Drug and Alcohol Dependence 125 (2012) 132–139

Contents lists available at SciVerse ScienceDirect

Drug and Alcohol Dependence

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

Response inhibition and psychomotor speed during methadone maintenance: impact of treatment duration, dose, and sleep deprivation

B.K. Bracken[a,b,*,3], G.H. Trksak[a,b,c,**,3], D.M. Penetar[a,b,c], W.L. Tartarini[a,c], M.A. Maywalt[c,1], C.M. Dorsey[b,c,2], S.E. Lukas[a,b,c]

[a] Behavioral Psychopharmacology Research Lab, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA
[b] Psychiatry, Harvard Medical School, Boston, 115 Mill Street, Belmont, MA 02478, USA
[c] Sleep Research Laboratory, McLean Hospital, 115 Mill Street, Belmont, MA 02478, USA

ARTICLE INFO

Article history:
Received 2 September 2011
Received in revised form 3 April 2012
Accepted 5 April 2012
Available online 30 April 2012

Keywords:
Methadone maintained
Sleep deprivation
Psychomotor performance
Impulsivity

ABSTRACT

Background: In opiate-dependent individuals, abstinence results in deficits in cognitive functioning, which may be exacerbated by medication-associated sleep disruption.
Method: To assess cognitive function and the influence of sleep deprivation (SD), 14 healthy control (HC) and 22 methadone maintained (MM) participants completed the continuous performance task (CPT) after a baseline night, a night of total SD, and two recovery sleep nights. The digit symbol substitution task (DSST) was administered at bedtime and in the morning. Secondary analyses separated MM participants into short- (<12 months; $n = 8$) and long-term (≥12 months; $n = 14$) treatment duration groups, and into low- (<80 mg; $n = 9$) and high-dose (≥80 mg; $n = 13$) groups.
Results: Linear mixed model ANOVAs revealed that there was no effect of SD. Across all days MM participants had more errors of omission, fewer correct responses, and slower reaction times (RTs) on the CPT, and fewer accurate substitutions on the evening and morning DSST. Short-term MM participants exhibited slower RTs on the CPT, and fewer correct substitutions on the evening DSST compared to long-term MM participants. Low-dose MM participants had slower RTs on the CPT than HCs and high-dose MM participants.
Conclusion: These data demonstrate that methadone-maintained individuals exhibit poorer performance on tasks of psychomotor speed and selective attention/impulsivity, but with longer-term treatment, performance appears to return toward control levels. Furthermore, while one day of SD was enough to alter subjective reports of sleep quality, cognitive function may be more resilient.

1. Introduction

Worldwide, 21.9 million people used opiates in 2008 (United Nations Office on Drugs Crimes, 2010). In the US, 1.9 million people are dependent on or abused prescription pain medications; 399,000 people meet these criteria for heroin (Substance Abuse and Mental Health Administration, 2010). Per year, there are 739,000 treatment admissions for prescription pain medication and 507,000 treatment admissions for heroin (Substance Abuse and Mental Health Services Administration, 2010). In the UK, there are 330,000 people who used heroin or cocaine; three quarters of adults seeking drug treatment are heroin addicts; and deaths from heroin are rising (National Treatment for Substance Misuse, 2009).

Methadone maintenance (MM) has been a standard opiate-dependence treatment for over 30 years. Once daily oral methadone is safe and efficacious at suppressing withdrawal symptoms and blocking euphoric effects associated with heroin administration (Committee for Methadone Program Administrators, 1997). MM positively impacts general health of opiate abusers, increasing treatment retention (Mattick et al., 2009), decreasing heroin use, improving health outcomes, and decreasing risky sexual behavior, HIV/AIDS, hepatitis and STDs (Committee for Methadone Program Administrators, 1997). MM increases productivity, decreases criminal activity (Hubbard et al., 1997; Gossop et al., 2005), and lowers mortality (Soyka et al., 2006, 2011).

In healthy volunteers, i.v. morphine increases subjective ratings of drug effect, but does not affect psychomotor speed (Hill and

* Corresponding author at: McLean Imaging Center, McLean Hospital/Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA. Tel.: +1 617 855 3911.
** Corresponding author at: McLean Imaging Center, McLean Hospital/Harvard Medical School, 115 Mill Street, Belmont, MA 02478, USA. Tel.: +1 617 855 2718; fax: +1 617 855 3711.
E-mail addresses: bbracken@mclean.harvard.edu (B.K. Bracken), gtrksak@mclean.harvard.edu (G.H. Trksak).
[1] Now at Sleep Health Centers, 41 North Road, Bedford, MA 01730, USA.
[2] Now in private practice, 1266 Main St., West Concord, MA 01742, USA.
[3] Both contributed equally to this work.

0376-8716/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.drugalcdep.2012.04.004

Zacny, 2000). Current heroin abusers perform worse on intra- and extra-dimensional set shifting and working memory tasks when compared to healthy controls (HCs; Ornstein et al., 2000). Memory and response inhibition decrements persist in initial (~2 weeks) MM therapy (Rapeli et al., 2007), but improvements on a subset of tasks including verbal learning and memory, visuospatial memory, psychomotor speed (Gruber et al., 2006), executive functioning (Soyka et al., 2008), and response inhibition (Soyka et al., 2010) are seen after several months of MM stabilization. However, reduced use of other drugs and alcohol, less harmful lifestyles, and learning effects may also contribute to improvements (Soyka et al., 2008). Even after stabilization on methadone, MM participants perform worse than HCs (Pirastu et al., 2006). In fact, higher methadone doses (Loeber et al., 2008) and more recent methadone administration (Curran et al., 2001) are associated with poorer performance. Even MM participants stably medicated for years perform worse than HCs and successfully abstinent heroin dependent individuals (Mintzer et al., 2005; Verdejo et al., 2005; Prosser et al., 2006).

Impaired sleep may contribute to reduced cognitive function (Schmutte et al., 2007). Methadone and heroin similarly disturb sleep, although methadone is about half as potent as heroin (Kay et al., 1981; Wang and Teichtahl, 2007). Disturbances to sleep architecture occur during all phases of opiate use (Wang and Teichtahl, 2007) with subjective sleep most disturbed at the end of opiate detoxification, and slowly normalizing by two weeks of abstinence (Beswick et al., 2003). In alcohol and cocaine-abusing populations, disturbed sleep is an important predictor of relapse (Brower et al., 1998; Conroy et al., 2006), and there are many indications that this is true in opiate-dependent populations as well (Gossop and Bradley, 1984; Staedt et al., 1996; Oyefeso et al., 1997).

To test whether deficits in cognitive functioning may be exacerbated by acute sleep disturbance, the present study examined impulse inhibition, psychomotor speed, subjective mood, sleep quality and sleep quantity before and after one baseline night of sleep, one night of total sleep deprivation (SD), and two recovery sleep nights (RE). To assess differences based on the duration of MM, secondary analyses divided participants into short- and long-term MM treatment duration groups. Finally, to assess differences based on methadone dose, secondary analyses divided participants were divided into low- and high-dose groups. A priori hypotheses were that all MM participants would perform more poorly on cognitive tasks than HCs at baseline, and that baseline differences would be exacerbated by SD. Short-term MM participants would perform most poorly, however after SD both long- and short-term groups would perform at a similar level. Finally, participants on a high dose of methadone would perform the most poorly, however after SD both high- and low-dose groups would perform at a similar level. These data were collected as part of a larger study to assess the effects of SD on sleep architecture and brain bioenergetics in MM participants (Trksak et al., 2010).

2. Methods

2.1. Participants

HCs and opiate-dependent participants actively enrolled in a MM program were recruited via newspaper, radio, online advertisements, or from the North Charles Mental Health and Addiction Services (Cambridge, MA). After initial phone screens, they visited the Sleep Research Laboratory at McLean Hospital where IRB approved informed consent was obtained. They underwent a physical examination (EKG, complete blood panel and test of liver function), drug urine screen (QuickTox Drug Screen Dipcard, Branan Medical Corporation, Irvine, CA), and pregnancy testing for females (Stanbio QuPID, Studio Laboratory, Boerne, TX). Pregnant participants were excluded. Participants were free of any current Axis I disorders (Structured Clinical Interview for DSM-IV Disorders; First et al., 1997), except opiate dependence for MM participants. Participants were free of primary sleep disorders, including sleep apnea and periodic limb movement disorder assessed with polysomnography. On study nights participants were again tested for drugs and pregnancy. Positive drug test results: baseline-3 cocaine, 3 benzodiazepines, 1 morphine, 1 THC; SD-2 cocaine, 4 benzodiazepines, 1 morphine, 1 THC, 2 PCP; RE 1–1 cocaine, 3 benzodiazepines, 1 THC; RE 2–4 cocaine, 5 benzodiazepines, 2 morphine, 1 PCP. The percentage of drug positive urines were not different between groups (short-term MM: 38%; long-term MM: 29%; low-dose methadone: 33%; high-dose methadone: 33%).

Participant completers were 14 HC adults (34 ± 3.1 years; $n = 7$ females), and 22 MM adults (39.5 ± 2.1 years; $n = 10$ females). There were no significant age or sex differences between HC and MM groups. Average treatment duration for the MM group was 16.1 ± 2.4 months. Within the MM group, 8 participants were categorized as short-term (MM < 12 months; age = 38 ± 3.6 years; 4 female), and 14 as long-term (MM ≥ 12 months; age = 40.3 ± 2.8 years; 6 female). This differentiation is based on previous findings and clinical relevance (Oviedo-Joekes et al., 2009; Peles et al., 2011a). There were no significant age or sex differences between short- and long-term treatment groups. Within the MM group, 9 participants were categorized as low-dose (dose < 80 mg; age = 45.6 ± 6.0 years; 6 female), and 13 as high-dose (dose ≥ 80 mg; age = 35.2 ± 10.2 years; 4 female). This differentiation is based on previous findings and clinical practices (Mohamad et al., 2010; Peles et al., 2011b). Low-dose participants were older than high-dose participants ($p = 0.014$), but there was no sex difference between MM groups. Participants in the short-term group were not more likely to be receiving a higher dose of methadone. The short-term MM group contained 6 participants on a high dose and 2 participants on a low dose of methadone. The long-term MM group contained 7 participants on a high dose and 7 participants on a low dose.

2.2. Experimental procedures

The continuous performance task (CPT) is designed to assess selective attention and impulsivity (Conners, 1994). 360 stimuli are presented in random order (10% targets). One key indicates the stimulus is a target; a different key indicates it is not a target. The digit symbol substitution task (DSST) is designed to assess psychomotor performance (Lezak et al., 2004). The participant completes a worksheet with a key containing symbols paired with numbers. Participants fill in as many symbols next to corresponding numbers as possible in 120 s.

On SD nights, participants remained awake for ≥36 h, supervised by a technician. On all other non-deprivation nights, total time in bed was 8 h. To assess cognitive function, participants were administered the CPT in the morning after a baseline night of sleep, a night of total SD, and two RE nights. The DSST was administered at bedtime and in the morning each day. To assess mood, participants were administered the Profile of Mood States (POMS; McNair et al., 1971) at bedtime and in the morning each day. To assess subjective sleep, participants were administered the Stanford Sleepiness Scale (SSS; Hoddes et al., 1972) and a visual analog scale (VAS) on which participants rated their current level of sleepiness (anchors: sleepy, alert). All tests were assessed in the morning before participants' daily dose of methadone or in the evening immediately before bed. All participants were stably medicated, and attended regular methadone clinic visits at the usual dosing time. Therefore, side effects and withdrawal symptoms were not measured.