Melatonin for perceived sleep disturbances associated with benzodiazepine withdrawal among patients in methadone maintenance treatment: a double-blind randomized clinical trial

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ABSTRACT

Aims To evaluate the effectiveness of melatonin in attenuating sleep difficulties during benzodiazepine (BDZ) withdrawal. Design Double-blind cross-over control study. Setting Methadone maintenance treatment clinic. Participants Eighty patients enrolled at a community methadone maintenance clinic recruited to a BDZ withdrawal programme. Intervention Melatonin (5 mg/day) or placebo: 6 weeks one arm, 1 week washout, 6 weeks other arm. Measurements Urine BDZ; self-reported Pittsburgh Sleep Quality Index (PSQI) and the Center for Epidemiologic Studies Depression (CES-D) questionnaires administered at baseline, and at 6, 7 and 13 weeks. Findings Sixty-one patients (77.5% in the ‘melatonin first’ condition and 75% in the ‘placebo first’ condition) completed 6 weeks of treatment, showing a similar BDZ discontinuation rate of 11/31 and 11/30, respectively. PSQI scores were significantly lower (indicating better sleep quality) in the 22 patients who discontinued BDZ (8.9 ± 0.9) than in 39 with urine BDZ (11.2 ± 0.7, P = 0.04). Sleep quality in patients who continued abusing BDZ improved more in the ‘melatonin first’ group than in the ‘placebo first’ group, with no differences in sleep quality improvement in patients who stopped BDZ. Conclusion Most improvement in sleep quality was attributed to BDZ discontinuation. Although melatonin did not enhance BDZ discontinuation, it improved sleep quality, especially in patients who did not stop BDZ.

Keywords Abuse, benzodiazepine, melatonin, methadone maintenance treatment (MMT), sleep, withdrawal.

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INTRODUCTION

The misuse of benzodiazepines (BDZ) is highly prevalent among illicit opioid users, including those enrolled in methadone maintenance treatment (MMT). Non-prescribed BDZ use among MMT patients ranged from 44 to 66% [1,2]. This clinical problem is associated with more severe dependence and serious health and behavioural problems which, when interacting with methadone, may induce both respiratory distress and cardiac arrhythmia [3]. In our clinic population, patients’ motivation to discontinue illicit BDZ use derives from their motivation to receive ‘take-home’ doses for self-administration, a clinic benefit that is granted only to those who abstain from all illicit drugs.

During the 1990s, an effort was made in our MMT clinic to study the prevalence, course and correlates of illicit BDZ use and to try to develop a BDZ maintenance programme with clonazepam (a high-potency and long half-life BDZ; 1 mg clonazepam = 20 mg of diazepam) similar to that implemented with methadone for heroin addiction [1,4,5]. However, this was not very successful: clonazepam was considered to have a higher dependence liability than other compounds and medication diversion became widespread (a problem also reported in the United States [6]).

Sleep disorders are common among illicit BDZ users: this phenomenon may be an initial cause of BDZ misuse in some individuals and its consequence in others [7,8]. Prolonged misuse of BDZ induces an alteration of sleep...
pattern and quality, with disturbed sleep worsening during BDZ withdrawal [8]. The sleep–wake cycle is a complex behaviour mediated by circadian rhythmicity and regulated by an endogenous pacemaker [9]. Endogenic melatonin (N-acetyl-5-methoxy-tryptamine) is a hormone that is produced and secreted nocturnally by the pineal gland. Melatonin is inhibited by light and thus synchronizes between the external light/dark effects and the internal biological clock of the body [10,11]. Its concentration in body fluids tends to decrease with age [12,13], in diverse pathological conditions [14] and following some medication treatments, including prolonged BDZ use [15].

Treatment with melatonin has been shown to improve sleep disturbances in the elderly [16,17], in chronic schizophrenia patients and among children with sleep-onset insomnia [18,19]. In these populations, melatonin was found to help sleep even in non-circadian sleep disturbances. The aim of the present double-blind cross-over study was to evaluate a possible contribution of melatonin in attenuating subjective complaints of sleep disturbances during a gradual BDZ withdrawal programme in an MMT population.

METHODS

Study design and setting

We conducted a double-blind cross-over control study with melatonin (5 mg/day) or placebo with patients enrolled in an MMT programme (the Adelson Clinics in Tel Aviv, Israel) who participated in a gradual BDZ (clonazepam) withdrawal programme. This MMT clinic has a 300-patient capacity and receives patients who meet DSM-IV criteria for opioid dependence and report self-administration of illicit heroin for 1 year or more. The characterization and effectiveness of the clinic has been reported elsewhere [20,21]. All patients who were admitted to the clinic between July 1993 and July 2004 were eligible for inclusion in the study. The study was approved by the Institutional Review Board (IRB) of the Tel Aviv Sourasky Medical Center. The managed BDZ withdrawal programme consisted of a run-in phase during which patients were instructed to taper down their BDZ dose independently until reaching the upper therapeutic limit (6 mg/day clonazepam or equivalent). Based on their self-report about their BDZ dose, each enrolled patient signed his/her informed consent and was enrolled in a standardized gradual clonazepam withdrawal programme (0.5 mg/week dose reduction) accompanied by either melatonin or placebo for 6 weeks, 1 week of washout (no melatonin or placebo), and then another 6 weeks of placebo or melatonin (each patient serving as his/her own control group). During study recruitment, one-third of the patients were consistently positive to BDZ (i.e. for more than 1 month). These patients were entered into the study without exception. Another 100 patients reported that they did not wish to stop BDZ use and declined to participate in the study. The BDZ users who did not participate the study were more like to use cocaine prior to admission to MMT (33.8%) compared with the study participants (17.4%, \( P = 0.02 \)), but in other respects were similar.

Study protocol

Each participant was assigned a container holding a 1.2-week supply of pills in numbered boxes (seven pills in each box) that were packed by the pharmacist. The boxes had melatonin/placebo in the first six boxes and placebo/melatonin in the last six boxes. The participants were given consecutive container numbers and each patient received only one box at a time once a week for 12 weeks, thus providing maximum control and follow-up. The codes for melatonin first/placebo first were known only to the pharmacist who prepared the sequence in a random manner and identified it to us only at the end of the study.

Evaluations

Urine samples were analysed for BDZ, opiates, methadone metabolite, cocaine (benzylecgonine), cannabis [delta-9-tetrahydrocannabinol (THC)] and amphetamines using enzyme immunoassay systems (DRI® and CEDIA®) [22]. The self-reported Pittsburgh Sleep Quality Index (PSQI) questionnaire was used to evaluate the quality and pattern of sleep. The PSQI differentiates ‘poor’ from ‘good’ sleep by measuring seven areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleep-inducing medication and daytime dysfunction over the preceding month. A global sum of >5 indicates a ‘poor’ sleeper (with a diagnostic sensitivity of 89.6% and specificity of 86.5% in distinguishing between good and poor sleepers) [23]. The internal reliability of Cronbach’s alpha (i.e. internal consistency, based on the average inter-item correlation) in our study ranged between 0.6 and 0.8 at the four time-points. The Center for Epidemiologic Studies Depression (CES-D) questionnaire for mood is a 20-item self-reported scale that assesses aspects of depressive mood that occurred during the previous week [24]. Responses are recorded on a Likert scale from 0 = ‘rarely or never’ to 3 = ‘most of the time or constantly’. The final CES-D score is the mean of the 20 responses. Internal reliability of the CES-D was good across the four time-points (Cronbach’s alpha, 0.8–0.9). The PSQI and CES-D were administered at baseline and after 6, 7 and 13 weeks (see trial profile, Fig. 1).
Participants
Between December 2004 and April 2006, 80 patients were enrolled into the study and assigned randomly to two groups: 40 patients who started on melatonin and 40 patients who started on placebo. Sixty-one patients (31 from the ‘melatonin-first’ group and 30 from the ‘placebo-first’ group) completed phase one (6 weeks). Forty-four patients completed all 13 weeks of the study, with no differences between groups (60% of the 40 ‘melatonin first’ group and 50% of the 40 ‘placebo first’ group (P = 0.5). The sample size was calculated for 100 patients, 50 in each arm, with α of 5% and power of 80% to find significant differences of ≈ 20% between the two arms. The limitation of the number of recruited patients, however, reduced the power.

BDZ cessation and relapse rate follow-up
Patients in our MMT clinic undergo repeated random and observed urine tests throughout the entire length of their treatment. This routine urine monitoring for drug abuse continued among the study subjects, who also underwent specific evaluations of BDZ in urine samples and sleep and mood states at study weeks 0, 6, 7 and 13. From the results of the urinalyses that were followed-up until 25 September 2006 (so that the maximal available time of follow-up measured from the beginning of recruitment in December 2004 could reach 21 months), we calculated duration to BDZ cessation (the time between the patient’s enrollment into the study until the first negative urine for BDZ), and the duration until relapse (the time between the cessation date and relapse as measured from the first positive BDZ following a period of negative findings).

Data analyses
Group differences between ‘melatonin first’ and ‘placebo first’ groups were analysed using one-way and repeated-measures analysis of variance (ANOVA, SPSS version 13). Categorical variables were presented as proportions and significant differences were analysed using Fisher’s exact test or χ². The duration to BDZ cessation and the duration until relapse were compared using Kaplan–Meier survival analysis with log rank to compare significant differences between groups and other variables. Variables that were associated significantly with duration until relapse (P < 0.05) were included in a Cox regression multivariate analysis and presented as odds ratio (OR) and associated 95% confidence intervals (CI).

RESULTS
Patient characteristics
Most (70%) of the 80 study patients were male. The mean age during study was 42.6 ± 1.2 years and the mean duration in MMT was 4.4 ± 0.4 years. Almost two-thirds (62.3%) were born in Israel, 78.2% were drug injectors, 62.5% were positive to hepatitis C virus (HCV) antibody, 15% to human immunodeficiency virus (HIV) and 5% had hepatitis B antigen. Almost half (48.8%) of the patients had other drug abuse in addition to BDZ in the month prior to study entry. Specifically, 25 had positive urine for opiates, 12 for cocaine, 14 for cannabis and five for amphetamines. With respect to life-time psychiatric diagnosis, nine patients (11.3%) had one of the psychotic disorders, 18 (22.5%) had an affective disorder, eight (10%) had an adjustment disorder; two (2.5%) had an organic brain disorder, 38 (47.5%) had no DSM-IV Axis I diagnosis (but all 38 had a DSM-IV Axis II personality disorder) and five (6.3%) had no DSM-IV Axis I and Axis II psychiatric diagnosis. There were no differences in the baseline characteristics of the two groups (data not shown).

At baseline, the ‘melatonin first’ and ‘placebo first’ groups had similar PSQI scores (13.8 ± 0.6) and CES-D scores (1.5 ± 0.1), and both scores correlated with each other (r = 0.4, P = 0.001). Sixty-one patients (76.3%) finished the first phase of the study (6 weeks: 77.5% of the ‘melatonin first’ group and 75% of the ‘placebo first’ group). After 6 weeks, 32.9% of all 76 patients in the study (four urine results were unknown) had no BDZ in urine, 36.1% of the 61 who stayed 6 weeks (35.5% of the ‘melatonin first’ group and 36.7% of the ‘placebo first’ group) and 20% of the 15 who had quit before 6 weeks (33.3% of the ‘melatonin first’ group and 11% of the

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Addiction
‘placebo first’ group). After 6 weeks, there were still no differences in mean PSQI and CES-D between the two groups. The mean PSQI score was, however, significantly lower in the 22 patients who discontinued BDZ (8.9 ± 0.9) compared to the 39 patients with urine BDZ (11.2 ± 0.7, ANOVA, F = 4.3, P = 0.04); 36 patients (92.3%) had disturbed sleep (PSQI > 5) among the patients compared with 15 (68.2%) of patients who discontinued BDZ (Fisher’s exact test, P = 0.03). There were no significant differences in the mean CES-D score (1.3 ± 0.1 versus 1.2 ± 0.1, P = 0.5).

The mean PSQI scores were reduced significantly (indicating sleep improvement) in both the ‘melatonin first’ (repeated measures, PSQI: 14.3 ± 0.6 and 10.2 ± 0.8) and the ‘placebo first’ (PSQI: 13.7 ± 0.7 and 10.5 ± 0.8) groups [F = 31.7 (df = 1) P < 0.0005] with no intergroup differences [F = 0.5 (df = 1) P = 0.5]. An interaction was found between BDZ abuse/cessation at 6 weeks and melatonin/placebo groups [F = 4.3 (df = 1) P = 0.04] (Table 1), indicating that sleep quality improved more in the ‘melatonin first’ group than in the ‘placebo first’ group in patients who continued BDZ abuse, but the extent of improvement was similar between the two groups in patients who stopped abusing BDZ after 6 weeks.

Forty-four patients (55%) finished the entire 13-week study. 24 (60%) in the ‘melatonin first’ group and 20 (50%) in the ‘placebo first’ group. The proportion of patients with no BDZ use at week 13 was similar for both groups: 29.2% in the ‘melatonin-first’ group and 30% in the ‘placebo-first’ group. Test scores at week 13 revealed no differences in mean PSQI and mean CES-D scores between the melatonin/placebo groups or between the BDZ cessation/abuse groups. The mean PSQI scores of these 44 patients was 13.9 ± 0.5 (week 0), 10.3 ± 0.6 (week 6), 11.9 ± 0.7 (week 8) and 11.6 ± 0.6 (week 13). The change between baseline and weeks 6, 7 and 13 reached a level of significance [F = 10.1 (df = 3) P < 0.0005]. There was also a significant increase between the mean scores at the end of week 6 and the end of week 7 (the 1 week of washout), but none between week 7 and week 13 (Fig. 2).

The mean change in sleep quality between the first phase (PSQI difference between week 6 and week 0) and the second phase (PSQI difference between week 13 and week 7) showed that subjective sleep improvement was significantly higher during the first phase compared to the second phase, independent of melatonin/placebo group or BDZ abuse after 6 weeks and 13 weeks. There was no significant change in subjective sleep quality in either group throughout phase 2 of the study.

**BDZ cessation and relapse rate follow-up**

A total of 63 patients stopped using BDZ between December 2004 and 25 September 2006. The mean cumulative time to BDZ cessation was 48.3 days (95% CI 28.9–67.8 days) and there was no difference between the two groups: 50.8 days (95% CI 24.1–77.6) for the ‘melatonin first’ group and 45.8 days (95% CI 17.2–74.4) for the ‘placebo first’ group (log rank 2 χ² = 0.8, P = 0.6). Separate analysis of the 44 patients who stopped within the study period also showed no group difference: 8.2 days (95% CI 3.1–13.3) for the ‘melatonin first’ subjects compared 11.2 days (95% CI 6.3–16.1) for the ‘placebo first’ subjects.
Disturbance in sleep quality was found to be related to increased age and female gender in the general population (for review see [26]). Among MMT patients, disturbance in sleep quality was associated with BDZ use, with any coexisting psychiatric diagnosis, with chronic pain, and with duration of opiate abuse before admission to MMT that was found to correlate to high methadone doses [27]. In the current study, comparing PSQI at baseline (before study onset) by these factors, no significant differences were found comparing by drug misuse, gender, duration of drug abuse before MMT, duration in MMT, methadone dose and psychiatric disorders (data not shown). This confirms the fact that BDZ abuse in itself
is one of the most prominent variables that induces sleep disturbance.

Importantly, the ‘melatonin first’ group had a significantly longer period of abstinence from BDZ than the ‘placebo first’ group. This is not surprising, as melatonin has been already found to improve sleep in other populations, such as the elderly [16,17], schizophrenic patients [18] and children [19].

The effect induced by melatonin was found here to be a delayed one. Thus, it is possible that the disrupted sleep mechanism of the subjects in the ‘melatonin first’ group had time to undergo ‘repair’, a process that could have helped the patients to stop abusing BDZ: this became apparent during the follow-up period after study closure. If this had been the case, however, we would expect that the ‘placebo first’ subjects would also show a similar delayed effect, but they did not. However, a decrease in adherence to medication treatment that probably increased over time could also be the case. This may create a situation in which the ‘melatonin first’ group succeeded in obtaining melatonin more than the ‘placebo first’ group.

BDZ use has been found to disturb the normal endogenous melatonin processes of secretion, binding [15,28] and synthesis, and to shift the day/night rhythmicity [29]. One study showed that melatonin supplement abrogated the suppression effect of melatonin binding caused by diazepam in a rat model [30]: this could explain the contribution of exogenous melatonin to sleep quality, even when BDZ use continued. Melatonin has also been reported to affect systems other than sleep. It has been reported to possess cytoprotective properties (due to its anti-oxidant and anti-apoptotic effects), as well as immune-enhancing and oncostatic properties. It was shown to be efficacious in the treatment of major depressive disorders and bipolar affective disorders (see review [31]). However, in the present study we did not assess this effect in our patients. Melatonin has also been found to induce analgesia (see review [32]), probably by increasing the release of beta-endorphin [33], an important issue in a population found to be affected by high prevalence of chronic pain [34] but, again, not assessed in the present study.

We found that our patients’ sleep actually improved during BDZ withdrawal phase, regardless of treatment arm. This finding is seemingly paradoxical, given that many people attempting withdrawal from BDZs on a prescribed reducing prescription of BDZs complain typically of worsening insomnia, even at the end of the detoxification. However, all published studies on BDZ discontinuation involved patients treated with dosages of BDZ within (or slightly above) therapeutic levels. One possible explanation of our finding is that asking our patients to taper rapidly from the extremely high doses they were abusing (20–30, some even 50 tablets of 2 mg clonazepam each day, which is equivalent to 2000 mg diazepam/day) to ‘only’ 6 mg/day (the required upper limit for entering the study, which is equivalent to 120 mg diazepam/day [35]) induced a rebound phenomenon (via cessation of negative feedback mechanisms on the ‘sleep gates’). This was then reinforced by the addition of melatonin at the beginning of the study. In that context, we consider the significant deterioration in sleep quality during the 1 week of washout as being suggestive of a psychological placebo effect of the act of pill-taking.

In conclusion, the 30% success rate in stopping BDZ use accompanied by the reported improvement in sleep quality, regardless of the accompanying treatment (melatonin or placebo), warrants further study on a larger group of patients and over a much longer period of time. The findings of the present study are obviously not attributable to melatonin alone, but probably to the efforts to discontinue BDZ abuse, with enhanced quality of sleep as a secondary benefit. Interestingly, although most reported improvement in sleep quality was attributed to BDZ discontinuation, melatonin showed a small contribution to sleep quality improvement among patients who continued to abuse BDZ.

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