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# SLEEP PROBLEMS AMONG PATIENTS ON METHADONE MAINTENANCE TREATMENT

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**Abstract**

Insomnia is the most prevalent sleep disorder in the general population, and is commonly encountered in medical practices. Subjective sleep complaints occur in 75-84% of methadone-maintained patients, and more than 50% of methadone-maintained patients reported use of medications to improve their sleep cycle. Studies of insomnia support a female predominance.

The Aim of this study was to evaluate insomnia and gender differences in insomnia among methadone-maintained patients in the Department for prevention and treatment of drug abuse and dependence, Psychiatric Hospital Skopje.

This was a cross-sectional study. Two groups of methadone-maintained patients were included: 73 males and 14 females. Participants were evaluated with Bergen Insomnia Scale (BIS), and Insomnia Severity Index.

The evaluation of subjects with BIS showed that 87.3% of subjects reported some sleep problems. There were significant differences between the groups related to item 3 on BIS with higher mean score for females. The total score for the Insomnia Severity Index scale showed that a larger number of females than males had moderate and severe insomnia. More females than males reported use of medications (90.5% used benzodiazepine), to help them with their sleep problems. Last month 36.8% of subjects used some substances and in 75% of cases it was alcohol, cannabis or both.

This study provided evidence that sleep disturbance and use of alcohol, cannabis, and benzodiazepines was highly prevalent among methadone-maintained patients. Female patients reported a significantly worse sleep cycle than males. Use/abuse of benzodiazepines in methadone-maintained patients does not resolve the problem of insomnia.

**Keywords:** opioids, methadone-maintained patients, insomnia

## Introduction

Insomnia is the most prevalent sleep disorder in the general population, and is commonly encountered in medical practices. Various studies worldwide have shown the prevalence of insomnia in the range of 10%-30% of the population; some studies report the prevalence of insomnia to be as high as 50%-60%[1,2]. Persons who use alcohol and other

drugs are at even greater risk of having insomnia. This is due to the negative effects of those substances or their withdrawal on normal sleep patterns. One study found that patients presenting to a medical clinic seeking treatment for sleep complaints were more likely to have problems with drug and/or alcohol use as compared to those without sleep complaints[3].

There are bidirectional relationships between insomnia and circadian rhythm disturbance with substance use disorders in terms that insomnia and circadian rhythm disturbance may increase substance use, dependence and relapses or *vice versa*, substance use results in circadian rhythm disturbance and may induce sleep problems[4].

Specifically relating to opioid drugs, the primary effect of short-term opioid administration on sleep is to hasten falling asleep, but the restfulness of sleep and total sleep time are reduced. The acute effects of opiates initially produce soporific effects, including increased daytime sleepiness and reduced sleep latency, but opiates cause sleep disruptions later in the night such as increased night awakenings due to acute withdrawal effects[4].

Alcohol is regularly used by more than 10% of the population to help them with sleep problems[5]. More than half of patients report that insomnia predated the onset of drinking by more than 10 years[6,7]. On the other hand, persons who use alcohol and other drugs are at high risk of sleep disorders because persistent use of substances can directly disrupt neurobiological systems that regulate sleep and wakefulness, potentially leading to insomnia[8].

Acute opioid use causes more frequent shifts in sleep states, increased arousals from sleep, an increase in non-rapid eye movement (NREM), and reductions in total sleep time, amount of slow wave sleep, and rapid eye movement (REM) sleep[9]. Although opioids are perceived as sedating, chronic opioid use can be disruptive to sleep quality. Long-term opioid use may lead to tolerance of some negative effects on sleep, although more serious insomnia may develop. Of some concern, many patients in methadone maintenance treatment (MMT) appear to have serious sleep disturbances. This can be of great concern, since lack of sleep can upset daytime activities and possibly influence drug relapse. It is believed that methadone may contribute to insomnia by disrupting normal sleep phases during the night; however, the exact reasons for this are unknown.

Subjective sleep complaints occur in 75-84% of methadone-maintained patients [10-12]. In one study, difficulties with prolonged sleep latency and poor sleep efficiency were the most common symptoms, and more than 50% of methadone-maintained patients reported use of medications to help them fall asleep[11]. Subjective sleep complaints in methadone-maintained patients have been corroborated by polysomnographic studies demonstrating poor sleep efficiency, decreased total sleep time, increased nighttime wakefulness, decreased REM and decreased slow wave sleep[11-14].

Sleep disturbances may persist long after discontinuation of opioids. One prospective study found that reductions in total sleep time, REM sleep, and slow wave sleep had not recovered to normal levels up to 12 months following opioid discontinuation[15]. Sleep is not immediately recovered even if drug or alcohol abstinence is achieved and, in fact, more normal sleep may require months or even years to return.

Other studies have identified an increased prevalence of sleep-related breathing disorders and irregular breathing patterns in patients who use opioids both acutely and chronically. These breathing disturbances may further disrupt sleep[11].

The neurobiology of sleep and substance use interconnects, such that alterations in one process have consequences for the other. Locus coeruleus is involved in arousal and also is a primary target of opioids. Locus coeruleus - norepinephrine neuronal activity is positively correlated to the state of arousal, and these neurons are most active during waking and are off during REM sleep. Locus coeruleus neurons are robustly activated during opioid withdrawal and this has implicated the locus coeruleus - norepinephrine system in opioid-withdrawal signs, including the hyperarousal and insomnia associated with withdrawal[16].

Another potential pathway to sleep disruption in MMT patients is opioid-induced reduction of the nucleoside adenosine in the basal forebrain. Reduced adenosine, a neurochemical modulator of the homeostatic drive for sleep, may be responsible for sleep disturbances in MMT patients[17,18]. Patients on methadone also have a high prevalence of depression and anxiety disorders, which independently and negatively affect sleep[19].

Studies of insomnia support a female predominance, with increased divergence of prevalence between men and women of older age[20]. Differences in sleep behavior and sleep disorders may not only be driven by biological factors but also by gender differences in the way how women and men report symptoms[21].

## Material and methods

### *Participants*

All participants in the study met the ICD-10 criteria for opiate addiction and were between 27-49 years of age.

Inclusion criteria: participants undertaking MMT for a minimum of 1 year and stabilized on their current dose for at least three months.

Exclusion criteria: patients/participants currently experiencing psychotic symptoms or being treated for bipolar disorder, schizophrenia, schizoaffective disorder, or schizophreniform disorder and self-reported current pregnancy or breastfeeding.

Two groups of methadone-maintained patients of both genders were included in the study with an intended choice: 73 males and 14 females, 87 in total with a mean age of 34.7 ± 4.7 years, receiving average methadone doses of 88.6 mg/day and an average of 106.2 ± 50.6 months being on treatment.

Female group consisted of 14 participants with a mean age of 36.3 ± 4.9 years, receiving an average methadone doses of 83.3 mg/day and an average of 103.3 ± 55.9 months being on treatment.

Male group consisted of 73 participants with a mean age of 34.3 ± 4.5 years, receiving an average methadone doses of 89.6 mg/day and an average of 106.8 ± 49.9 months being on treatment.

The study was approved by the Human Research Ethics Committee, Ss. Cyril and Methodius University in Skopje, Faculty of Medicine in Skopje (No: 03-3951/9) and a signed informed consent was obtained from all participants.

### *Methods*

Participants were evaluated with Bergen Insomnia Scale (BIS), and Insomnia Severity Index. In order to provide data regarding demographic attributes, duration of treatment, methadone dose, use of benzodiazepines and other substances, route of administration, bedtime, wake time, sleep duration, and self-medication with sleep medications and psychoactive substances, non-standardized self-report questionnaire was used.

The Bergen Insomnia Scale has six items, of which the first three pertain to sleep onset, maintenance, and early morning wakening insomnia, respectively. The last three items refer to not feeling adequately rested, experiencing daytime impairment, and being dissatisfied with current sleep [22]. A cut-off value of 30 min is used to define wake time as insomnia. Participants stated the number of days per week in which they experienced various sleep problems in the last month between 0 and 7 on an 8-point scale. The lowest score that can be taken from the scale is 0 and the highest score is 42.

The Insomnia Severity Index- (ISI) is composed of seven items that evaluate: the severity of sleep-onset (initial), sleep maintenance (middle), early morning awakening (terminal) problems, satisfaction with current sleep pattern, interference with daily functioning, noticeability of impairment attributed to the sleep problem, and level of distress

caused by the sleep problem. Each of these items is rated on a five-point Likert scale (0 = not at all, 4 = extremely) and the time interval is in the last 2 weeks. Total scores range from 0 to 28, with high scores indicating greater insomnia severity (0–7 = No clinically significant insomnia, 8–14 = Subthreshold insomnia, 15–21 = Clinical insomnia - of moderate severity, 22–28 = Clinical insomnia - severe. The ISI is available in three different versions: patient (self-administered), significant others and clinician [23].

Outcomes were analyzed for all participants and for male and female groups.

*Study Design and Outcomes*

The study was conducted in the Department for prevention and treatment of drug abuse and dependence, Psychiatric Hospital Skopje. To accomplish the aim of this study, we undertook a cross-sectional study. The primary aim was to evaluate sleep problems and gender differences in sleep problems among patients in mixed gender methadone-maintenance treatment.

*Statistical analysis*

Descriptive and analytical statistical methods were used for statistical analysis of the results.

The following methods of descriptive statistics (parametric and non-parametric) were used to describe the obtained results: frequency, percentages, arithmetic mean (mean value), and standard deviation. The following analytical statistical methods - statistical tests (parametric and non-parametric) were used to test the null hypothesis and make valid conclusions:

- Student's T-test for 2 large unpaired samples
- Mann-Whitney U test of inversion
- $x^2$ test as a contingency table and as a test of agreement.

The levels of probability of realization of the null hypothesis according to the international standards of biomedical sciences was 0.05 and 0.01. The stars mean the level of significant difference between both groups (**p<0.01, *p<0.05).

**Results**

The mean age of subjects was 34.7±4,7; it was 36.3 years (±4.9) in the female group, and 34.3 (±4.5) years old in the male group, i.e., there was no significant difference in age between the two groups (p= 0.16). The mean duration of treatment of all subjects was 106.3 months; male participants had longer duration of treatment (106.8 months) than female (103.3 months), but the groups statistically did not differ in length of treatment (p= .81). According to the methadone dose, there were no statistically significant differences between the two groups (p = .43). The mean dose in all subjects was 88.6 mg; 83.3 mg and 89.6 mg in female and male groups, respectively. The use of benzodiazepine (BZD) during lifetime, in the last 6 months and in the last month among both groups is illustrated in Table 1.

**Table 1.** Benzodiazepine use during lifetime, in the last 6 months and in the last month in both groups

| BZD use | Lifetime use (%) | | Last 6 months (%) | | Last month (%) | |
|---|---|---|---|---|---|---|
| | Yes | No | Yes | No | Yes | No |
| Total | 96.6 | 3.4 | 60.9 | 39.1 | 52.9 | 47.1 |
| Males | 95.9 | 4.1 | 58.9 | 41.1 | 50.7 | 49.3 |
| Females | 100 | 0 | 71.4 | 28.6 | 64.3 | 35.7 |
| p-value | .97 | | .38 | | .35 | |

Regarding the benzodiazepine use in different periods of life, although a higher percentage of females compared to males used benzodiazepines, the two groups did not differ statistically.

The intravenous benzodiazepine use in both groups is presented in Table 2.

**Table 2.** Route of administration of benzodiazepines in different periods of life in both groups

| Rout | Lifetime use (%) | | | Last 6 months use (%) | | | Last month use (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | i.v. | other | NA | i.v. | other | NA | i.v. | other | NA |
| Total | 74.7 | 21.8 | 3.4 | 16.1 | 44.8 | 39.1 | 4.6 | 48.3 | 47.1 |
| Males | 76.7 | 19.2 | 4.1 | 13.7 | 45.2 | 41.1 | 4.1 | 46.6 | 49.3 |
| Females | 64.3 | 35.7 | 0 | 28.6 | 42.8 | 28.6 | 7.2 | 57.1 | 35.7 |
| p-value | | .35 | | | .35 | | | .61 | |

*NA- not applicable (no BZD use)

In terms of intravenous drug use in different periods of life, the groups also did not differ significantly.

The illicit drug/alcohol/polydrug use during lifetime, in the last 6 months and in the last month among both groups is shown in Table 3.

**Table 3.** Drug/alcohol/ polydrug use during lifetime, in the last 6 months and in the last month in both groups

| Drug/alcohol use | Lifetime use (%) | | Last 6 months use (%) | | Last month use (%) | |
|---|---|---|---|---|---|---|
| | Heroin | Polydrug | Yes | No | Yes | No |
| Total | 16.1 | 83.9 | 44.8 | 55.2 | 36.8 | 63.2 |
| Males | 17.8 | 82.2 | 47.9 | 52.1 | 39.7 | 60.3 |
| Females | 7.1 | 92.9 | 28.6 | 71.4 | 21.4 | 78.6 |
| p-value | .54 | | .29 | | .31 | |

The groups did not differ in the way of drug administration and a larger number of both females (92.8%) and males (90.4%) used drugs intravenously during their lifetime.

Regarding the drugs/substances used, 87.2% of participants used drugs in the last 6 months; 86% of males and 100% of females used drugs, marijuana, alcohol or both. Over the last month 36.8% of participants, 39.7% of males and 21.4% of females used some illegal drugs or alcohol, and 78% (79% of males and 67% of females) used alcohol, cannabis or both. According to drug use, in the last month of treatment there was no statistical difference between the two groups (p=.79).

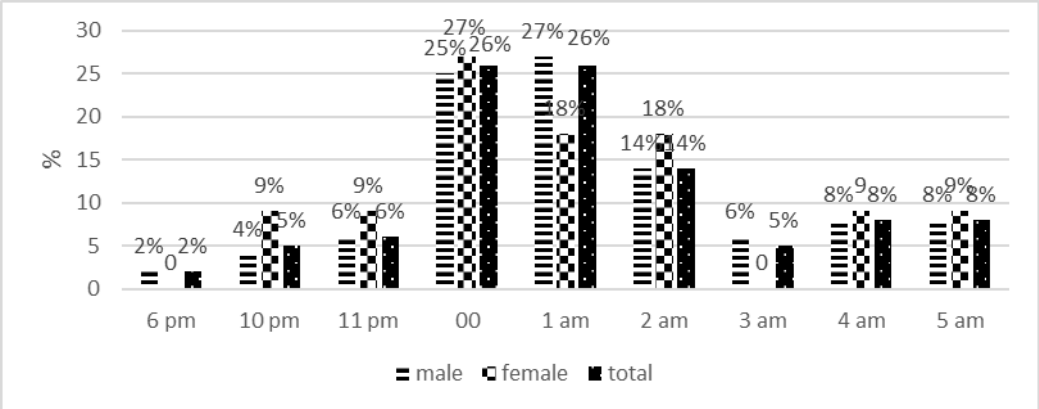


**Fig. 1**. Bed time

Participants answered that they went to bed from 6 pm to 5 am, most of them went between midnight and 2 am (Figure 1 and woke up from 4 am to 2 pm; females woke up from 4 am to 11 am, and males from 4 am to 2 pm (Figure 2).

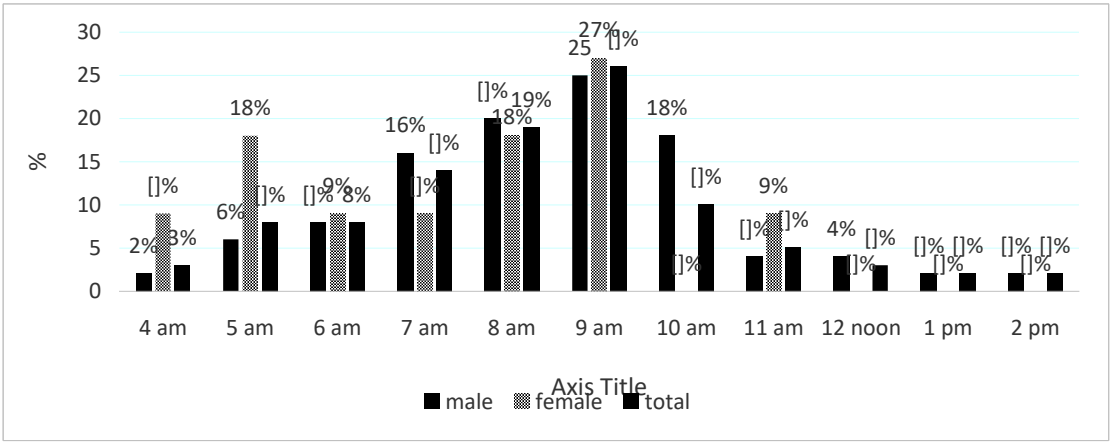


**Fig. 2**. Waking time

The sleep duration lasted 2-9 hours – mean 6.27 ± 2.05 in females and 2-12 hours - mean 7.22 ± 2.23 in males, although females slept one hour less than males on average. However, there was no statistically significant difference related to sleep duration in both groups (p = .2).

The evaluation of subjects with the Bergen Insomnia Scale showed that 87.3% of patients reported some sleep problem, 73.5% reported some sleep problems more than one day per week, and 46% reported some sleep problem every day related to six items about sleep onset, maintenance, early morning wakening insomnia, not feeling adequately rested, experiencing daytime impairment, and being dissatisfied with current sleep. All females had some problem with sleep; 85.7% reported some sleep problems more than one day per week, and half of them reported some sleep problem every day compared to male group where 83.6% reported some sleep problem, 72.6% reported some sleep problems more than one day per week, and 45.2% reported some sleep problem every day. The analysis showed that there were significant differences in the mean scores between the groups for Item 3 related to "wake up earlier and then could not fall asleep again"; females had problem with this 3.4 days a week and males 1.6 days a week (p =.012*). Although all other mean scores, except the first one, were higher in females compared to males; the mean score in females was 2.32 ± 2.72, in males 1.99 ± 2.65 and in all subjects 2.04 ± 2.66, hence groups did not differ significantly (p=.3). The mean value of the total composite score for the Bergen Insomnia

**Table 4.** Means scores, standard deviations and p value for BIS

| During the past month, how many days a week: | Male M±SD | Female M±SD | p |
|---|---|---|---|
| 1.You are not able to fall asleep within 30 minutes, after you switched off the light? | 2.6±2.9 | 2.3±2.9 | .70 |
| 2. Do you stay awake for more than 30 minutes when you woke up at night? | 1.7±2.6 | 2.8±2.8 | .14 |
| 3. Do you wake up at least 30 minutes earlier than you are supposed to wake up and then could not fall asleep again? | 1.6±2.4 | 3.4±2.8 | .012 * |
| 4.You feel like you did not take enough rest after getting up? | 2.7±2.9 | 3.4±2.9 | .38 |
| 5. Do you feel sleepy/tired in a manner that shall affect your school/job or private life? | 1.5±2.2 | 2.3±2.7 | .25 |
| 6. Are you dissatisfied with your sleep? | 1.9±2.7 | 2±2.3 | .85 |

Scale was 12.64 ± 12.49 (16.21 ± 12.56 in females and 11.96 ± 12.45 in males) and these differences were not statistically significant (p=.24).

The mean scores for 6 items at the BIS, standard deviations and p value for both groups are presented in Table 4.

The percentage of participants by gender who endorsed each item response is shown in Table5.

**Table 5.** Percentage of participants by gender who endorsed each item response

| Item ISI | Item response choice[1] | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | | 1 | | 2 | | 3 | | 4 | |
| | m | f | m | f | m | f | m | f | m | f |
| falling asleep | 43.1 | 33.3 | 23.1 | 0 | 16.9 | 41.7 | 7.7 | 8.3 | 9.2 | 16.7 |
| staying asleep | 58.5 | 33.3 | 13.8 | 16.7 | 16.9 | 0 | 4.6 | 41.7 | 6.2 | 8.3 |
| early awakening | 66.2 | 41.7 | 15.4 | 16.7 | 9.2 | 8.3 | 1.5 | 25 | 7.7 | 8.3 |
| satisfaction | 23.1 | 33.3 | 38.5 | 0 | 23.1 | 16.7 | 7.7 | 25 | 7.7 | 25 |
| noticeable | 66.2 | 58.3 | 12.3 | 8.3 | 12.3 | 8.3 | 4.6 | 16.7 | 4.6 | 8.3 |
| worry | 63.1 | 33.3 | 12 | 25.3 | 15.4 | 25 | 3 | 8.3 | 6.2 | 8.3 |
| interference | 53.8 | 33.3 | 12.3 | 8.3 | 16.9 | 25 | 10.8 | 25 | 6.2 | 8.3 |

[1]Items (1–3) 0 - no problem; 1- mild; 2 - moderate; 3 - severe; 4 - very severe
[1]Item (4) 0 - very satisfied; 1 - satisfied; 2 - neutral; 3 - dissatisfied; 4 - very dissatisfied
[1]Items (5–7) 0 - not at all; 1- a little; 2 - somewhat; 3 - much; 4 - very much

The distribution of participants by gender according to the total score on the Insomnia Severity Index scale is showed in Table 6.

**Table 6.** Percentage of participants by gender according to the total score on the ISI

| Total score | Males % | Females % | Total % |
|---|---|---|---|
| 0-7 no clinically significant insomnia | 67.7 | 33.3 | 62.3 |
| 8-14 subthreshold insomnia | 15.4 | 25 | 16.9 |
| 15-21 clinical insomnia (moderate severity) | 12.3 | 33.3 | 15.6 |
| 22-28 clinical insomnia (severe) | 4.6 | 8.3 | 5.2 |

P<.01**

The analyses of the total score of participants on the ISI showed that 62.3% of participants had no clinically significant insomnia, 16.9% had subthreshold insomnia, 15.6% had clinical insomnia (moderate severity) and 5.2% had clinical insomnia (severe). Related to gender, 67.7% of males and 33.3% of females had no clinically significant insomnia, 15.4% of males and 25% of females had subthreshold insomnia, 12.3% of males and 33.3% of females had moderate insomnia and 4.6% of males and 8.3% of females had severe insomnia. The percentage of males who did not have clinically significant insomnia was higher compared to females, who had more subthreshold, moderate and severe insomnia than males. The two groups differed statistically significantly in terms of the severity of their insomnia problems evaluated by the Insomnia Severity Index (p<.01**).

Almost half of the participants in the study (48.3%) reported use of medications to help them with sleep; this percentage was higher in females (57.1%) than in males (46.6%), but this difference was not statistically significant (p= .15).

Ninety percent of those who reported use of medications to help with sleep (91% of males and 87.5% of females) used benzodiazepines.

## Discussion

The results obtained in our study have shown a very high prevalence of sleep disturbances among subjects on opioid agonist treatment, 87% of all subjects; 100% of

females and 83% of males reported some sleep problems related to sleep onset, maintenance, early morning wakening insomnia, not feeling adequately rested, experiencing daytime impairment, and being dissatisfied with current sleep. This is much higher than in the general population (10-30%) and even higher (50-60%)[1,2], but it is in accordance with the literature where subjective sleep complaints occurred in 75-84% of methadone-maintained patients[10-12,19,24]. About half of the subjects, 46% (50% of females and 45.2% of males) reported some sleep problems 7 days a week in the last month, which is again higher than in the general population[19].

Analysis of ISI scores showed that overall 5.2% of subjects had severe insomnia, 15.6% had moderate insomnia and 16.9% had subthreshold insomnia. Sixty-three percent of subjects did not have insomnia, and this percentage is higher than that presented in other studies which included patients with co-morbid mood disorders[25].

Coping with insomnia in methadone-maintenance treatment with medication, alcohol and drugs is usual and patients reported use of medications to improve their sleep[11,12,19,24]. Almost half of the subjects, a larger number of females than males reported use of medications to help them with sleep, and 90% used benzodiazepine. Also, almost all subjects, more fameles than males, used benzodiazepine during lifetime and more than a half used benzodiazepine in the last six months and in the last month of treatment. Over the last month of treatment, more than a third of the subjects, a larger number of males than females, used some illegal drug or alcohol and it was mostly alcohol, cannabis, or both. This is consistent with the literature which reports that drug addiction can lead to insomnia, but also insomnia can contribute to alcohol or illegal drug use and relapse [4,24,26-30]. Benzodiazepines do not resolve the problem of insomnia and lead to long-life abuse of benzodiazepines, dependance and long-life insomnia in vast majority of methadone-maintained patients. Tolerance develops relatively quickly for the sedative, and hypnotic actions of benzodiazepines. Many studies have addressed the physical dependence of benzodiazepines and their abuse potential, and it may pose a problem to reduce the dose after chronic use related to physical dependence [31].

Since opioids including methadone appear to affect sleep, patients on methadone might accept some degree of sleep disturbance as a normal part of the addiction recovery process. However, it is also vital to consider that a return to more normal sleep patterns would require stabilized methadone maintenance and may take a great deal of time[15].

Although the ideal amount of sleep can vary from person to person, healthy adults aged 26-64 sleep 7-9 hours[32]. In our study, females slept 2-7 hours, an average of 6.27 hours, and men 2-12 hours, an average 7.2 hours. Most of the subjects had irregular sleep/wake timing, often with late bedtimes or even reversed schedules. This is in accordance with literature that suggests bidirectional effects; that is, substance abuse results in circadian rhythm disturbance, and circadian rhythm disturbance leads to increased substance use and greater potential for abuse and/or dependence [4].

Related to gender differences, our study found that females had more severe sleep problems than males and higher precentage of them had moderate and severe insomnia than males. These results are in correlation with some other studies [20,21,33], but on the contrary, there are studies reporting that higher scores on Pittsburgh Sleep Quality Index were not correlated with gender, and that insomnia and excessive day sleep did not differ by sex [12,19]. This study has several limitations, including a small sample size, collection of data from self-administered questionnaires, and lack of objective sleep measurements.

## Conclusion

This study provides evidence that sleep disturbance as well as the use of alcohol, cannabis, and benzodiazepines is highly prevalent among patients involved in opioid agonist treatment. Female patients reported a significantly worse sleep cycle than males. Since opioids

including methadone appear to affect sleep, patients on methadone may have to accept some degree of sleep disturbance as a normal part of the addiction recovery process. Use/ abuse of benzodiazepines in methadone-maintained patients is potentialy lethal and does not resolve the problem of insomnia.

*Conflict of interest statement*. None declared.

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