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Comparison of psychiatric disorders in addicted patients treated with buprenorphine, methadone, and opium tincture in Iran

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Abstract

Background: The aim of this study was to comparing the complications (depression, anxiety, sleep disorders and sexual dysfunction) of buprenorphine, methadone and opium tincture as an alternative drug treatment in patients referred to the National Center for Addiction Studies of Tehran during 2020–2021. This cross-sectional study was conducted on 197 patients referred to the National Center for Addiction Studies of Tehran who were treated with one of the alternative treatments of opioids buprenorphine ($n = 24$), methadone ($n = 116$), and opium tincture ($n = 57$) during 2020–2021. Three questionnaires were used to assess the side effects of drugs including Anxiety and Depression Hospital Scales (HADS), AIS (Athens insomnia scale) and the International Index of Erectile Function (IIEF). Data were analyzed using Stata 14.0. The multinomial logistic regression model was used in order to compare complications in the three groups and adjusted odds ratio (OR) with 95% confidence interval (CI) were estimated.

Results: The mean age in the buprenorphine, methadone and opium tincture groups were 46.80 ± 9.90 , 48.31 ± 13.33 and 55.30 ± 10.34 years, respectively. The numbers of men were 17 (70.80), 90 (77.60), and 50 (78.70); respectively. Multinomial logistic regression model showed $OR = 0.73$ (95% CI 0.61–0.88) for anxiety in the methadone group in compared to buprenorphine. Likewise, $OR = 1.22$ (95% CI 1.001–1.48) and $OR = 1.34$ (95% CI 1.10–1.63) was observed for sleep disorder in the methadone and opium tincture groups in compared to buprenorphine; respectively.

Conclusions: Sleep disturbance in buprenorphine group is less than opium tincture and methadone. Also, anxiety in the methadone group was lower than the buprenorphine, however, there was no significant difference between the three groups in term of sexual function and depression. In addition to control measures for sleep disorders in receiving methadone and buprenorphine, the cohort studies with a higher sample size are recommended.

Keywords: Depression, Anxiety, Sleep disorders, Sexual dysfunction, Buprenorphine, Methadone and opium tincture

Background

Substance abuse is one of the most serious social health problems that Iran has experienced in recent decades. Iran has a long border with the world's largest producer of opium and heroin, Afghanistan, which has intensified drug addiction [1]. Studies show that 2.8% of Iran's population over the age of 15 is addicted, while the global average is about 0.5% [2]. The 2015 report by the Iranian

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Drug Control Headquarters shows that 280,000 of the population aged 15–64 are addicted to drugs [3]. A significant number of road traffic accidents and crimes are related to drug use [4].

To address drug addiction, the government launched harm reduction and treatment programs, such as maintenance therapy in 2002. The most common drug methods for the treatment of drug dependence are detoxification and maintenance therapy with agonist and antagonist drugs and alpha 2 adrenergic agonists, which have increased the frequency of use of agonists due to good efficacy [5]. Methadone and buprenorphine are the most effective alternative drugs for maintenance treatment in drug addicts. These drugs prevent withdrawal symptoms and reduce the urge to use drugs. In addition, they reduce the rate of death and physical illness and social and mental problems caused by drug use [6, 7]. The choice of maintenance treatment (methadone or buprenorphine or other drugs) depends on various factors such as patient preference, therapist's opinion, access to the drug and the cost of treatment; however, it varies in different countries [8]. One of the important factors influencing patients' candidacy for maintenance therapy is the amount of high-risk behaviors of drug-dependent patients. Evidence suggests that both methadone and Buprenorphine are effective in reducing risk behaviors [9].

In Iran, in addition to methadone and buprenorphine, treatment with opium tincture is also used. Opium tincture is based on harm reduction policies to control dependence on opium and juice, which is the most widely used drug in Iran [10]. One of the purposes of prescribing opium tincture is to prevent opioid-dependent patients from taking substances such as heroin and methamphetamine and to use it as a good alternative to opium in addition to methadone and buprenorphine-containing therapies [11]. There are different reports on the effectiveness of each of these treatments. Some studies have found methadone treatment more effective and some maintenance therapy with buprenorphine [12–14]. Each of these maintenance treatments may have side effects. For example, one of the most common side effects of methadone has been reported as sexual dysfunction. Some studies have shown that methadone recipients had lower levels of sexual desire and intercourse satisfaction than buprenorphine recipients [15]. A number of patients treated with methadone and buprenorphine have also reported sleep disorders [16]. Therefore, considering that the profile of side effects and effects of each method are different from each other and in Iran, no comparison has been made between these three types of treatments and it is not clear which treatment has fewer side effects, the aim of this study was to comparing the complications of buprenorphine, methadone and opium tincture as

an alternative drug treatment in patients referred to the National Center for Addiction Studies of Tehran during 2020–2021.

Methods

Study design and subjects

This cross-sectional study designed to comparing the complications of buprenorphine, methadone and opium tincture as an alternative drug treatment in patients referred to the National Center for Addiction Studies of Tehran during 2020–2021. The study population was a patients referred to the National Center for Addiction Studies of Tehran for alternative treatment who were treated with one of the alternative treatments of opioids buprenorphine, methadone, and opium tincture during 2020–2021. Sampling method was convenience and 197 consecutive patients in three groups of buprenorphine ($n = 24$), methadone ($n = 116$), and opium tincture ($n = 57$) were included in the study. Inclusion criteria included drug addiction, age 18 and older, and informed consent. Exclusion criteria also included psychiatric illnesses under a specific medication regimen and lack of informed consent.

Data collection

Data was obtained through interviews with participants. In addition to demographic variables, three questionnaires were used to assess the side effects of drugs. First, Anxiety and Depression Hospital Scales (HADS) which used to assess anxiety and depression disorders in patients. This questionnaire has 14 questions (7 questions related to anxiety and 7 related to depression) that assess the presence and severity of depression and anxiety in patients in the past week. Each question has a score between 0 and 3 therefore, the scores of depression and anxiety subscales range from 0 to 21. For both subscales, normal 0–7 score, 8 to 10 mild, 11 to 15 moderate, and 16 to 21 severe are considered. The questionnaire has already been validated and reliable in Iran [17].

Second, AIS (Athens insomnia scale) questionnaire that applied to check sleep disorder in participants. This questionnaire evaluates three main signs of insomnia including problems in starting sleep, problems in maintaining sleep and waking up early in the last month which includes 8 questions with a score range of 0 to 24 and has been valid and reliable in Iran [18]. Third, the International Index of Erectile Function (IIEF) which was used to measure male sexual function which includes 15 questions and 5 scales: 1—erectile function (6 questions with a score range of 5 to 30), 2—orgasm function (2 questions with a score range of 0 to 10), 3—sexual desire (2 questions with a score range of 4 to 10), 4—intercourse satisfaction (3 questions with a score range of 0 to 15) and

overall satisfaction (2 questions with a score range of 4 to 10). High scores indicate better sexual performance and low scores also implies sexual dysfunction. Similarly, this questionnaire has been standardized in Iran [19].

Statistical analysis

Data were analyzed using Stata software version 14.0 (Stata Corp, College Station, TX, USA). For descriptive analyses, the mean, standard deviation (SD), and number (%) were reported. The Multinomial logistic regression model was used in order to compare complications in the three groups of buprenorphine, methadone, and opium tincture under study and finally adjusted odds ratio (OR) with 95% confidence interval (CI) were estimated and P value < 0.05 was considered as statistical significance.

Ethics considerations

Before data collection, the aims of the research were explained to the patients, then informed consent was obtained from them. In addition, this study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Semnan University of Medical Sciences (Iran).

Results

A total of 197 patients in three groups of buprenorphine ($n = 24$), methadone ($n = 116$), and opium tincture ($n = 57$) were studied. Table 1 shows demographic characteristic of patients under study, as can be seen, the mean age in the buprenorphine, methadone and opium tincture groups were 46.80 ± 9.90 , 48.31 ± 13.33 , and 55.30 ± 10.34 years, respectively. The numbers of men were 17 (70.80), 90 (77.60), and 50 (78.70);, respectively. The mean scores of anxiety in these groups were 7.41 ± 3.11 , 6.12 ± 3.71 , and 7.51 ± 4.92 , respectively. Likewise, the mean scores of depression were 9.12 ± 4.60 , 10.56 ± 3.49 , and 10.68 ± 3.80 ; respectively. For sleep disorders were 3.71 ± 2.79 , 5.53 ± 3.61 , and 5.68 ± 3.96 . Other details of these variables can be seen in Table 1.

The International Index of Erectile Function (IIEF) was also used to measure male sexual function in this study. Table 2 shows the descriptive characteristics of the dimensions of this questionnaire. As can be seen, the highest mean scores for the four dimensions of erectile function, orgasm function, sexual desire, and intercourse satisfaction were related to the group treated with buprenorphine. However, the highest mean scores for overall satisfaction was related to the opium tincture group.

Table 3 shows anxiety and depression Hospital Scales (HADS) according normal, mild, moderate and severe in participants under study. As can be seen, people in

the methadone group had less anxiety disorder (mild to severe) than other groups. But depressive disorder is less common in the buprenorphine group than in other groups.

The multinomial logistic regression model was used in order to compare anxiety, depression, sleep disorders, and sexual function as important complications in the three groups of buprenorphine, methadone, and opium tincture. This model adjusts the effect of potential confounding variables (such as demographic variables) and shows the actual effect of the variable under consideration. Table 4 shows adjusted odds ratio (OR) and 95% CI derived from multinomial logistic regression model, as can be seen, after adjusting for the confounding variables, there was a statistically significant difference between the three groups in terms of anxiety and sleep disorders (P value < 0.05). As is clear, OR = 0.73 (95% CI 0.61–0.88) for anxiety means that the odds of anxiety in the methadone group is 27% lower than the buprenorphine (as a reference group). Likewise, after adjusting for the confounding variables, OR = 1.22 (95% CI 1.001–1.48) and OR = 1.34 (95% CI 1.10–1.63) for sleep disorder means that the odds of sleep disorder in the methadone and opium tincture groups is 1.22 and 1.34 times higher than the buprenorphine (as a reference group), respectively.

Discussion

In many countries around the world, a common treatment for people with opioid use disorder is opioid replacement therapy, known as alternative or maintenance therapy [20]. We designed this study to compare the complications (depression, anxiety, sleep disorders and sexual dysfunction) of buprenorphine, methadone, and opium tincture as an alternative drug treatment in patients referred to the National Center for Addiction Studies of Tehran during 2020–2021. Multinomial logistic regression model showed a statistically significant difference between the three groups in terms of anxiety and sleep disorders (P value < 0.05), so that the odds of anxiety in the methadone group (OR = 0.73; 95% CI 0.61–0.88) was 27% lower than the buprenorphine. Likewise, odds of sleep disorder in the methadone and opium tincture groups were 1.22, (OR = 1.22; 95% CI 1.001–1.48) and 1.34 (OR = 1.34; 95% CI 1.10–1.63) times higher than the buprenorphine group, respectively.

Methadone is one of the opioid analgesics whose most important effects on the central nervous system include analgesia, euphoria, and sedation [21]. Our study showed anxiety in the methadone group is 27% (OR = 0.73; 95% CI 0.61–0.88) lower than the buprenorphine. This finding was consistent with some studies conducted in this field [22–24]. For example,

Table 1 Demographic characteristics of participants under study

Quantitative variables		Groups	Number	Mean	S.D*	Min	Max
Age (year)		Buprenorphine	24	46.80	9.90	22	61
		Methadone	116	48.31	13.33	21	84
		Opium tincture	57	55.30	10.34	31	82
Duration of medication (months)		Buprenorphine	24	9.75	12.72	1	48
		Methadone	116	60.86	64.91	1	266
		Opium tincture	57	18.28	28.65	1	44
Dosage (ml)		Buprenorphine	24	3.33	1.92	1	10
		Methadone	116	18.15	7.54	5	40
		Opium tincture	57	16.95	9.62	3	50
Anxiety score		Buprenorphine	24	7.41	3.11	3	15
		Methadone	116	6.12	3.71	0	18
		Opium tincture	57	7.51	4.92	1	18
Depression score		Buprenorphine	24	9.12	4.60	0	19
		Methadone	116	10.56	3.49	2	20
		Opium tincture	57	10.68	3.80	2	16
Sleep disorder score		Buprenorphine	24	3.71	2.79	0	9
		Methadone	116	5.53	3.61	0	19
		Opium tincture	57	5.68	3.96	1	16
Sexual function score		Buprenorphine	24	44.17	21.24	7	67
		Methadone	116	35.37	20.93	6	72
		Opium tincture	57	36.00	21.85	5	67
Qualitative variables		Groups					
Sex	Female	Buprenorphine		Methadone		Opium tincture	
	Male	7 (29.20)		26 (22.40)		7 (12.30)	
	Total	17 (70.80)		90 (77.60)		50 (78.70)	
Education	Academic	24 (100)		116 (100)		57 (100)	
	Nonacademic	2 (8.30)		23 (19.8)		6 (10.50)	
	Total	22 (91.70)		93 (80.20)		51 (89.50)	
Marital status	Married	24 (100)		116 (100)		57 (100)	
	Single	18 (75)		76 (65.50)		44 (77.20)	
	Total	6 (25)		40 (34.50)		13 (22.80)	
Occupation	Employed	24 (100)		116 (100)		57 (100)	
	Unemployed	16 (66.70)		99 (85.30)		53 (93.00)	
	Total	8 (33.30)		17 (14.70)		4 (7.00)	
	Total	24 (100)		116 (100)		57 (100)	

S.D standard deviation

the study of Dehkordi et al., with the aim of investigating the effect of methadone on depression, anxiety, and quality of life of addicts in Iran, indicates a reduction in situational anxiety after methadone administration [24]. The study by Almasi et al. Also showed that the mean score of anxiety decreased significantly after methadone administration (39.40 vs. 20.41) [23]. However, compared to some other studies, this alignment was not observed. A study in Finland with the aimed to comparing psychological disorders in patients treated with methadone and buprenorphine showed

that anxiety and cognitive complications were lower in buprenorphine receptors than methadone [7]. In France, Fatseas et al. showed that the level of anxiety with buprenorphine did not change significantly compared to other maintenance treatments such as methadone [25]. The reasons for these discrepancies may be due to different study design characteristics such as measurement tools, study methods, sample sizes, and clinical features.

The results of this study showed that odds of sleep disorder in the methadone and opium tincture groups were

Table 2 Dimensions of the International Index of Erectile Function (IIEF) in male under study

Quantitative variables	Groups	Number	Mean	S.D*	Min	Max
Erectile function	Buprenorphine	24	19.41	10.01	2	30
	Methadone	116	14.35	10.11	1	30
	Opium tincture	57	14.20	10.30	1	30
Orgasm function	Buprenorphine	24	6.23	4.04	0	10
	Methadone	116	4.14	3.99	0	10
	Opium tincture	57	3.86	3.92	0	10
Sexual desire	Buprenorphine	24	6.35	1.69	2	8
	Methadone	116	4.91	2.20	1	10
	Opium tincture	57	5.94	1.82	1	10
Intercourse satisfaction	Buprenorphine	24	6.18	3.77	0	10
	Methadone	116	5.19	4.99	0	15
	Opium tincture	57	5.10	5.23	0	14
Overall satisfaction	Buprenorphine	24	6.00	3.24	2	10
	Methadone	116	6.77	2.37	2	10
	Opium tincture	57	6.90	2.60	2	10

*S.D standard deviation

Table 3 Anxiety and Depression Hospital Scales (HADS) in participants under study

Qualitative variables		Groups		
		Buprenorphine	Methadone	Opium tincture
Anxiety	Normal	14 (58.3)	78 (67.2)	32 (56.1)
	Mild	5 (20.8)	27 (23.3)	9 (15.8)
	Moderate	5 (20.8)	8 (6.9)	11 (19.3)
	Severe	0 (0)	3 (2.6)	5 (8.8)
Depression	Normal	7 (29.2)	21 (18.1)	10 (17.5)
	Mild	9 (37.5)	37 (31.9)	14 (24.6)
	Moderate	7 (29.2)	52 (44.8)	26 (45.6)
	Severe	1 (4.2)	6 (5.2)	7 (12.3)

1.22 (OR = 1.22; 95% CI 1.001–1.48) and 1.34 (OR = 1.34; 95% CI 1.10–1.63) times higher than the buprenorphine group; respectively. This finding was consistent with the results of a number of studies. A study in Vietnam showed moderate prevalence of poor sleep quality (26.6%) in methadone users. In addition, the study showed there was a significant relationship between duration of methadone use and poor sleep quality, so that with increasing methadone duration, the likelihood of experiencing low sleep quality increases [26]. In study by Kelly E. Dunn et al. aimed to investigate the frequency and correlates of sleep disturbance in methadone and buprenorphine-maintained patients in the USA indicated that sleep disorders are similar in patients receiving methadone and buprenorphine [27]. In a another study by Rapeli et al. in Finland, the results showed that sleep disorders in buprenorphine receptors were lower

than in patients treated with methadone [7]. Generally, various studies have reported the prevalence of sleep disorders in patients treated with methadone from 70 to 99% [28, 29]. A cohort study in Taiwan reported a 19.1% incidence for sleep disorders two years after follow-up in methadone-treated patients [30]. A number of studies have linked sleep problems in methadone patients to psychological problems, so that increasing psychological problems increases the likelihood of poor sleep quality [31, 32]. This phenomenon may be due to hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis, because when addicted people experience stressful or depressive conditions, this axis becomes active, followed by concealing slow-wave sleep and poor quality sleep [33–35]. Therefore, controlling and managing psychological problems in patients treated with maintenance such as methadone and opium tincture may be helpful.

Table 4 Comparison of complications in the three groups under study by multinomial logistic regression model

Variable	Group	Adjusted OR	95% CI	P value
Age	Buprenorphine	Reference	–	–
	Methadone	1.001	0.94–1.05	0.958
	Opium tincture	1.10	1.04–1.18	0.001
Sex	Buprenorphine	Reference	–	–
	Methadone	1.42	0.53–3.80	0.381
	Opium tincture	2.94	0.90–9.60	0.074
Duration of medication	Buprenorphine	Reference	–	–
	Methadone	1.04	1.004–1.07	0.026
	Opium tincture	1.007	0.97–1.04	0.693
Marital status	Buprenorphine	Reference	–	–
	Methadone	2.06	0.53–8.01	0.298
	Opium tincture	1.87	0.41–8.43	0.415
Education	Buprenorphine	Reference	–	–
	Methadone	0.19	0.03–1.17	0.073
	Opium tincture	0.44	0.06–2.99	0.405
Occupation	Buprenorphine	Reference	–	–
	Methadone	0.45	0.12–1.66	0.229
	Opium tincture	0.14	0.03–0.67	0.014
Anxiety	Buprenorphine	Reference	–	–
	Methadone	0.73	0.61–0.88	0.001
	Opium tincture	0.91	0.77–1.08	0.292
Depression	Buprenorphine	Reference	–	–
	Methadone	1.17	0.98–1.39	0.080
	Opium tincture	1.09	0.90–1.30	0.369
Sleep disorder	Buprenorphine	Reference	–	–
	Methadone	1.22	1.001–1.48	0.048
	Opium tincture	1.34	1.10–1.63	0.004
Sexual function	Buprenorphine	Reference	–	–
	Methadone	0.98	0.95–1.02	0.360
	Opium tincture	1.01	0.98–1.05	0.383

OR odds ratio

95% CI 95% confidence interval

In the present study, there was no statistically significant difference in term of sexual function between the three groups of buprenorphine, methadone, and opium tincture. In the study of Bonhomme et al. in Atlanta, the incidence of erectile dysfunction in people treated with methadone and buprenorphine was not significantly different [36]. Similarly, consistent with our study, a study by Hallinan R et al. showed no significant difference in erectile dysfunction in men receiving methadone and buprenorphine maintenance treatment [37]. However, a number of other studies were not in line with this result [16, 38, 39]. The causes of this discrepancy may be due to measurement tools, study methods, sample sizes, and clinical features. Researchers in this study recommend conducting cohort studies with a higher sample size.

These studies have a number of strengths and weaknesses. Perhaps its most important strength is the simultaneous study of depressive, anxiety, sleep, and sexual disorders in the three groups receiving methadone, buprenorphine and opium tincture maintenance treatment. The study has limitations. This was a cross-sectional study with different and relatively low sample sizes in a number of groups and only once measuring complications, therefore, longitudinal studies with high and equal sample size are recommended in order to carefully investigate the causal relationships of drug and complications. Finally, in this study, it was not possible to collect information about female sexual dysfunction (due to shame and heavy atmosphere in society), which should be considered in interpreting the results.

Conclusions

This study showed that sleep disturbance in buprenorphine group is less than opium tincture and methadone. However, there was no significant difference between the three groups in term of sexual function and depression. In addition to control measures for sleep disorders in receiving methadone and buprenorphine, the cohort studies with a higher sample size are recommended.

Abbreviations

HADS: Anxiety and Depression Hospital Scales; AIS: Athens insomnia scale; IIEF: International Index of Erectile Function; OR: Odds ratio; CI: Confidence interval.

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Authors' contributions

ZB and NS designed the study. NS and MMKH supervised the study. ZB and NS processed the data. MMKH did the statistical analysis. NS and MMKH interpreted the results. ZB and NS wrote the original draft. NS and MMKH review and edit the final draft. All authors have read and approve the final manuscript.

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Availability of data and materials

Access to the data of this study is not restricted.

Declarations

Ethics approval and consent to participate

This study was performed according to the principles expressed in the Declaration of Helsinki and was approved by the Deputy of Research and Ethics Committee of Semnan University of Medical Sciences (Iran).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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