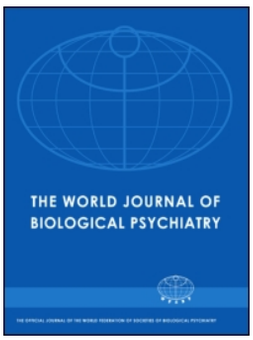

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ORIGINAL INVESTIGATION

Prolonged-release melatonin versus placebo for benzodiazepine discontinuation in patients with schizophrenia or bipolar disorder: A randomised, placebo-controlled, blinded trial

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Abstract

Objectives. We assessed if prolonged-release melatonin can facilitate withdrawal of long-term benzodiazepine usage in patients with schizophrenia or bipolar disorder. *Methods.* Randomised, placebo-controlled, blinded, parallel superiority trial of 24 weeks duration. Participants were randomised to prolonged-release melatonin 2 mg daily versus matching placebo and were continuously guided to gradually reduce their usual benzodiazepine dosage. The primary outcome was mean benzodiazepine daily dosage at 24 weeks. Secondary outcomes included pattern of benzodiazepine dosage over time, benzodiazepine cessation proportion, and benzodiazepine withdrawal symptoms. *Results*. In total, 86 patients (21–74 years) were enrolled: 42 were randomised to melatonin versus 44 to placebo. We found no significant effect of melatonin on mean benzodiazepine dosage at 24 weeks (melatonin group 8.01 mg versus placebo group 5.72 mg diazepam equivalents; difference between means –2.29; 95% CI –5.78 to 1.21; $P = 0.20$). Benzodiazepine cessation proportion was 38.1% (16/42) in the melatonin group versus 47.7% (21/44) in the placebo group (OR 0.64; 95% CI 0.26 to 1.56; $P = 0.32$). Prolonged-release melatonin had no effect on benzodiazepine withdrawal symptoms. *Conclusions.* Benzodiazepine dosage was comparably low between the groups after 24 weeks of guided gradual dose reduction. In this context, prolonged-release melatonin did not seem to further facilitate benzodiazepine discontinuation.

Key words: *benzodiazepine, discontinuation, cessation, melatonin, schizophrenia*

Introduction

Continuous benzodiazepine prescriptions are frequent in patients suffering from mental illness (Zandstra et al. 2004; Huthwaite et al. 2013), despite a lack of evidence of therapeutic benefit (Dold et al. 2012; Baldwin et al. 2013). In the acute treatment of psychosis-induced agitation and aggression, benzodiazepines are warranted as efficient sedating agents (Gillies et al. 2013). Beyond the acute setting, benzodiazepines are mainly prescribed to treat symptoms of insomnia and anxiety. International treatment guidelines recommend only short-term treatment (days to weeks) with benzodiazepines (Baldwin et al. 2013), but prescriptions often continue for extended periods representing an additional burden of adverse reactions. These include sedation, risk of falls, psychological and physical dependence, development of tolerance, risk of addiction, decline of cognitive abilities, and increased risk of dementia (Wu et al. 2009; Billioti de et al. 2012; Dold et al. 2012; Baldwin et al. 2013). In addition, recent observational studies have found an association of increased mortality with benzodiazepine–antipsychotic combination treatment in patients with schizophrenia (Baandrup et al. 2010; Tiihonen et al. 2012). Previously, a number of different co-medications were investigated as facilitators of benzodiazepine discontinuation, but as yet no systematic reviews with meta-analyses have been able to

Trial registration: *ClinicalTrials NCT01431092.*

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unambiguously identify efficient drugs (Voshaar et al. 2006; Denis et al. 2006; Parr et al. 2009). Thus, currently no drugs are licensed to facilitate benzodiazepine discontinuation.

Melatonin is a naturally occurring nocturnal hormone with a short half-life and sleep promoting and circadian regulatory effects (Pacchierotti et al. 2001; Srinivasan et al. 2006). Prolonged-release melatonin (PRM), a formulation that releases melatonin gradually in the gut, mimics the physiological profile of endogenously secreted melatonin with high concentrations throughout the night when administered at bedtime. PRM is licensed in Europe and other countries for treatment of primary insomnia in adults above 55 years (Wade et al. 2007). Supplementary melatonin is associated with minimal adverse reactions (Buscemi et al. 2005, 2006) and several possible therapeutic effects, including sleep regulatory, anti-inflammatory, neuroprotective and pro-cognitive properties (Maldonado et al. 2009).

Research suggests that benzodiazepine treatment is associated with reduced melatonin secretion (Kabuto et al. 1986; Hajak et al. 1996) and that people with schizophrenia and bipolar disorder suffer from reduced or abnormally timed secretion of melatonin as compared to healthy controls (Harvey 2008; Maldonado et al. 2009; Anderson and Maes 2012). Supplementary melatonin, in particular PRM, is therefore a candidate drug when aiming to facilitate discontinuation of long-term benzodiazepine use, especially in patients with schizophrenia or bipolar disorder due to the disrupted secretory pattern of endogenous melatonin. This indication for melatonin has not previously been investigated in chronically medicated mentally ill patients.

Objective

In the current randomised SMART (Schizophrenia Melatonin-Associated Reduction of benzodiazepine Treatment) trial, we investigated the efficacy of add-on PRM compared with placebo as facilitator of reduction or discontinuation of chronic use of benzodiazepines or benzodiazepine-like drugs in patients diagnosed with schizophrenia or bipolar disorder.

Method

Design

The SMART trial is a single-centre, randomised, placebo-controlled, blinded, two-armed, parallel group superiority trial with a 1:1 allocation ratio and a trial duration of 24 weeks. Because we expected slow tapering rates in the trial population, we chose this treatment duration not to miss any differences between the intervention groups, and to ensure that a sizeable fraction of the participants would be able to cease their benzodiazepine treatment within the time limits.

The trial protocol was published prior to inclusion of the first patient (Baandrup et al. 2011). The trial was conducted in accordance with the latest version of the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines for clinical trials. The trial was approved by the Committee on Biomedical Research Ethics of The Capital Region in Denmark (H-1-2011-025), the Danish Medicines Agency (EudraCT 2010-024065-46), and the Danish Data Protection Agency (RHP-2011-07: 01217).

Participants and setting

Participants were recruited from the secondary mental health care in the Capital Region of Denmark. Recruitment was mainly from outpatient services, but inpatients were also allowed into the trial. Only two of the participants were inpatients when they were included in the trial but they did not remain hospitalised throughout the trial period. Many patients were approached for the first time while they were admitted, but inclusion was most often some weeks after discharge. After complete description of the study to the subjects, written informed consent was obtained.

Inclusion criteria

- Age 18 years or above.
- An ICD-10 (International Classification of Diseases, 10th edition) diagnosis of schizophrenia (F20), schizoaffective disorder (F25), or bipolar disorder (F31). Bipolar patients were required to be euthymic at the time of inclusion.
- Treatment with antipsychotic drug(s) for at least 3 months before inclusion.
- Treatment with one or more benzodiazepine derivatives or benzodiazepine-related drugs for at least 3 months before inclusion.
- Fertile women: negative pregnancy test at baseline and the use of safe contraceptives (intrauterine devices or hormonal contraception) throughout the trial period.
- Written informed consent.

Exclusion criteria

- Known aggressive or violent behaviour.
- Mental retardation, pervasive developmental disorder, or dementia.

- Epilepsy, terminal illness, severe somatic co-morbidity, or inability to understand Danish.
- Allergy to compounds in the trial medication (melatonin, lactose, starch, gelatine, and talc).
- Hepatic impairment.
- Pregnancy or nursing.
- Lack of informed consent.

Changes to methods after trial commencement

Due to a slow recruitment rate, we adjusted a few of the eligibility criteria 4–6 months after recruitment began: an upper age limit of 55 years and not currently being treated for alcohol or substance abuse were annulled; bipolar disorder (in euthymic phase at inclusion) and treatment with benzodiazepine related drugs (zolpidem, zopiclone and zaleplon) were added as inclusion criteria. We decided to add the benzodiazepine-related drugs because their mode of action, side effect profile and risk of addiction is similar to that of the benzodiazepines. Towards the end of the trial, the target number of participants was raised from 80 to 86 to replace a few patients who left the trial very early.

Experimental intervention and comparator

After informed consent and baseline examinations, all trial participants were instructed to gradually reduce their usual benzodiazepine dosage (including benzodiazepine-related drugs) at an approximate rate of 10–20% every second week. This rate of benzodiazepine tapering has been recommended internationally (Ashton 2005). We aimed for this withdrawal rate as the first steps of tapering. Subsequently, withdrawal rate was decided upon in close collaboration with each participant. If necessary, the discontinuation could be temporarily paused, but participants were continuously encouraged to continue the withdrawal process. If treated with short-acting benzodiazepine derivatives (elimination half-life 24 h or less), the participants were offered the possibility to switch to a long-acting benzodiazepine (diazepam substitution, run-in phase) before beginning trial medication.

We examined participants at baseline and after 8, 16 and 24 weeks. These examinations were conducted at the research unit hosting the trial or as a home visit according to the preference of each participant. A total of 13 participants chose the option of home visits for the regular assessments. None of these participants lived independently, and they hardly ever left the institutions in which they lived. In between these visits, we contacted the participants weekly by telephone to adjust the benzodiazepine dose reduction and provide information and general support. All trial procedures were delivered individually.

Trial medication (PRM, Circadin® 2 mg versus matching placebo) was initiated in parallel with the gradual benzodiazepine dose reduction. The participants were instructed to ingest the trial medication approximately 2 h before bedtime and, if possible, following a light meal. Treatment with trial medication continued throughout the trial period including the follow-up assessment after 24 weeks, irrespective of the final benzodiazepine dosage. Hereafter, the trial medication was abruptly discontinued.

It was our aim to keep the co-medication (any medication apart from benzodiazepines) constant during the trial period, but any changes in co-medication prescribed by the participants' usual caregivers were allowed for the benefit of limited attrition.

Compliance with study medication expressed as compliance rate ($100 \times$ number of tablets taken/number of tablets prescribed) was monitored in all trial participants using tablet count at the end of the trial.

Outcomes and assessments

The primary outcome was the mean daily dosage of benzodiazepines (including benzodiazepine related-drugs) at 24 week follow-up. Benzodiazepine daily dosage was expressed in diazepam equivalents because this measure is the national conversion standard and, additionally, because this benzodiazepine equivalence is generally used in the field. Secondary outcomes included pattern of benzodiazepine dosage over time (8, 16 and 24 weeks), benzodiazepine cessation proportion at 24 weeks, and benzodiazepine withdrawal symptoms as measured using the Benzodiazepine Withdrawal Symptom Questionnaire (BWSQ-2) (Tyrer et al. 1990). Measures of electrophysiology (early information processing), neurocognition, objective and subjective sleep evaluations, social functioning, psychopathology and quality of life will be reported elsewhere.

For safety reasons, we included measurement of routine laboratory tests, physical examination, ECG and registration of adverse events (AEs). In addition, we measured the plasma concentration of benzodiazepines at 24 weeks in participants who managed to discontinue benzodiazepine use within the trial period. We registered any co-medication at baseline and at 8, 16 and 24 weeks follow-up. Antipsychotic dosage was expressed as olanzapine equivalents (Gardner et al. 2010).

Randomisation and data entry

Central randomisation was performed by the Copenhagen Trial Unit (CTU) with computer-generated, permuted randomisation allocation sequence with

varying block sizes of 6, 8 and 10. The allocation sequence and block sizes were kept unknown to the investigator. Allocation ratio was 1:1. The investigator contacted the CTU and provided a personal pin code, participant civil registration number, participant trial identification number, and the value of the stratification variable of benzodiazepine dosage (low ($\leq$15 mg diazepam equivalents) or high ($>$15 mg diazepam equivalents)) at baseline. Then the randomisation was announced as a trial medication container number and confirmation sent by e-mail. All data were double entered into the OpenClinica database managed and hosted by CTU.

Blinding

Trial participants, staff, and outcome assessors were blinded to the allocated treatment. We maintained blinding using matching placebo and an independent unit to perform the randomisation and do the packaging and labelling of the trial medication. Both PRM and placebo were encapsulated in lactose-containing gelatine capsules to optimise the blinding. Thus, the placebo was matched to the study medication for taste, smell, colour, size and solubility. CTU held the randomisation code and the trial was not un-blinded until all data were registered, primary analyses finished and conclusions drawn (Gotzsche 1996).

Sample size estimation

Data directly illustrating the distribution of benzodiazepine dosage in schizophrenia or bipolar patients after participating in a discontinuation trial was not available in the literature. When estimating the sample size, we therefore applied our own unpublished data from a comprehensive chart review including registration of benzodiazepine dosage in 99 consecutive outpatients diagnosed with schizophrenia. In brief, under certain assumptions and a claim to be able to detect a statistically significant difference of minimum 8 weeks between the two intervention groups with regard to average duration of adherence to the discontinuation plan with 90% power, we reached a conservative estimate of 40 patients in each group. A more detailed description of the sample size estimation is included in the published trial protocol (Baandrup et al. 2011).

Statistical analysis

We used SAS version 9.3 for statistical analyses. All analyses were adjusted by the protocol specified stratification variable (baseline diazepam equivalents $>$15 mg, yes/no) and the baseline value of the dependent outcome variable. All analyses were intention to treat. Two-sided 5% significance tests were used. We analysed the primary outcome using the univariate general linear model. As sensitivity analysis, we used a non-parametric test (Mann–Whitney). The efficacy of the intervention with respect to benzodiazepine cessation proportion (follow-up dose: 0) was analysed using a logistic regression analysis.

We assessed the time course (8, 16 and 24 weeks) of benzodiazepine dosage and BWSQ-2 score using the mixed model with repeated measures (MMRM). Prior to the analysis, we examined if the distributions of the outcome defined by intervention and time followed a normal distribution with reasonable approximation. Since there were few timed measurements, we applied an unstructured covariance matrix in the analyses.

For patients leaving the trial early, the actual benzodiazepine dosage at 24 weeks was collected from patient files and the same procedure was followed in case of missing visits at week 8 and 16. For the BWSQ-2 score, if only one item was missing this item was set to zero, and if more items were missing the total score was set equal to missing. Missing values will not lead to bias when the MMRM is applied if data are missing at random.

Results

Participant flow and characteristics

The first patient visit took place in February 2012 and the last patient visit in June 2014. Out of 155 patients screened, 86 were randomised: 42 to PRM versus 44 to placebo. The mean age of the 69 excluded patients was 50.9 years and 40.6% were men. Figure 1 illustrates the flow of participants through the trial (CONSORT diagram). Only one patient was switched to a long-acting benzodiazepine (diazepam) before tapering began.

The intervention groups were similar with regard to baseline demographic and clinical characteristics (Table I). The mean duration of benzodiazepine treatment was 10 years in both groups and the main indication was anxiety and distress. Benzodiazepine mean dosage at baseline was similar between the treatment groups (24.5 mg (SD 20.1) in the PRM group and 23.1 mg (SD 14.1) in the placebo group).

Benzodiazepine dosage, cessation rate and withdrawal symptoms

No values were missing for the primary outcome. We found no significant effect of PRM on the primary outcome: mean benzodiazepine daily dosage at

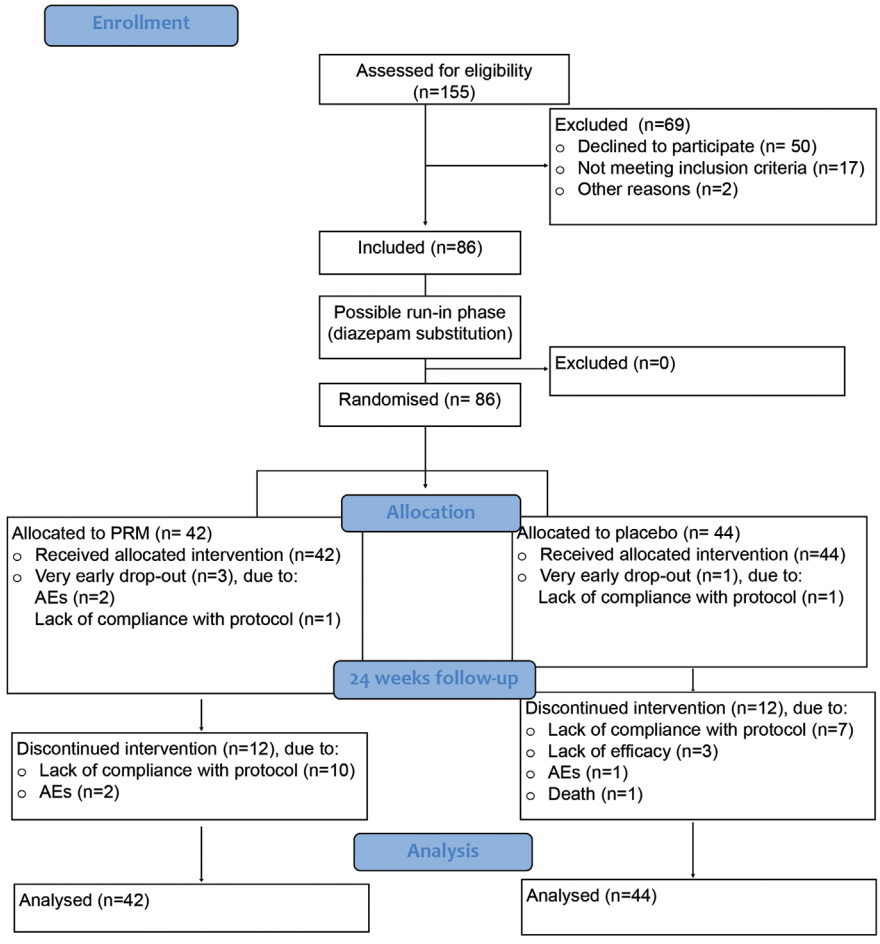

Figure 1. The CONSORT diagram. Flow of participants through the trial. AE, adverse event.

24 weeks was 8.01 mg (95% CI 5.51 to 10.5) in the PRM group versus 5.72 mg (95% CI 3.25 to 8.19) diazepam equivalents in the placebo group; the difference between means was –2.29 mg (95% CI –5.72 to 1.21; $P = 0.20$). The distribution of the data for the visit at 24 weeks deviated somewhat from the normal distribution, but the main result was confirmed in the planned sensitivity analysis: the P value of the corresponding non-parametric test was 0.25.

We did not find any significant difference in benzodiazepine cessation proportion between the two groups: 38.1% (16/42) in the PRM group versus 47.7% (21/44) in the placebo group (OR = 0.64; 95% CI 0.26 to 1.56; P = 0.32; PRM group as reference group).

Table II presents the results of the MMRM analyses. As expected, there was a highly significant main effect of time ($P < 0.0001$), i.e., benzodiazepine daily dosage steadily declined throughout the trial period in both intervention groups (Figure 2). There was no significant effect of intervention × time (coefficient of the interaction = 1.09; 95% CI –0.38 to 2.57; $P = 0.14$). There was a main effect of the stratification variable (coefficient = 5.29; 95% 1.52 to 9.05; $P = 0.007$; low dosage as reference group), i.e., higher benzodiazepine dosage at baseline was associated with higher dosage at endpoint. Regarding benzodiazepine withdrawal symptoms (BWSQ-2), all fixed effects except for the main effect of the baseline value were insignificant. Thus, no effect of supplementary PRM on the time course of BWSQ-2 could be demonstrated (Table II).

The mean total antipsychotic daily dosage at endpoint was 18.9 mg (SD 9.5) olanzapine equivalents in the PRM group versus 24.7 mg (SD 23.3) in the placebo group. As such, antipsychotic daily dosage decreased in both intervention groups during the trial, but the reductions were not statistically significantly different when comparing the mean difference in dosage between the groups.

Compliance

Compliance was similar between groups (Mann–Whitney, $P = 0.78$). In the PRM group, the median compliance rate was 99% with a range between 53%

Table I. Baseline demographic and clinical characteristics.

	Prolonged-release melatonin $N = 42$		Placebo $N = 44$	
	N	%	*N*	%
Men	23	55	25	57
Ethnic origin				
Caucasian	39	93	41	93
Non-caucasian	3	7	3	7
Diagnosis				
Paranoid schizophrenia	31	74	36	82
Non-paranoid schizophrenia	2	5	4	9
Schizoaffective disorder	3	7	0	0
Bipolar affective disorder	6	14	4	9
Smoking status				
Smoker	31	74	28	65
Previous smoker	6	14	11	26
Never smoker	5	12	4	9
Alcohol, number of drinks per week				
0–5	33	79	30	68
6–15	6	14	10	23
≥16	3	7	4	9
Substance abuse				
Current	3	7	6	14
Previous	19	46	16	36
Never	20	48	22	50
Somatic co-morbidity				
None	12	29	17	39
Diabetes type II	10	24	9	21
Chronic obstructive lung disease	2	5	6	14
Miscellaneous	18	29	12	27
Education, years in school				
7–10	17	40	22	50
11–15	21	50	16	36
≥16	4	10	5	11
Marital status				
Married	4	10	4	9
Divorced	10	24	4	9
Never married	28	67	36	82
Housing				
Living independently	30	71	25	57
Supported housing	2	5	1	2
Institution	10	24	18	41
Occupational status				
Employed	1	2	0	0
Financial aid/cash subsidies	1	2	3	7
Disability pension	37	88	38	86
Other	3	7	3	7
Benzodiazepine treatment				
One benzodiazepine	31	74	36	82
Two benzodiazepines[a]	11	26	8	18
Clonazepam	27	64	25	57
Diazepam	1	2	4	9
Oxazepam	16	38	11	25
Nitrazepam	3	7	3	7
Lorazepam	0	0	1	2
Zopiclone	4	10	4	9
Zolpidem	2	5	4	9
Benzodiazepine, indication for first prescription				
Anxiety, distress	35	83	34	77
Insomnia	5	12	6	14
Mania	1	2	1	2

(*Continued*)

Table I. (*Continued*)

	Prolonged-release melatonin $N = 42$		Placebo $N = 44$	
	N	%	*N*	%
Alcohol abuse	0	0	1	2
Unknown	1	2	2	5
Antipsychotic drug treatment				
One antipsychotic	26	62	19	43
Two antipsychotics	14	33	19	43
≥Three antipsychotics	2	5	6	15
Antidepressant drug treatment				
≥ One antidepressant	25	60	24	55
Mood stabiliser drug treatment				
≥ One mood stabiliser	18	43	11	25
Anticholinergic drug treatment				
≥ One anticholinergic drug	4	10	12	27
	Mean	SD	Mean	SD
Age (years)	47.9	8.7	49.4	12.3
Duration of illness (years)	21.9	10.9	21.8	10.1
PANSS total score	64.9	16.2	65.0	12.0
PSP total score	45.1	10.5	41.6	10.0
BWSQ-2 total score	11.3	9.0	8.6	9.0
Benzodiazepine treatment duration (years)	10.4	7.7	10.5	6.8
Benzodiazepine daily dosage (mg diazepam equivalents)	24.5	20.1	23.1	14.1
Antipsychotic daily dosage (mg olanzapine equivalents)	22.0	19.3	27.9	21.4
Body mass index (kg/m^2)	30.3	6.4	30.1	6.4

BWSQ-2, Benzodiazepine Withdrawal Symptom Questionnaire; PANSS,Positive and Negative Syndrome Scale; PSP, Personal and Social Performance Scale.

[a]The most frequent benzodiazepine combinations were oxazepam or clonazepam in combination with zopiclone or zolpidem.

and 100%. In the placebo group, the median compliance rate was 98% with a range between 26% and 100%. Non-parametric statistics were used because data were not normally distributed.

We measured the plasma benzodiazepine concentration in all participants with benzodiazepine cessation at endpoint, except for three patients where blood sampling was not possible due to logistic reasons. In all measured samples, plasma benzodiazepine concentration was zero confirming compliance with the discontinuation process.

Safety and tolerability

The overall occurrence of adverse events (AEs) did not differ between the PRM group and the placebo group (Table III). Likewise, rates of serious adverse events (SAEs) were comparable between intervention groups. Only two of the reported AEs were considered related to the study medication, and one of these was reported as a suspected unexpected serious adverse reaction (SUSAR). The SUSAR consisted of acute severe hyponatremia with confusion and seizures developed within few days after study

Table II. Estimates, 95% confidence intervals and *P* values of coefficients of the type 3 fixed-effect MMRM analyses.

	Dependent variable					
	Benzodiazepine dosage			BWSQ-2		
Covariates	Estimate	95% CI	*P*	Estimate	95% CI	*P*
Baseline value	0.37	0.26 to 0.48	<0.0001	0.64	0.48 to 0.80	<0.0001
Strata (low compared to high baseline bzd dosage)	5.29	1.52 to 9.05	0.007	−0.018	−1.81 to 1.77	0.98
Intervention	−0.033	−2.67 to 2.61	0.98	−0.39	−2.14 to 1.37	0.66
Time	−3.14	−3.89 to 2.40	<0.0001	−0.018	−0.66 to 0.63	0.96

BWSQ-2, Benzodiazepine Withdrawal Symptom Questionnaire.

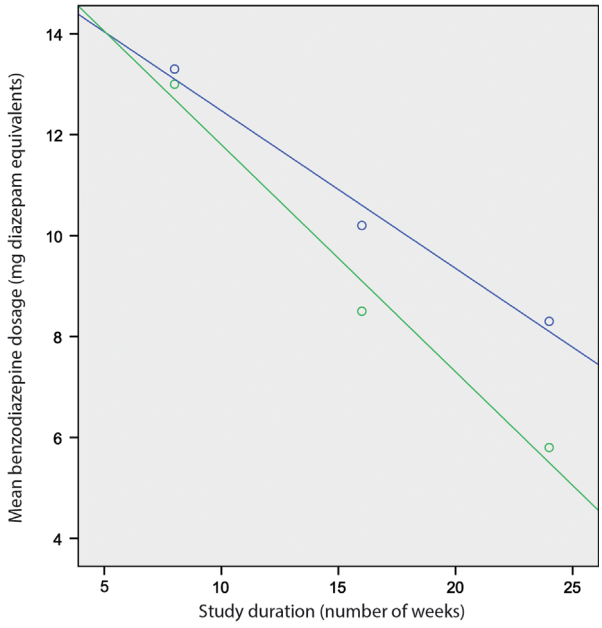

Figure 2. Benzodiazepine daily dosage. Estimated linear time course of the mean benzodiazepine daily dosage (mg diazepam equivalents) in the two intervention groups. Prolonged-release melatonin group = upper (blue) line. Placebo group = lower (green) line. There was no statistically significant difference between the groups ($P = 0.20$).

inclusion. Hyponatremia is listed in the summary of product characteristics as a rare adverse reaction. In this patient, a cannabis abuse with malnutrition was also believed to contribute to the clinical picture. The other AE considered related to the study medication was one patient with gastrointestinal symptoms related to lactose intolerance with increased intensity of symptoms after starting study medication. Only three of reported AEs led to discontinuation. All reported AEs in the suicidal ideation category were associated with hospitalisation (mostly of brief duration) and were therefore categorised as SAEs. None of these reported suicidal ideation events led to trial discontinuation and all the patients involved were described with a pattern of fluctuating suicidal ideation also prior to inclusion in the trial.

One patient died four days before the 24-week follow-up visit. The cause of death was a severe alcohol–disulfiram reaction not related to trial medication or trial participation.

Results from the physical examination including ECG were similar between groups from baseline to week 24. Clinically significant laboratory abnormalities were observed with similar frequency in both treatment groups and included mainly dyslipidaemia and elevations in glucose in patients already diagnosed with diabetes. Mean values of body mass index, abdominal width, blood pressure and pulse were similar between intervention groups both at baseline and at endpoint.

Discussion

This is the first randomised clinical trial investigating the efficacy of add-on melatonin compared with placebo to facilitate benzodiazepine discontinuation in patients with schizophrenia or bipolar disorder. Furthermore, it is the hitherto largest trial investigating the efficacy of melatonin for this specific indication. We found that PRM did not facilitate benzodiazepine withdrawal in terms of dosage reduction or cessation proportion at 24-week follow-up.

One possible limitation of our trial was the trial duration. Benzodiazepine dosage steadily declined throughout the trial period and in case of an extended trial period, the treatment groups might have separated. A more long-term follow-up of the participants with regard to benzodiazepine dosage will be necessary to evaluate if discontinued patients actually manage to stay off future benzodiazepine treatment. Recent studies investigating long-term outcome after successful discontinuation of benzodiazepines in older community-dwelling adults found relapse rates of resumed benzodiazepine use of, respectively, 43% at 24-month follow-up (Morin et al. 2005) and 41% at 10 years follow-up (de Gier et al. 2011). Another possible limitation was the fixed dose PRM regimen applied in the trial. The optimal melatonin dosing interval for treatment of insomnia (which is the main indication for melatonin treatment) has not been established. The 2-mg dose of PRM was used in this trial because this was the licensed dose for the approved condition (primary insomnia in elderly people) and because a pharmacokinetic study found that 2 mg of a slow-release melatonin preparation resulted in high, near physiological plasma levels sustained for 5–7 h in most healthy individuals (Aldhous et al. 1985). However, some patients might have benefitted from higher doses if a flexible dose regimen had been applied. The strengths of the current trial include the rigor of methodology resulting in a low risk of bias in terms of sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective outcome reporting (Savovic et al. 2012).

Add-on melatonin when discontinuing benzodiazepines has previously been investigated in two randomised clinical trials recruiting long-term benzodiazepine users mainly from general practice. One of the trials used the immediate release formulation of melatonin (5 mg 4 h before bedtime) and did not find any effect on benzodiazepine

Table III. Distribution of adverse events (AEs)[a] in the intervention groups.

	Prolonged-release melatonin $N = 42$		Placebo $N = 44$	
	N	%	*N*	%
Patients with one AE	15	35.7	12	27.2
Patients with two AEs	7	16.7	11	25.0
Patients with three AEs	3	7.1	3	6.8
Patients with four AEs	1	2.4	2	4.6
Patients with one serious AE	11	26.2	6	13.6
Patients with two serious AEs	1	2.4	4	9.1
Discontinuation due to AEs	2*	4.8	1**	2.3
AEs by body system				
Central nervous:				
Exacerbation of psychiatric symptoms (mainly psychotic symptoms and anxiety)	2	4.8	2	4.6
Mood changes	3	7.1	1	2.3
Suicidal ideation	3	7.1	2	4.6
Somnolence	4	9.5	2	9.1
Alcohol abuse	2	4.8	2	4.6
Cardiovascular	3	7.1	4	9.1
Digestive	8	19.1	4	9.1
Urogenital	0	0	4	9.1
Musculo-sceletal	3	7.1	3	6.8
Whole body:				
Influenza	3	7.1	0	0

[a]Reported in ≥ 5% of patients (≥ 2 patients) in either treatment group.
*One patient discontinued due to severe hyponatremia and one due to gastrointestinal symptoms related to lactose intolerance.
**One patient discontinued due to dizziness.

discontinuation proportion at 1-year follow-up (40% in both groups) in a total sample of 38 adult patients from general practice using benzodiazepines as sleeping medication for more than 3 months (Vissers et al. 2007). The other trial used PRM (2 mg 2 h before bedtime) and found a significantly higher discontinuation proportion in the PRM group (78%) compared with the placebo group (25%) at 6-week follow-up in a total sample of 34 long-term benzodiazepine users living independently and not cognitively impaired (Garfinkel et al. 1999). The failure of the melatonin immediate release trial might be due to the short elimination half-life and the need of most patients to stabilise sleep across the entire night and not only initially. Compared with these trials, a definite strength of our trial was the larger sample size. Another obvious contributor to the discrepancy between the current results and the result from the previous PRM trial is the trial population. It must be expected that the psychiatric morbidity and the lower functional level of the participants in the current trial would decrease the impact of a relative mild medication as melatonin compared with studies conducted in general practice.

The mean duration of benzodiazepine treatment prior to enrolment was 10 years, reflecting a lack of compliance with national and international recommendations of only short-term benzodiazepine treatment. The reasons for such long-term prescriptions may be manifold, but probably include a therapeutic nihilism regarding the ability of severely mentally ill patients to taper benzodiazepine treatment. The success in obtaining substantial benzodiazepine dose reductions in both intervention groups as demonstrated in our present trial suggests that withdrawal should be initiated in more patients. The total daily dosage of antipsychotics decreased non-significantly from baseline to endpoint in both intervention groups. Consequently, there was no indication that reduced/ceased use of benzodiazepines was substituted by increased use of antipsychotics.

The neutral findings of our trial may be explained by the severity of the illness of included patients and the nature of the applied gradual dose reduction regimen. People with schizophrenia suffer from a variety of symptoms (psychotic, negative and affective), cognitive disturbances and functional impairments, and merely succeeding to be included and staying in the trial was a major accomplishment for

most of the participants. When taking into consideration that the participants had been treated with benzodiazepines for a decade and had considered it a more or less integrated part of themselves, it was remarkable how dedicated and involved in the trial the patients became when they were informed about the adverse reactions of chronic benzodiazepine use. This engagement was also reflected in the rates of trial completion and benzodiazepine cessation in both treatment groups, which were higher than in most other discontinuation studies. A review of benzodiazepine discontinuation trials found an overall cessation proportion of 22–28% in studies recruiting patients from general practice or outpatient settings with only minor psychiatric morbidity (Parr et al. 2009). In the current trial, the mean benzodiazepine daily dosage at follow-up was comparably low between the intervention groups, indicating that the closely monitored gradual dose reduction regimen applied in this trial was successful in itself. It was possible to reduce the benzodiazepine dosage markedly, and for many patients to cease chronic benzodiazepine treatment, within 6 months, when a gradual and continuously guided taper regimen was applied. However, in this context of closely guided and monitored benzodiazepine dose reduction it was not possible to show an additional facilitating effect of add-on treatment with PRM.

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Statement of Interest

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