian version produced by Mapi Research Institute _ID2505 [20]. IIEF covers five domains of male sexual function: erectile function (EF), intercourse satisfaction (IS), orgasm, desire (OD), overall satisfaction (OS). For evaluation of erectile dysfunction was used EF domain with ranging values between severe, moderate, mild and no dysfunction[21].

Methadone usage

Methadone maintenance treatment (MMT) consists of everyday use of methadone, taken as a syrup. Every ml syrup of methadone contains 10 mg active component. During their treatment patients go through three stages. First stage is Introduction period: Induction the patient to the MMT. During this stage an individual dose is contributed to each patient. Second stage is rehabilitation period with continuous treatment and relatively stable dose. Each patient has own dose which is determined by the clinical features assessed form psychiatrist. Third stage is the Conclusive period. During this period the dose is reduced, and a period of cessation is fixed. The patients included to the investigation are in their rehabilitation period with continuous treatment with an individual dose. Mean daily dose and mean duration of MMT were investigated. We tried to elucidate better the methadone exposure of patients, so we integrated a pioneer index and named it *Index of Methadone Exposure (IME).* This index has never been used by any research teams before. The index is formed by multiplying mean daily dose and mean duration of MMT.

Data analysis

Data were expressed as mean± standard deviation (SD) when normally distributed, as medians (quartiles) for parameters with non-normal distribution, and as percentages when categorical. Correlations were assessed using Spearman's or Pearson's method. Differences between more than two groups were assessed with one-way ANOVA or Kruskal-Wallis test. For comparisons of means between groups unpaired two-sided Student's T or Mann–Whitney U- tests were used depend on distribution of parameters. Stepwise multiple linear or logistic regressions were applied for multivariate analysis, whenever appropriate. The statistical analysis was performed using a SPSS statistical processing program (SPSS Inc., IBM SPSS Statistics, Version 21.0). In the hypothesis test, for a level of significance where the zero hypothesis was rejected, the standard value $p \leq 0.05$ was chosen.

III. Results

Metabolic and hormonal assays

The patient and control group were matched for age and BMI. Table 1 presents socio-demographic, clinical, hormonal, and biochemical parameters for both groups.

Table 1 Clinical and laboratory parameters of investigated patients and healthy controls. A statistical analysis comparing patients and controls has been performed. ** p <0.05; **p <0.01; *** p <0.0001*

Clinical and laboratory parameters	MMT patients n=119	Controls n=22	P value
Age (years)	31.63±4.13	30.18±1.47	0.107
BMI	23.74±3.48	24.68±3.00	0.239
LH (IU/L)	5.67±3.16	3.68±1.46	0.004**; t=2.88
FSH (mIU/ml)	6.34±8.43	4.061.99	0.176
Testosterone (ng/ml)	3.99±1.97	5.11±1.56	0.02*; t=-2.51
Estradiol (pmol/L)	106.71±65.48	124±49.29	0.09
Inhibin B (μIU/mL)	203.80±91.93	191.74±93.0	0.57
T/LH	0.85±0.46	1.54±0.84	0.000***;t=-5.53

InhB/FSH	65.21±68.66	61.97±45.73	0.662
DHEAS (µg/dL)	222.33±101.03	500.14±69.82	0.000***;t=-11.19
Prolactin (µg/L)	156.15±83.25	215.33±101.90	0.016*;t=-2.50
Glucose (mmol/l)	5.29±0.61	4.93±0.40	0.026*, t=0.25
IRI (µIU/mL)	8.75±5.06	8.38±5.12	0.81
HOMA - IR	2.07±1.22	1.82±1.08	0.47
Cholesterol (mmol/l)	5.03±1.50	4.92±0.59	0.80
TG (mmol/l)	1.41±0.93	1.41±0.90	0.99
HDL-chol (mmol/l)	1.32±0.44	1.44±0.55	0.41
LDL-chol (mmol/l)	3.06±1.20	2.84±0.74	0.50

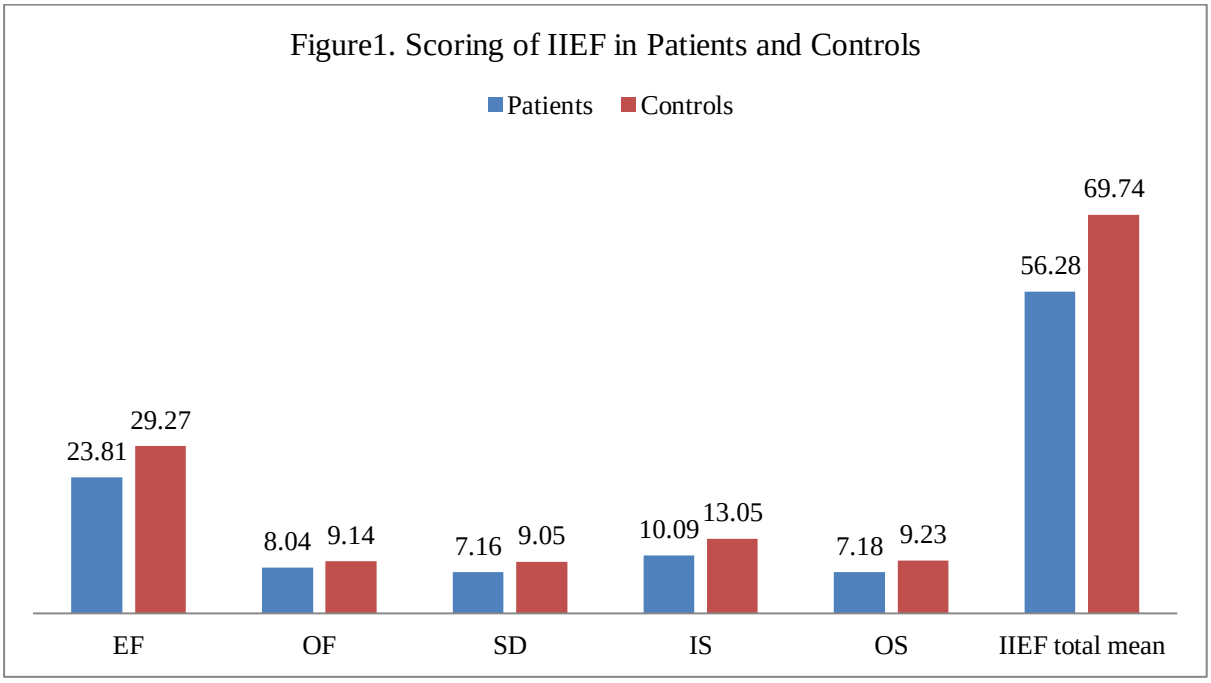
Comparing patients and controls for metabolic parameters we found a statistically significant differences only in glucose levels with slightly elevated but statistically significant values in patients' group. However, the values of glucose in both groups were in the reference laboratory range. Also, no difference was found in HOMA-IR.

Patients showed lower levels of testosterone and increased levels of LH compared with the controls. Also, T/LH ratio was significantly lower in the patients' group compared to the controls. DHEA-S was significantly lower in patients undergoing chronic MMT. No significant differences in FSH and Inhibin B levels were found between the groups. PRL was significantly lower in patients' group.

The recommendations of the 5th International Congress of Sexual Medicine held in Paris in 2009 and involving 190 multidisciplinary experts from 33 countries and the Endocrine Society (USA, 2010) set limits for low total testosterone of 300 to 350 ng / dL or 3.0 to 3.5 ng/ml, and patients with testosterone lower than 230 ng/dL need to have testosterone replacement therapy [22, 23]. If we use 3.5 ng / ml as a lower limit for normal testosterone levels, 57 patients (47.9%) and only 2 healthy subjects (9.1%) had a testosterone deficiency status. Using a lower limit of 3 ng / ml, 40 patients or 33.6% of the patient group and one healthy person (4.5%) were associated with testosterone deficiency. 18 subjects from the patient group (15.13%) cover the criteria for initiating testosterone replacement therapy (testosterone lower than 230 ng/dL).

Erectile function

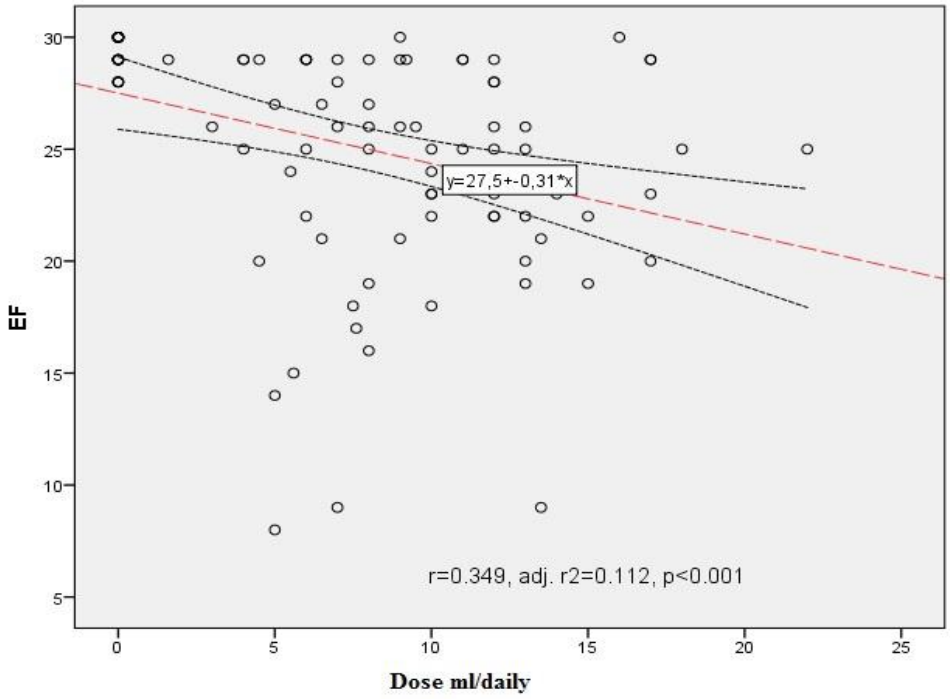
When analyzing results from the IIEF survey we established significantly lower total scores on the scale for all components of the survey in the patients as compared to the group of controls (P<0.05). The results are presented in Figure 1.



The total means score criterion EF (23.81) in the investigated group of patients indicated ED of slight degree with mild dysfunction (EF score between 22-25).

In our study we did not find any correlation between the components of the survey for erectile function evaluation and testosterone nor prolactin levels. We evaluated the influence of parameters of MMT on the EF component. A linear regression model with a negative correlation between the mean daily methadone dose and the EF component was shown (Figure 2). Other factors of MMT – duration and exposure did not show any correlation with the EF component.

Figure 2. Linear regression model of the component EF and mean daily dose of MMT



Methadone usage and previous heroin abuse

Mean daily dose of MMT for the investigated patients is 9.85±4.12 ml/daily (98.5 mg/daily). Our clinical data is similar to the reported daily average daily dose in Bulgaria which is 100 mg / day [24]. Mean duration of MMT is 35.02±25.85 months. Reported average duration of treatment according to different sources vary widely from 12-36 months up to 7 years [22, 23]. Calculating *IME* we found mean values of 374.35±375.08. A subgroup analyze was made using median of the parameter *Index of Methadone Exposition* as an integration parameter of methadone usage. Patients were divided into the following groups: Group One- Patients with low exposition to methadone (with value of *IME* <264) and Group Two- Patients with high exposition to methadone (with value of *IME* ≥264). Each of the parameters of hypothalamus-pituitary-gonad axis, glucose and lipid metabolism was compared between the groups with low and high exposition to methadone. No statistically significant difference was found in any of the investigated indicators. Mean duration of heroin addiction prior MMT is 6.32±3.68 years.

IV. Discussion

Androgen deficiency among drug addicts who undergo MMT is a condition reported in several clinical trials [25,16]. Reported evidence suggests a direct suppressive effect of methadone on the hypothalamus, resulting in suppression of testosterone levels [26]. The occurrence of hypogonadotropic hypogonadism with low levels of gonadotropins and suppression of testosterone synthesis and secretion is one of the most commonly reported endocrine effects of chronic opioid use affecting males [27]. Opioids are thought to lead to disturbances in pulse gonadotropin secretion as well as to influence receptor sensitivity and anterior pituitary response to GnRH, both mechanisms resulting in qualitative and quantitative disturbances in LH and FSH secretion, respectively to lowering testosterone levels [28].

The results of our study support the reported androgen deficiency data but reveal a direct toxicopharmacological action of methadone on the testes, suppressing testosterone levels and increasing LH. The hormonal constellation of elevated LH levels, low testosterone and the T / LH ratio are in favour of direct

disturbance of Leydig cell function. According to A. Jakubovic, methadone has a direct suppressive effect on ribonucleic acid synthesis (RNA) and proteins [29]. According to data from other studies, a negative influence on testicular function with suppression of testosterone levels and deterioration of seminal fluid parameters, were observed in heroin-addicted persons undergoing MMT[16]. Probably the mechanism of suppressing the HPA during MMT is combined: central and peripheral[1]. The occurrence of hypogonadotropic hypogonadism in chronic opioid exposure by a mechanism of increasing serum prolactin levels by hypothalamic tuberoinfundibular dopaminergic (TIDA) neurones, quoted in some clinical studies[29, 30], was not confirmed by our study.

Our clinical data support a variety of scientific studies reporting a suppressive effect of long-term use of methadone on DHEA-S secretion[31, 32].

We did not find any functional disturbance in testicles with no statistically differences in levels of Inhibin B between patients and controls. A sperm analyzes is needed for more complex evaluation.

OPIAD (opioid induced androgen deficiency) occurs several hours after opioid administration. Mendleson et al.[33] report suppression of testosterone levels by more than 50% after 7 to 9 hours of administration of 30-80 mg of oral opioid (acetyl methadone analog of methadone) in drug addicts. Scatter levels of testosterone are also found in several patients, these levels are maintained for an average of about 24 hours, and then returned to normal for a period of 48 to 72 hours. In our patients, blood samples for the studies performed were taken between 1 and 2 hours after methadone intake when is the absorption peak but not the peak in serum concentration and the suppressing effect on the gonad axis. The transient methadone suppressive effect on the HPA and the restoration of normal levels of gonadotrophins and peripheral gonadal hormones has been proven by other authors. Woody showed that testosterone levels reached the lowest values on average 5½ hours after oral methadone administration. After a period of 24 hours, testosterone returns to baseline values[34]. This may explain the results of our study showing higher levels of LH in methadone patients. It can be assumed that the blood-sampling period is with the lowest levels of methadone in the blood, resulting in an independent release of the HPA axis from its suppressive effect and rise in the levels of gonadotropic hormones. However, the axis is chronic and prolonged suppressed so the levels of peripheral hormones cannot be recovered immediately to baseline. For a more complex and detailed assessment of this observed mechanisms testosterone level, sex hormone binding globulin and albumin should be investigated by comparing free and bioavailable testosterone with serum-methadone levels. A shortcoming of this study is not having results of gonad hormones of the heroin addicts prior initiating MMT. It cannot be distinguished whether the negative effects on HPA are due to MMT or previous heroin abuse prior treatment.

Sexual activity serves as a natural satisfaction, enjoyment and positive emotion in humans and animals. Sexual behaviour is a collection of stimulatory and suppressive mechanisms in the brain[35]. There are a number of mechanisms of brain stimulation involving multiple neurotransmitters, with dopamine being best studied over time in research[36]. One of the first evidences is improving sexual behaviour and increasing libido in patients treated for Parkinson's disease with dopamine precursor L-dopa (3,4-dihydroxy-l-phenylalanine). It is the TIDA system dysfunction triggered by the chronic methadone influence and the change in the pulsatility of GnRH may be one of the possible pathophysiological mechanisms for the occurrence of septic dysfunction even without an absolute increase in serum prolactin levels.

Sexual behaviour and desire are not only influenced by biological factors such as levels of gonad hormones and prolactin. The psychogenic component and social support can have a strong influence on sexual desire and behaviour[35]. Drug addicts combine multiple negative social-household factors that obviously exert a suppressive effect on the sexual function of this contingent. Although sexual dysfunction is not a life-threatening phenomenon, it should not be overlooked, as it may result in refusal to adhere to therapy, change in social life, and the quality of life of patients undergoing methadone replacement therapy[36].

V. **Conclusions**:

Overall, the results from our study reveal an androgen deficient state in male undergoing chronic MMT with decreased levels of testosterone and DHEA-S. As regards to the mechanism of testosterone suppression we observed a direct toxic effect on gonads leading to lower testosterone levels and a rise in LH levels. Patients performing chronic methadone treatment are presented with worsening erectile function compared to the control group of clinically healthy men of the same age. According to the assessment system of the IIIEF survey, drug addicts in the current clinical trial have a moderate degree of erectile dysfunction. From the factors analyzed, the average daily dose of methadone treatment has the most negative impact on all indicators of erectile function. It is obvious that endocrine regulation is not the most important thing regarding erectile function.

References

[1]. Daniell HW. Hypogonadism in men consuming sustained-action oral opioids. *J Pain.* 2002; 3(5): 377-84.
[2]. Novaira HJ, Ng Y, Wolfe A, Radovick S. Kisspeptin increases GnRH mRNA expression and secretion in GnRH secreting neuronal cell lines. *Mol Cell Endocrinol* 2009; 311: 126–134. 43
[3]. Paice JA, Penn RD, Ryan WG. Altered sexual function and decreased testosterone in patients receiving intraspinal opioids. *J Pain Symptom Manage.* 1994; 9(2): 126-31.
[4]. Rajogopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Hypogonadism and sexual dysfunction in male cancer survivors receiving chronic opioid therapy. *J Pain Symptom Manage.* 2003; 26(5):1055-61.
[5]. Rajogopal A, Vassilopoulou-Sellin R, Palmer JL, et al. Symptomatic hypogonadism in male survivors of cancer with chronic exposure to opioids. *Cancer.* 2004; 100(4): 851-8.
[6]. Lafisca S, Bolelli G, Franceschetti F, Danieli A, Tagliaro F et al. Free and bound testosterone in male heroin addicts. *Arch Toxicol Suppl.* 1985;8:394-7 7.
[7]. Palha AP, Esteves M. A study of the sexuality of opiate addicts. J Sex Marital Ther. 2002;28:427–37.
[8]. Comparison of prevalence between self-reported erectile dysfunction and erectile dysfunction as defined by five-item International Index of Erectile Function in Taiwanese men older than 40 years. Wu CJ, Hsieh JT, Lin JS, Hwang TI, Jiann BP, Huang ST, Wang CJ, Lee SS, Chiang HS, Chen KK, Lin HD
[9]. Erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment. Hallinan R, Byrne A, Agho K, McMahon C, Tynan P, Attia J J Sex Med. 2008 Mar; 5(3):684-92.
[10]. Adequacy of sexual performance in men maintained on methadone. Hanbury R, Cohen M, Stimmel B Am J Drug Alcohol Abuse. 1977; 4(1):13-20.
[11]. Methadone maintenance and male sexual dysfunction. Brown R, Balousek S, Mundt M, Fleming M J Addict Dis. 2005; 24(2):91-106.
[12]. Fabbri A, Jannini EA, Gnessi L, Moretti C, Ulisse S, Franzese A, et al. Endorphins in male impotence: Evidence for naltrexone stimulation of erectile activity in patient therapy. *Psychoneuroendocrinology* 1989;14:103-11.
[13]. Ramdurg S, Ambekar A, Lal R. Sexual dysfunction among male patients receiving buprenorphine and naltrexone maintenance therapy for opioid dependence. J Sex Med. 2011;10:1743–61.
[14]. G. Ragni et al. Gonadal function in male heroin and methadone addicts International Journal of Andrology, 1988, 11, pages 93-100
[15]. Daniell HW. DHEAS deficiency during consumption of sustained action prescribed opioids: Evidence for opioid-induced inhibition of adrenal androgen production. *J Pain* 2006; 7(12): 901-907. 67
[16]. Ragni G, De Laurentis L, Bestetti O, Sghedoni D, Gambaro V Gonadal function in male heroin and methadone addicts. *International Journal of Andrology.* 1988; 11: 93–100.
[17]. Manchikanti L. National drug control policy and prescription drug abuse: facts and fallacies. *Pain Physician.* 2007; 10: 399–424
[18]. Stewart B. L. Methadone-Drug Interactions. *Pain Treatment Topics.* January 2006; 17-21.
[19]. Teoh JB, Yee A, Danaee M, Ng CG, Sulaiman AH. Erectile Dysfunction Among Patients on Methadone Maintenance Therapy and Its Association With Quality of Life. J Addict Med. 2017 Jan/Feb;11(1):40-46.
[20]. Rosen RC, Riley A, et all. The international index of erectile function (IIEF): a multidimensional scale for assessment of erectile dysfunction. Urology. 1997 Jun; 49(6):822-30.
[21]. Cappelleri JC, Siegel RL, Osterloh IH, Rosen RC. Relationship between patient self-assessment of erectile function and the erectile function domain of the International Index of Erectile Function. Urology. 2000; 56:477-481.
[22]. Bhasin S, Cunningham GR, Hayes FJ,Matsumoto AM, Snyder PJ, Swerdloff RS, et al. Testosterone therapy in men with androgen deficiency syndromes: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2010;95(6):2536–59. doi:10.1210 /jc.2009-2354.
[23]. Montorsi F, Adaikan G, Becher E, Giuliano F, Khoury S, Lue TF, et al. Summary of the recommendations on sexual dysfunctions in men. *J Sex Med.* 2010;7(11):3572–88. doi:10.1111/j.1743- 6109.2010.02062.x.
[24]. Annual report of NCN for 2014 (Годишен доклад на НЦН за 2014 г.) available at: http://www.ncn-bg.org/docs/reports/Report_NCN_2014_Internet.pdf
[25]. Vescovi PP et al. Effects of dopamine receptor stimulation on opiate-induced modifications of pituitary-gonadal function. *Horm Res.* 1985;21:155–9.
[26]. Adams ML, Sewing B, Forman JB, Meyer ER, Cicero TJ. Opioid-induced suppression of rat testicular function. *J Pharmacol Exp Ther.* 1993;266:323–8.
[27]. Schug SA, Zech D, Grond S. Adverse effects of systemic opioid analgesics. *Drug Saf.* 1992;7(3):200–13.
[28]. de la Rosa RE, Hennessey JV Hypogonadism and methadone: hypothalamic hypogonadism after long-term use of high-dose methadone. *Endocr Pract.* 1996 2:4–7.
[29]. Jakubovic A, McGeer EG. Narcotics and rat testicular metabolism. *Mol Pharmacol.* 1979 Nov;16(3):970-80.
[30]. Van Vugt DA, Meites J Influence of endogenous opiates on anterior pituitary function. Fed Proc. 1980 Jun; 39(8):2533-8.
[31]. Reid RL, Hoff JD, Yen SS, and Li CH. Effects of exogenous _h-endorphin on pituitary hormone secretion and its disappearance rate in normal human subjects. *J Clin Endocrinol Metab.* 1981 52:1179–1184.
[32]. Abs R, J Verhelst, J Maeyaert, et al. Endocrine consequences of long-term intrathecal administration of opioids. *J Clin Endocrinol Metab* 2000; 85:2215–2222.
[33]. Mendelson JH, Inturrisi CE, Renault P, Senay EC: Effects of acetylmethadol on plasma testosterone. *Clin Pharmacol Ther.* 1976 19:371-374.
[34]. Woody G, McLellan T, O'Brien C, et al. Hormone secretion in methadone-dependent and abstinent patients. *NIDA Res Monogr.* 1988;81:216–23.
[35]. Pfaus JG. Pathways of sexual desire. *J Sex Med.* 2009; 6: 1506–1533. doi: 10.1111/j.1743-6109.2009.01309.x 81
[36]. Levine SB. The nature of sexual desire: a clinician's perspective. *Arch Sex Behav.* 2003; 32: 279–285.

Sava Petrov, et. al. "Evaluation of Gonad Function in Men Undergoing Methadone Treatment Hypothalamus-Pituitary-Gonad axis and erectile function in patients on Methadone Maintenance Treatment (MMT)." *IOSR Journal of Nursing and Health Science (IOSR-JNHS)*, 10(06), 2021, pp. 48-54.