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IMPACT OF BUPRENORPHINE THERAPY ON THE NORMALIZATION OF SEXUAL FUNCTION AND STATES OF ANXIETY

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Abstract: According to certain, studies, chronic opioid use has a major impact on the function of the hypothalamic-pituitary-adrenal axis. Hypogonadism occurs in more than half of male opioid users and elevated cortisol levels in approximately one-fifth of addicts. Buprenorphine as a kappa opioid antagonist reduced release of adrenocorticotropic hormone and in these way was reducing anxiety and depression in heroin addicts. The AIM of our research was to determinate the impact of buprenorphine therapy on sexual function and anxiety.

Materials and methods: The cross-sectional study included 19 male and 1 female patients on buprenorphine therapy aged between 25-51years with a diagnosis of F11.22. The patients were evaluated in the Day hospital for treatment of drug abuse, department of Psychiatric Hospital Skopje. Sociodemographic characteristics (age, marital status, years of education, employment) of patients were determined using a questionnaire specially designed for the study. The anxiety state of the patients was determined using the Hamilton Anxiety Rating Scale consisting of 14 items. Sexual dysfunction was determinate by Scale for Quality of Sexual Function (QSF) as an outcome measure for both genders. The results were analyzed statistically using descriptive methods, the t-test for independent samples. The correlation between the observed variables was tested using Spearman's rank correlation coefficient (rho). A significance level of 0.05 was used to determine statistically significant differences and associations. Statistical analysis was performed using SPSS for Windows, version 25. The results show inverse correlation between duration of buprenorphine treatment with the score of anxiety r=-0,411; p=0,072 and with sexual dysfunction r=-0,192; p=0,418. Also in our study we got inverse correlation between the buprenorphine doses with the score of anxiety r=-0,136; p=0567 and with sexual dysfunction r=-0,528; p=0,017. But in both cases we got results without statistically significances. Conclusion: Longer buprenorphine treatment with adequate doses give lower scores of sexual dysfunction and anxiety.

Keywords: Buprenorphine therapy, duration of treatment, doses, sexual dysfunction, anxiety.
Field: Psychiatry (addiction diseases)

1. INTRODUCTION

Increased heroin use has resulted in the development of opiate addiction, which according to the World Health Organization ranks highly compared to other diseases. According to certain, although still insufficiently explained, studies, chronic opioid use has a major impact on the function of the hypothalamic-pituitary-adrenal axis.

Hypogonadism occurs in more than half of male opioid users and elevated cortisol levels in approximately one-fifth of addicts. Therefore, periodic evaluation of the gonadal and adrenal axis at least once a year is recommended (Afrasiabi M.A et all, 1989; Friso V et all, 2020).

As one of the treatments used worldwide in the treatment of opiate addiction is buprenorphine therapy.Buprenorphine is a drug with high affinity for mu opioid receptor as a agonist , kappa opioid receptor as antagonist and has some affinity for at delta opioid receptors in high concentration as an antagonist .All of them receptor are found in the somatosensory and limbic processing zones in the brain(BeErshad AK et all,214; Falcon E et all,2021) . According to the literature, buprenorphine is considered to have a much smaller effect on the hypothalamic-pituitary-adrenal axis than heroin and methadone therapy. A frequency of dopamine increase after treatment with buprenorphine is only 25%, unlike the effect of heroin, which is 60% (Bodkin J.A. et all 2005; Han J., 2022).

Also compared to methadone and heroin, buprenorphine is known to be associated with significantly lower testosterone levels changes and thus lower rates of sexual dysfunction. The results obtained in certain preclinical studies indicate the antidepressant and anxiolytic effects of buprenorphine through its kappa receptor. There is also evidence that it is involved in the release of serotonin (Leander J, 2007).

In support of these claims are the data on the effects of buprenorphine in terms of its influence on reduced release of adrenocorticotropic hormone as well as cortisol, which findings also confirm the

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practical possibility of reducing anxiety and depression in heroin addicts treated with this type of therapy (Bodkin J.A et all,2005).

So the AIM of our research was precisely to see the impact of buprenorphine therapy on sexual functioning and anxiety.

2. MATERIALS AND METHODS

The cross-sectional study included 19 male and 1 female patients aged between 25-51years with a diagnosis of F11.22. The patients were evaluated in the Day hospital for treatment of drug abuse, department of Psychiatric Hospital Skopje. All the patients was treated with buprenorphine therapy 2-32 mg day/doses and they were on the treatment duration of 1,5-10 years. The inclusion criterion was the presence of opioid dependence, criteria for exclusion were: chronic liver and renal diseases, AIDS, HIV infection, or other chronic organic disorders. All respondents signed a written consent to participate before the start of the research. Confidentiality of information was assured.

As follow-up, all these patients received routine medical examination, which included urine analysis and serology for Hepatitis C and HIV infection. Sociodemographic characteristics (age, marital status, years of education, employment) of patients were determined using a questionnaire specially designed for the study.

The anxiety state of the patients was determined using the Hamilton Anxiety Rating Scale consisting of 14 items. Each item is scored on the scale of 0 without symptoms to 4 severe symptomatology. The total range is 0-56; score >17 indicated anxiety.

Sexual dysfunction was determinate by the Scale for Quality of Sexual Function (QSF) as an outcome measure for both genders. The scale consists of 30 specific items and eight general questions Total score ranges from 5 to 30, score of 19 more suggestive of sexual dysfunction. Statistical analysis Categorical and continuous variables are presented as means with standard deviations and percentages. The t-test was used to compare mean values, while associations between categorical variables were tested using the chi-square test. The correlation between the observed variables was tested using Spearman's rank correlation coefficient (rho). A significance level of 0.05 was used to determine statistically significant differences and associations. Statistical analysis was performed using SPSS for Windows, version 25.

3. RESULTS

Table 1 presents the socio demographic characteristics, buprenorphine therapy profile, and the average scores for anxiety and sexual dysfunction among patients enrolled in the buprenorphine substitution program.

Table 1. Socio demographic and clinical characteristics of patients in the buprenorphine substitution program.

Parameter	M±SD /N (%)
Age (years)	56,5 ±5,9
Gender (M/F)	19/1 (95%/5%)
Marital status (Y/N)	9/11 (45%/55%)
Employment (Y/N)	13/7 (65%/35%)
Education (years)	11,6±2,6
Buprenorphine (mg)	17,5±9,19
Treatment duration (years)	4,98 ±2,1
Anxiety score	15,8±6,4
Sexual dysfunction score	17,5±4,4

Source: Authors

Anxiety was insignificantly association with sex (female), unemployment, marital status (unmarried),

shorter duration of buprenorphine treatment, fewer years of education, or sexual dysfunction Sexual dysfunction was significantly associated with unemployment and a shorter duration of buprenorphine treatment (Table 2).

Table 2. Correlation of anxiety and sexual dysfunction scores with socio demographic characteristics and buprenorphine treatment dosage/duration.

Parameter	Employment	Marital	Treatment	Education	Bup.dose	Anxiety	SexDysf
Anxiety score (Spearman ρ)	-0,185	-0,089	-0,411	-0,081	-0,136	/	0,139
P level	0,435	0,71	0,072	0,735	0,567	/	0,558
Sex.dysf.score Spearman ρ	-0,585**	-0,254	-0,192	0,192	-0,528*	0,139	/
P level	0,007**	0,28	0,418	0,418	0,017*	0,558	/

* Correlation is significant at the 0.05 level (2-tailed).** Correlation is significant at the 0.01 level (2-tailed).
Source: Authors

Patients with sexual dysfunction receive a significantly lower daily dose of buprenorphine and a slightly shorter, but not statistically significant, duration of substitution therapy compared to those without sexual dysfunction. Patients with anxiety receive a slightly lower buprenorphine dose and have a shorter duration of therapy, though these differences are not statistically significant (Table 3).

Table 3. Distribution of anxiety and sexual dysfunction according to daily buprenorphine dosage and duration of buprenorphine therapy.

	Yes/No (N)	M±SD	t	df	P
Sex. dysfunction. /Buprenorphine. dosage	Y (6)	10.67±8.548	2.443	18	0.025*
	N (14)	20.43±8.045			
Anxiety / Buprenorphine. dosage	Y (6)	14.33±8.8	1.009	18	0.327
	N (14)	18.9±9.3			
Sex. dysfunction. /Buprenorphine . treatment duration .	Y (8)	5,25±2.9	0.466	18	0.647
	N (12)	4,79±1.5			
Anxiety/ Buprenorphine . treatment duration .	Y (6)	3,9±2.7	-1.517	18	0.147
	N (14)	5,4±1.7			

Source: Authors

There was no significant association between anxiety and marital or employment status, although anxiety was more common among unmarried and unemployed patients. Sexual dysfunction showed a significant association with both anxiety and unemployment, while its association with marital status was not statistically significant—however, it was more frequently observed among unmarried patients (Table 4).

Table 4. Association of socio demographic characteristics with anxiety and sexual dysfunction.

Parameter	Anxiety	X2	df	P
Married	22.2%	0.471	0	0.492
Unmarried	36.4%			
Employed	15.4%	3.778	1	0.052
Unemployed	57.1%			
No sex. dys.	33.3%	5.488	1	0.019*
Sex. dys.	66.7%			
	Sex dys.	**X2**	**df**	**P**
Married	11.1%	2.781	1	0.157
Unmarried	45.5%			
Employed	7.1%	8,802	1	0.003*
Unemployed	77.4%			

Source: Authors

4. DISCUSSION

The AIM of our research was precisely to see the impact of buprenorphine therapy on sexual functioning and anxiety in heroin addicts. According to the results obtained in our study, there is a inverse correlation between the duration of buprenorphine treatment and the anxiety scale r=-0,411;p=0,72, as well as inverse correlation between the buprenorphine dose and the anxiety scale r=-0,136; p=0,567.

This means that with longer treatment and higher doses, a lower anxiety score is obtained. This result also correlates with results obtained in other studies that refer to the knowledge that long-term treatment with an adequate buprenorphine dose achieves stabilization of the patient's neuroendocrine system (BeErshad AK et all, 2021; Bodkin J.A et all, 2005; Falcon E et all, 2021; Kosten TR et all, 1990).

Buprenorphine, as an agonist of opiate kappa receptors, acts suppressive on the hypothalamic-pituitary adrenal axis, which is responsible for the release of adrenocorticotropic hormone, which stimulates the production of ACTH from the anterior pituitary gland, leading to the secretion of cortisol (Han J ,2022; Farahbakhsh ZZ.et all, 2023)

Also, according to certain research, buprenorphine also participates in the secretion of serotonin, which once again confirms its significant anxiolytic effect through kappa receptors (Falcon E et all, 2021).

But, the results obtained in our study do not correlate with some results in preclinical studies that indicate that treatment shorter than a year and with a low dose of 2 mg reduces anxiety in heroin addicts (Kosten TR et all, 1990; Leander J 2007).

However, it must be noted that the anxiolytic effect of buprenorphine opens up other challenges. Most often, young people from the general population are increasingly starting to experiment with buprenorphine in order to overcome anxiety, which is a serious public social problem and leads to the possible development of addiction.

Compared to opiates, according to some research, it is known that buprenorphine exerts less suppression of the gonadal hormone (Friso V et all, 2020). According to some studies, it is known that chronic use of opioids causes hypogonadism and it was present in more than half, that is, in 63% of the subjects, while during treatment with buprenorphine therapy, that percentage was much lower (Han J ,2020; Leander J, 2007).

Also, compared to methadone, buprenorphine has been found to have significantly less effect on testosterone reduction and thus sexual dysfunction. According to some research, kappa receptors play an important role in this condition through their inhibitory effect on the secretion of ACTH hormone, which is in turn responsible for the secretion of gonadal hormones (Afrasiabi M.A et all, 1989; Bodkin J.A et all, 2005; Farahbakhsh ZZ. et all, 2023).

In fact, in our study we also found inverse correlation between the duration of treatment r=-0,192; p= 0,418 and the dose of therapy with score of sexual dysfunction r=--0,528 p= 0,17 . This speaks to the effectiveness of buprenorphine therapy: the longer the treatment and the adequate doses give the lower sexual dysfunction scores.

However, what we, as the authors of this study, want to emphasize is that despite adequate buprenorphine therapy for more than a year, 30% of patients still had high anxiety scores. That can be explained by the persistence of comorbid disorders.

Also in our study we got the results who show that anxiety was more common among unmarried and unemployed patients but without statistical significances p=0,435;p=0,71 . So we can conclude that the family and social environment have an influence on the occurrence of anxiety. Maybe family support and improved social opportunities would be reduced this conditions.

5. CONCLUSION

This study show that we got the inverse correlation between buprenorphine therapy and score of sexual dysfunction and anxiety in patients. So, the longer treatment with the adequate doses give lower sexual dysfunction and anxiety scores, because buprenorphine as a kappa opioid antagonist receptor diminished the anxiety and sexual dysfunction. But, we may also concluded that 30% of patients still had high anxiety scores. That can be explained by the persistence of some comorbid conditions.

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