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Measuring Objective and Subjective Sleep during Lisdexamfetamine Treatment of Acute Methamphetamine Withdrawal: A Feasibility Study

Liam S. Acheson[a, b, c] Christopher Gordon[d, e] Rebecca McKetin[a] Jonathan Brett[f, g] Michael Christmass[h, i] Craig Rodgers[b] Nicholas Lintzeris[j, k, l] Adrian Dunlop[j, m, n] Michael Farrell[a] Steven Shoptaw[o] Nadine Ezard[b, c, j] Krista J. Siefried[a, b, c]

[a]The National Drug and Alcohol Research Centre (NDARC), The University of New South Wales, Sydney, NSW, Australia; [b]Alcohol and Drug Service, St Vincent's Hospital Sydney, Sydney, NSW, Australia; [c]The National Centre for Clinical Research on Emerging Drugs (NCCRED), c/o the University of New South Wales, Sydney, NSW, Australia; [d]Susan Wakil School of Nursing and Midwifery, The University of Sydney, Sydney, NSW, Australia; [e]CIRUS Centre for Sleep and Chronobiology, Woolcock Institute of Medical Research, University of Sydney, Sydney, NSW, Australia; [f]Clinical Pharmacology and Toxicology, St Vincent's Hospital Sydney, Sydney, NSW, Australia; [g]St. Vincent's Clinical School, The University of New South Wales, Sydney, NSW, Australia; [h]Next Step Drug and Alcohol Services, Perth, WA, Australia; [i]National Drug Research Institute, Curtin University, Perth, WA, Australia; [j]New South Wales Drug and Alcohol Clinical Research and Improvement Network (DACRIN), Sydney, NSW, Australia; [k]Drug and Alcohol Services, Sydney, NSW, Australia; [l]Specialty of Addiction Medicine, The University of Sydney, Sydney, NSW, Australia; [m]Drug and Alcohol Clinical Services, Newcastle, NSW, Australia; [n]School of Medicine and Public Health, The University of Newcastle, Newcastle, NSW, Australia; [o]Department of Family Medicine, The University of California Los Angeles, Los Angeles, CA, USA

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Abstract

Introduction: Sleep disturbance is common during methamphetamine (MA) use and withdrawal; however, the feasibility of combined subjective-objective measurement of sleep-wake has not been shown in this population. Actigraphy is a well-established, non-invasive measure of sleep-wake cycles with good concordance with polysomnography. This study aimed to investigate the feasibility and utility of using actigraphy and sleep diaries to investigate sleep during MA withdrawal. ***Methods:*** We conducted a feasibility and utility study of actigraphy and sleep diaries during a clinical trial of lisdexamfetamine for MA withdrawal. Participants were inpatients for 7 days, wore an actigraph (Philips Actiwatch 2) and completed a modified Consensus Sleep Diary each morning. Participants were interviewed between days 3–5. ***Results:*** Ten participants (mean age 37 years, 90% male) were enrolled. No participant removed the device prematurely. Participants interviewed (n = 8) reported that the actigraph was not difficult or distracting to

karger@karger.com
www.karger.com/ear

Correspondence to:
Liam S. Acheson, liam.acheson@svha.org.au

wear or completion of daily sleep diary onerous. Actigraphic average daily sleep duration over 7 days was 568 min, sleep onset latency 22.4 min, wake after sleep onset (WASO) 75.2 min, and sleep efficiency 83.6%. Sleep diaries underreported daily sleep compared with actigraphy (sleep duration was 56 min ($p = 0.008$) and WASO 47 min ($p < 0.001$) less). Overall sleep quality was 4.4 on a nine-point Likert scale within the diary. ***Conclusions:*** Continuous actigraphy is feasible to measure sleep-wake in people withdrawing from MA, with low participant burden. We found important differences in self-reported and actigraphic sleep, which need to be explored in more detail.

Introduction

Currently, there are no approved medications indicated for methamphetamine (MA) withdrawal. A particular challenge in managing withdrawal from MA is the sleep disturbances that occur during the withdrawal process [1]. These impairments in sleep-wake behaviours are amongst the most undesirable symptoms of MA withdrawal [1] and have been postulated to drive post-withdrawal substance use [2]. It is therefore imperative that any pharmacotherapies that are used in the management of MA withdrawal can successfully ameliorate related sleep disturbances.

Evaluation of whether pharmacotherapies can ameliorate sleep disturbances requires accurate, objective, and detailed data on sleep-wake behaviours. This is difficult in the context of MA withdrawal. The gold-standard in sleep measurement, polysomnography (PSG) includes multiple concurrent measurements of electroencephalogram, electro-oculogram, and electromyogram but can also include electrocardiogram, pulse oximetry, airflow, and respiratory measures used in the diagnosis of sleep disorders [3]. PSG is resource intensive, typically conducted in a sleep laboratory, and is therefore costly and impractical for use in the context of a drug withdrawal management unit [4]. The use of subjective sleep assessment, such as sleep diaries are commonly used, but these rely on participant recall do not provide the granularity of objective data needed for a thorough assessment of sleep-wake behaviour in MA withdrawal. Further, there are well-defined differences in subjective and objective sleep which are common in people with insomnia, attention-deficit hyperactivity disorder, and depression, all of which are found in people who use MA [5, 6]. It has thus been recommended that these measures be combined [7].

An alternative and potentially more feasible approach involves combining subjective sleep measures with actigraphy. Actigraphy collects continuous objective sleep-wake data via a wearable device (typically wrist-worn) and is the gold-standard of sleep measurement in ambulatory settings. In healthy sleepers, actigraphic measurement of sleep and wake has comparable accuracy to PSG [8]. Although actigraphy has been utilised in pre-clinical laboratory studies, no clinical trials investigating treatments of MA use or dependence have included actigraphy, nor attempted to combine subjective and objective sleep measures [9].

This study examined the feasibility and utility of actigraphy in a clinical trial investigating lisdexamfetamine for the treatment of MA withdrawal over a 7-day admission to hospital. Data were compared to sleep patterns recorded from a conventional and validated sleep diary, the Consensus Sleep Diary (CSD) [10].

Materials and Methods

Study Design and Procedures

An exploratory analysis of actigraphy and daily sleep diary data from an open-label, single-arm clinical trial of lisdexamfetamine (LDX) for the treatment of acute MA withdrawal. The 7-day trial involved a tapering dose of LDX, beginning at 250 mg oral once daily, reducing by 50 mg per day to 50 mg once daily on day 5. Inpatient treatment-as-usual consisted of withdrawal symptom management and supportive care. Participants were at least 18 years of age, had a current DSM-5 MA use disorder, and were voluntarily presenting to inpatient MA withdrawal treatment. This study protocol is described in detail and outcomes reported elsewhere [11].

Feasibility and Utility

The feasibility of continuous actigraphy and daily sleep diaries was defined as (i) actigraph time on wrist, (ii) participant feedback via qualitative interview on difficulties encountered wearing the device and completing the diary, and (iii) utility as the proportion of useable actigraphy data and missed sleep diaries.

One-on-one, semi-structured interviews focused on understanding participant experiences of trial participation (including measurement of outcomes) were conducted in person between days three and six of admission to allow participants to experience and reflect on study methods. All interviews were conducted face-to-face by the study coordinator (L.S.A.), in a private clinic room within the withdrawal unit, transcribed verbatim, and coded in NVivo (v12, Lumivero, Denver, CO). Other qualitative data are reported elsewhere.

Sleep Measures

Actigraphy

All participants were provided with an actigraph (Phillips Actiwatch 2®, Philips Respironics, Murrysville, PA) on admission. Actigraphs recorded participant movement and ambient light levels to calculate sleep-wake periods. Participants were instructed to wear the device continuously from admission to discharge, with participants allowed to remove the device to shower. Actigraphic data were scored using Philips Actiware (Version 6.0.9, Philips

Table 1. Substance use history

Duration of MA use, median (IQR[a]), years	13.6 (10.1–19.3)
Age first used MA, median (IQR), years	21.5 (18.25–26.5)
Days used in last 28 days, median (IQR), days	23 (20–28)
Quantity used per day[a], median (IQR), g	0.6 (0.2–0.7)
Other recent substance use (any use last 28 days)	
Tobacco, *n* (%)	3 (30)
Alcohol, *n* (%)	3 (30)
GHB[b], *n* (%)	5 (50)
Cannabis, *n* (%)	5 (50)
Benzodiazepines, *n* (%)	1 (10)
Ecstasy, *n* (%)	1 (10)
Amyl nitrate, *n* (%)	1 (10)

[a]Interquartile range. [b]Gamma hydroxybutyrate.

Table 2. Mean sleep summary statistics across 7-day admission

	Sleep diary mean (SD[a])	Actigraph mean (SD)	Effect size mean difference (95% CI[b])	*p* value
Total sleep time, min[c]	509.1 (184.3)	567.6 (162.1)	−58.5 (−101.4 to −15.7)	**0.008**
Sleep onset latency, min	28.1 (53.3)	22.4 (29.4)	5.7 (−8.1 to 19.4)	0.410
WASO, min	28.5 (43.3)	75.2 (53.9)	−46.6 (−59.3 to −33.9)	<**0.001**
Efficiency, %	83.6 (16.0)	83.6 (9.6)	0.04 (−4.9 to 4.9)	0.986
Quality (1–9)	4.4 (1.8)	*		

[a]Standard deviation. [b]Confidence interval. [c]Minutes. *Not recorded by device.

Respironics, Murrysville, PA) according to standardised scoring methods for actigraphy (scoring refers to the defining and categorising of sleep epochs).

Sleep Diary

Participants completed a modified CSD [10] each morning on waking. The sleep diary was modified by removing items related to work or exercise (due to hospitalisation) and medications for sleep aid (as all medications were recorded in inpatient medication charts). Subjective sleep quality is determined by a 9-point Likert scale in the CSD, where lower scores indicate better sleep.

The difference in recorded measures of actigraphy and sleep diaries in terms of total sleep time (TST), sleep onset latency (SOL), wake after sleep onset (WASO), sleep efficiency, and subjective sleep quality were assessed. TST is defined as the total amount of sleep time scored during the total recording time. SOL is the duration of time from attempting to fall asleep to falling asleep. WASO is the total duration of wakefulness between initially falling asleep and finally waking. Sleep efficiency is the ratio of total time asleep to the total rest interval expressed as a percentage.

Analysis

Quantitative feasibility and utility were analysed using descriptive statistics. Differences in mean total actigraphy and sleep diary measures (TST, SOL, WASO, and sleep efficiency) were compared using paired *t*-tests ($\alpha = 0.05$) with mean difference and 95% confidence intervals (95% CI) reported. All data were analysed in SPSS (Version 26, IBM, Armonk, NY). Qualitative data were thematically analysed, an approach involving separating interview data into core themes to develop a cohesive narrative, and re-iterating through, and reflecting on, the data to further refine themes [12].

Results

Ten participants were enrolled in this trial, nine male and one female, and median age was 37.1 years (interquartile range 31.7–41.9). No participant reported history of psychosis or sleep disorders. Detailed data on participant's substance use history are reported in Table 1.

Feasibility and Utility of the Measure

Seven of the 10 participants wore the actigraph continuously from admission to discharge. Three participants removed the device once each to shower, for an average of 21 min (maximum time off wrist 31 min). All participants completed the CSD each morning during their admission and answered all questions.

In qualitative interviews ($n = 8$), no participant indicated the actigraph was distracting or difficult to wear. All participants reported that the device did not impact their ability to sleep or receive medical care. Daily sleep diaries were not considered onerous, and no one provided any negative feedback regarding sleep assessment. The combined measures were acceptable to participants in this trial.

Sleep Data

An annotated example of the continuous data obtained from the actigraph can be seen in online supplementary Figure 1 (for all online suppl. material, see https://doi.org/10.1159/000536328) and summary sleep data in Table 2. Average sleep diary TST was 58.5 min less (95% CI −101.4, −15.7, $p = 0.008$) and WASO 46.6 min less (95% CI −59.3, −33.9, $p < 0.001$) than actigraphic sleep. There was no difference in SOL (mean difference 5.7 min, 95% CI −8.1, 19.4, $p = 0.41$) or sleep efficiency (mean difference 0.04%, 95% CI −4.9, 4.9, $p = 0.986$). Changes in the average sleep-wake measures over the 7-day period can be seen in online supplementary Figure 2.

Conclusion

We found actigraphy and sleep diaries showed feasibility and utility for use during clinical trials of MA withdrawal treatment. This provided objective and subjective non-invasive measurement of sleep-wake behaviour in a manner highly acceptable to our participants.

Medical-grade actigraphy requires minimal financial investment (from approximately $400 per device) for a reusable wearable measurement device which requires little technical oversight. Compared to PSG, which costs over $600 per study (based on Australian health costs) (and would require an estimated minimum of $20,000 to establish excluding building and staffing costs) [13], actigraphy is both a practical and cost-effective method of determining objective sleep assessment for research in the addictions. Further, modern actigraphy software automatically scores sleep data using validated algorithms [14], meaning analysis and interpretation for research purposes may be undertaken by non-specialist staff, whereas PSG requires an overnight sleep technician to oversee the study, and a sleep medicine specialist to review and evaluate the sleep data and associated measurements.

When interpreting the actigraphic and sleep diary data from this study, lisdexamphetamine treatment would have impacted on sleep patterns. Further, some participants received diazepam and olanzapine during their admission for symptom management. Actigraphy and sleep diaries lack the electroencephalography measures acquired in PSG, making analysis of sleep microarchitecture difficult. However, this is of less importance for clinical trials assessing improvements in overall sleep patterns. The cost of actigraphy may discourage some researchers and limited sample size and gender imbalance reduce generalisability of these results.

Actigraphy and sleep diaries represent a feasible method of sleep measurement in clinical trials. This methodology could be employed in both research and clinical settings with minimal burden on practitioners and patients, and implementation may lead to new and important findings. Simple analysis and interpretation of research data require minimal training due to the automation in modern actigraphy scoring software; however, specialist sleep advice should still be sought for clinical interpretation.

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Statement of Ethics

This study protocol was reviewed and approved by the St. Vincent's Hospital Sydney Human Research Ethics Committee, approval number 2020/ETH02039. Written informed consent was obtained from all study participants for participation in this study.

Conflict of Interest Statement

L.S.A. is supported by an NDARC PhD Scholarship. M.F. has received unrestricted funding for research purposes from Indivior and Sequiiris. S.S. has received clinical research supplies from Alkermes. N.E. and K.J.S. are employed by NCCRED. No other investigators have any conflicts of interest to declare.

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Author Contributions

L.S.A. conceptualised the study. L.S.A. led data acquisition under supervision of N.E. and K.J.S. L.S.A., C.G., R.M., J.B., M.C., C.R., N.L., A.D., M.F., S.S., N.E., and K.J.S.

contributed to the study protocol and final methodology. L.S.A. analysed the data and prepared the first draft of the manuscript under the supervision of C.G., N.E., K.J.S., R.M., L.S.A, C.G., R.M., J.B., M.C., C.R., N.L., A.D., M.F., S.S., N.E., and K.J.S. contributed to the writing of the manuscript and its review.

Data Availability Statement

The data that support the findings of this study are not publicly available due to the small sample size and potential for re-identification of participants but are available from the corresponding author (L.S.A.) upon reasonable request.

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