Abstract: Abstinence-based treatment of opioid use disorder has always been faced with the probability of an increase in craving, which potentially results in relapse. Moreover, sleep problems are predominant among patients with abstinence treatment. A sample of twenty-six male subjects with opioid use disorder were selected from a residential treatment center for substance use disorders in 2017 in Mashhad, Iran. Opioid craving was evaluated using obsessive-compulsive drug use scale (OCDUS) at four-time points (days 1, 10, 20, and 30) during abstinence. Also, they were asked to report their total sleep time. The participants with an average age of 32.5 ± 8.0 years reported the use of opium and heroin to be as high as 2.0 ± 1.2 g per day and 1.5 ± 0.9 g per day, respectively. Abstinence induced a non-significant gradual decrease in self-reported craving during one month (p > 0.05). Also, they experienced significant declines in total sleep time over the first ten days (p = 0.008). The univariate analysis of variance showed no significant changes in craving after adjustment for total sleep time (p > 0.05). Insignificant reductions in opioid craving after detoxification persisted throughout the 30 days of abstinence.

1. Introduction
Opioid use disorder (OUD) is a long-term, relapsing condition caused by the problematic pattern of opioid use, and considered a leading public health issue all over the world, and attributed to a marked mortality as well as morbidity (GBD 2016 Causes of Death Collaborators, 2017; United Nations Office on Drugs and Crime, 2019b). The most recent evidence concerning the health consequence of drug use has shown that it causes 42 million years of “healthy” life lost, the considerable part of which arises from opioid use disorder (United Nations Office on Drugs and Crime, 2019b).

Subjects: Behavioral Psychology; Addiction Disorders - Adult; Addictions and Substance Use

Keywords: abstinence; craving; opioid; self-report; sleep

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PUBLIC INTEREST STATEMENT
This study addressed the issue of opioid use disorder during 30-day abstinence and how this treatment affects the patients’ craving and total sleep time. The findings indicated that craving remained constant until day 20, followed by a slow reduction for the next ten days. As for total sleep hour, there was a sharp fall in the first ten days, which further recovered to the initial amount at the end of the treatment period.
Crime, 2019a). Chronic drug use is related to the craving for the drug (Sinha, 2009), which enhances vulnerability to addiction (Sinha, 2008). The very indispensable element of OUD is the formation of long-lasting craving (American Academy of Pain Medicine, the American Pain Society, & the American Society of Addiction Medicine, 2001; Kosten & George, 2002; Schuckit, 2016), for either prescription opioids or illicitly acquired heroin or opiate. It continues following detoxification to enhance relapse (Ahmadi & Razeghian Jahromi, 2017; Gerra et al., 2006; Maremmani et al., 2011; Sadock, Sadock, & Ruiz, 2015). Although the existing literature has not yet clarified a universally agreed definition of drug craving, some studies suggest that it refers to an intrusive, irresistible desire or overwhelming sense of compulsion to use or seek a drug due to a pleasant or rewarding experience superimposed on a negative emotion (Auriacombe, Serre, Denis, & Fatséas, 2019; Dematteis et al., 2017; Koob & Le Moal, 2008). Craving plays an essential role in the motivational models of addiction (Tiffany & Wray, 2012) and is the central part of dependence syndromes. Noteworthy, it has been added to the latest DSM-5 classification system for substance use disorders (Hasin et al., 2013). Interestingly, the recent definition of opioid dependence has been revised by incorporating the concept of craving into the International Classification of Diseases, ICD 11 (World Health Organization, 2018).

Sleep problems may play a key role in the pattern of relapse and affect critical endpoints such as the capacity to finish treatment (Kampman et al., 2001). A relationship between sleep and treatment in case of substance use disorder (SUD) may not be unexpected due to the contribution of sleep physiology to the brain function and effects of several common neurotransmitter systems in the various brain regions on sleep. Moreover, modification of sleep and wakefulness includes many structures, for example, the brain stem, hypothalamus, basal forebrain, etc., and action of various neurotransmitters, such as GABA, glutamate, adenosine, etc. (Brown, Basheer, McKenna, Strecker, & McCarley, 2012). It has been reported that patients receiving prescription opioids for the management of pain experienced more disturbances in sleep and it took longer for them to fall asleep when compared with those participants who had pain but were not prescribed any opioids (Morasco, O’Hearn, Turk, & Dobscha, 2014). A similar pattern was observed in subjects with prescription opioid dependence in which they took longer to fall asleep and complained of less sleep as well as less efficient sleep, even following three days of the abstinence treatment (Hartwell, Pfeifer, McCauley, Moran-Santa Maria, & Back, 2014).

Opioid dependence is associated with sleep disturbances that persist over time, even if the person discontinues drug abuse (Asaad, Ghanem, Samee, & El-Habiby, 2011). Intensely few studies have investigated the impact of abstinence from opioids on sleep quantity (Angarita, Emadi, Hodges, & Morgan, 2016). In a case-control study, Asaad et al. showed a drop in sleep duration for opioid-dependent male patients following three weeks of abstinence (Asaad et al., 2011).

To the best of our knowledge, there have been no research studies to date that evaluate how craving changes as a result of initiating abstinence. Also, empirical information is lacking on whether and when the initiation of abstinence may increase or decrease craving in OUD treatment. With the lack of evidence, some clinicians are more reluctant to initiate abstinence. Therefore, empirical findings on the timing and degree of change not only will culminate in positive expectations about abstinence goals but also enable the clinicians to better guide patients in planning the treatment options they have. This study investigated changes in craving over one month of start of the abstinence treatment.

2. Method

2.1. Participants

This was a cross-sectional, observational study, including a convenient sample of 30 male individuals recruited from those admitting into abstinence-based outpatient OUD treatment at Kowsar medium-term residential SUD (substance use disorder) treatment center, Mashhad, Iran. This research involved male participants to avoid the gender-associated differences in craving as
a result of hormonal changes throughout the menstrual cycle (Nicolas et al., 2019). The DSM-5 was applied to verify OUD in participants with self-report drug use who primarily sought treatment. Within two weeks of admission, they were also evaluated using the Clinical Opiate Withdrawal Scale (COWS), as well as a 10-panel drug test. Thereafter, they entered five-day buprenorphine detoxification. The inclusion criteria were: (a) an age range of 18–64 years, (b) positive urine test for morphine at the beginning of entry to the center, (c) no signs or symptoms of withdrawal at the beginning of the study, (d) no individual or concurrent use of other non-opioid psychedelic drugs at moderate and severe intensities in the previous year (according to DSM-5), (e) avoiding the use of hypnotics, cannabinoids, crystal, amphetamine-like psychostimulants, and alcohol within one week before the study, (f) no history of psychotic disorders, anxiety and mood disorders. The Symptom Checklist-90-Revised (SCL-90-R) was utilized for the presence of psychiatric symptoms. The following factors would exclude patients from the study: (a) after the first negative result for morphine, the screening test for substance use became positive during follow-up; (b) patient developed psychosis symptoms that prevented them from informed and satisfactory participation; (c) patient was willing to receive pharmaceutical aids or abandon the abstinence-based treatment plan in the center; (d) there was a high risk of suicide at initial clinical interview; (e) patient contracted a severe physical disease or used medicines (except for screened drugs) interfering with sleep.

2.2. Instruments

2.2.1. Maudsley addiction profile (MAP)
This questionnaire evaluated the subjects for four aspects: opioids and alcohol use, health risk behaviors, physical and mental health, as well as personal and social functioning (Marsden et al., 1998).

2.2.2. Symptom checklist-90-revised (SCL-90-R)
The SCL-90-R was initially developed by Derogatis and contained 90 items to assess the following subscales: somatization, obsessive-compulsive disorder, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychoticism (Tomiioka, Shimura, Hidaka, & Kubo, 2008). In the study by Ardakani et al. from Iran, it has been confirmed as a good unitary measure for the assessment and screening of mental disorders (Ardakani et al., 2016).

2.2.3. Obsessive-compulsive drug use scale (OCDUS)
The OCDUS, a self-completed questionnaire, is composed of 12 questions that assess an individual’s level of craving for an opioid in the past week (Franken, Hendriks, & van den Brink, 2002). This questionnaire was validated in Persian by Hassani-Abharian et al. (Hassani-Abharian, Mokri, Ganjgahi, Oghabian, & Ekhtiari, 2016). Questions 1, 2, 7, and 8 represent the first factor called “desire and mental preoccupation with drugs”; items 3 and 9 constitute the second factor called “effect of desire for drug, and drug-related thoughts on the patient’s work and life”; and questions 4, 6, 11, and 12 are included in the third factor called “motivation, emotion, and lack of control”; the fourth factor called “resistance to drug use” consists of questions 5 and 10. Participants were requested to show to what extent every question applies to them using 5-point Likert formats. Scores of individual questions were combined to obtain a total score of the subscales.

2.3. Procedure
Primarily, the participants were examined in terms of substance use disorder (history and pattern of use), withdrawal symptoms, comorbid psychological disorders, physical health status, total sleep time, and craving for drug use. Detailed information about demographics, medical history, mental and physical diseases, along with the patent of drug use were gathered using MAP at the beginning of the study. During one month of abstinence on the 1st, 10th, 20th, and 30th days, all the patients were assessed in terms of total sleep time, craving, and urine toxicology test by OCDUS and 10-panel drug test. The toxicology panel included morphine, amphetamine,
methamphetamine, methadone, tetrahydrocannabinol, tramadol, benzodiazepine, buprenorphine, cocaine, and tricyclic antidepressants.

2.4. Ethical consideration
The ethics committee of Tehran University of Medical Sciences approved this study (No IR.TUMS.REC.1394.1060). The written consent was taken from the participants after an explanation of the methods and purpose of the research.

2.4.1. Statistical analysis
Data were collected and then processed using the SPSS software (version 16, USA). The data were described by descriptive statistics (mean, standard deviation (SD), median, interquartile range (IQR), frequency, and percentage). The Wilcoxon signed-rank test was used for comparing the mean scores between days of abstinence (10th, 20th, 30th days) and baseline. Afterward, the difference in the mean scores of OCDUS and total sleep times was evaluated at these four-time points applying the Friedman test. Furthermore, ANCOVA was used to adjust the possible influence of total sleep time on the OCDUS findings. A p-value of less than 0.05 was considered statistically significant.

3. Results
This study included a convenient sample of 30 male participants who were recruited from the Kowsar medium-term residential SUD treatment center in Mashhad. Using the SCL-90-R, four patients were identified with depression or anxiety and subsequently removed from the study. Accordingly, 26 participants with OUD were confirmed with an average age of 32.5 ± 8.0 years and a mean treatment duration of 1.6 ± 0.9 years. The mean age of first use was 25.08 ± 7.34 (Minimum: 15; Maximum: 43) years old. The demographic characteristics of the study subjects are presented in Table 1.

| Characteristics                  | Total N = 60 |
|----------------------------------|--------------|
| Age, year, Mean ± SD*            | 32.5 ± 8.0   |
| Treatment** duration, year, Mean ± SD| 1.6 ± 0.9    |
| Monthly salary, rial, Mean ± SD  | 5,000,000 ± 2,828,428 |
| Married, n (%)***                | 9 (34.6)     |
| Education, n (%)                 |              |
| Illiterate                       | 2 (7.7)      |
| Primary school                   | 5 (19.2)     |
| High school                      | 19 (73.1)    |
| Employment, n (%)                |              |
| Unemployed                       | 2 (7.7)      |
| Self-employed                    | 24 (92.3)    |
| History of incarceration, n (%)  | 7 (26.9)     |
| Family history of drug use, n (%)| 13 (50.0)    |
| Type of opioid used, n (%)       |              |
| Opium                            | 25 (96.2)    |
| Heroin                           | 1 (3.8)      |
| Health insurance, n (%)          | 20 (76.9)    |

*SD: standard deviation; ** Opioid agonist maintenance treatment. ***Frequency (percentage).
The participants in this study were all male (100%), 65.4% single, and 73.1% with secondary education. The majority of the subjects were self-employed, with an average monthly salary of 5,000,000 ± 2,828,428 rials. The pattern of opioid use was opium with a mean use of 2.0 ± 1.2 g per day and heroin with a mean use of 1.5 ± 0.9 g per day.

As can be seen in Figure 1, the mean scores of the first factor decreased in response to abstinence however these changes did not reach a significant level on days 10 (mean ± SD: 1.7 ± 0.4; median (IQR): 2.0 (1.0); p = 0.157), 20 (mean ± SD: 1.8 ± 0.4; median (IQR): 2.0 (1.0); p = 0.317), and 30 (mean ± SD: 1.5 ± 0.5; median (IQR): 2.0 (2.0); p = 0.058) when compared with the baseline (mean ± SD: 2.1 ± 0.3; median (IQR): 2.0 (1.0)). Similarly, there was an insignificant decline in the mean scores of the second factor upon the initiation of abstinence on days 20 (mean ± SD: 2.0 ± 0.1; median (IQR): 2.0 (1.5); p = 0.102) and 30 (mean ± SD: 1.7 ± 0.0; median (IQR): 2.5 (3.0); p = 0.070) when compared with the baseline (mean ± SD: 2.3 ± 0.0; median (IQR): 2.0 (1.0)). It remained unchanged on day 10 (mean ± SD: 2.3 ± 0.1; median (IQR): 2.0 (2.0)).

On the other hand, in Figure 1, abstinence was associated with an insignificant increase in the mean scores of the third factor on days 10 (mean ± SD: 3.0 ± 0.4; median (IQR): 3.0 (0.0); p = 0.564) and 20 (mean ± SD: 3.0 ± 0.1; median (IQR): 3.0 (0.0); p = 0.317) when compared with the baseline (mean ± SD: 2.9 ± 0.3; median (IQR): 3.0 (0.0)). It showed no change on day 30 (mean ± SD: 2.9 ± 0.3; median (IQR): 3.0 (0.0)). Likewise, abstinence led to a rise in the mean scores of the fourth factor however these were not statistically significant on days 10 (mean ± SD: 3.8 ± 0.3; median (IQR): 3.0 (0.0); p = 0.655), 20 (mean ± SD: 3.9 ± 0.5; median (IQR): 4.0 (0.0); p = 0.180), and 30 (mean ± SD: 4.0 ± 0.3; median (IQR): 4.0 (1.0); p = 0.102) when compared with the baseline (mean ± SD: 3.7 ± 0.5; median (IQR): 4.0 (1.0)).

As for Figure 2, the total score of craving was in decline over 30 days of abstinence, though statistically insignificant (p > 0.05). The results of Spearman’s rank correlation test revealed no marked relationship between total craving score and duration of drug use (p > 0.05). Through the abstinence period, the participants experienced considerably fewer sleep hours in the first ten days (p = 0.008). The same decrease occurred till the end of abstinence however it was insignificant (p > 0.05). The Spearman’s rho between total sleep time and duration of opioid use was statistically significant at the baseline (rho = 0.605, p = 0.037).

The findings of the Friedman test indicated that the opioid abstainer at baseline had a higher total score of craving as opposed to the other three points ($\chi^2 = 4.156, p = 0.245$). Also, there was no significant difference among the mean scores of the first ($\chi^2 = 4.875, p = 0.181$), second...
In opioid agonist maintenance treatment, reductions in craving are expected once the patient becomes stable, which relies on the pharmacologic properties of opioids and treatment duration. For example, Ling et al. showed changes in craving using Visual Analog Craving Scale at baseline, after a 2-week buprenorphine induction/stabilization phase, and after the 16-week behavioral treatment phase. They found gradual reductions of craving in opioid-dependent participants over time (Ling, Hillhouse, Ang, Jenkins, & Fahey, 2013). More promising findings were observed by Willner-Reid et al. on patients undergoing methadone maintenance therapy, and combined cognitive-behavioral therapy and contingency management. Notably, linear reductions occurred in heroin craving throughout 12 weeks however, there was a limitation concerning the lack of a control arm. In this study, heroin craving “right now” was rated on a four-point scale (NO!!, no??, yes??, YES!!) (Willner-Reid et al., 2016).

When it comes to abstinence-based treatments, gradual or sharp decreases have been obtained, mainly due to different research designs. Applying three different instruments to measure craving (i.e., Visual Analogue Scale Craving, OCDUS, and Desires for Drug Questionnaire), Dijkstra et al. observed that

\[ \chi^2 = 4.814, p = 0.186 \), third \( \chi^2 = 1.200, p = 0.753 \), and fourth \( \chi^2 = 4.224, p = 0.238 \) factors at the four-time points. After adjustment for total sleep time, no difference was still found in the mean score of OCDUS \( p = 0.505 \). In the adjusted model, the difference in craving was 0.40 on day 10, 0.37 on day 20, and 0.88 on day 30 versus the baseline craving on day 1 (Table 2).

4. Discussion

Opioid-specific evidence is lacking for the link between clinical changes in craving and an abstinence-based treatment approach. The present study was intended to assess the timing and magnitude of change in self-reported craving in response to abstinence from opioids. The participants experienced reductions in the total score and first factor (i.e., desire and mental preoccupation with drugs) since the 10\textsuperscript{th} day of abstinence, and decreases in the second factor (i.e., effect of desire for drug and drug-related thoughts on the patient's work and life) since the 20\textsuperscript{th} day of abstinence. Moreover, the third factor (i.e., motivation, emotion, and lack of control) gradually increased up to the 20\textsuperscript{th} day of abstinence, while the fourth factor (i.e., resistance to drug use) was on the rise over one month of abstinence. Despite the ups and downs of self-reported craving, the progression of abstinence carried no marked effect on the patient experience of craving. On the contrary, the opioid abstainer reported notably fewer sleep hours within ten days of abstinence. The adjusted model showed that sleep carried no effect on the addicts' craving score.

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Table 2. Craving scores and adjusted differences among the opioid abstainers

| Day of abstinence | 1    | 10   | 20   | 30   | Comparison between days 10 and 1 | Comparison between days 20 and 1 | Comparison between days 30 and 1 | Total score of OCDUS | p-value |
|------------------|------|------|------|------|----------------------------------|----------------------------------|----------------------------------|----------------------|---------|
|                  | 11.0 ± 0.4 | 10.8 ± 0.6 | 10.7 ± 0.4 | 10.2 ± 0.7 | 0.40 (.124 to 2.08) | 0.37 (.22 to 1.96) | 0.88 (.07 to 2.46) | 11.0 ± 0.4 | .245   |

a Friedman test; b univariate analysis of variance adjusting for total sleep time.
craving reduced insignificantly in opioid-dependent patients during detoxification (Dijkstra, De Jong, Krabbe, & van der Staak, 2008). This study corroborated our findings by the use of OCDUS. On the contrary, Shi et al. indicated that self-reported heroin craving by the Assessment of Psychological Craving Rating Scale decreased considerably in heroin addicts during the first month of abstinence (Shi et al., 2009). Such a difference may arise from the instrument used and small sample size. There has been some evidence in a various setting including opioid pain-killer prescriptions. Garland et al. have demonstrated that mindfulness on patients under opioid treatment for chronic pain significantly lowered opioid craving at post-treatment in comparison to baseline. Despite reductions, opioid craving at a 3-month follow-up was comparable to baseline (Garland et al., 2014). These inconsistent results can be justified considering participants who were chronic pain patients, use of visual analogue scale for the measurement of desire for opioids, sample size, and distinct measurement points (baseline, 8th week after treatment, and 3-month follow-up).

Another prominent factor is the presence of drug cues. Indeed, continuous changes in reward and memory brain circuitry, which are related to drug dependence, resulting in sensitivity to drug-linked during abstinence (Koob & Mason, 2016; Volkow, Fowler, & Wang, 2004). Furthermore, impairment in the regulation of the hypothalamic-pituitary-adrenal axis caused by opioid dependence is correlated to enhanced sensitivity to stressors during abstinence (G. Koob & Kreek, 2007). Such abstinence-related influences on reward and stress response systems may explain the subjective experiences reported by study participants during protracted abstinence, and the constant desire for drugs even in case patients are in residence and living far from social, drug use-related, environmental stimuli of craving (Ferguson & Shiffman, 2009; Kober & Mell, 2015). In contrast with the general situation of tonic desire for drug, it is more likely that episodic craving takes place, suggesting that a lack of consistency exists in craving during abstinence following external or internal cues (Ferguson & Shiffman, 2009). As realized, drug cues generate an incentive motivation for drugs (Robinson & Berridge, 2008), even after one month of abstinence (Childress, McLellan, & O'Brien, 1986). Not to mention that the participants of the present study were selected from a residential center for opioid users with no access to illegal and non-prescription drugs. Thus, the total scores of OCDUS for them were less than previous reports.

This study for the first time indicated the lowering effect of abstinence on total sleep time among opioid addicts. Previously, reductions in total sleep time were found in patients withdrawing from non-prescription opioids (Hartwell et al., 2014). Mehtry et al. in a case-control study documented that opioid-dependent patients experienced decreases in total sleep time after one week of abstinence (Mehtry, Nizamie, Parvez, & Pradhan, 2014). In could be concluded that abstinence might not worsen opioid craving but did reduce total sleep time. Moreover, the improvement of craving is more likely to depend on sample size, type of participants recruited and tools used and, not surprisingly, the presence of cues related to opioids. Total sleep time carried no effect on craving for opioid during abstinence. This study had some limitations; its sample size was approximately small that may potentially affect changes in craving during treatment. The use of a self-report instrument to rate their cravings could be a potential source of bias since such measurements were impacted by their success in not using opioids and also altered by moods during the study period; accordingly, real-time assessment of craving is proposed for future investigations. As for the strengths of the present study, daily craving was assessed during 30 days of abstinence, giving many data points appropriate for analyses that addressed within-person differences over time.

Funding
The authors hereby express their gratitude toward the authorities of the Office of Vice-Chancellor for Global Strategies and International Affairs, Tehran University of Medical Sciences for their financial supports (fund number: 94-03-103-30184).

Competing Interests
The authors report no conflicts of interest and have no proprietary interest in any of the materials mentioned in this article.
Citation information
Cite this article as: Effects of abstinence from opioids on self-reported craving and sleep, Hamidreza Fathi, Ali Yoonessi, Amir Rezaei Ardani, Reza Mojzaee & Fanborz Rezaeitalab, Cogent Psychology (2020), 7: 1713440.

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