HHS Public Access

Author manuscript

Drug Alcohol Depend. Author manuscript; available in PMC 2022 August 04.

Published in final edited form as:

Drug Alcohol Depend. 2020 February 01; 207: 107698. doi:10.1016/j.drugalcdep.2019.107698.

Multimodal Assessment of Sleep in Men and Women During Treatment for Opioid Use Disorder

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Abstract

Background.—Sleep disturbance is common in patients with opioid use disorder (OUD) receiving medication for addiction treatment. Differences between patients on the two primary agonist medications—methadone and buprenorphine—are not well understood.

Methods.—In patients receiving either methadone or buprenorphine treatment for OUD, we examined sleep continuity and architecture using ambulatory monitoring to gather both an objective measure (daily sleep EEG; M = 5.76 days, SD = 1.46) and a subjective measure (daily sleep diary; M = 54.10 days, SD = 25.10) of sleep.

Results.—Patients treated with buprenorphine versus methadone did not differ on any measure of sleep continuity or architecture. Women had longer EEG-derived total sleep time than men (d = −0.68, 95% CI −1.32 to −0.09), along with lower %N2 (d = 0.94, 95% CI 0.34 to 1.64) and greater %N3 (d = −0.94, 95% CI −1.61 to −0.32). Self-reported sleep differed from EEG-derived estimates: wake after sleep onset was greater by EEG than by diary (d = 2.58, 95% CI 1.74 to 3.63), and total sleep time and sleep efficiency were lower by EEG than by diary (d for sleep time = 2.93, 95% CI 2.06 to 4.14; d for efficiency = 1.69, 95% CI 0.98 to 2.49).

Conclusions.—Patients treated with buprenorphine or methadone did not substantively differ in ambulatory measures of sleep. With both medications, there was a discrepancy between objective and subjective sleep measures. Further confirmatory evidence would inform the development of sleep-related recommendations for OUD patients undergoing agonist treatment.

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Contributors

KLP, DHE, and PHF designed the study. KLP, DHE, WJK, KAP, and DA collected the data. PHF, CJM, DHE, and MTS ran and/or reviewed the analyses. PHF led the manuscript writing. All other authors contributed to manuscript writing and/or editing. All authors reviewed and approved the final manuscript.

Conflict of Interest

No conflict declared.

Keywords

Sleep; ecological momentary assessment; opioid use disorder; buprenorphine; methadone; sex differences

1. Introduction

Sleep disturbance is a frequently reported symptom among patients with opioid use disorder (OUD) on medication for addiction treatment. Two opioid agonist medications are currently approved in the United States: methadone, a full μ agonist, and buprenorphine, a partial μ agonist commonly co-formulated with the μ antagonist naloxone to discourage misuse. Between 70–85% of patients treated with methadone report poor sleep quality (Hartwell et al., 2014; Hsu et al., 2012; Peles et al., 2006; Stein et al., 2004). The perception of poor sleep quality persists through long-term treatment with methadone (Nordmann et al., 2016), suggesting that sleep disturbance is not simply attributable to medication adjustments common in early treatment. Stark abnormalities in sleep architecture—including deficiencies in rapid-eye movement (REM) sleep and slow-wave sleep—have been observed in patients on methadone compared to healthy controls (Teichtahl et al., 2001; Wang et al., 2005). Less is known about sleep among patients treated with buprenorphine. One small prospective study reported that sleep improved over the first 90 days on buprenorphine/naloxone (Zheng et al., 2016). Given that acute administration of μ agonists can directly impair sleep by altering sleep-wake regulation and sleep architecture (Dimsdale et al., 2007; Kay et al., 1981; Pickworth et al., 1981), it is possible that differences in receptor binding between methadone and buprenorphine could yield different sleep effect profiles. To our knowledge, only one study has compared sleep disturbance as a function of methadone versus buprenorphine treatment for OUD (Dunn et al., 2018), finding no substantial differences between groups on the Medical Outcomes Survey Sleep Disturbance Scale (Hays et al., 2005). In the present study, we compared OUD patients undergoing either methadone or buprenorphine/naloxone treatment on objective and subjective ambulatory measures of sleep for two reasons. First, repeated ambulatory measures may provide a more complete picture of sleep than single occasion measures. Second, the collection of both objective and subjective data affords an opportunity to evaluate differences across modalities, which can inform clinical assessment standards. Prior work has documented differences in objective and subjective sleep estimates in individuals with insomnia (Carskadon et al., 1976; Hauri and Wisbey, 1992) and in large community samples (Silva et al., 2007). Relevant to our study population, many of whom used cocaine in addition to opioids, differences in objective and subjective sleep estimates have been shown in individuals who have recently discontinued heavy cocaine use (Hodges et al., 2017; Morgan et al., 2006). Whereas individuals with insomnia have been shown to underestimate total sleep time and overestimate the frequency and duration of nocturnal awakenings (Carskadon et al., 1976; Hauri and Wisbey, 1992) relative to PSG, recently abstinent heavy cocaine users show the opposite pattern of subjective-objective discrepancies in sleep (Hodges et al., 2017; Morgan et al., 2006).

Objective sleep parameters are known to predict risk for relapse in patients with alcohol use disorder (Brower et al., 1998; Clark et al., 1998; Gann et al., 2001), but less is known about the association of sleep disturbance and illicit opioid relapse during treatment with agonist medications. A series of findings from experimental sleep deprivation studies, however, show that acute sleep disruption reliably attenuates positive emotional functioning (Finan et al., 2017) and behavioral responses to monetary rewards (Finan et al., 2019), and alters the functional connectivity of the nucleus accumbens in response to pain and rewarding music (Seminowicz et al., 2019). These studies offer compelling preliminary evidence that acute sleep disruption creates vulnerabilities in the brain reward system that may influence illicit opioid use behaviors.

We conducted an ambulatory monitoring study in patients with OUD treated with either methadone or buprenorphine/naloxone, using both a daily sleep diary (for up to 17 weeks) and home sleep electroencephalography (EEG; for up to 1 week) while patients were actively engaged in treatment. For brevity, we will refer to the buprenorphine/naloxone combination as buprenorphine. Our primary goal was to investigate differences in sleep continuity and architecture across medications and evaluate the extent to which those measures were associated with illicit opioid use (both self-reported and objectively verified). Based upon previous literature, we hypothesized that sleep disturbance would be greater with methadone than with buprenorphine, and that illicit opioid use would be associated with greater sleep disturbance across participants. We also examined whether measures of sleep continuity would differ between assessment types (sleep diary versus sleep EEG). Given Morgan and colleagues' prior work with people who use cocaine chronically (Hodges et al., 2017; Morgan et al., 2006), we expected that EEG-derived measures of sleep continuity would be worse than self-reported sleep continuity, providing a novel test of the "occult insomnia" hypothesis in patients on opioid agonist medications for OUD.

2. Methods

2.1. Overview

This was a sub-study of a parent study conducted at the National Institute of Drug Abuse's Intramural Research Program (NIDA IRP) in Baltimore, MD. Participants were either (1) seeking addiction treatment and subsequently enrolled in an office-based outpatient treatment (OBOT) program at the NIDA IRP outpatient treatment research clinic, or (2) were already receiving treatment elsewhere (TE) in the community. Participation in both arms involved treatment with methadone or buprenorphine and the completion of the assessments described herein. The source of the treatment differed in the OBOT and TE cohorts, but the study methods and data collection were otherwise similar. The analyses reported here were not focused on differences between the OBOT and TE cohorts, nor on the overall efficacy of methadone and buprenorphine. Rather, we focus on ambulatory measures of sleep obtained through the course of treatment in both cohorts, the extent to which they varied between participants receiving methadone and buprenorphine, and their degree of association with opioid use over the course of treatment. The study was approved by the local IRB, and all participants signed informed consent prior to enrollment. Greater details on the study procedures are presented in the Supplementary Materials.

2.2. Participants

Participants were 55 adults with OUD. Participants were recruited via fliers at local outpatient treatment facilities and newspaper advertisements.

Because the main aims of the parent study involved assessing environmental influences on behavior (not discussed here), participants had to have a home address in Baltimore City, or report working or spending most of their waking hours in Baltimore City while having a home address in an adjacent county. Participants in the OBOT cohort also had to meet the following criteria: (1) age between 18 and 75; (2) physically dependent on opioids (by positive urine and/or frank opioid withdrawal). Participants in the Treatment Elsewhere (TE) cohort had to be documented to be receiving methadone or buprenorphine treatment for opioid addiction at a community substance abuse treatment program. TE participants gave consent for NIDA research staff to confirm community treatment participation.

Candidates for the OBOT cohort were excluded if they presented with: (1) A history of any DSM-5 psychotic disorder or bipolar disorder, or current untreated Major Depressive Disorder; (2) Current dependence on alcohol or sedative-hypnotic, e.g. benzodiazepine (by DSM-5 criteria); (3) Cognitive impairment severe enough to preclude informed consent or valid self-report; (4) Any condition that would interfere with urine collection; (5) medical illness (e.g., cirrhosis, nephrotic syndrome, etc.) or medications (e.g., glucocorticoids, adrenal extract supplements, etc.) that, in the view of the investigators, would complicate medical management or compromise participation in research. Candidates for the TE cohort, who were receiving medical management elsewhere, were subject only to exclusion criteria 1, 3, and 4, as criteria 2 and 5 were designed for the safe administration of opioid agonist therapy within the NIDA clinic.

2.3. Procedures

2.3.1. Sleep Monitoring Procedures

2.3.1.1. EMA: A study smartphone was issued to each participant for use throughout the study, up to 16 weeks for the OBOT cohort and up to 8 weeks for the TE cohort. The EMA items assessed a broader range of topics (mood, stress, drug use and craving, pain, and pleasurable events) than we address in the current analyses. We focus here on sleep-related items and on self-reports of illicit opioid use. The questions (Table 1) asked participants to report on the previous night's sleep, following a standard sleep diary (Carney et al., 2012).

On average, participants completed 54.1 days of diaries (SD=25.1). Participants in the OBOT group completed 88.5 days (SD=17.1) on average, and those in the TE group completed 41.2 days (SD=11.8).

2.3.1.2. Home Sleep EEG: Participants were trained to use a home sleep EEG monitor, the Sleep Profiler (Advanced Brain Monitoring, Inc.). The Sleep Profiler provides 3 channels of frontal EEG, in addition to a sensor for head movement, quantitative estimates of snoring, and estimates of nocturnal pulse rate. This device has been validated as an acceptable alternative to full polysomnography (Finan et al., 2016; Levendowski et al., 2017). It is designed for home use and can be easily applied and operated without the

assistance of a polysomnography technician. Participants were asked to wear the device for 7 consecutive nights, and compliance was good (75%; 294/392 possible nights). Participants were incentivized with $10 per night they successfully collected sleep data and given a $30 bonus if they collected data on all seven.

The Sleep Profiler includes autoscoring software that decomposes the EEG signal into power spectral bands and identifies sleep stages in 30-second epochs. This autoscore procedure, which we used in this study, has been shown to have strong agreement with a trained human scoring concurrently acquired polysomnography (Levendowski et al., 2017).

Groups did not differ in duration of sleep profiler use [$t(49) = .41$, $p = .69$]. To verify whether there was a "first night effect" with the EEG, paired t-tests compared sleep continuity and architecture parameters between the first night and other nights. There were no significant differences, suggesting there was not a first night effect. More detailed results are summarized in Supplementary Material (Supplementary Table 1).

2.3.2. Measures

2.3.2.1. Sleep Continuity: Sleep continuity was measured via the sleep diary and home sleep EEG. The sleep diary included items assessing the previous night's bedtime, wake time, and time out of bed (each using 12-hour clock AM/PM convention); minutes of sleep onset latency (SOL); and minutes of wake after sleep onset (WASO). From those items, we used standard formulas (Carney et al., 2012) to calculate subjective estimates of total sleep time (TST), in minutes, and sleep efficiency (SE), in percent of time in bed. Each row of data was inspected for systematic errors that would lead to illogical/implausible calculated indexes (e.g., sleep efficiency > 100%; SOL or WASO > time in bed; wake time earlier than bed time). Implausible indexes that could not be remedied by a simple fix (e.g., changing an incorrectly entered "AM" or "PM") were treated as missing data.

The Sleep Profiler automatically calculates objective estimates of SOL, TST, WASO, and SE via the EEG signal.

2.3.2.2. Sleep Quality: A single sleep diary item assessed sleep quality on a 0–10 scale, with 0 = "Extremely poor (shallow, unrefreshing)" and 10 = "Excellent (deep, refreshing"): "Please rate your overall sleep quality last night.

2.3.2.3. Sleep Architecture: Sleep architecture could only be assessed through objective readings from the Sleep Profiler. These included the percent of TST spent in each of the 4 sleep stages: N1, N2, N3 (slow wave sleep), and REM.

2.3.2.4. Illicit Opioid Use: Illicit opioid use was assessed both through EMA and through twice-weekly or thrice-weekly urine screens during clinic visits. As described earlier, in the EMA data, illicit opioid use was measured multiple times per day using random and fixed prompts, as well as event-contingent reports. If a participant endorsed any one of these illicit opioid use items in a day, we coded that the participant used an illicit opioid on that day. We then calculated the percent of total completed EMA days on which illicit opioid use was reported. For urine screen data, we expressed illicit opioid use as the percent

of positive urines across assessment occasions. On average, participants provided 30 days (SD = 12.3) of urine samples. Among these urine samples, 3.3% of them were invalid. On both measures, the outcome of interest was use/detection of any opioid other than the one prescribed for OUD. The bi-variate correlation between the two illicit opioid use measures was .77 indicating strong correlation.

2.4. Data Analytic Strategy

Data were pooled across the OBOT and TE cohorts. Sleep continuity and architecture measures were aggregated across measurement occasions to create a single value for each measure. Primary analyses were analyses of covariance (ANCOVAs); the main categorical predictor of interest was Medication Group (methadone, buprenorphine), and each model controlled for sex and for a baseline summary measure of pain severity. Pain severity was controlled for because 20 participants reported chronic pain at screening, which is consistent with normative data suggesting that between 37–62% of patients with OUD on medication-assisted treatments have chronic pain (Dunn et al., 2015; Jamison et al., 2000; Rosenblum et al., 2003). Sex was controlled for because there are known sex differences in both sleep disturbance (Zhang and Wing, 2006) and substance-use behaviors (Becker et al., 2017). When the dependent variable was sleep architecture (%N1, %N2, etc.), we additionally controlled for TST in order to account for variable TST across the different sleep-stage percentages.

In additional models examining whether sleep measures were associated with illicit opioid use, the main predictor of interest was a continuous variable for either self-reported opioid use or urine-verified opioid use (described above), which replaced the factor Medication group. Each model controlled for pain severity (coded as a person-level summary measure) and sex.

Measures that were acquired by both home EEG and subjective diary (SOL, WASO, SE, and TST) were compared with paired-sample t-tests.

Four participants were missing EEG data, and two additional participants were missing BPI pain severity data. Consequently, the final sample size for diary analysis was 53 participants, and the final sample size for EEG analysis was 49 participants.

Analyses were conducted in SPSS version 25. All tests were two-tailed. F values and degrees of freedom were used to calculate Cohen *d* effect sizes and 95% confidence intervals. We did not follow up null findings by calculating Bayes factors (Dienes, 2014) because we had no *a priori* estimates of effect sizes against which to test a hypothesis of no effect.

3. Results

3.1. Sample Characteristics

Demographics and other sample characteristics are presented in Table 2. The buprenorphine group had a higher percentage of men than the methadone group ($p = .04$). No other demographic feature was significantly different between groups.

3.2. Sleep Continuity and Quality

Sleep continuity and quality measures, acquired via daily diary and home sleep EEG, are presented in Table 3.

3.2.1. Differences Between Medication Groups—Medication groups did not significantly differ in sleep continuity and quality obtained from either diary estimates or EEG estimates, (see Table 3), when controlling for sex and pain severity. On some of the EEG-derived indices, the buprenorphine group may have had slightly better sleep than the methadone group (Cohen *d* effect sizes in the absolute range of .38 to .47, with wide confidence intervals that crossed 0, and *p* values no lower than .12). This small difference was not reflected in subjective ratings from the sleep diaries.

3.2.2. Effects of Covariates—Pain severity was inversely associated with subjectively rated sleep quality, $F(1,49) = 4.94$, $p = .03$, and marginally associated with diary TST, $F(1,49) = 3.86$, $p = .06$. Men tended to have lower sleep quality than women, though this was statistically significant only for EEG-derived TST, $F(1,45) = 5.19$, $p = .03$.

3.3. Sleep Architecture

Measures of sleep architecture, acquired via home sleep EEG, are presented in Table 4.

3.3.1. EEG-Based Comparison Between Medication Groups—There were no statistically significant ($p < .05$) differences between methadone- and buprenorphine-treated participants. Participants on buprenorphine had a slightly lower %N3 (slow wave sleep) than participants on methadone, along with a slightly higher %N2 (a shallower stage of sleep). Again, the Cohen *d* effect sizes were modest (.34 to .39, with wide confidence intervals that crossed 0), and the *p* values were no lower than .19.

3.3.2. Effects of Covariates—Pain severity was marginally associated with a greater %N2, $F(1,45) = 3.77$, $p = .06$, and more weakly with a lower %N3, $F(1,45) = 2.67$, $p = .11$. Men had greater %N2 than women, $F(1,45) = 10.04$, $p = .003$, and lower %N3, $F(1,45) = 9.85$, $p = .003$).

3.4. Associations of Illicit Opioid Use with Sleep Continuity and Architecture

Neither self-reported nor urine-detected use of illicit opioids was significantly associated with diary- or EEG-derived sleep measures, and no orderly trends appeared (data not shown). To verify whether different drugs of abuse were associated with sleep, we ran a series of sensitivity analyses that collectively demonstrated that neither illicit opioid use, cocaine use, nor their combined use was significantly associated with sleep (results are summarized in the Supplementary Material under the header “Urine Toxicology Sensitivity Analyses” and Supplementary Tables 2a–c).

3.5. Differences Between Home EEG and Diary Measures of Sleep Continuity

In paired-sample t-tests, WASO ($t[50] = -9.11$, $p < .001$; $d = 2.58$; [CI 1.74, 3.63]) and TST ($t[50] = 10.37$, $p < .001$; $d = 2.93$; [CI 2.06, 4.14]) were lower, and SE ($t[50] = 5.96$, $p < .001$; $d = 1.69$; [CI 0.98, 2.49]) was higher in self-report compared to EEG. SOL did not

significantly differ between modalities (t[50]= 1.00, p =.32; d = −0.28; [CI −0.88, 0.29]). The differences between objective and subjective measures can be seen, broken down by medication group, in Table 3. In sensitivity analyses, even when the sleep diary data were limited to those days when sleep profiler data were also available, there were no significant changes in these findings (data provided in the Supplementary Material).

To determine whether the subjective reports were compromised by response habituation, we used t-tests to compare the first 2 weeks of reporting with the rest of the reporting period, which continued for up to 14 additional weeks. Together, these data (presented in the Supplementary Material, under the header “Sleep Diary Response Habituation”) reflect a high degree of concordance between early and later reporting periods and suggest that the duration of measurement did not systematically bias the diary-derived results.

4. Discussion

We used ambulatory monitoring to evaluate sleep in patients with OUD treated with either methadone or buprenorphine, with the primary goal of comparing groups on aggregated measures of sleep continuity, quality, and architecture obtained from a multimodal assessment paradigm. The results suggest that individuals on buprenorphine and methadone treatments did not substantively differ in any sleep parameter. Another key finding was that objective, EEG-based estimates of sleep continuity in OUD patients showed more disturbed sleep (i.e., lower TST and SE, and higher WASO) than the patients’ subjective, diary-based estimates.

Our ambulatory monitoring methods afforded an opportunity to examine sleep as it unfolds in OUD patients’ daily lives. We are only aware of one prior study of differences in sleep as a function of methadone and buprenorphine treatment (Dunn et al., 2018). That study characterized sleep from a single-occasion questionnaire that assessed perceived sleep disturbance, and the results, like ours, were trends suggesting that sleep disturbance may be modestly greater with methadone than with buprenorphine. This difference, if present, may reflect a difference between methadone’s full agonism at μ-opioid receptors versus buprenorphine’s partial agonism. Indeed, evidence suggests that agonist induction directly impairs sleep [for a review, see: (Wang and Teichtahl, 2007)].

The strongest person-level predictor of sleep was sex: women had longer EEG-derived TST than men, along with lower % N2 and higher % N3 (slow-wave sleep). These findings are consistent with prior PSG-based data in healthy adult samples, which have similarly shown that women had longer TST (Bixler et al., 2009; Goel et al., 2005), lower %N2 (Redline et al., 2004), and both higher %N3 (Bixler et al., 2009; Goel et al., 2005; Redline et al., 2004) and higher overall slow-wave activity (Dijk et al., 1989), a more general marker of sleep depth. Because our sample was predominantly male (75%), and the buprenorphine group had more men than the methadone group (87% vs. 62%), it is possible that these underlying sex differences in sleep continuity and architecture may have obscured medication-related differences in sleep that would have otherwise been observed with a larger, more balanced sample.

Self-applied, home-based sleep EEG is a relatively new option for sleep assessment that removes some of the barriers associated with traditional laboratory PSG and home PSG, both of which are expensive and require technical assistance to administer. In the present study, participants were monetarily incentivized to use the Sleep Profiler for 7 consecutive nights, and overall adherence was good, with participants using the device on average for approximately 5 nights. These data show that home sleep EEG is feasible in patients being treated for OUD.

We complemented the objective EEG measures with daily sleep diaries, which were found to be discordant with the EEG measures. The association of daily sleep diaries and PSG varies across clinical and demographic contexts (Kaplan et al., 2017). For example, among aging men and women without frank sleep complaints, subjective reports of sleep continuity were more consistent with PSG-derived estimates for men than for women (Vitiello et al., 2004). Patients with primary insomnia and/or psychophysiologic insomnia (Carskadon et al., 1976; Edinger and Fins, 1995) and obstructive sleep apnea (McCall et al., 1995) tend to *over*-report nocturnal wake periods and *under*-report TST compared to objectively verified estimates acquired through PSG and actigraphy. The opposite pattern was seen in our study, which is consistent with prior work in individuals becoming abstinent from heavy use of cocaine, who reported good perceived sleep quality despite progressively worsening PSG-derived estimates of sleep continuity (Morgan et al., 2006). Those findings have since been extended, showing that recently abstinent people who chronically use cocaine overreport TST and underreport SOL and WASO during 2 weeks in an inpatient sleep laboratory without access to cocaine (Hodges et al., 2017). Our study offers similar findings from OUD patients on opioid agonist treatment: higher WASO and lower TST on aggregate measures of home sleep EEG acquired over multiple nights, relative to aggregate measures of sleep diaries acquired over multiple weeks. These results may point to a generalized phenomenon whereby people with SUDs who are not currently using illicit substances continue to have demonstrably poor sleep, yet fail to perceive it fully. Notably, however, one prior study compared a week of sleep-diary data with a subsequent one or two nights of home PSG in OUD and found good concordance (Sharkey et al., 2011). Thus, additional research is necessary to clarify the methodological differences responsible for these different patterns of results.

Clinical and Research Implications

One hypothesis generated by these results is that the partial mu agonist buprenorphine may have similar sleep disrupting effects as the full agonist methadone. Notably, our buprenorphine preparation included naloxone, raising the question of whether buprenorphine alone would have yielded different results. There is evidence that naloxone given intravenously at doses of 4–14 mg disrupts sleep (Cianchetti et al., 1984; Sitaram and Gillin, 1982). However, the addition of naloxone is likely to have had little effect on response to buprenorphine due to the differences in their pharmacokinetics and receptor activities. The ratio of naloxone to buprenorphine was specifically designed to have minimal effects in the combination product when used sublingually, as demonstrated in analgesic and subjective effect studies comparing buprenorphine alone and in combination with naloxone (Harris et al., 2000; Roily et al., 1986; Strain et al., 2000; Vanacker et al., 1986).

Another interpretation of the results of this study is that self-reported sleep continuity estimates of patients with OUD in treatment may not be accurate: latent disturbances may be present in patients who report sleep patterns conforming to normative population estimates. If this finding is replicated, it could have broad clinical implications for identifying and managing sleep disturbance in this population, such as prioritizing passive, objective sleep monitors over self-report.

However, we reach these conclusions tentatively and cannot endorse changes to clinical practice prior to replication, for several reasons. First, the discordance between objective and subjective estimates of sleep continuity could be at least partly driven by error in either or both measurements. For example, we cannot rule out the possibility that the elevated estimates of sleep continuity from the sleep diary were due to recall error brought about by evening assessment of the previous night's sleep: sleep diaries are optimally administered upon awakening, but design priorities of the parent study prevented that. Similarly, we cannot rule out that the attenuated estimates of sleep continuity from our home sleep EEGs were a result of participants' removing the devices before returning to sleep. Notably, though, EEG-derived WASO was very high in our participants, and this cannot be readily explained by premature device removal, because it requires at least one additional sleep period before the final awakening is registered. Finally, although the Sleep Profiler has been previously validated in healthy volunteers and people with sleep disturbance (Levendowski et al., 2017), it has not been validated among OUD patients receiving treatment. Reproducing the present findings in a larger sample with a similarly multimodal approach to sleep assessment would provide the confirmatory evidence necessary to develop guidelines for assessing and treating sleep-continuity disturbance in patients with OUD receiving opioid agonist treatment.

The present study had other limitations that should be minimized in attempts at replication or extension. First, the study was not a randomized controlled trial, and therefore cannot provide direct causal information about the influence of methadone or buprenorphine on sleep, or how such an association would be represented across measurement modalities. Second, because of the complexity of the parent study, the timing and duration of measurement across sleep measurement modalities was unequal across participants and medication groups. Additionally, daily doses of buprenorphine and methadone for participants recruited from community clinics were not under our control and may have fluctuated without our knowledge. We also could not control for any effects that may be driven by the time since stabilization on opioid agonist therapy. Another limitation was that patients were not formally assessed for sleep apnea, and the Sleep Profiler devices did not have features to monitor sleep-related breathing, so we do not know the extent to which sleep-continuity estimates were driven by undetected apnea. Future studies could include a formal in-lab sleep study to diagnose central and/or obstructive sleep apnea, which are prevalent in individuals who chronically use opioids (Walker et al., 2007; Wang et al., 2005; Webster et al., 2007). Additionally, several ambulatory sleep-related breathing monitors are now available— including a more recent version of the Sleep Profiler—so future studies may incorporate these measurements into the intensive longitudinal assessment battery. Finally, most of our findings concerning the absences of associations are tentative due to the modest size of our sample. These limitations, however, are partially balanced by the

strength of sample heterogeneity introduced by our community-based recruitment, which should positively influence the generalizability of the results.

4.1. Summary and Conclusion

Home-based multimodal measures of sleep were either not different or only modestly and inconsistently different between patients treated with buprenorphine/naloxone versus methadone. With either medication, patients evidenced a positive misperception of sleep quality, whereby their subjective estimates of sleep continuity were significantly better (greater TST, lower WASO) than objective estimates. The findings, if replicated, may help guide recommendations for managing sleep in patients with OUD.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding: This work was supported by the Intramural Research Program of the National Institute on Drug Abuse, and a career development grant awarded to PHF (NIH/NIDA K23DA035915), and postdoctoral training grant for CJM (NIH/NINDS T32NS070201).

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Highlights

- Patients treated with buprenorphine versus methadone did not differ on sleep
- EEG revealed shorter and more disrupted sleep than patients self-reported
- Sex differences were observed; men had shorter and less deep sleep than women

Table 1.

EMA Sleep Questions

Please tell us about your sleep **last night**.

1) What time did you go to bed last night? (lights out with the intention of going to sleep)_____am/pm

2) After turning out the lights, how many minutes did it take you to fall asleep? _____ mins.

3) How many awakenings did you have last night? _____ (do not include final awakening)

4) Please add up the total amount of time you were awake during the middle of the night _____mins.

(Don't include time it took you to fall asleep)

5) What was the time of your **final** awakening_____ am/pm (woke up and did not return to sleep)?

6) What time did you get out of bed _____ am/pm (time actually got out of bed to start day)?

7) Please estimate how many hours and minutes you slept last night:

Total Sleep Time _____ hrs. and _____mins.

8) Please rate your overall **sleep quality** last night on the following scale.

0	1	2	3	4	5	6	7	8	9	10
Extremely Poor Sleep Quality (Shallow, Unrefreshing)										Excellent Sleep Quality (Deep, Refreshing)

These items were presented on a smartphone; participants were prompted by the phone to answer the questions daily within one hour of their self-reported bed time.

Table 2.

Sample Characteristics

	Methadone (N=26)	Buprenorphine (N=29)	*P*	Total N=55
Age *	49.9 (7.9)	48.2 (10.4)	.51	49.0 (9.3)
Sex (% Male) *	62	86	**.04**	75
Race * % AA % Caucasian % Other	 58 39 4	 48 45 7	.74	 53 42 6
Education *				
% Some HS	15	7	.79	11
% HS degree or GED	62	69		66
% Some College	19	21		20
% College Grad	4	3		4
% EMA-Reported Opioid Use Days **	22.5 (21.9)	21.2 (28.4)	.85	21.8 (25.3)
% Positive Urines **	33.1 (33.1)	45.3 (41.0)	.23	39.5 (37.6)
Dosage (mg/day) **	81.7 (31.1)	14.2 (6.0)	N/A	N/A

Note. HS = High School. N/A = Not applicable.

* at enrollment

** during the study

Table 3.

Sleep Continuity and Quality

	M (SD) for whole sample	M(SD) for methadone pts	M(SD) for buprenorphine pts	ANCOVA: bup vs. meth (controlling for pain severity and sex)	*d* (95% CI) for bup vs. meth (positive: meth > bup; negative: bup > meth)	*d* for pain severity	*d* for sex *(positive: M > F; negative: F > M)*
SOL (mins) (higher is worse) Diary EEG	23.75 (15.52) 20.00 (17.26)	22.18 (12.49) 20.73 (18.11)	25.04 (17.76) 19.36 (16.80)	F = 0.28, p = .61 F = 0.22, p = .64	−0.15 (−0.71, 0.42) 0.14 (−0.44, 0.73)	0.26 (−0.29, 0.84) −0.34 (−0.95, 0.23)	0.06 (−0.50, 0.62) 0.25 (−0.32, 0.86)
WASO (mins) (higher is worse) Diary EEG	24.38 (20.66) 106.18 (61.61)	22.87 (17.93) 118.51 (65.61)	25.63 (22.92) 95.28 (56.90)	F = 0.03, p = .87 F = 2.53, p = .12	−0.05 (−0.60, 0.52) 0.47 (−0.11, 1.09)	0.39 (−0.17, 0.97) 0.07 (−0.50, 0.57)	0.23 (−0.34, 0.79) 0.35 (−0.23, 0.95)
TST (mins) (higher is better) Diary EEG	410.70 (98.27) 249.31 (72.99)	418.11 (96.00) 241.00 (60.96)	404.56 (101.38) 256.66 (82.69)	F = 0.23, p =.63 F = 1.86, p = .18	0.14 (−0.42, 0.71) −0.41 (1.02, 0.17)	−0.56 (−1.17, 0.00) −0.10 (−0.69, 0.48)	0.06 (−0.50, 0.62) −0.68 (−1.32, − 0.09)*
SE (%) (higher is better) Diary EEG	.81 (.11) .67 (.16)	.82 (.09) .65 (.17)	.80 (.12) .69 (.16)	F = 0.13, p = .72 F = 1.61, p = .21	0.10 (−0.46, 0.67) −0.38 (−1.00, 0.19)	−0.51 (−1.12, 0.04) −0.10 (−0.69, 0.48)	−0.14 (−0.71, 0.42) −0.47 (−1.09, 0.11)
Sleep Quality (0–10) (higher is better) Diary	5.98 (1.99)	6.11 (1.63)	5.88 (2.26)	F = 0.08, p = .78	0.08 (−0.48, 0.65)	−0.63 (−1.24, −0.07)*	−0.05 (−0.60, 0.52)

Note. EEG=electroencephalograph; SOL= Sleep Onset Latency; WASO=Wake After Sleep Onset; TST=Total Sleep Time; SE=Sleep Efficiency. *p* values were obtained from a general linear model in which Medication group was the factor and pain severity and sex were covariates. Cohen *d* effect sizes are model adjusted; they were calculated from the F values, not the raw means.

Sample size for diary measures: 53 (24 methadone, 29 buprenorphine). df's for F tests = 1,49.

Sample size for EEG measures: 49 (23 methadone, 26 buprenorphine). df's for F tests = 1,45.

* p ≤ .05, 2-tailed.

Table 4.

Sleep Architecture

	M (SD) for whole sample	M(SD) for methadone pts	M(SD) for buprenorphine pts	ANCOVA : bup vs. meth (controlling for pain severity, sex, TST)	*d* (95% CI) for bup vs. meth (positive: meth > bup; negative: bup > meth)	*d* for pain severity	*d* for sex *(positive: M > F; negative: F > M)*
%N1	19.16 (8.42)	19.09 (8.41)	19.22 (8.59)	F = 0.19, p = .66	−0.13 (−0.73, 0.44)	0.17 (−0.40, 0.78)	0.08 (−0.50, 0.67)
%N2	50.01 (13.57)	46.29 (13.74)	53.30 (12.78)	F = 1.75, p = .19	−0.39 (−1.00, 0.19)	0.58 (0.00, 1.22)*	0.94 (0.34, 1.64)*
%N3	16.58 (17.04)	20.70 (20.37)	12.93 (12.74)	F = 1.28, p = .26	0.34 (−0.23, 0.95)	−0.49 (−1.12, 0.09)	−0.94 (−1.61, −0.32)*
%REM	14.25 (7.37)	13.91 (7.75)	14.55 (7.17)	F = 0.08, p = .77	−0.09 (−0.67, 0.50)	−0.13 (−0.71, 0.46)	−0.29 (−0.89, 0.30)

Note. *p* values were obtained from a general linear model in which Medication group was the factor and pain severity, sex, and TST (not shown) were covariates.

Sample size: 49 (23 methadone, 26 buprenorphine). df's for F tests = 1,45. Cohen *d* effect sizes are model adjusted; they were calculated from the F values, not the raw means.

* p ≤ .05, 2-tailed.