Psychiatry Research 240 (2016) 163–169

Contents lists available at ScienceDirect

Psychiatry Research

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

Objective and subjective sleep quality: Melatonin versus placebo add-on treatment in patients with schizophrenia or bipolar disorder withdrawing from long-term benzodiazepine use

Lone Baandrup [a,*], Birte Yding Glenthøj [a], Poul Jørgen Jennum [b]

[a] Center for Neuropsychiatric Schizophrenia Research (CNSR) & Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), Copenhagen University Hospital, Mental Health Center Glostrup, Mental Health Services, Capital Region of Denmark, DK-2600 Glostrup, Denmark
[b] Rigshospitalet, Danish Center for Sleep Medicine, Department of Clinical Neurophysiology, Faculty of Health Sciences, University of Copenhagen, DK-2600 Glostrup, Denmark

ARTICLE INFO

Article history:
Received 2 March 2015
Received in revised form
29 March 2016
Accepted 15 April 2016
Available online 15 April 2016

Keywords:
Polysomnography
Severe mental illness
Sleep architecture
Sleep continuity
Insomnia

ABSTRACT

Benzodiazepines are frequently long-term prescribed for the treatment of patients with severe mental illness. This prescribing practice is problematic because of well-described side effects including risk of dependence. We examined the efficacy of prolonged-release melatonin on objective and subjective sleep quality during benzodiazepine discontinuation and whether sleep variables were associated with benzodiazepine withdrawal. Eligible patients included adults with a diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder and long-term use of benzodiazepines in combination with antipsychotics. All participants gradually tapered the use of benzodiazepines after randomization to add-on treatment with melatonin versus placebo. Here we report a subsample of 23 patients undergoing sleep recordings (one-night polysomnography) and 55 patients participating in subjective sleep quality ratings. Melatonin had no effect on objective sleep efficiency, but significantly improved self-reported sleep quality. Reduced benzodiazepine dosage at the 24-week follow-up was associated with a significantly decreased proportion of stage 2 sleep. These results indicate that prolonged-release melatonin has some efficacy for self-reported sleep quality after gradual benzodiazepine dose reduction, and that benzodiazepine discontinuation is not associated with rebound insomnia in medicated patients with severe mental illness. However, these findings were limited by a small sample size and a low retention rate.

1. Introduction

Sleep disturbances and comorbid anxiety symptoms represent important obstacles in the treatment of patients with severe mental illness; thus, long-term benzodiazepines are frequently prescribed (Zandstra et al., 2004; Huthwaite et al., 2013). When administered for more than a few weeks, it is often difficult to discontinue benzodiazepine use due to the development of dependence and associated distressing withdrawal symptoms (O'brien, 2005). International treatment guidelines recommend only short-term treatment with benzodiazepines (Baldwin et al., 2013); however, prescriptions often continue long-term, generating additional side effects, including sedation, risk of falls, decline of cognitive abilities, and increased risk of dementia (Wu et al., 2009; Billioti de et al., 2012; Dold et al., 2012; Gallacher et al., 2012; Baldwin et al., 2013; Billioti de et al., 2014). Most benzodiazepines directly affect sleep by inhibiting stage 3 (N3) and rapid eye movement (REM) sleep and increasing the amount of stage 2 (N2) sleep (Hollister et al., 1993; Parrino and Terzano, 1996). Consequently, benzodiazepines potentially aggravate the disrupted sleep pattern identified in mentally ill patients (Monti and Monti, 2004; Abad and Guilleminault, 2005; Cohrs, 2008). Numerous observational studies have indicated increased mortality associated with the use of anxiolytic and hypnotic drugs (Mallon et al., 2009; Kripke et al., 2012; Weich et al., 2014), whereas studies controlling for underlying psychiatric disorders have not replicated this association (Jaussent et al., 2013).

Melatonin is a naturally occurring hormone secreted from the pineal gland in response to darkness (Maldonado et al., 2009). This hormone supports the maintenance of sleep and a regular sleep-wake cycle. Melatonin is sold as an over-the-counter drug in many countries. Although this hormone has a short elimination half-life, melatonin is licensed in Europe (and other countries) as a prolonged-release formulation for the short-term treatment of

* Corresponding author.
E-mail address: lone.baandrup@regionh.dk (L. Baandrup).

http://dx.doi.org/10.1016/j.psychres.2016.04.031
0165-1781/

primary insomnia in adults aged 55 years and older (Wade et al., 2007). Prolonged-release melatonin (PRM) maintains high melatonin concentrations throughout the night when administered at bedtime, thus mimicking the physiological profile of endogenously secreted melatonin. No signs of tolerance or withdrawal effects have been reported in trials of up to six months in duration (Lemoine et al., 2007; Wade et al., 2010). The effect of immediate-release melatonin as a therapeutic aid in sleep disturbances has been extensively investigated (Buscemi et al., 2005, 2006), but solid evidence only exists for an effect in sleep phase disorders, particularly jet lag (Herxheimer and Petrie, 2002), and delayed sleep phase disorder (van Geijlswijk et al., 2010), including sleep disturbances in children with ADHD (Bendz and Scates, 2010). Theoretically, the administration of supplementary melatonin might facilitate benzodiazepine tapering, reflecting the sleep stabilizing effect of this hormone and a range of other potentially beneficial effects, including cognitive improvement, antipsychotic enhancing effects through anti-inflammatory and anti-oxidative effects (Maldonado et al., 2009; Manda and Reiter, 2010), and a reported ability to reduce antipsychotic side effects, such as tardive dyskinesia and metabolic syndrome (Anderson and Maes, 2012; Modabbernia et al., 2014).

In this paper, we report the secondary sleep outcomes from a randomized clinical trial with the main aim of evaluating if PRM facilitates the withdrawal of chronic benzodiazepine use in patients with schizophrenia or bipolar disorder. Only a subset of the total sample (86 subjects) enrolled in the trial agreed to participate in the sleep recordings, which were not mandatory for trial participation. The prioritization of the co-examinations and co-outcomes was described in the published SMART trial protocol (Baandrup et al., 2011). The main outcome of the trial, endpoint benzodiazepine dosage based on all 86 participants, has been reported elsewhere (Baandrup et al., 2015).

The aim of the sleep examinations was to evaluate whether add-on treatment with PRM during the tapering of chronic benzodiazepine treatment improves objectively measured sleep efficiency and self-reported sleep quality compared with placebo. In addition, we hypothesized a more marked effect on sleep recordings of benzodiazepine dose reduction compared with supplementary PRM. Specifically, we hypothesized that a benzodiazepine dose reduction would be associated with the reversal of benzodiazepine-induced sleep changes, i.e., increased amounts of N3 and REM sleep and a decreased amount of N2 sleep (Baandrup et al., 2011).

2. Methods and materials

2.1. Study design and participants

This study was a single-center, randomized, double-blinded clinical trial conducted at a university hospital research department in the Capital Region of Denmark with a catchment area of 1,700,000 inhabitants. The patients were primarily recruited from outpatient mental health services. Participants eligible for the trial were 18 years or older; had an ICD-10 (*International Classification of Diseases, 10th edition)* diagnosis of schizophrenia, schizoaffective disorder, or bipolar mood disorder (euthymic at inclusion); were treated daily with at least one antipsychotic drug and at least one benzodiazepine or benzodiazepine-like drug for a minimum of three months; did not present with current violent or aggressive behavior; were not diagnosed with mental retardation, pervasive developmental disorder, dementia, hepatic impairment, terminal illness, severe somatic comorbidity, or epilepsy; were able to understand Danish; and were not allergic to any compounds in the trial medication. Fertile women were only included if not pregnant or nursing and using safe contraceptives throughout the trial period.

2.2. Experimental intervention and comparator

All participants received oral and written information about the trial before providing written informed consent. After baseline examinations, all trial participants gradually reduced their usual benzodiazepine dosage (including benzodiazepine-like drugs) at an approximate rate of 10–20% dose reduction every second week. Subsequently, we continuously adjusted the discontinuation rate according to the individual experience of withdrawal symptoms. It was possible to halt the discontinuation temporarily when considered necessary by the participant or investigator. We examined the participants at baseline and after 8, 16, and 24 weeks. In between visits, the participants were contacted by telephone on a weekly basis to adjust the benzodiazepine dose reduction regimen and to provide information and general support. If participants developed insomnia, we provided sleep hygiene advice, but systematic cognitive-behavioral treatment approaches were not offered.

Trial medication (PRM 2 mg or matching placebo) was initiated once daily in parallel with the gradual benzodiazepine dose reduction after baseline assessments. The participants were instructed to ingest the trial medication approximately two hours before bedtime and preferentially following a light meal. Treatment with trial medication continued throughout the trial period, including a follow-up assessment after 24 weeks, irrespective of the individual final dosage of benzodiazepine. Hereafter, the trial medication was abruptly discontinued. The participants, investigators, caregivers and outcome assessors were all blinded.

Any co-medication (i.e., medication other than benzodiazepines and benzodiazepine-like drugs) was permitted. We did not differentiate between benzodiazepines administered as anxiolytics or hypnotics. We aimed at keeping the co-medication constant during the trial period, but clinically necessary changes, according to the usual caregiver team, were permitted for the benefit of limited attrition.

2.3. Sleep recordings

Sleep examinations were conducted between February 2012 and June 2014 at the Danish Center for Sleep Medicine at Glostrup Hospital. Each subject underwent a full-night unattended in-home polysomnography (PSG) in accordance with the 2007 guidelines of the American Academy of Sleep Medicine (AASM) (Iber et al., 2007). Montage was generally performed on weekdays between 12:00 and 15:00. The impedance of each electrode was maintained below 10 kΩ, and the electroencephalogram was sampled at a frequency of 256 Hz. PSG was performed using portable equipment (Trackit) (www.cephalon.dk/). Polysomnographic recordings were performed before the initiation of the benzodiazepine taper and at the 24-week follow-up. The participants recorded a sleep diary, stating the time of lights off and lights on for three consecutive nights: the first night, both PSG and actigraphy recordings were performed and, the following two nights, only actigraphy was conducted. The actigraphy data will be reported elsewhere.

The PSG comprised electroencephalography (with frontal, central, and occipital derivations), vertical and horizontal electrooculography, surface electromyography of the submentalis and tibialis anterior muscles, nasal air flow, temperature of in- and exhaled air, pulse oximetry, respiratory inductance plethysmography (measuring the effort to breath), and electrocardiography.

A trained neurophysiologist and a neurologist specialized in sleep medicine visually scored the sleep recordings in 30 second epochs according to AASM criteria (Iber et al., 2007). The sleep continuity parameters were reported in minutes, and the macro architectural variables were reported as the percentage of the total sleep time.

2.4. Self-reported sleep quality

All participants were evaluated using the Pittsburgh Sleep Quality Index (PSQI) at baseline and at the 24-week follow-up. PSQI is a questionnaire that is designed to measure sleep quality in psychiatric populations and comprises nineteen self-rated items generating seven component scores (subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction) that combine to yield one global score (range 0–21) of self-reported sleep quality (Buysse et al., 1989). Higher scores indicate worse sleep, and a score above five indicates poor sleep quality (Backhaus et al., 2002; Buysse et al., 1989). The PSQI has been psychometrically validated in different populations, with findings of high test-retest reliability, high correlations with sleep log data, and high to moderate correlations between global and component scores (Carpenter and Andrykowski, 1998; Backhaus et al., 2002). The PSQI has previously been applied in studies of sleep disturbances in schizophrenia patients (Hofstetter et al., 2005; Ritsner et al., 2004). In the present study, we analyzed the global score and three selected components (subjective sleep quality, sleep disturbances, and daytime dysfunction).

2.5. Outcomes

In this subsample of participants, we primarily investigated the effect of PRM on sleep efficiency and the PSQI global score. Sleep efficiency is the ratio of the total sleep time to time in bed. Secondarily, we investigated the association of the benzodiazepine dosage at 24 weeks with changes in the total sleep time, sleep latency, REM latency, time awake after sleep onset, number of awakenings, sleep