Journal of Psychiatric Research 130 (2020) 260–272

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Effects of treatment of sleep disorders on sleep, psychological and cognitive functioning and biomarkers in individuals with HIV/AIDS and under methadone maintenance therapy

Mostafa Alikhani [a], Alireza Ebrahimi [b], Vahid Farnia [a], Habibolah Khazaie [b], Farnaz Radmehr [a], Elahe Mohamadi [a], Omran Davarinejad [a], Kenneth Dürsteler [d], Dena Sadeghi Bahmani [b,c,e], Serge Brand [a,b,c,f,g,*]

[a] Substance Abuse Prevention Research Center, Health Institute, Kermanshah University of Medical Sciences, Kermanshah, Iran
[b] Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
[c] University of Basel, Psychiatric Clinics, Center for Affective, Stress and Sleep Disorders, Basel, Switzerland
[d] University of Basel, Psychiatric Clinics, Division of Substance Use Disorders Basel, Switzerland
[e] Departments of Physical Therapy, University of Alabama at Birmingham, Birmingham, AL, USA
[f] University of Basel, Department of Sport, Exercise and Health, Division of Sport Science and Psychosocial Health, Basel, Switzerland
[g] Tehran University of Medical Sciences, School of Medicine, Tehran, Iran

ARTICLE INFO

Keywords:
Human immunodeficiency virus
Methadone maintenance therapy
Trazodone
Sleep hygiene training
Cortisol
Cognitive performance

ABSTRACT

Background: Poor sleep is a major complaint of people with human immunodeficiency virus (HIV) and acquired immune deficiency syndrome (AIDS) and undergoing methadone maintenance therapy (MMT). We tested the impact of three different sleep-improving interventions (trazodone; sleep hygiene training; sleep hygiene training + trazodone) on sleep, psychological functioning and biomarkers in males with HIV and undergoing MMT.

Methods: A total of 75 male outpatients (mean age: 39.6 years) participated in a 12 week intervention. Participants were randomly assigned to one of the following conditions: trazodone 50 mg/d (TRAZ); sleep hygiene training (SHT); sleep hygiene training and trazodone (SHT + TRAZ). At baseline, and six and 12 weeks later, participants completed questionnaires covering subjective sleep and daytime sleepiness, and symptoms of depression and anxiety. In parallel, their cognitive performance (working memory; sustained attention) was assessed. Biomarkers (cortisol, BNDF, $CD4^{+}$) were assessed at baseline and at the end of the study.

Results: Over time, sleep disturbances decreased and daytime functioning and overall sleep quality improved. More specifically, both sleep disturbances and daytime functioning improved in the two SHT conditions from baseline to week 6. Daytime functioning remained stable from week 6 to week 12. Over time, in all conditions symptoms of depression and anxiety declined from baseline to week 6 and remained lower from week 6 to week 12. Daytime sleepiness, symptoms of insomnia and sleep-disordered breathing remained unchanged. Sustained attention performance improved over time from baseline to week 6 and remained high through to week 12. Biomarkers remained unchanged.

Conclusions: In males with HIV and undergoing MMT, treating sleep disturbances over a period of six to 12 weeks had a positive impact on aspects of sleep disturbance, symptoms of depression and anxiety, and cognitive performance. The results indicate that sleep hygiene training, either as stand-alone or in combination with trazodone, can produce positive results.

1. Introduction

Individuals with opioid use disorder (OUD) sharing needles and having unprotected sex with multiple partners are at increased risk of acquiring human immunodeficiency virus (HIV), and of suffering subsequently from both acquired immunodeficiency syndrome (AIDS) and

* Corresponding author. University of Basel, Psychiatric Clinics (UPK), Center for Affective, Stress and Sleep Disorders (ZASS), 4002, Basel, Switzerland.
E-mail address: serge.brand@upk.ch (S. Brand).

https://doi.org/10.1016/j.jpsychires.2020.07.043
Received 8 June 2020; Received in revised form 23 July 2020; Accepted 29 July 2020
Available online 2 August 2020

hepatitis C virus (HCV). HIV, AIDS and HCV require life-long treatment.

Methadone-maintenance therapy (MMT) now plays a key role in decreasing drug use and drug-related behavior such as sharing needles, working for commercial sex, having unprotected sex with multiple partners, and committing drug- and sex-related crimes (Gowing et al., 2006; Wodak and McLeod, 2008). In a recent meta-analysis and prospective cost-effectiveness study, Zhang et al. (2019) reported on 134 studies of Chinese MMT programs published between 2004 and 2015. They concluded that the Chinese MMT programs were cost-effective, as negative behavior related to drug-related harm significantly decreased. Additionally, applying an estimation model, they calculated that $1037 of MMT-related investment prevented about 29,463 new HIV infections, 130,563 new HCV infections, and 10,783 deaths related to HIV, HCV and drug-related harm. Thus, MMT programs were highly effective in reducing HIV/AIDS and HCV epidemics and damaging drug-related behavior, in increasing the overall health of people living with HIV, and in avoiding other health problems in this group. Similarly, Karki et al. (2016), in their systematic review, concluded that MMT led to a dramatic drop in injected drug use, in sharing needles, in new cases of people with HIV, AIDS and HCV, and in commercial sex work. On the other hand, adherence of HIV sufferers to MMT programs remains a challenge.

As regards the arrangements for methadone maintenance therapy in Iran, Bastani et al. (2019) noted that Iran has developed the most robust harm reduction infrastructure in the Middle East. Typically, low-threshold drop-in centers offer free sterile needles, syringes and condoms to between 170 and 230 thousand people who inject drugs. In addition, about 6000 MMT programs are delivering care to about half a million of people with OUD . In other countries, about 60% of those in the HIV and OUD categories and also undergoing MMT relapse and reuse drugs within the first three months (Zhang et al., 2019). High recidivism rates are also a major concern in Iran (Bastani et al., 2019; Pashaei et al., 2013). Bastani et al. (2019) observed that social and structural barriers, and the use of other illicit drugs, particularly amphetamine-like drugs (see also Zhang et al., 2019), may be partly responsible for these rates. Pashaei et al. (2013) found that cognitive-behavioral interventions were effective in reducing relapse rates from 63.6% in a control condition to 36.4% in an intervention condition.

MMT also have disadvantages. Thus methadone in common with other opioids leads to altered sleep patterns; impaired sleep is already a major health problem for HIV sufferers (Gutierrez et al., 2019; Low et al., 2014; Hahmood et al., 2018; Patterson et al., 2019). Hahmood et al., 2018 observed that in HIV and opioid use disorder cases between 56% and 73% had sleep-related issues; this compares to 10%–30% in the general population (Low et al., 2014). Patterson et al. (2019) reported that, compared to a healthy population, HIV sufferers were more likely to experience poor sleep. This high risk of poor sleep might be related to use of antiretroviral medication (for a contrary opinion see Hahmood et al., 2018 or to excessive tobacco use (Patterson et al., 2019), while a potentially life-long highly irregular sleep-wake pattern associated with a chaotic life style might also contribute to a generally poor sleep pattern. In the same vein, Gamaldo et al. (2013) argued that psychiatric and psychosocial issues such as symptoms of depression, perceived stress, social exclusion, and poverty also resulted in poor sleep. Likewise, Gutierrez et al. (2019) reported that, compared to a healthy population, up to 75% of HIV cases self-reported sleep disturbances. Typical indicators were more fragmented sleep, reduced sleep efficiency, and a longer sleep onset latency. Furthermore, 20–95% of those with HIV reported symptoms of insomnia, though it was unclear whether poor sleep in these cases meant sleep disturbances or insomnia or both (Low et al., 2014). In the light of these observations the first aim of the present study was to improve the sleep of HIV patients undergoing MMT. To this end participants were assigned to one of three different interventions (trazodone (TRAZ); sleep hygiene training (SHT); sleep hygiene training + trazodone (SHT + TRAZ; see details below).

Suffering from HIV/AIDS and undergoing MMT is also related to an increased risk of sleep apnea (Gutierrez et al., 2019; Kunisaki et al., 2015; Teichtahl and Wang, 2007; Wang and Teichtahl, 2007). Wang and Teichtahl (2007) estimated that up to 30% of HIV and OUD OUD cases suffer from central sleep apnea (CSA) (Wang et al., 2005), while obstructive sleep apneas (OSAs) may also be involved. As a general observation, opioids are respiration-depressing, leading to abnormal awake and ventilatory responses to hypercapnia and hypoxia. Wang and Teichtahl (2007) reported two findings. First, there is an association between higher CSA and higher methadone blood concentrations. Second, imaging studies of HIV patients under long-term MMT showed structural brain damage, particularly in the mid brain of the brain stem, the location of the central respiratory controller. These results suggested that regular and long-term use of opioids such as methadone may harm those brain regions responsible for central respiratory functioning. In the light of these observations we asked whether sleep-improving interventions could have a positive impact on subjective and self-rated dimension of OSAs. Therefore, the second aim of the present study was to investigate the influence of sleep-improving interventions on participants' self-rated sleep-disordered breathing.

As a general rule, restoring sleep is also associated with better cognitive functioning (Curcio et al., 2006; Devore et al., 2016; Killgore et al., 2008; Leong et al., 2019; Lo et al., 2016; Lowe et al., 2017; Van Dongen et al., 2003; Wardle-Pinkston et al., 2019; Wu et al., 2018). As regards those with HIV, Hahmood et al., 2018 showed in their experimental study an association between sleep disturbances and poor cognitive performance. Byun et al. (2016) reported a similar pattern. Given this, the third aim of the present study was to investigate the extent of the relation between sleep and cognitive performance and whether improvements in sleep would be associated with improvements in working memory and sustained attention.

Symptoms of depression are also associated with poor cognitive performance (Norell-Clarke et al., 2014; Sater et al., 2015), with poor sleep (Alvaro et al., 2013; Baglioni et al., 2010; Fava, 2004; Goldstein and Walker, 2014; Manber and Chambers, 2009; Nutt et al., 2008; Rumble et al., 2015) and with anxiety (Alvaro et al., 2013; Cox and Olatunji, 2016; Hertenstein et al., 2018). The fourth aim of the present study was therefore to determine whether interventions to improve sleep would also reduce symptoms of depression and anxiety.

Next, HIV patients undergoing MMT have reported poor sleep, which was associated with higher daytime sleepiness (Low et al., 2014) and fatigue (Faraut et al., 2018). The fifth aim of the study was to investigate whether sleep-improving interventions would also result in reductions in daytime sleepiness.

Studies including both healthy samples and individuals with major depressive disorders have shown poor sleep to be associated with higher cortisol concentrations (Hatzinger et al., 2008, 2012, 2010; Hori et al., 2011) and lower brain-derived neurotrophic factor (BDNF) concentrations (Mikoteit et al., 2019; Monteiro et al., 2017), while improvements in sleep have been associated with a downregulation of cortisol concentrations and an up-regulation of BDNF concentrations. Given these findings, the sixth aim of the study was to examine whether sleep-improving interventions would also have a positive impact on cortisol and BDNF.

We examined three strategies for improving sleep, a pharmacological intervention (trazodone (TRAZ)), a psychoeducational intervention (sleep hygiene training (SHT), and the combination of these interventions (SHT + TRAZ).

Trazodone is a serotonin antagonist and reuptake inhibitor (SARI) used to treat major depressive disorders and anxiety disorders. Given its sleep-inducing and sleep-stabilizing properties (Everitt et al., 2018), trazodone is also administered as a sleeping-promoting medication.

Sleep hygiene training as a proxy for psychoeducational interventions is proven to be effective (Åslund et al., 2018; Ballesio et al., 2018; Chung et al., 2018; Murawski et al., 2018; Thakral et al., 2020; Trauer et al., 2015; van Straten et al., 2018). Gee et al. (2019) concluded from their systematic review and meta-analysis that sleep hygiene

training also has positive effects with respect to symptoms of depression.

We employed a combination of sleep hygiene training and trazodone intake as the third strategy.

To summarize, for those with HIV and OUD , MMT has proved to be an effective and harm-reducing intervention. However, people with HIV also have poor sleep, impaired cognitive performance, and symptoms of depression and anxiety. Both trazodone and sleep hygiene training have been shown to improve sleep characteristics. Given this, the main aim of the present study was to investigate the degree of positive effect of sleep-improving interventions (TRAZ, SHT; SHT + TRAZ) on sleep, daytime sleepiness, symptoms of depression and anxiety, cognitive performance and biomarkers in a sample of male HIV patients receiving MMT.

Five hypotheses and one research questions were formulated. As a preliminary statement and given the lack of previous studies in this field and with these forms of sleep-improving interventions, we had no specific expectations as regards the relative superiority of trazodone, sleep hygiene training, or their combination.

Following others (Gutierrez et al., 2019; Low et al., 2014; Hahmood et al., 2018; Patterson et al., 2019), our first hypothesis was that sleep-improving interventions would benefit subjective sleep in this patient group.

Second, following others (Byun et al., 2016; Killgore, 2010; Leong et al., 2019; Hahmood et al., 2018; Wardle-Pinkston et al., 2019) we expected that these sleep-improving interventions would improve cognitive performance.

Third, on the basis of previous research (Alvaro et al., 2013; Cox and Olatunji, 2016; Hertenstein et al., 2018; Nutt et al., 2008; Rumble et al., 2015) we anticipated that the interventions would reduce symptoms of depression and anxiety.

Fourth, following others (Byun et al., 2016; Faraut et al., 2018; Low et al., 2014), we hypothesized that the interventions would reduce daytime sleepiness.

Fifth, based on previous research (Hatzinger et al., 2010; Hori et al., 2011; Lemola et al., 2015; Mikoteit et al., 2019), we expected the interventions to result in decreased cortisol concentrations and increased BDNF concentration.

Finally, we examined whether the sleep-improving interventions would alter the symptoms of sleep apnea, as it appears that sleep apnea in this patient group is an issue of the central neuronal respiratory controller (Gutierrez et al., 2019; Teichtahl and Wang, 2007; Wang and Teichtahl, 2007; Wang et al., 2005).

We believe that results from this study may be of clinical and practical importance given that restoring sleep is crucial for daily functioning, and that this is also true for HIV patients undergoing MMT.

2. Methods

2.1. Study procedure

Male outpatients with HIV and receiving MMT at the Mehr Sina Clinic of the Kermanshah University of Medical Sciences (KUMS; Kermanshah, Iran) were approached to participate at the study. Potential participants were informed about the study aims and the confidential data handling. Thereafter, they signed a written informed consent. Participants were randomly assigned to one of the following study conditions: administration of trazodone 50 mg/d (TRAZ), sleep hygiene training (SHT); sleep hygiene + 50 mg/d trazodone (SHT + TRAZ). At the beginning of the study (baseline), after six weeks and then after 12 weeks, participants completed questionnaires on sleep and sleep-related dimensions, and on symptoms of depression and anxiety. In parallel, we ran objective tests of participants' cognitive performance (verbal working memory; sustained attention). At baseline and at the end of the study blood samples were taken to assess the following biomarkers: Cortisol, BDNF, and $CD4^{+}$.

The Ethical Committee of the Kermanshah University of Medical Sciences (ethics committee reference number: kums.rec.1395.255) approved the study, which was performed in accordance with the seventh revision of the Declaration of Helsinki (World Medical Association, 2013). The study was registered at the Iranian Register for Clinical Trials (itct.ir: IRCT2016110923705N8).

2.2. Samples

Fig. 1 presents the flow chart for participants' recruitment and study condition assignments.

A total of 130 possible participants were approached. Of these 55 (42.31%) were excluded: Either they did not fulfill the inclusion criteria (see below) or they declined to participate. Seventy-five participants were assigned to one of the three study conditions (see below).

In the TRAZ condition (N = 25), one participant dropped out after allocation, two had dropped by week 6, and three had dropped by week 12; thus 19 participants in this condition completed the study. In the SHT condition (N = 25), two dropped out after allocation, five dropped by week 6, and seven dropped by week 12; thus, 11 of these participants completed the study. In the SHT + TRAZ condition (N = 25), three dropped out after allocation, two dropped out by week 6, and four dropped out by week 12; thus 16 of these participants completed the study. Overall, 46 (61.3%) of the original 75 participants completed the study.

2.3. Randomization

As in previous studies (Farnia et al., 2019; Jahangard et al., 2018), randomization was accomplished using the software randomization.com to create a list to assign 75 participants randomly to one of the three study conditions. Thereafter, a psychologist not otherwise involved in the study managed the assignments.

2.4. Sample size calculation

The sample size calculation was performed with G*Power® (Faul et al., 2007). Based on previous results (Hahmood et al., 2018), the following parameters were defined: effect size: 0.18 (Cohen's f for ANOVAs); alpha error probability: 0.05; power: 0.80; number of groups: 3; number of measurements: 3. These parameters give a total sample size of 66. However, to allow for drop-outs, the sample size was set at 75 participants.

2.5. Methadone maintenance therapy

All patients were in receipt of methadone weekly at therapeutic dosages (mean: 40mg/w; see also (Farnia et al., 2019).

2.6. Trazodone medication

Participants in the TRAZ and SHT + TRAZ condition took trazodone 50 mg/d every morning throughout the study.

2.7. Sleep hygiene training

A clinical psychologist experienced in sleep hygiene education provided sleep hygiene training in small groups of eight to ten participants. Training took place once a week for 50–60 min at the Mehr Sina Clinic. Basic topics were: "What is a normal sleep schedule?", "Why is it important to have a regular sleep schedule?"; "Which techniques help us to maintain a stable sleep schedule, to fall asleep and to feel more refreshed in the morning?"; "Dos and Don'ts before going to sleep"; "How to get rid of "bad" thoughts to fall asleep"; and similar. Topics were discussed, solutions were elaborated, and sleep-improving techniques were practiced during the sessions. Additionally, participants were encouraged to keep a sleep log and to exercise relaxation techniques at home, though "home work" was not explicitly checked to

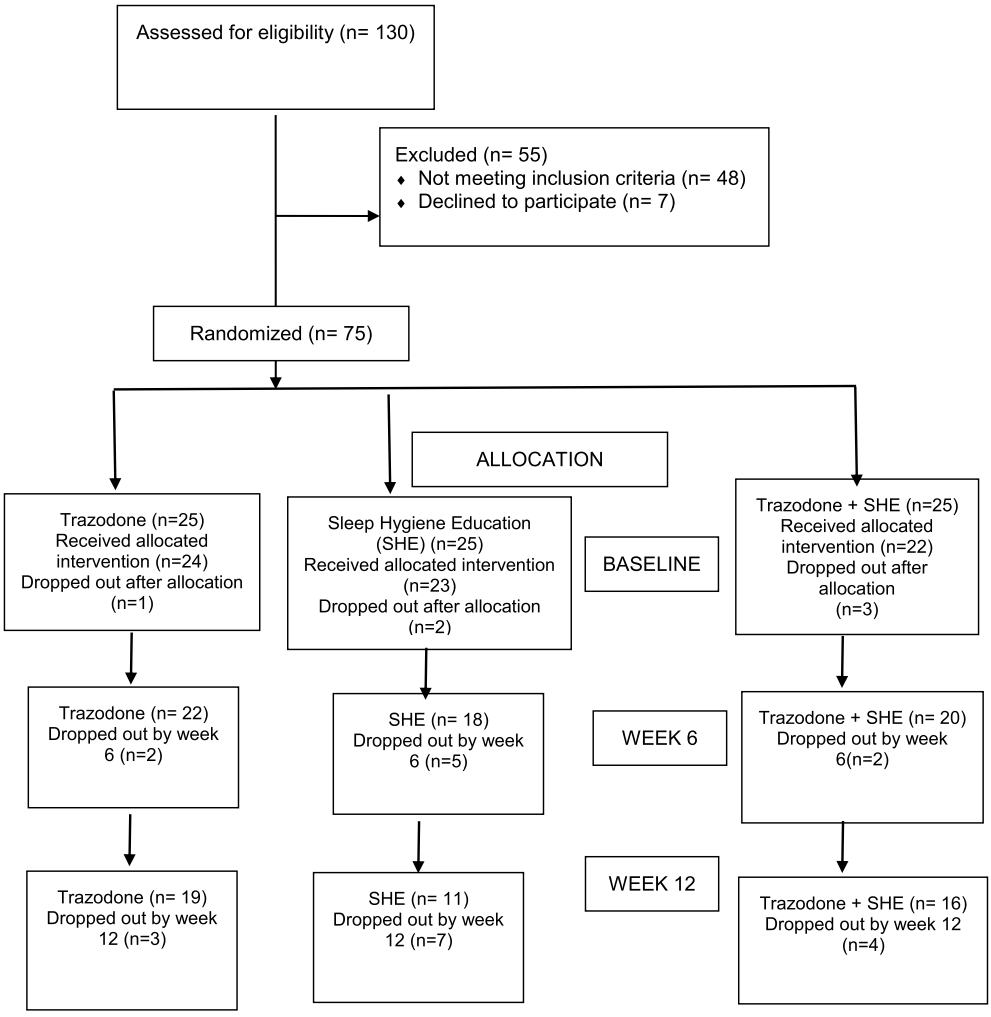

Fig. 1. CONSORT diagram showing the flow of participants through each stage.

avoid drop-out through feelings of shame, insecurity or being overly supervised.

2.8. Tools

2.8.1. Sociodemographic, anthropometric, and illness-related information

Participants reported on their age (in years), socioeconomic status (low; medium; high), civil status (single; married; divorced), highest educational level (compulsory school; high school; diploma; higher diploma), employment status (yes; no) and substance use (opioids; opioids + stimulants; opioids + hallucinogens). The following anthropometric variables were measured: waist circumference (cm), neck circumference (cm); BMI (kg/m^2). The following illness-related information was taken from the most recently available medical records: duration of HIV diagnosis (years); age at commencement of methadone treatment (years); duration of methadone treatment (years); duration of substance use (years).

2.8.2. Sleep and daytime sleepiness

2.8.2.1. Subjective sleep: Pittsburgh Sleep Quality Index (PSQI (Buysse et al., 1989). The PSQI is a self-report scale that is completed in 5 min. It consists of 19 items and contains seven subscales (subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbance, sleeping medication, daytime dysfunction), each weighted equally on a scale from 0 to 3, with higher scores indicating poorer sleep quality. The seven components are then summed to obtain an overall PSQI score, ranging from 0 (good sleep quality) to 21 (poor sleep quality). Total scores of ≥5 reflect poor sleep, associated with considerable sleep complaints. Farrahi et al. (2012) have validated the psychometric properties of the Farsi version (Cronbach's alpha = .85).

2.8.2.2. Symptoms of insomnia. Subjective insomnia was assessed with the Insomnia Severity Index (ISI; Bastien et al., 2001; Gerber et al., 2016). This questionnaire is a seven-item screening measure for insomnia. The items, answered on 5-point Likert scales ranging from 0 (=not at all) to 4 (=very much), refer in part to the Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 2013) criteria for insomnia by assessing difficulty falling asleep, difficulty remaining asleep, early morning awakenings, impaired daytime performance, low satisfaction with sleep, and worry about sleep. The higher the overall score, the more the participant is assumed to suffer from insomnia (Cronbach's alpha = 0.89).

2.8.2.3. Daytime sleepiness. To assess daytime sleepiness, participants completed the Epworth Sleepiness Scale (ESS; (Johns, 1991), which consists of ten items rating the odds of dozing off during different activities. Answers are given on 4-point rating scales (0–3), with higher sum scores reflecting greater daytime sleepiness. The sum score ranges from 0 to 30 points; a global score greater than 10 indicates excessive daytime sleepiness. ESS scores were treated as continuous. The Cronbach's α for the present sample was 0.89.

2.8.2.4. Sleep-disordered breathing. The Berlin Questionnaire (Netzer et al., 1999) is a self-rating questionnaire designed to assess risk of suffering from Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS). The items are as follows. Category 1: 1. "Do you snore?" (yes/no/I don't know); 2. "Your snoring is …" (as loud as normal breathing/as loud as talking/louder than talking); 3. "How often do you snore?" (almost every day/3–4 times a week/1–2 times a week/1–2 times a month/-rarely or never). 4. Has your snoring ever bothered other people?" (yes/no/I don't know); 5. Has anyone noticed that you stop breathing during sleep?" (almost every day/3–4 times a week/1–2 times a week/1–2 times a month/rarely or never). Category 2: 6. "How often do you feel tired or fatigued after your sleep?" (almost every day/3–4 times a week/1–2 times a week/1–2 times a month/rarely or never). 7. "During your waking time, do you feel tired, fatigued or not up to par?" (almost every day/3–4 times a week/1–2 times a week/1–2 times a month/rarely or never). 8. "Have you ever nodded off or fallen asleep while driving a vehicle?" (yes/no). If your answer is 'yes'; 9. How often does it occur? (almost every day/3–4 times a week/1–2 times a week/1–2 times a month/rarely or never). Category 3: 10. "Do you have high blood pressure?" (yes/no/I don't know). High risk for Obstructive Sleep Apnea/Hypopnea Syndrome (OSAHS) is taken to exist when there are persistent symptoms (more than three or four times per week) in categories 1 and 2, and hypertension (P140/90 mmHg or use of medication) or BMI P30 kg/m^2 in category 3. Categories 1 and 2 are positive when the sum of all items is 2. Individuals are classified as having high risk for OSAHS if scores are positive in two or more categories. Individuals scoring positive in only one or none of the categories are classified as low risk. The sum score was treated as a continuous variable.

2.9. Self-report of depressive symptoms: Beck Depression Inventory (BDI)

Participants completed the Beck Depression Inventory (Beck et al., 1961) Farsi version (for psychometric properties of the Farsi version see (Ghassemzadeh et al., 2005). This inventory samples self-reported symptoms of depression. The questionnaire consists of 21 items and asks about different aspects such as depressive mood, loss of appetite, sleep disorders, suicidality and similar. Each question has a set of at least four possible responses, ranging in intensity; e.g., 'sadness': 0 = 'I do not feel sad'; 1 = 'I feel sad'; 2 = 'I am sad all the time and I can't snap out of it'; 3 = 'I am so sad or unhappy that I can't stand it.', and with higher scores reflecting greater severity of depressive symptoms (Cronbach's alpha = .89).

2.10. Self-report of symptoms of anxiety

Symptoms of anxiety were assessed with the Beck Anxiety Inventory (BAI; Beck et al., 1988). Hossein Kaviani and Mousavi (2008) have reported robust and reliable psychometric properties for the Farsi version of this inventory. The BAI consists of 21 items addressing typical cognitive, emotional and bodily signs of anxiety such a fear of the worst happening, numbness and tingling, or sweating not due to heat. Answers are given on 4-point rating scales with the anchor points 0 (= not at all) and 3 (= severely/it bothers me a lot), and with higher sum scores reflecting more marked symptoms of anxiety (Cronbach's alpha = 0.81). Respondents were categorized as follows (Hossein Kaviani and Mousavi, 2008; Beck et al., 1988): 0–9: minimal anxiety; 10–16: mild anxiety; 17–29: moderate anxiety; 30–63: severe anxiety.

2.11. Cognitive testing

2.11.1. Verbal working memory

The Digit Span subtest of the Wechsler Adult Intelligence Scale (WAIS-IV; Wechsler, 2008) was administered to assess verbal working memory. This task has two conditions. In the forward condition, sequences of digits of increasing length have to be repeated in the same order as presented. In the backward condition, digit sequences have to be repeated in reverse order.

2.11.2. Sustained attention

To assess sustained attention, we employed the d2-test (Brickenkamp, 2002). The test consists of the following tasks. There are 14 lines consisting of symbols. Symbols may be d or p with no, one, two, three or four small lines. The participant must mark within 20sec as many as possible of the symbols consisting of a d and two small lines. Crossing a d with two small lines equals a correct answer; crossing a d with one, three or four lines, or crossing a p, or missing a d with two lines are all treated as errors. In the present study, we considered only the correct responses.

2.12. Cortisol, BDNF, $CD4^+$

At the beginning and 12 weeks later, participants' blood samples were taken at 8am on an empty stomach. Blood sampling was performed intravenously from the inner fold of the elbow, though in some participants due to a lack of accessible blood vessels in this location blood samples were taken from the back of the hand or foot.

All blood samples were sent to Farabi Hospital Laboratory of the Kermanshah University of Medical Sciences (Kermanshah, Iran) and serum was isolated by a centrifugal device. All serums were stored until completion of the study at −20 °C in a special refrigerator for storage of biomarkers in the Sleep Disorders Research Center (KUMS; Kermanshah, Iran).

Enzyme-linked immune sorbent assay (ELISA) kits based on the Biotin double antibody sandwich technology were employed to assay the Human Cluster Of differentiation4 (CD4), Human Cortisol, and Brain-Derived Neurotrophic Factor (BDNF). Cortisol and BDNF ELISA kits were produced by Biston Teb Company (Kermanshah, Iran) on behalf of Zell Bio GmbH (Germany), while the CD4 ELISA kit was provided by Tarvand Sina Headquarters Company (Esfahan, Iran) on behalf of EASTBIOPHARM (USA). All cortisol, BDNF, and $CD4^+$ analyses were performed in the laboratory of Imam Reza Clinic (Kermanshah, Iran). Further information on detailed laboratory analyses are available as supplementary files.

2.13. Statistical analysis

Statistical analyses were not performed per protocol, but by intent-to-treat, with the last observation carried forward (LOCF) method.

The primary outcome variables were sleep related. These included sleep quality and sleep quantity (Pittsburgh Sleep Quality Index), symptoms of insomnia (Insomnia Severity Index), daytime sleepiness (Epworth Sleepiness Scale), sleep disordered breathing (Berlin questionnaire).

Secondary outcome variables were psychological and cognitive dimensions and physiological biomarkers.

a) Psychological dimensions: Symptoms of depression as assessed by the Beck Depression Inventory; symptoms of anxiety as assessed by the Beck Anxiety Inventory
b) Cognitive dimensions: Working memory (digit span forward and backward); measure of selective and sustained attention and visual scanning speed from the d2-test.
c) Physiological markers: Cortisol; BDNF, $CD4^+$.

Differences across treatment conditions in age and duration of illness were assessed via one-way ANOVAs. A series of ANOVAs for repeated measures was performed with the following factors: Group (TRAZ; SHT; SHT + TRAZ) and Time (baseline; week 6; week 12); dependent variables were sleep quality (PSQI), symptoms of insomnia (ISI), daytime sleepiness (ESS), sleep-disordered breathing (Berlin); depression (BDI), anxiety (BAI): working memory (digit span forward and backward),

sustained attention (d2). For physiological dimensions the factor Time had two values (baseline; week 12); dependent variables were: cortisol-, BDNF-, and $CD4^+$ levels. In case of deviation from sphericity, ANOVAs were computed using Greenhouse-Geisser corrected degrees of freedom, though the original degrees of freedom are reported with the relevant Greenhouse-Geisser epsilon value (ε).

For ANOVAs, effect sizes are reported as partial eta squared (η_p^2), with $0.01 < \eta_p^2 < 0.059$ indicating small [S], $0.06 < \eta_p^2 < 0.139$ indicating medium [M], and $\eta_p^2 > 0.14$ indicating large [L] effect sizes.

All statistical computations were performed with SPSS® 25.0 (IBM Corporation, Armonk NY, USA) for Apple Mac®.

3. Results

3.1. Sociodemographic and illness-related information

Table 1 provides the descriptive and inferential statistical indices for age and HIV-related information for the three conditions. These indices are not repeated in the text.

No descriptive or statistically significant differences were found between the three groups (TRAZ, SHT, SHT + TRAZ) as regards age, BMI, waist circumference, neck circumference, duration of the HIV diagnosis, age at methadone treatment onset, duration of methadone treatment, duration of substance use, socioeconomic status, civil status, highest educational level or type of substance use.

3.2. Subjective sleep parameters (PSQI; ISI, ESS), over time (baseline, week 6, week 12) and between and within groups (TRAZ, SHT; SHT + TRAZ)

Table 2 provides a descriptive statistical overview, while Table 3 provides the inferential statistical overview for the dimensions of sleep over time and across the three groups. These indices are not repeated in the text.

3.2.1. Pittsburgh Sleep Quality Index

No significant or descriptive mean differences were observed over time or between groups for sleep latency, sleep efficiency, sleep medication or sleep quality.

There was a significant between-group difference in sleep duration; post-hoc analyses with Bonferroni-Holm corrections for p-values showed that sleep duration improved significantly in the SHT + TRAZ condition.

Sleep disturbances significantly decreased over time, but not between groups. However, post-hoc analyses with Bonferroni-Holm corrections for p-values showed that sleep disturbances decreased significantly from baseline to week 6 in both SHT and SHT + TRAZ conditions (see Fig. 2).

Daytime dysfunction significantly decreased over time, but not between groups. However, post-hoc analyses with Bonferroni-Holm corrections for p-values showed that sleep disturbances decreased significantly from baseline to week 6 in the SHT and SHT + TRAZ conditions (see Fig. 3). Furthermore, daytime dysfunction remained low across time in the SHT + TRAZ condition.

The Pittsburgh Sleep Quality Index overall scores decreased significantly over time, but without differences between groups (see Fig. 4).

3.3. Insomnia (ISI) and daytime sleepiness (ESS)

There were no significant or descriptive mean differences over time or between groups in these variables.

3.4. Self-rated symptoms of depression and anxiety

Tables 4 and 5 provide the descriptive and inferential statistical indices of self-rated symptoms of depression and anxiety separately for the three time points and for the three groups.

Symptoms of depression and anxiety reduced over time; there was no group or time by group-interaction effect. Post-hoc analyses with Bonferroni-Holm corrections for p-values showed that symptoms of depression and anxiety decreased from baseline to week 6, and thereafter remained unchanged.

3.5. Working memory (digit span forward and backward) and sustained attention (d2-test)

Tables 6 and 7 provide the descriptive and inferential statistical overview of cognitive performance scores for working memory (digit span forward and backward) and sustained attention (d2-test).

For working memory, the performance for digit span forward did not

Table 1
Descriptive and statistical overview of sociodemographic variables separately by treatment condition.

	Groups			
	Trazodone	Sleep hygiene training	Trazodone + sleep hygiene training	Statistics
N	24	23	22	
	M (SD)	M (SD)	M (SD)	
Age (years)	37.71 (6.38)	39.78 (6.26)	41.27 (6.44)	$F(2, 66) = 1.82$
BMI	21.24 (3.30)	21.77 (2.40)	2.50 (2.75)	$F(2, 66) = 1.13$
Waist circumference (cm)	74.75 (17.51)	69.17 (16.85)	70.00 (16.83)	$F(2, 66) = 0.73$
Neck circumference (cm)	36.37 (2.89)	38.21 (5.35)	35.22 (7.99)	$F(2, 66) = 1.57$
Duration of HIV diagnosis (years)	12.29 (7.48)	13.82 (7.73)	15.04 (6.24)	$F(2, 66) = 0.85$
Age at methadone treatment (years)	30.50 (7.08)	30.57 (8.93)	33.91 (8.53)	$F(2, 66) = 1.27$
Duration of methadone treatment (years)	9.38 (16.21)	9.61 (7.65)	8.18 (6.64)	$F(2, 66) = 0.10$
Duration substance use (years)	16.46 (5.97)	19.13 (7.86)	18.14 (9.25)	$F(2, 66) = 0.71$
	n/n/n	n/n/n	n/n/n	
Socioeconomic status (low/medium/high)	13/11/0	17/6/0	17/5/0	$X^2(N = 69, df = 4) = 1.06$
Civil status (single/married/divorced)	10/9/4	9/10/4	12/10/0	$X^2(N = 69, df = 4) = 8.58$
Highest educational level (compulsory school/high school/diploma/high diploma)	3/8/12/1	6/3/13/1	8/2/11/1	$X^2(N = 69, df = 6) = 11.16$
Occupation (yes/no)	22/11	17/16	20/13	$X^2(N = 69, df = 2) = 1.72$
Substance use (opium/opium + stimulants/opium + hallucinogens)	15/6/3	11/8/4	15/4/3	$X^2(N = 69, df = 4) = 2.26$

Table 2
Descriptive overview of sleep dimensions (Pittsburgh Sleep Quality Index; Insomnia Severity Index; Epworth Sleepiness Scale; Berlin questionnaire), separately by assessment time (baseline, week 6, week 12), and group (trazodone; sleep hygiene training; trazodone + sleep hygiene training).

	Assessment times								
	Baseline			Week 6			Week 12		
	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ
N	**24**	**23**	**22**	**22**	**18**	**20**	**19**	**11**	**16**
Pittsburgh Sleep Quality Index	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)
Sleep latency	3.21 (1.67)	3.39 (1.75)	2.90 (2.14)	3.17 (1.55)	3.09 (1.62)	2.50 (1.74)	2.75 (1.67)	3.30 (1.72)	3.09(1.85)
Sleep duration	1.12 (1.03)	1.65 (1.11)	1.27 (1.12)	0.95 (0.81)	1.61 (0.94)	1.09 (1.06)	1.00 (0.83)	1.35 (0.83)	1.04 (0.90)
Sleep efficiency	75.70 (12.64)	80.29 (14.78)	78.48 (13.39)	80.90 (10.17)	79.90 (11.41)	80.35 (24.71)	80.79 (12.27)	83.06 (11.93)	83.73 (20.90)
Sleep disturbances	10.71 (4.47)	11.04 (4.30)	11.14 (4.84)	9.96 (4.48)	8.78 (4.18)	9.09 (4.83)	9.62 (4.70)	8.70 (4.64)	9.40 (5.40)
Sleep medications	1.37 (1.24)	1.26 (1.10)	0.81 (0.91)	1.50 (1.32)	1.17 (1.37)	0.81 (1.18)	1.25 (1.26)	1.21 (1.28)	0.73 (1.12)
Daytime dysfunction	2.57 (1.65)	2.86 (1.93)	2.29 (1.85)	2.00 (1.51)	1.81 (1.26)	2.12 (1.57)	2.17 (1.56)	1.77 (1.11)	2.05 (1.77)
Subjective sleep quality	1.58 (0.97)	1.87 (0.87)	1.41 (1.05)	1.25 (0.90)	1.70(0.82)	1.50(0.86)	1.33 (0.96)	1.70 (0.76)	1.68 (0.84)
PSQI overall score	10.41 (3.28)	10.70 (3.02)	9.45 (4.69)	9.37 (3.24)	9.78 (3.10)	8.18 (3.25)	9.00 (3.78)	9.38 (3.41)	8.25 (3.26)
Insomnia Severity Index	12.79 (5.96)	13.60 (60.61)	13.59 (6.56)	11.21 (4.75)	13.78 (4.47)	12.86 (5.86)	12.17 (5.00)	13.87(4.99)	11.77 (6.42)
Epworth Sleepiness scale	5.92 (4.96)	4.87 (4.14)	6.09 (4.45)	6.37 (3.98)	4.74 (4.22)	6.72 (4.62)	5.58 (4.36)	4.35 (3.50)	6.90 (4.52)
Berlin	1.96 (1.78)	1.91 (1.90)	1.95 (1.49)	1.83 (1.52)	1.52 (1.80)	1.77 (1.51)	1.46 (1.28)	1.35 (1.80)	2.04 (2.10)

Notes: TRAZ=trazodone ; SHT = sleep hygiene training ; SHT + TRAZ : sleep hygiene training + trazodone; PSQI = Pittsburgh Sleep Quality Inventory.

Table 3
Descriptive and inferential statistical indices of physiological scores.

	Inferential statistics									
	Time			Group			Time × Group interaction			Greenhouse-Geisser ε
	F	η_p^2	[ES]	F	η_p^2	[ES]	F	η_p^2	[ES]	
Pittsburgh Sleep Quality Index										
Sleep latency	F(1, 61) = 0.56	0.008	[S]	F(2, 61) = 0.58	0.017	[S]	F(2, 61) = 0.79	0.023	[S]	0.92
Sleep duration	F(1, 61) = 1.44	0.021	[S]	F(2, 61) = 3.04*	0.085	[M]	F(2, 61) = 0.70	0.021	[S]	0.95
Sleep efficiency	F(1, 61) = 2.32	0.034	[S]	F(2, 61) = 0.19	0.006	[S]	F(2, 61) = 0.37	0.011	[T]	0.88
Sleep disturbances	F(1, 61) = 5.41**	0.076	[M]	F(2, 61) = 0.038	0.001	[S]	F(2, 61) = 0.39	0.012	[T]	0.98
Sleep medications	F(1, 61) = 0.24	0.004	[T]	F(2, 61) = 2.33	0.066	[S]	F(2, 61) = 0.16	0.005	[T]	1.00
Daytime dysfunction	F(1, 61) = 4.83**	0.068	[M]	F(2, 61) = 0.12	0.004	[S]	F(2, 61) = 0.25	0.008	[T]	0.95
Subjective sleep quality	F(1, 61) = 0.72	0.011	[T]	F(2, 61) = 1.60	0.20	[S]	F(2, 61) = 1.08	0.032	[S]	0.94
PSQI overall score	F(1, 61) = 4.42*	0.063	[M]	F(2, 61) = 1.40	0.041	[M]	F(2, 61) = 0.13	0.004	[T]	0.96
Insomnia Severity Index	F(1, 61) = 0.72	0.001	[T]	F(2, 61) = 0.80	0.024	[S]	F(2, 61) = 0.68	0.020	[S]	0.97
Epworth Sleepiness scale	F(1, 61) = 0.33	0.005	[T]	F(2, 61) = 1.59	0.046	[S]	F(2, 61) = 0.46	0.014	[T]	0.93
Berlin	F(1, 61) = 1.70	0.025	[S]	F(2, 61) = 0.28	0.009	[S]	F(2, 61) = 0.87	0.026	[S]	0.95

Notes: * = p < .05; ** = p < .01; [S] = small effect size; [M] = medium effect size.

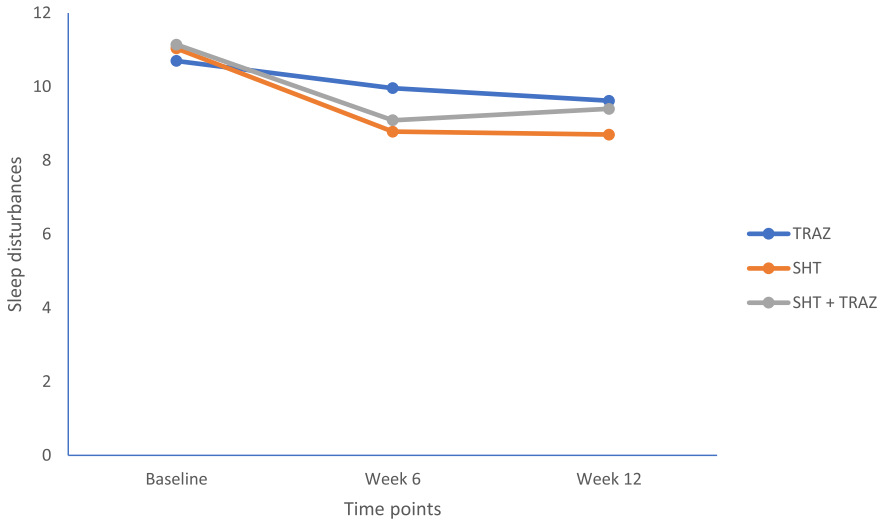

Fig. 2. Sleep disturbances over time and between groups. Points are means. A lower score reflects fewer sleep disturbances. TRAZ = trazodone (n = 19); SHT = sleep hygiene training (n = 11); SHT + TRAZ = sleep hygiene training + trazodone (n = 16).

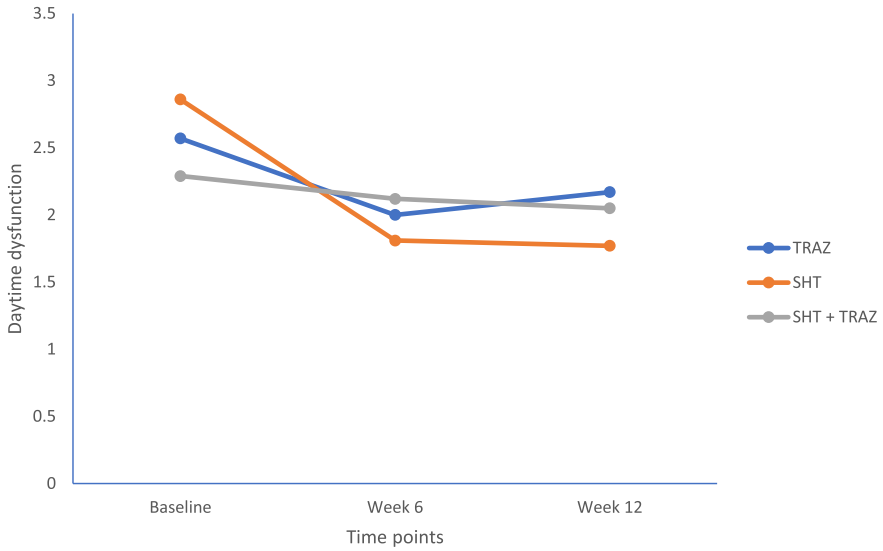

Fig. 3. Daytime dysfunction over time and between groups. Points are means. A lower score reflects lower daytime dysfunction. TRAZ = trazodone (n = 19); SHT = sleep hygiene training (n = 11); SHT + TRAZ = sleep hygiene training + trazodone (n = 16).

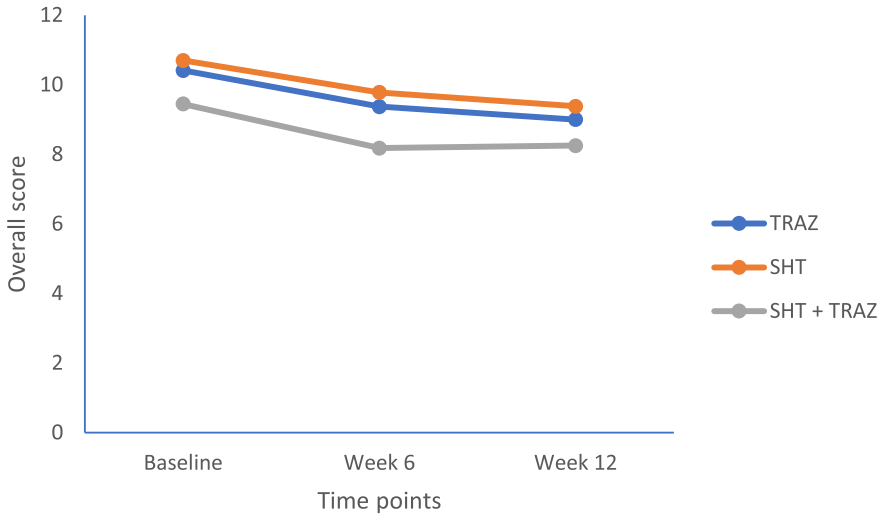

Fig. 4. Overall scores over time and between groups. Points are means. A lower score reflects a lower daytime dysfunction. TRAZ = trazodone (n = 19); SHT = sleep hygiene training (n = 11); SHT + TRAZ = sleep hygiene training + trazodone (n = 16).

Table 4
Descriptive overview of depression and anxiety scores, separately by assessment time (baseline; week 6; week 12), and group (trazodone; sleep hygiene training; trazodone + sleep hygiene training).

	Assessment times								
	Baseline			Week 6			Week 12		
	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ
N	**24**	**23**	**22**	**22**	**18**	**20**	**19**	**11**	**16**
	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
Depression	17.08 (6.74)	17.30 (7.74)	17.09 (9.72)	15.16 (8.96)	16.39 (10.60)	15.54 (9.62)	15.50 (8.43)	14.65 (10.61)	15.59 (7.53)
Anxiety	24.54 (12.15)	25.26 (11.69)	24.63 (15.33)	21.83 (12.57)	20.78 (11.73)	19.77 (10.43)	25.12 (13.42)	21.60 (12.79)	19.90 (12.30)

Notes: TRAZ = trazodone; SHT = sleep hygiene training; SHT + TRAZ = sleep hygiene training + trazodone.

differ across time or between groups.

For the more difficult task of backward digit span performance declined over time in all groups.

For sustained attention (d2-test; correct items), performance improved over time, irrespective of group. Post-hoc analyses after Bonferroni-Holm corrections for p-values showed that performance improved from baseline to week 6 but remained unchanged from week 6 to week 12.

Table 5
Descriptive and inferential statistical indices of symptoms of depression and anxiety.

	Factors									
	Time			Group			Time × Group interaction			Greenhouse-Geisser
	F	η_p^2	[EF]	F	η_p^2	[EF]	F	η_p^2	[EF]	ε
Depression	F(2, 132) = 3.10*	0.045	[S]	F(2, 66) = 0.04	0.001	[T]	F(4, 121) = 0.33	0.010	[T]	0.94
Anxiety	F(2, 132) = 4.56*	0.065	[M]	F(2, 66) = 0.28	0.009	[T]	F(4, 132) = 0.74	0.022	[S]	0.94

Notes: * = $p < 0.05$; EF = effect size; T = trivial effect size S = small effect size, M = medium effect size.

Table 6
Descriptive overview of cognitive performance scores, separately by assessment time (baseline, week 6, week 12), and group (trazodone; sleep hygiene training; trazodone + sleep hygiene training).

	Assessment times								
	Baseline			Week 6			Week 12		
	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ
N	**24**	**23**	**22**	**22**	**18**	**20**		**19**	**11**
Cognitive performance	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
D2 (correct answers)	106.48 (26.26)	99.60 (33.30)	109.95 (28.70)	115.70 (35.55)	103.17 (37.22)	123.14 (27.61)	115.34 (39.82)	110.13 (33.56)	122.09 (25.30)
Digit span forward	5.00 (1.72)	5.13 (1.79)	5.13 (1.64)	5.66 (1.66)	4.74 (2.02)	5.54 (1.94)	5.66 (1.55)	5.04 (1.87)	5.72 (1.93)
Digit span backward	4.75 (1.35)	4.30 (1.32)	4.81 (1.53)	4.16 (1.04)	4.04 (1.26)	4.31 (1.35)	4.25 (0.99)	3.87 (1.29)	4.45 (1.56)

Notes: TRAZ = trazodone; SHT = sleep hygiene training; SHT + TRAZ = sleep hygiene training + trazodone.

Table 7
Descriptive and inferential statistical indices of cognitive performance scores.

	Factors									
	Time			Group			Time × Group interaction			Greenhouse-Geisser
Cognitive performance	F	η_p^2	[ES]	F	η_p^2	[ES]	F	η_p^2	[ES]	ε
d2 (correct answers)	F(1, 64) = 10.80**	0.14	[L]	F(2, 66) = 1.45	0.044	[S]	F(2, 64) = 1.11	0.034	[S]	1.00
Digit span forward	F(2, 132) = 1.86	0.027	[S]	F(2, 66) = 0.79	0.023	[S]	F(4, 132) = 1.36	0.040	[S]	0.95
Digit span backward	F(2, 132) = 4.95**	0.070	[M]	F(2, 66) = 1.11	.033	[S]	F(4, 121) = 0.25	0.008	[S]	0.98

Notes: ** = $p < .01$; S = small effect size, M = medium effect size; L = large effect size.

Table 8
Descriptive and inferential statistical indices of physiological scores.

	Groups						Inferential statistics								
	Baseline			Study end											
	TRAZ	SHT	SHT + TRAZ	TRAZ	SHT	SHT + TRAZ	Time			Group			Time × Group interaction		
N	24	23	22	**19**	**11**	16									
	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	M (SD)	F	η_p^2	[EF]	F	η_p^2	[EF]	F	η_p^2	[EF]
Cortisol	7.30 (7.14)	8.19 (7.67)	6.46 (5.25)	5.98 (5.16)	5.88 (4.36)	6.17 (4.18)	F(1, 61) = 1.76	.028	[S]	F(2, 61) = 0.15	.005	[T]	F(2, 61) = 0.71	.011	[T]
BDNF	0.32 (0.07)	0.34 (0.12)	0.51 (0.92)	0.49 (0.98)	0.47 (0.79)	0.25 (0.08)	F(1, 61) = 0.04	.001	[T]	F(2, 61) = 0.03	.001	[T]	F(2, 61) = 1.50	.047	[S]
$CD4^+$	2.86 (3.12)	2.51 (1.90)	2.96 (2.31)	2.55 (2.09)	2.53 (1.24)	3.16 (2.07)	F(1, 61) = 0.01	.001	[T]	F(2, 61) = 0.49	.016	[T]	F(2, 61) = 0.22	.007	[T]

Notes: TRAZ = trazodone; SHT = sleep hygiene training; SHT + TRAZ: sleep hygiene training + trazodone.
BDNF = brain derived neurotrophic factor; $CD4^+$ = cluster of differentiation 4. T = trivial effect size; S = small effect size.

3.6. Biomarkers

Table 8 provides the descriptive and inferential statistical indices for the biomarkers cortisol, BDNF, and $CD4^+$ for the three groups (TRAZ, SHT, SHT+TRAZ SHT) and for the two assessment time points (baseline; week 12).

Cortisol, BDNF and $CD4^+$ did not change significantly or descriptively over time, between the groups, or between groups over time (interaction effect).

4. Discussion

The key findings of the present study were that among a sample of males with HIV and opioid use disorder and undergoing regular methadone maintenance therapy, sleep-improving interventions had positive effects on aspects of self-reported sleep, symptoms of depression and anxiety, and cognitive performance. More specifically and compared to treatment with trazodone alone (TRAZ), sleep hygiene training (SHT) and the combination of sleep hygiene training and trazodone (SHT +

TRAZ) led to observable improvements after six weeks and these improvements were sustained for a further six weeks. Thus, it appeared that SHT (stand alone or in combination with TRAZ) led to improvements in sleep and affect, while all three interventions had positive effects on cognitive performance. We therefore believe that the present results add to the current literature in an important way; the results are of clinical and practical importance, because they show that sleep-promoting interventions are both feasible and beneficial for those with HIV and OUD and undergoing MMT.

Five hypotheses and one research question were formulated and each of these is considered in turn.

Our first hypothesis was that sleep-improving interventions would enhance subjective sleep among male HIV patients undergoing MMT, and this hypothesis was generally supported. Over time, sleep disturbances decreased, and both sleep quality and daytime functioning improved. In these respects the present findings accord with previous studies (Gutierrez et al., 2019; Low et al., 2014; Hahmood et al., 2018; Patterson et al., 2019). However, we expand upon this previous work in showing that sleep hygiene training (SHT) in particular had positive effects. Compared to administration of TRAZ alone, SHT and SHT + TRAZ reduced sleep disturbances and improved sleep quality, along with daytime functioning, within six weeks of their introduction and sustained these improvements for a further six weeks. The evidence available from the study is unable to shed direct light on the psychological and physiological mechanisms that might explain these improvements, though we consider some possibilities below.

Our second hypothesis was that sleep-promoting interventions would improve cognitive performance, and this was supported for sustained attention, but not for working memory. Nevertheless, our findings are consistent with other research (Byun et al., 2016; Killgore, 2010; Leong et al., 2019; Hahmood et al., 2018; Wardle-Pinkston et al., 2019), but go further in that the improvements were found irrespective of the type of sleep-promoting intervention. Unfortunately, again we cannot draw any direct conclusions about psychophysiological mechanisms that might underlie these effects and the fact that sustained attention improved but working memory did not is an added complication. For want of direct evidence, the following admittedly speculative possibilities are advanced. First, it may be that improvement in sustained attention occurred as a consequence of improved daytime functioning and improved sleep quality. However, this possibility does not explain, why there was no improvement in working memory. Second, it is possible that improvements in sustained attention were epiphenomena of training effects, though such effects have not so far been found for the d2-test (Brickenkamp, 2002) while training effects should also have occurred for working memory. Third, the outcome variable for the d2-test was the sum of correct items within a set time; incorrect answers were not scored. Taking incorrect answers into consideration might have produced another pattern of results.

Our third hypothesis was that sleep-improving interventions would reduce symptoms of depression and anxiety, and this was fully supported. Thus, while the present findings replicate other work (Alvaro et al., 2013; Cox and Olatunji, 2016; Hertenstein et al., 2018; Nutt et al., 2008; Rumble et al., 2015), for the following reasons they also take matters further. First, these improvements were obtained with a patient group not previously studied in this way. Second, the improvements were observable within six weeks of initiating treatment, and third they were sustained for a further six weeks. Gee et al. (2019) found from their systematic review and meta-analysis that non-pharmacological sleep interventions reduced symptoms of depression. However, it is not surprising that there were reductions in symptoms of both depression and anxiety. Transdiagnostic psychotherapy (Norton et al., 2013; Norton and Paulus, 2016; Norton and Roberge, 2017; Pearl and Norton, 2017) is based on propositions that cognitive-emotional improvements are not diagnosis-specific, that there is a substantial overlap in symptoms of depression and anxiety, and that improvements on one dimension (e.g., depression) will therefore be accompanied by improvements on another (e.g., anxiety).

Our fourth hypothesis was that sleep-improving interventions would reduce daytime sleepiness, but this was not supported. Thus, our findings here do not match those from previous research (Byun et al., 2016; Faraut et al., 2018; Low et al., 2014). In this context, we also found no improvement in insomnia scores. The following are possible reasons for the lack of effects here. First, the tools might be too coarse-grained to detect subtle changes. Second, participants may have had difficulties distinguishing between daytime sleepiness and fatigue. Third, there was really no change in daytime sleepiness.

Our fifth hypothesis was that sleep-improving interventions would decrease cortisol concentration and increase BDNF concentration but this was not supported. Again, therefore, our results do not match previous findings (Hatzinger et al., 2010; Hori et al., 2011; Lemola et al., 2015; Mikoteit et al., 2019). The following are possible explanations for our failure to find these effects. First, the physiological condition of males with HIV and OUD and undergoing MMT might be too deteriorated for a 12-week intervention to produce any improvement. Second, it is in the nature of the psychology-physiology-trade-off that changes on a cognitive-emotional level will not necessarily be associated with observable changes at a physiological level. This pattern has been observed for individuals with major depressive disorders and undergoing ECT and physical activity exercise; Salehi et al. (2016) found that although symptom severity reduced following interventions, these cognitive-emotional improvements were entirely unrelated to changes in BDNF concentrations. Similarly, Gerber et al. (2016) reported that for individuals with major depressive disorders, improvements on a non-pharmacological stress challenge were unrelated to cortisol concentrations. In the present study also it appears cognitive-emotional and sleep-related improvements were unrelated to changes in key biomarkers such as cortisol and BDNF.

Our research question concerned the capacity of sleep-improving interventions to alter symptoms of sleep -disordered breathings. The answer was no. The following are possible reasons for this lack of any effect. First, sleep-disordered breathing was assessed by self-reports, which by default can be imprecise and biased. Second, even if participants accurately reported symptoms of OSAs, previous work has shown that OSAs in HIV patients receiving MMT are an issue of the central neuronal respiratory controller (Gutierrez et al., 2019; Teichtahl and Wang, 2007; Wang and Teichtahl, 2007; Wang et al., 2005). Given this, it is highly unlikely that sleep-improving medications or psycho-educative strategies could produce changes in the central neuronal respiratory controller or that they could counteract the effect of methadone on these neuronal regions and processes.

Improvements in sleep-related dimensions were found most clearly in the SHT and SHT + TRAZ conditions, and this deserves particular attention. First, it is possible that psycho-educative group interventions in themselves support and enhance cognitive-emotional and behavioral functioning. For example, Pashaei et al. (2013) showed that, among opioid dependent patients undergoing MMT, relapse rates for drug use were significantly lower among those regularly involved in cognitive-behavioral group interventions than among those in the control condition. Second, Zhang et al. (2019) noted that, among opioid-dependent and HIV patients, daytime structures and social adherence to group activities and interventions produced improvements in life style. It is possible that in the present study such cognitive-emotional, behavioral, social and structural interventions likewise helped to improve participants' daytime structures and activities. Third, as mentioned above, sleep improvements could be an epiphenomenon or a co-occurring effect or both of reductions in depression and anxiety.

The novelty of the findings should be balanced against the following limitations. First, sleep disordered breathing such as obstructive sleep apnea syndrome (OSAS) was only subjectively assessed with the Berlin Questionnaire (Netzer et al., 1999), though this questionnaire is not a diagnostic tool; it merely estimates an individual's risk of suffering from

OSAS and provides only an approximate estimation of risk. However, Hassamal et al. (2016) observed that OSAS is a common issue for individuals undergoing MMT, and it not only has adverse effects on sleep quality but also on a wide range of physiological and psychological functions. Indeed, OSAS is of critical concern because both in children and adults it is associated with an increased risk of systemic comorbidities such as cardiovascular diseases, hypertension, metabolic syndrome, and cognitive impairments (Dewan et al., 2015; Pedrosa et al., 2014). The most important epidemiological risk factors for OSAS are obesity and male gender (Davies, 1990; Reichmuth et al., 2005). Furthermore, OSAS plays an important role in the emergence and maintenance of hypertension, while snoring is a risk factor for hypertension independent of body mass index, apnea/hypopnea index (AHI), or age (Khazaie et al., 2018). Given this, future studies should assess OSAS in an accurate and objective fashion.

Second, studies in psychotherapy show that behavioral change is difficult to achieve and requires modifications at the cognitive-emotional level (Grawe, 2004, 2007; Grawe et al., 1994). Given this, it remains unclear to what extent the interventions produced cognitive-emotional changes related to sleep habits, including the motivation and capacity to translate the substance of instructions during SHT into behavior.

Third, in order to improve sleep patterns and well-being, Merrill et al. (2007) employed an intensive, four week program involving 10 h of moderate to vigorous physical activity and regular cognitive-behavioral psycho-educative training in stress-management and emotion regulation. Compared to the baseline condition, participants (N = 2624; age range: 30–80 years) displayed improvements in sleep duration, sleep quality, and coping with stress and emotion. Given their findings it is possible that for individuals with HIV undergoing MMT and with fluctuating wake-sleep-patterns this very intensive form of intervention might have produced greater changes in their sleep and psychological functioning.

Fourth, the study design was such that participants were always aware of which study condition they had been assigned to; thus, it is conceivable that outcome expectations and motivational cognitive-emotional processes might have biased the outcome.

Fifth, and relatedly, it is also possible that latent and unassessed physiological, psychological and behavioral dimensions might have biased two or more dimensions in the same or opposite direction.

Sixth, future studies should make a more thorough assessment of participants' sleep habits, and cognitive-emotional characteristics related to sleep, in particular those related to pre-sleep (Harvey, 2000; Harvey and Payne, 2002; Harvey and Tang, 2012) and sleep-procrastination (Herzog-Krzywoszanska and Krzywoszanski, 2019; Li et al., 2020; Nauts et al., 2019; van Eerde and Venus, 2018).

Seventh, for cultural (wards are gender-separated) and methodological reasons (investigating a homogeneous sample), we assessed only males. Our findings are therefore not generalizable to females with HIV and undergoing MMT, and future studies should also assess females.

Eighth, while we were unable to find improvements on all dimensions, notably OSAS, daytime sleepiness, insomnia, working memory performance and biomarkers such as cortisol, BDNF and $CD4^{+}$, we also found no further deterioration. A control condition with no interventions or social support would therefore have been helpful to settle whether the zero-improvements on these dimensions were in fact preventions of additional deterioration.

Last, to explore and detect associations between sleep patterns, depression, anxiety, cognitive performances, and biomarkers between and within the three study groups and over time, a series of correlational computations would have been a reasonable option. However, such analyses were considered to be too fine-grained. Accordingly, such results were not reported.

5. Conclusions

In a clinical sample of males with HIV and opioid use disorder (OUD) and undergoing methadone maintenance therapy (MMT) (MMMMT (MMT), specific sleep-improving interventions improved sleep, reduced symptoms of depression and anxiety and enhanced cognitive performance. Beneficial changes were most apparent when sleep hygiene training was included.

Funding source

The entire study (research project 95491) was performed without external funding. The Sleep Disorders Research Center, the Vice Chancellor for Research and Technology of the Kermanshah University of Medical Sciences (Kermanshah, Iran) financially supported the present study.

Author statements

All authors declare that they have substantively contributed to the study design, the performance of the study, including patient recruitment, patients' assessments, data gathering, statistical analysis, writing the drafts, the final version, and the resubmission of the revised version.

Declaration of competing interest

All authors declare no conflicts of interest.

Acknowledgements

We thank Nick Emler (University of Surrey, Surrey UK) for proofreading the manuscript. Additionally, we thank the Sleep Disorders Research Center and Clinical Research Development Unit (CRDU) of the Emam Khomeini, the Mohammad Kermanshahi and the Farabi Hospital (University of Medical Sciences, Kermanshah; Iran) for their support, cooperation and assistance throughout the execution of the study.

References

Alvaro, P.K., Roberts, R.M., Harris, J.K., 2013. A systematic review assessing bidirectionality between sleep disturbances, anxiety, and depression. Sleep 36 (7), 1059–1068.

American Psychiatric Association, 2013, fifth ed.. Diagnostic and Statistical Manual of Mental Disorders. DSM 5. American Psychiatric Association, Arlington VA.

Åslund, L., Arnberg, F., Kanstrup, M., Lekander, M., 2018. Cognitive and behavioral interventions to improve sleep in school-age children and adolescents: a systematic review and meta-analysis. J. Clin. Sleep Med. : JCSM: Off. Pub. Am. Acad. Sleep Med 14 (11), 1937–1947.

Baglioni, C., Spiegelhalder, K., Lombardo, C., Riemann, D., 2010. Sleep and emotions: a focus on insomnia. Sleep Med. Rev. 14 (4), 227–238.

Ballesio, A., Aquino, M., Feige, B., Johann, A.F., Kyle, S.D., Spiegelhalder, K., Lombardo, C., Rücker, G., Riemann, D., Baglioni, C., 2018. The effectiveness of behavioural and cognitive behavioural therapies for insomnia on depressive and fatigue symptoms: a systematic review and network meta-analysis. Sleep Med. Rev. 37, 114–129.

Bastani, P., Marshall, B.D.L., Rahimi-Movaghar, A., Noroozi, A., 2019. The risk environments of people who use drugs accessing two harm reduction centers in Tehran, Iran: a qualitative study. Int. J. Drug Pol. 63, 90–96.

Bastien, C.H., Vallieres, A., Morin, C.M., 2001. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep Med. 2 (4), 297–307.

Beck, A.T., Epstein, N., Brown, G., Steer, R.A., 1988. An inventory for measuring clinical anxiety: psychometric properties. J. Consult. Clin. Psychol. 56 (6), 893–897.

Beck, A.T., Ward, C.H., Mendelson, M., Mock, J., Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatr. 4, 561–571.

Brickenkamp, R., 2002. Test d2- aufmerksamkeits-belastungstest. Hogrefe, Göttingen GER.

Buysse, D.J., Reynolds 3rd, C.F., Monk, T.H., Berman, S.R., Kupfer, D.J., 1989. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatr. Res. 28 (2), 193–213.

Byun, E., Gay, C.L., Lee, K.A., 2016. Sleep, fatigue, and problems with cognitive function in adults living with HIV. J. Assoc. Nurses AIDS Care : J. Assoc. Nurses AIDS Care 27 (1), 5–16.

Chung, K.F., Lee, C.T., Yeung, W.F., Chan, M.S., Chung, E.W., Lin, W.L., 2018. Sleep hygiene education as a treatment of insomnia: a systematic review and meta-analysis. Fam. Pract. 35 (4), 365–375.
Cox, R.C., Olatunji, B.O., 2016. A systematic review of sleep disturbance in anxiety and related disorders. J. Anxiety Disord. 37, 104–129.
Curcio, G., Ferrara, M., De Gennaro, L., 2006. Sleep loss, learning capacity and academic performance. Sleep Med. Rev. 10 (5), 323–337.
Davies, R., 1990. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apnoea syndrome. Eur. Respir. J. 3 (5), 509–514.
Devore, E.E., Grodstein, F., Schernhammer, E.S., 2016. Sleep duration in relation to cognitive function among older adults: a systematic review of observational studies. Neuroepidemiology 46 (1), 57–78.
Dewan, N.A., Nieto, F.J., Somers, V.K., 2015. Intermittent hypoxemia and OSA: implications for comorbidities. Chest 147 (1), 266–274.
Everitt, H., Baldwin, D.S., Stuart, B., Lipinska, G., Mayers, A., Malizia, A.L., Manson, C.C., Wilson, S., 2018. Antidepressants for insomnia in adults. Cochrane Database Syst. Rev. 5 (5), Cd010753.
Faraut, B., Malmartel, A., Ghosn, J., Duracinsky, M., Leger, D., Grabar, S., Viard, J.P., 2018. Sleep disturbance and total sleep time in persons living with HIV: a cross-sectional study. AIDS Behav. 22 (9), 2877–2887.
Farnia, V., Alikhani, M., Ebrahimi, A., Golshani, S., Sadeghi Bahmani, D., Brand, S., 2019. Ginseng treatment improves the sexual side effects of methadone maintenance treatment. Psychiatr. Res. 276, 142–150.
Farrahi Moghaddam, J., Nakhaee, N., Sheibani, V., Garrusi, B., Amirkafi, A., 2012. Reliability and validity of the Persian version of the Pittsburgh sleep quality index (PSQI-P). Sleep & breathing = Schlaf & Atmung 16 (1), 79–82.
Faul, F., Erdfelder, E., Lang, A.G., Buchner, A., 2007. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav. Res. Methods 39 (2), 175–191.
Fava, M., 2004. Daytime sleepiness and insomnia as correlates of depression. J. Clin. Psychiatr. 65 (Suppl. 16), 27–32.
Gamaldo, C.E., Spira, A.P., Hock, R.S., Salas, R.E., McArthur, J.C., David, P.M., Mbeo, G., Smith, M.T., 2013. Sleep, function and HIV: a multi-method assessment. AIDS Behav. 17 (8), 2808–2815.
Gee, B., Orchard, F., Clarke, E., Joy, A., Clarke, T., Reynolds, S., 2019. The effect of non-pharmacological sleep interventions on depression symptoms: a meta-analysis of randomised controlled trials. Sleep Med. Rev. 43, 118–128.
Gerber, M., Lang, C., Lemola, S., Colledge, F., Kalak, N., Holsboer-Trachsler, E., Puhse, U., Brand, S., 2016. Validation of the German version of the insomnia severity index in adolescents, young adults and adult workers: results from three cross-sectional studies. BMC Psychiatr. 16, 174.
Ghassemzadeh, H., Mojtabai, R., Karamghadiri, N., Ebrahimkhani, N., 2005. Psychometric properties of a Persian-language version of the Beck depression inventory–second edition: BDI-II-Persian. Depress. Anxiety 21 (4), 185–192.
Goldstein, A.N., Walker, M.P., 2014. The role of sleep in emotional brain function. Annu. Rev. Clin. Psychol. 10, 679–708.
Gowing, L.R., Farrell, M., Bornemann, R., Sullivan, L.E., Ali, R.L., 2006. Brief report: methadone treatment of injecting opioid users for prevention of HIV infection. J. Gen. Intern. Med. 21 (2), 193–195.
Grawe, K., 2004. Psychological Therapy. Hogrefe Publisher, Göttingen GER.
Grawe, K., 2007. Neuropsychotherapy: How the Neurosciences Inform Effective Psychotherapy. Hogrefe Publisher, Göttingen GER.
Grawe, K.D., R, Bernauer, F., 1994. Development of Pychotherapy - from the Confession to Profession. Hogrefe, Göttingen GER.
Gutierrez, J., Tedaldi, E.M., Armon, C., Patel, V., Hart, R., Buchacz, K., 2019. Sleep disturbances in HIV-infected patients associated with depression and high risk of obstructive sleep apnea. SAGE Open Med 7, 2050312119842268.
Hahmood, Z., Hammond, A., Nunez, R.A., Irwin, M.R., Thames, A.D., 2018. Effects of sleep health on cognitive function in HIV+ and HIV- adults. J. Int. Neuropsychol. Soc. 24 (10), 1038–1046.
Harvey, A.G., 2000. Pre-sleep cognitive activity: a comparison of sleep-onset insomniacs and good sleepers. Br. J. Clin. Psychol. 39 (Pt 3), 275–286.
Harvey, A.G., Payne, S., 2002. The management of unwanted pre-sleep thoughts in insomnia: distraction with imagery versus general distraction. Behav. Res. Ther. 40 (3), 267–277.
Harvey, A.G., Tang, N.K., 2012. (Mis)perception of sleep in insomnia: a puzzle and a resolution. Psychol. Bull. 138 (1), 77–101.
Hassamal, S., Miotto, K., Wang, T., Saxon, A.J., 2016. A narrative review: the effects of opioids on sleep disordered breathing in chronic pain patients and methadone maintained patients. Am. J. Addict. 25 (6), 452–465.
Hatzinger, M., Brand, S., Perren, S., Stadelmann, S., von Wyl, A., von Klitzing, K., Holsboer-Trachsler, E., 2008. Electroencephalographic sleep profiles and hypothalamic-pituitary-adrenocortical (HPA)-activity in kindergarten children: early indication of poor sleep quality associated with increased cortisol secretion. J. Psychiatr. Res. 42 (7), 532–543.
Hatzinger, M., Brand, S., Perren, S., Stadelmann, S., von Wyl, A., von Klitzing, K., Holsboer-Trachsler, E., 2010. Sleep actigraphy pattern and behavioral/emotional difficulties in kindergarten children: association with hypothalamic-pituitary-adrenocortical (HPA) activity. J. Psychiatr. Res. 44 (4), 253–261.
Hatzinger, M., Brand, S., Perren, S., von Wyl, A., Stadelmann, S., von Klitzing, K., Holsboer-Trachsler, E., 2012. Pre-schoolers suffering from psychiatric disorders show increased cortisol secretion and poor sleep compared to healthy controls. J. Psychiatr. Res. 46 (5), 590–599.
Hertenstein, E., Feige, B., Gmeiner, T., Kienzler, C., Spiegelhalder, K., Johann, A., Jansson-Frojmark, M., Palagini, L., Rucker, G., Riemann, D., Baglioni, C., 2018. Insomnia as a predictor of mental disorders: a systematic review and meta-analysis. Sleep Med. Rev. 43, 96–105.
Herzog-Krzywoszanska, R., Krzywoszanski, L., 2019. Bedtime procrastination, sleep-related behaviors, and demographic factors in an online survey on a polish sample. Front. Neurosci. 13 (963).
Hori, H., Teraishi, T., Sasayama, D., Ozeki, Y., Matsuo, J., Kawamoto, Y., Kinoshita, Y., Hattori, K., Higuchi, T., Kunugi, H., 2011. Poor sleep is associated with exaggerated cortisol response to the combined dexamethasone/CRH test in a non-clinical population. J. Psychiatr. Res. 45 (9), 1257–1263.
Hossein Kaviani, H., Mousavi, A.S., 2008. Psychometric properties of the Persian version of Beck anxiety inventory (Bai). Tehran Univ. Med. J. 66 (2), 136–140.
Jahangard, L., Sadeghi, A., Ahmadpanah, M., Holsboer-Trachsler, E., Sadeghi Bahmani, D., Haghighi, M., Brand, S., 2018. Influence of adjuvant omega-3-polyunsaturated fatty acids on depression, sleep, and emotion regulation among outpatients with major depressive disorders - results from a double-blind, randomized and placebo-controlled clinical trial. J. Psychiatr. Res. 107, 48–56.
Johns, M.W., 1991. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep 14 (6), 540–545.
Karki, P., Shrestha, R., Huedo-Medina, T.B., Copenhaver, M., 2016. The impact of methadone maintenance treatment on HIV risk behaviors among high-risk injection drug users: a systematic review. Evid Based Med. Public Health 2.
Khazaie, H., Negahban, S., Ghadami, M.R., Sadeghi Bahmani, D., Holsboer-Trachsler, E., Brand, S., 2018. Among middle-aged adults, snoring predicted hypertension independently of sleep apnoea. J. Int. Med. Res. 46 (3), 1187–1196.
Killgore, W.D., 2010. Effects of sleep deprivation on cognition. Prog. Brain Res. 185, 105–129.
Killgore, W.D., Kahn-Greene, E.T., Lipizzi, E.L., Newman, R.A., Kamimori, G.H., Balkin, T.J., 2008. Sleep deprivation reduces perceived emotional intelligence and constructive thinking skills. Sleep Med. 9 (5), 517–526.
Kunisaki, K.M., Akgün, K.M., Fiellin, D.A., Gibert, C.L., Kim, J.W., Rimland, D., Rodriguez-Barradas, M.C., Yaggi, H.K., Crothers, K., 2015. Prevalence and correlates of obstructive sleep apnoea among patients with and without HIV infection. HIV Med. 16 (2), 105–113.
Lemola, S., Perkinson-Gloor, N., Hagmann-von Arx, P., Brand, S., Holsboer-Trachsler, E., Grob, A., Weber, P., 2015. Morning cortisol secretion in school-age children is related to the sleep pattern of the preceding night. Psychoneuroendocrinology 52, 297–301.
Leong, R.L.F., Cheng, G.H., Chee, M.W.L., Lo, J.C., 2019. The effects of sleep on prospective memory: a systematic review and meta-analysis. Sleep Med. Rev. 47, 18–27.
Li, X., Buxton, O.M., Kim, Y., Haneuse, S., Kawachi, I., 2020. Do procrastinators get worse sleep? Cross-sectional study of US adolescents and young adults. SSM Popul Health 10, 100518.
Lo, J.C., Groeger, J.A., Cheng, G.H., Dijk, D.J., Chee, M.W., 2016. Self-reported sleep duration and cognitive performance in older adults: a systematic review and meta-analysis. Sleep Med. 17, 87–98.
Low, Y., Goforth, H., Preud'homme, X., Edinger, J., Krystal, A., 2014. Insomnia in HIV-infected patients: pathophysiologic implications. AIDS Rev. 16 (1), 3–13.
Lowe, C.J., Safati, A., Hall, P.A., 2017. The neurocognitive consequences of sleep restriction: a meta-analytic review. Neurosci. Biobehav. Rev. 80, 586–604.
Manber, R., Chambers, A.S., 2009. Insomnia and depression: a multifaceted interplay. Curr. Psychiatr. Rep. 11 (6), 437–442.
Merrill, R.M., Aldana, S.G., Greenlaw, R.L., Diehl, H.A., Salberg, A., 2007. The effects of an intensive lifestyle modification program on sleep and stress disorders. J. Nutr. Health Aging 11 (3), 242–248.
Mikoteit, T., Brand, S., Eckert, A., Holsboer-Trachsler, E., Beck, J., 2019. Brain-derived neurotrophic factor is a biomarker for subjective insomnia but not objectively assessable poor sleep continuity. J. Psychiatr. Res. 110, 103–109.
Monteiro, B.C., Monteiro, S., Candida, M., Adler, N., Paes, F., Rocha, N., Nardi, A.E., Murillo-Rodriguez, E., Machado, S., 2017. Relationship between brain-derived neurotrofic factor (bdnf) and sleep on depression: a critical review. Clin. Pract. Epidemiol. Ment. Health : CP & EMH 13, 213–219.
Murawski, B., Wade, L., Plotnikoff, R.C., Lubans, D.R., Duncan, M.J., 2018. A systematic review and meta-analysis of cognitive and behavioral interventions to improve sleep health in adults without sleep disorders. Sleep Med. Rev. 40, 160–169.
Nauts, S., Kamphorst, B.A., Stut, W., De Ridder, D.T.D., Anderson, J.H., 2019. The explanations people give for going to bed late: a qualitative study of the varieties of bedtime procrastination. Behav. Sleep Med. 17 (6), 753–762.
Netzer, N.C., Stoohs, R.A., Netzer, C.M., Clark, K., Strohl, K.P., 1999. Using the Berlin Questionnaire to identify patients at risk for the sleep apnea syndrome. Ann. Intern. Med. 131 (7), 485–491.
Norell-Clarke, A., Jansson-Frojmark, M., Tillfors, M., Harvey, A.G., Linton, S.J., 2014. Cognitive processes and their association with persistence and remission of insomnia: findings from a longitudinal study in the general population. Behav. Res. Ther. 54, 38–48.
Norton, P.J., Barrera, T.L., Mathew, A.R., Chamberlain, L.D., Szafranski, D.D., Reddy, R., Smith, A.H., 2013. Effect of transdiagnostic cbt for anxiety disorders on comorbid diagnoses. Depress. Anxiety 30 (2), 168–173.
Norton, P.J., Paulus, D.J., 2016. Toward a unified treatment for emotional disorders: update on the science and practice. Behav. Ther. 47 (6), 854–868.
Norton, P.J., Roberge, P., 2017. Transdiagnostic therapy. Psychiatr. Clin. 40 (4), 675–687.
Nutt, D., Wilson, S., Paterson, L., 2008. Sleep disorders as core symptoms of depression. Dialogues Clin. Neurosci. 10 (3), 329–336.
Pashaei, T., Shojaeizadeh, D., Rahimi Foroushani, A., Ghazitabatabae, M., Moeeni, M., Rajati, F., E, M.R., 2013. Effectiveness of relapse prevention cognitive-behavioral

model in opioid-dependent patients participating in the methadone maintenance treatment in Iran. Iran. J. Public Health 42 (8), 896–902.
Patterson, F., Connick, E., Brewer, B., Grandner, M.A., 2019. HIV status and sleep disturbance in college students and relationship with smoking. Sleep health 5 (4), 395–400.
Pearl, S.B., Norton, P.J., 2017. Transdiagnostic versus diagnosis specific cognitive behavioural therapies for anxiety: a meta-analysis. J. Anxiety Disord. 46, 11–24.
Pedrosa, R.P., Barros, I.M., Drager, L.F., Bittencourt, M.S., Medeiros, A.K.L., Carvalho, L. L., Lustosa, T.C., Carvalho, M.M., Ferreira, M.N., Lorenzi-Filho, G., 2014. OSA is common and independently associated with hypertension and increased arterial stiffness in consecutive perimenopausal women. Chest 146 (1), 66–72.
Reichmuth, K.J., Austin, D., Skatrud, J.B., Young, T., 2005. Association of sleep apnea and type II diabetes: a population-based study. Am. J. Respir. Crit. Care Med. 172 (12), 1590–1595.
Rumble, M.E., White, K.H., Benca, R.M., 2015. Sleep disturbances in mood disorders. Psychiatr. Clin. 38 (4), 743–759.
Sater, R.A., Gudesblatt, M., Kresa-Reahl, K., Brandes, D.W., Sater, P.A., 2015. The relationship between objective parameters of sleep and measures of fatigue, depression, and cognition in multiple sclerosis. Multiple Sclerosis J. Exp. Trans. Clin. 1, 2055217315577828.
Teichtahl, H., Wang, D., 2007. Sleep-disordered breathing with chronic opioid use. Expet Opin. Drug Saf. 6 (6), 641–649.
Thakral, M., Von Korff, M., McCurry, S.M., Morin, C.M., Vitiello, M.V., 2020. Changes in dysfunctional beliefs about sleep after cognitive behavioral therapy for insomnia: a systematic literature review and meta-analysis. Sleep Med. Rev. 49, 101230.
Trauer, J.M., Qian, M.Y., Doyle, J.S., Rajaratnam, S.M., Cunnington, D., 2015. Cognitive behavioral therapy for chronic insomnia: a systematic review and meta-analysis. Ann. Intern. Med. 163 (3), 191–204.
Van Dongen, H.P., Maislin, G., Mullington, J.M., Dinges, D.F., 2003. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. Sleep 26 (2), 117–126.
van Eerde, W., Venus, M., 2018. A daily diary study on sleep quality and procrastination at work: the moderating role of trait self-control. Front. Psychol. 9, 2029.
van Straten, A., van der Zweerde, T., Kleiboer, A., Cuijpers, P., Morin, C.M., Lancee, J., 2018. Cognitive and behavioral therapies in the treatment of insomnia: a meta-analysis. Sleep Med. Rev. 38, 3–16.
Wang, D., Teichtahl, H., 2007. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med. Rev. 11 (1), 35–46.
Wang, D., Teichtahl, H., Drummer, O., Goodman, C., Cherry, G., Cunnington, D., Kronborg, I., 2005. Central sleep apnea in stable methadone maintenance treatment patients. Chest 128 (3), 1348–1356.
Wardle-Pinkston, S., Slavish, D.C., Taylor, D.J., 2019. Insomnia and cognitive performance: a systematic review and meta-analysis. Sleep Med. Rev. 48, 101205.
Wechsler, D., 2008. Wechsler Adult Intelligence Scale, 4th. Pearson Assessment., San Antonio, TX.
Wodak, A., McLeod, L., 2008. The role of harm reduction in controlling HIV among injecting drug users. AIDS 22 (Suppl. 2), S81–S92 (Suppl 2).
World Medical Association, 2013. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. Jama 310 (20), 2191–2194.
Wu, L., Sun, D., Tan, Y., 2018. A systematic review and dose-response meta-analysis of sleep duration and the occurrence of cognitive disorders. Sleep Breath. 22 (3), 805–814.
Zhang, L., Zou, X., Xu, Y., Medland, N., Deng, L., Liu, Y., Su, S., Ling, L., 2019. The decade-long Chinese methadone maintenance therapy yields large population and economic benefits for drug users in reducing harm, HIV and HCV disease burden. Front Public Health 7, 327.