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The effects of buprenorphine/naloxone maintenance treatment on sexual dysfunction, sleep and weight in opioid use disorder patients

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ABSTRACT

Opioid use disorder is a growing social problem. Different agents are used in the treatment of this disorder. One of these agents is buprenorphine / naloxone combination that includes buprenorphine and naloxone in a ratio of 4:1. Although used successfully in opiate maintenance treatment, buprenorphine / naloxone could have some side effects that might affect the treatment. The present study aimed to examine the effects of buprenorphine /naloxone opiate maintenance treatment on sexual dysfunction, sleep and bodyweight in patients diagnosed with opioid use disorder and to draw the attention of clinicians to the adverse effects of the treatment. The study group included 107 inpatients who were diagnosed based on The Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) and received treatment for opioid use disorder. On admission to the hospital and at the end of the 4th month, a Sociodemographic and Clinical Data Form, the Pittsburgh Sleep Quality Index (PSQI) and the Arizona Sexual Life Scale (ASEX) were applied to all patients. Patients were weighed, and their weight was recorded on the day of admission to the hospital and at the end of the 4th month. The data recorded at the beginning and during the treatment of the same group were compared. The mean age of 107 patients was 24.55 ± 4.27. Overall ASEX scores were 12.98 ± 4.33 before treatment and 15.03 ± 6.61 at 4 months ($p < 0.001$). The mean patient bodyweight was 63.86 ± 8.78 kg before the treatment and 68.49 ± 8.65 kg at the 4th month of the treatment ($p < 0.001$). Total PSQI scores were 8.87 ± 3.53 before the treatment and 6.85 ± 3.29 at the 4th month of the treatment ($p < 0.001$). The study findings demonstrated that after 4 months of buprenorphine /naloxone treatment, total ASEX scores and bodyweight of the patients increased and total PSQI scores decreased. These results demonstrated that sexual problems and bodyweight of the patients increased after the buprenorphine /naloxone treatment and sleep-related problems decreased, albeit still prevalent. These potential side effects should be included with other information about buprenorphine that is given to patients as they may influence interest in starting or continuing treatment.

1. Introduction

Buprenorphine / naloxone is a 4:1 combination of buprenorphine, a partial mu receptor agonist, and naloxone, an opioid antagonist. It is commonly used in the treatment of opioid use disorder. It was reported that opioid maintenance treatment in opioid use disorder was effective in reducing mortality, criminal activities and use of other substances, and in improving psychosocial functions (Ball and Ross, 2012). buprenorphine / naloxone maintenance treatment was showed to be associated with good treatment retention and significantly reduced opioid use (Finch et al., 2007). In a study conducted by Bell et al. (2004), It was reported that buprenorphine maintenance treatment was well tolerated, retention in treatment was long at 6 months and most subjects were still in treatment at 18 months of the trial. Also heroin use during treatment was very uncommon. But, it is not without side effects. They are usually mild, however severe side-effects could develop in a few patients. Side-effects of buprenorphine / naloxone include headaches, constipation, insomnia, abdominal pain, nausea, sweating, anxiety, muscle pain and changes in appetite (Can et al., 2012).

Sexual dysfunction was first defined by Masters and Johnson (1966). In sexual dysfunction, partners could not engage in sexual intercourse due to reduced sexual desire, arousal or orgasm (Araujo et al., 2010). Short or long-term sexual dysfunction is observed in individuals who use opioids (Peugh and Belenko, 2001). In males, opioids lead to hypogonadism by affecting the hypothalamic-pituitary-adrenal axis, and cause reduced libido and erectile dysfunction (Ajo et al., 2017). The use of opioids actually induces sexual dysfunction over time by negatively affecting sexual functions (Peugh and Belenko, 2001).

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The long-term use of opioid antagonists or full agonists in opioid use disorder maintenance treatment is known to cause side-effects that could result in abandoning the treatment (Parvaresh et al., 2015; Ramdurg et al., 2015). It was suggested that the side-effects of buprenorphine / naloxone were milder when compared to other agents used in opioid use disorder maintenance treatment such as methadone or naltrexone (Wang et al., 2015; Zheng et al., 2016). In the current study, the findings demonstrated that sexual problems and bodyweight of the patients increased after the buprenorphine /naloxone treatment and sleep-related problems decreased, albeit still prevalent. To the best of our knowledge, there are only a few studies in literature that compared the pre-treatment status of the patients and the side-effects induced by buprenorphine / naloxone treatment (Abs et al., 2000; Ajo et al., 2017; Ramdurg et al., 2015). The present study aimed to draw the attention of clinicians to the adverse effects of buprenorphine / naloxone treatment in opioid use disorder.

2. Method

Approval for the study was granted by the Local Ethics Committee. The study group included 107 patients who applied to Mental Health and Diseases Hospital, Alcohol and Substance Use Disorder Treatment and Research Center Polyclinic. The patients were diagnosed with opioid use disorder based on the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) (Association, 2013). All patients included to the study were consecutively admitted males due to the conditions of the hospital where the study was conducted. The addictive substances used by the study group before treatment included heroin in 28 (26.2%) cases, heroin and cannabis in 15 (14%) cases, and 64 (59.8%) cases abused more than two substances. They were all started on buprenorphine / naloxone in the hospital after detoxification and then followed up with outpatient treatment for 4 months. None of the patients dropped out of the treatment and they were evaluated on the 4th month after admission to the hospital and prescription of buprenorphine / naloxone. Based on the urine samples, which were routinely analyzed once a month before prescription of buprenorphine / naloxone, it was determined that the patients were free of the substances of abuse. Buprenorphine levels in the urine, which are also routinely measured during the admission to prescribe buprenorphine / naloxone, confirmed that the patients were still on buprenorphine / naloxone treatment. The study procedures were in accordance with the ethical standards of the Institutional and National Committee on Human Experimentation and with the Helsinki Declaration of 1975, as revised in 2000 (Riis, 2000). Informed consent was obtained from all patients participated in the study. The first interviews were conducted after the admission procedures and before the detoxification procedures with the participants. The second interviews were held at the end of the 4th month of buprenorphine / naloxone maintenance treatment.

Inclusion criteria required that all participants should be 18–65 years old and diagnosed with opioid use disorder based on DSM-5. Patients with any other DSM-5 disorders, a history or current neurological or physical disease (diabetes, hypertension, epilepsy, neuroendocrine diseases, other metabolic diseases, etc.), used antihypertensive, antidepressant, tranquilizer, anticholinergic or antipsychotic drugs were excluded from the study.

On admission and at the end of the 4th month, a Sociodemographic and Clinical Data Form, Pittsburgh Sleep Quality Index (PSQI) and the Arizona Sexual Experiences Scale (ASEX) were applied to all patients. Patients' bodyweights were recorded on the day of admission to the hospital and at the end of the 4th month.

The Arizona Sexual Experiences Scale (ASEX) (McGahuey et al., 2000) is a self-assessment scale that includes 5 items to assess sexual desire, arousal, vaginal lubrication/penile erection, orgasm and satisfaction with the orgasm. The ASEX is scored between 1–6 (no disorder- complete dysfunction) points in a Likert-type scale for each sexual function. Possible total score ranges between 5 and 30. A total ASEX score of 19 or greater, any one item with an individual score of 5 or 6, three or more items with individual scores of 4 have been found to be highly correlated with diagnosed sexual dysfunction.

The Pittsburgh Sleep Quality Index (PSQI) is used to evaluate the sleep quality of patients. Definition and objective measurement of sleep quality entails a difficult and complex clinical procedure. The PSQI is a 19-item self-assessment scale that evaluates sleep quality and sleep disorders in a time period of one month (Agargun, 1996). It has 7 component scores: subjective sleep quality, sleep latency, duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. There are five additional questions that are completed by a bed partner if there is one. They are not used in the scoring. The cut-off value is 5 and a total PSQI score of ≥ 5 are considered as sleep disorders. The diagnostic sensitivity is of 89.6% and specificity is of 86.5% (Buysse et al., 2008).

2.1. Statistical analysis

The Paired Samples t-test was used in the analysis of the variables. Pearson correlation coefficient was used to examine correlations between the scores. A significance level of $p < 0.05$ was considered as statistically significant.

3. Results

Initially, 120 patients with at least a 1-year history of opioid use and physiologically dependent to opioids were included in the study. A total of 13 patients were excluded; 3 for personal reasons and 10 for not meeting the inclusion criteria. Therefore, analyses were conducted with 107 patients. The mean age of the participants was 24.55 ± 4.27. The sociodemographic data for the study group are presented in Table 1.

The ASEX total scores were 12.98 ± 4.33 before buprenorphine / naloxone maintenance treatment and 15.03 ± 6.61 at 4 months after the treatment ($p < 0.001$). The ASEX sexual function scores and total ASEX scores measured before buprenorphine / naloxone and at 4 months after buprenorphine / naloxone administration are presented in Table 2. The mean patient bodyweight was 63.86 ± 8.78 kg before buprenorphine / naloxone maintenance treatment and 68.49 ± 8.65 kg at the 4th month ($p < 0.001$). Total PSQI scores were 8.87 ± 3.53 before buprenorphine / naloxone maintenance treatment and 6.85 ± 3.29 at the 4th month ($p < 0.001$). The bodyweight measurements, total PSQI scores and PSQI subscale scores are presented in Table 2. Following the detoxification process, the mean buprenorphine / naloxone dose was 3.79 ± 2.76 mg/day (minimum 2 mg/day – maximum 8 mg/day).

Table 1
Patient demographic data.

Buprenorphine/naloxone (n = 107)	
Age [years; mean (range)]	24.6 (18–42)
Highest educational level (n):	
Illiterate	10 (9.3%)
Elementary school	18 (16.8%)
Middle school	55 (51.4%)
High school	14 (13.1%)
University	10 (9.3%)
Occupational status (n):	
Employed	41 (38.3%)
Unemployed	66 (61.7%)
Marital status (n):	
Married	27 (25.2%)
Single	80 (74.8%)
Legal issues:	
Civil	42 (39.3%)
Penal	65 (60.7%)

Table 2
The ASEX (Arizona Sexual Experience Scale) and the PSQI (The Pittsburgh Sleep Quality Index) scores with regards to sexual stages and the mean changes of sleep and weight before BNX and after 4 months of BNX.

Items	Before BNX (Mean ± SD)	After BNX (Mean ± SD)	*t*	*p*
Weight (kg)	63.86 ± 8.78	68.49 ± 8.65	−15.59	<0.001
ASEX (men) component				
Sexual drive	2.50 ± 1.24	3.01 ± 1.56	−4.58	<0.001
Psychological arousal	2.64 ± 1.19	3.11 ± 1.44	−5.06	<0.001
Erection	2.59 ± 1.24	3.03 ± 1.44	−3.79	<0.001
Ease of orgasm	2.66 ± 1.11	2.93 ± 1.39	−2.42	0.017
Orgasm satisfaction	2.59 ± 1.15	2.95 ± 1.59	−2.74	0.007
ASEX total	12.98 ± 4.33	15.03 ± 6.61	−4.90	<0.001
PSQI component				
Subjective sleep quality	1.86 ± 0.85	1.00 ± 0.79	14.32	<0.001
Sleep latency	1.76 ± 0.95	1.21 ± 0.96	6.81	<0.001
Sleep duration	0.91 ± 1.07	0.75 ± 1.09	1.35	0.179
Habitual sleep efficiency	0.77 ± 1.09	0.78 ± 1.06	−0.08	0.941
Sleep disturbance	0.98 ± 0.14	0.89 ± 0.32	3.31	0.001
Sleeping medication use	0.80 ± 1.12	0.80 ± 0.96	0.00	1.000
Daytime dysfunction	1.79 ± 0.91	1.43 ± 0.74	3.87	<0.001
PSQI total	8.87 ± 3.53	6.85 ± 3.29	6.51	<0.001

BNX: Buprenorphine/Naloxone; SD: Standard Deviation

4. Discussion

Buprenorphine/naloxone is a combination drug used in opioid use disorder maintenance treatment. Buprenorphine has a safer side-effect profile when compared to full agonists including headaches, constipation, insomnia, abdominal pain, nausea, sweating, anxiety, muscle pains, changes in appetite, and sexual dysfunction (Can et al., 2012). Sexual dysfunction due to buprenorphine treatment hasn't been well-studied. In a previous study on opioid use disorder patients treated with buprenorphine, it was reported that at least one sexual dysfunction was observed in 83% of the subjects (Ramdurg et al., 2015). In the current study, the same rate was 64.2%. In the current study, ASEX was used to assess the sexual functions. It was determined that the total scores before buprenorphine maintenance treatment and at the end of 4 months after buprenorphine maintenance treatment were above the cut-off value. Consistent with findings in previous studies in the literature, this result affirmed sexual dysfunction in opioid use (Abs et al., 2000; Aggarwal et al., 2016; Ajo et al., 2017; Ramdurg et al., 2015; Wong et al., 2011). In a study by Wong et al. (2011), serum free testosterone values of males who used and did not use opioids were compared and it was reported that the serum free testosterone levels were lower in the patients using opioids. In the current study, a statistically significant difference was determined between the total ASEX scores obtained before buprenorphine maintenance treatment and at the end of 4 months of buprenorphine maintenance treatment. There was an increase in the total ASEX scores after 4 months of buprenorphine maintenance treatment. A statistically significant increase was observed in ASEX subscale scores, namely sexual desire, psychological arousal, erection and ease of orgasm scores, at the end of 4 months when compared to the scores before buprenorphine maintenance treatment. Although an increase was observed in the orgasm satisfaction subscale, the variance was not statistically significant.

Opioid maintenance treatment appears to be related with sexual dysfunctions by reducing serum levels of testosterone among men (Mendelson et al., 1976; Mendelson and Mello, 1975). In males, drugs used in opioid maintenance treatment may act via: (1) affecting hypothalamic and pituitary regulatory hormones (LH, FSH, GnRH), (2) elevation of serum prolactin, (3) suppressing production of testosterone with direct action on the testes. Since opioids of abuse are known to cause sexual dysfunctions themselves, the discussion why buprenorphine might be increasing sexual dysfunctions in opioid use disorder patients is not clear yet. Since, there are only few studies have examined the prevalence of sexual dysfunctions among patients treated with buprenorphine. To clarify sexual adverse effect of buprenorphine, more research is needed (Brown and Zueldorff, 2007).

Studies demonstrated that sexual life is affected by factors such as age and education level; sexual dysfunctions frequency increases with age and decreases as education level decreases (Degauquier et al., 2012). It was reported that probability of the presence of any level of sexual dysfunctions between the ages of 40 and 70 was 26% (Feldman et al., 1994). The mean age and education level of the patients in the current study were not at a value that would significantly change the findings; the mean age of the patients was 24.55 and the majority of patients (57%) were middle school graduates. Since all the patients were smokers before buprenorphine maintenance treatment, this was not considered to be a confounding factor.

Sleep disorder is frequently described by patients on opioid use disorder maintenance treatment. In a study on patients receiving methadone maintenance treatment by Parvaresh et al. (2015), sleep-related complaints were reported at a rate of 67%. The reduction in acetyl choline expression induced by methadone, a mu receptor agonist, could lead to a reduction in sleep quality through suppression of inhibitor GABAergic transmission and reduction of nucleoside adenosine in some regions of the brain (Ajo et al., 2017). The impact of buprenorphine on sleep disturbance is unclear. In the current study, a statistically significant decrease was determined between total PSQI scores and PSQI subscales scores (subjective sleep quality, sleep latency, conditions affecting sleep, and diurnal sleepiness) at the end of 4 months of buprenorphine maintenance treatment when compared to the pre- buprenorphine maintenance treatment scores. Albeit not statistically significant, a reduction was also observed in the duration of sleep, effectiveness of sleep and use of sleeping tablet scores. In the current study, 26 (24%) patients had total PSQI scores above the PSQI cut-off value before buprenorphine maintenance treatment and the total PSQI scores fell below the cut-off value at the end of the 4th month of buprenorphine maintenance treatment. This suggested that buprenorphine maintenance treatment had positive regulatory effects on lifestyle conditions due to the biological effect of buprenorphine-naloxone, or the addiction treatment itself could have led to the improvement in sleep quality. In a study conducted by Zheng et al. (2016), the authors reported improvement in both sleep and depression after starting buprenorphine maintenance treatment. They applied the Medical Outcomes Study (MOS-Sleep) Sleep Scale, 5-item Supplemental Sleep Scale (SSS), and the Beck Depression Inventory II (BDI-II) on the day 0, 30, 60 and 90 of the experiment. The results demonstrated that patients reported significant progressive improvement in Sleep scale subscales and BDI-II scale. In the current study, it was determined that there was a correlation between sleep complaints and the buprenorphine-naloxone

dose. However the mechanism with which buprenorphine improves sleep quality is not clear (Wang et al., 2015).

There are a few studies that investigated the effects of long-term opioid use disorder treatment on weight change. In a study by Karp et al. (2014), low-dose buprenorphine was administered for 8 weeks to patients diagnosed with resistant depressive disorder, and although this led to a reduction in Montgomery–Asberg Depression Scale scores, no weight gain was reported. In the current study, a statistically significant increase in bodyweight was determined at the end of 4 months of buprenorphine maintenance treatment when compared to the pre- buprenorphine maintenance treatment weight of the patients. In clinical observations, an increase was observed in the appetite of the patients on buprenorphine maintenance treatment. In a study conducted with methadone, the study group exhibited a statistically significant increase in bodyweight after 6 months of methadone treatment (Parvaresh et al., 2015). Further studies are required to determine whether the increase in weight observed during opioid use disorder maintenance treatment was a side-effect of the medication or it was due to lifestyle improvements with the acquisition of regular and healthy nutritional habits during the treatment process.

Buprenorphine maintenance treatment is widely used in patients diagnosed with opioid use disorder. It is effective on reducing mortality, the criminal behavior, and the use of other substances by the patients (Martin and Finlayson, 2012). Randomized clinical trials have demonstrated that buprenorphine-naloxone is safe and reduce the use of opioids and the craving for opioids among the persons with opioid use disorder (Fudala et al., 2003; Johnson et al., 1995). It is mentioned by Ling et al. (1998) that for the maintenance treatment of opioid use disorder, buprenorphine will be a useful and welcome addition to methadone, 1 alpha acetylmethadol (LAAM), and naltrexone.

But the side-effects of the medicine could affect the treatment. Although buprenorphine-naloxone has safer side-effect profile and well tolerated when compared to full agonists, it is showed in the current study that it affects the sexual functions adversely. Weight gain may be encouraging at the beginning of the treatment but it should be taken into consideration in long term. Therefore buprenorphine-naloxone seems to lead to the improvement in sleep quality in the current study. It would be beneficial to consider the side effects of buprenorphine maintenance treatment in opioid use disorder to improve the treatment compliance.

The present study has certain limitations. Due to the conditions of the hospital where the study was conducted, only male patients were assessed, and the number of patients was relatively small. The presence of a control group to compare the findings would be beneficial for the study findings.

Declarations of interest

The authors declare that there are no conflict of interests.

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