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ORIGINAL PAPER

Neurocognitive performance, subjective well-being, and psychosocial functioning after benzodiazepine withdrawal in patients with schizophrenia or bipolar disorder: a randomized clinical trial of add-on melatonin versus placebo

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Abstract Chronic benzodiazepine use is common in patients with mental illness and is associated with cognitive impairment. It is unclear whether benzodiazepine-induced cognitive impairment is reversible. Amelioration of cognitive dysfunction may be facilitated during benzodiazepine tapering by add-on melatonin due to its anti-inflammatory and neuroprotective properties. We examined how melatonin and benzodiazepine withdrawal affect cognition, subjective well-being, and psychosocial functioning. Eighty patients with schizophrenia or bipolar disorder were randomized to add-on treatment once daily with either prolonged-release melatonin or placebo in a 24-week, double-blind clinical trial. All participants gradually tapered usual benzodiazepine dosage in a closely monitored treatment setting. We used the Brief Assessment of Cognition in Schizophrenia (BACS) to assess neurocognitive performance with additional assessments of subjective well-being and psychosocial functioning. BACS composite and subscale scores (except motor speed) significantly improved in parallel with benzodiazepine dose reduction, but there was no additional effect of melatonin. Cognitive performance was still markedly impaired post-tapering compared with normative data. Neither benzodiazepine withdrawal nor treatment group affected subjective well-being or psychosocial functioning. In conclusion, add-on melatonin does not seem to affect cognition, well-being, or psychosocial functioning in patients with severe mental illness. The observed improvement in cognitive performance could not be distinguished from retest effects, which may in turn have been facilitated by the benzodiazepine tapering.

Keywords Neurocognition · Benzodiazepine · Melatonin · Schizophrenia · Bipolar disorder

Introduction

Patients with schizophrenia show marked neurocognitive impairments across most cognitive domains, e.g., verbal memory, working memory, motor speed, attention, executive functions, and verbal fluency [1]. The cognitive deficits observed generally range from 1.2 to 0.6 standard deviations below healthy controls in both first episode and chronic patients [2, 3]. Composite scores tend to be between 2.5 and 1.5 standard deviations below healthy controls [4]. In patients with bipolar disorder, cognitive deficits across all neuropsychological domains are reported in the euthymic state ranging from 0.8 to 0.5 standard deviations, with particularly marked impairment in verbal learning and memory [5]. Various pharmacological add-ons have been investigated as potential cognitive enhancers in schizophrenia, but none has yet proved to substantially improve cognitive performance [6].

A complicating matter in studies of cognition in patients with severe mental illness is the possible contribution of ongoing medication. Benzodiazepines are frequently prescribed for this patient population owing to high rates of comorbid insomnia and anxiety. On immediate exposure, benzodiazepines cause sedation and psychomotor slowing and thus impair cognition to varying degrees in the short-term [7]. In addition to immediate effects, impaired long-term cognitive functioning has also been reported as a

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side effect of chronic use (more than 3 months) [8, 9]. This long-term cognitive effect has been observed across all measured domains, with effect sizes ranging from −1.30 to −0.42 and a mean weighted effect size of −0.74 [8].

It is unclear whether benzodiazepine-induced cognitive impairment is reversible following benzodiazepine discontinuation [10]. This issue has recently gained further importance after several observational studies reporting an increased risk of dementia associated with chronic benzodiazepine use [11–14]. Such observational studies are potentially influenced by confounding by indication, i.e., that benzodiazepines are prescribed for conditions indicative of an early stage of dementia, which in clinical practice overlap with usual indications for benzodiazepine use (e.g., anxiety and insomnia) [15]. However, several studies trying to adjust for confounding factors have reported similar findings with a dose effect, suggesting that the association might be causal [12].

Melatonin is a naturally occurring nocturnal hormone, implicated in sleep induction and circadian rhythm regulation [16]. It also has a range of other potentially therapeutic benefits, including anti-inflammatory and neuroprotective properties [17]. Since immune system alterations are reported in schizophrenia [18], melatonin might act to stabilize the immune system, thus having a pro-cognitive effect via its antioxidative properties [19]. Furthermore, melatonin modulates stress effects on cognition via action on the stress response and cortisol secretion [19]. Add-on melatonin might therefore facilitate the reversal of cognitive dysfunction during benzodiazepine tapering.

In this study, we aimed to examine the effects of prolonged-release melatonin and benzodiazepine dose reduction/discontinuation on neurocognitive functioning in patients with schizophrenia or bipolar disorder. The primary outcome measure was global cognitive performance. We also obtained secondary outcome measures to investigate specific neurocognitive domains, subjective well-being, and psychosocial functioning. The secondary outcomes aimed to measure quality of life (patient-reported outcomes) and all-round daily functioning, in addition to the objective measure of a neuropsychological test battery.

Methods

Design and participants

A single-center, randomized, double-blind clinical trial was conducted at a University Hospital Research Department in the Capital Region of Denmark with a catchment area of 1,700,000 inhabitants. Patients were mainly recruited from outpatient services. The trial period was from February 2011 to June 2014. 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 3 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 at a sufficient level to be tested validly; and were not allergic to any compounds in the trial medication. Fertile women were only included if not pregnant or nursing and if using safe contraceptives throughout the trial period.

We present the results of repeated assessments of neurocognitive functioning, subjective well-being, and psychosocial functioning. A total of 86 patients were enrolled in the study. Here, we report results from a subsample of 80 patients who participated in baseline cognitive testing (which was not mandatory for trial participation). The overall primary objective of the trial was to evaluate whether prolonged-release melatonin can facilitate benzodiazepine withdrawal in medicated patients with schizophrenia or bipolar disorder. These results have been published elsewhere [20]. In this previous publication, we reported that prolonged-release melatonin had no effect on withdrawal rate or discontinuation. The prioritization of the co-examinations and co-outcomes was described in the published SMART trial protocol [21].

Experimental intervention and comparator

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 fortnightly. Hereafter, the discontinuation rate was continuously adjusted according to the individual experience of withdrawal symptoms. We examined participants at baseline and after 8, 16, and 24 weeks. We contacted the participants weekly by telephone to adjust the benzodiazepine dose reduction regimen and to provide information and general support.

Trial medication (2-mg prolonged-release melatonin, Circadin®, or matching placebo) once daily was initiated in parallel with the gradual reduction of benzodiazepine. Treatment with trial medication continued throughout the trial period, including the follow-up assessments after 24 weeks, irrespective of the individual final dosage of benzodiazepine. Participants, investigators, caregivers, and outcome assessors were blinded to treatment allocation. The number of tablets of trial medication was counted at each visit to assess compliance. Plasma benzodiazepine

concentration was measured in all participants with benzodiazepine cessation at endpoint to confirm compliance with the discontinuation process.

Any co-medication (i.e., medication other than benzodiazepines and benzodiazepine-like drugs) was allowed. We aimed to keep the co-medications constant during the trial period, but clinically necessary changes (as judged by the usual caregiver team) were allowed to limit attrition as much as possible.

Cognitive assessment

The Brief Assessment of Cognition in Schizophrenia (BACS) is a neurocognitive test battery developed to assess the cognitive domains that are most impaired and most strongly correlated with functional outcome in schizophrenia [1]. It was specifically designed to measure treatment-related changes in cognition, e.g., in medication trials. The assessment takes approximately half an hour, and composite scores have demonstrated high test–retest reliability. The BACS cognitive battery comprises six subtests in the respective targeted domains: verbal memory (list learning), working memory (digit sequencing), motor speed (token motor test), verbal fluency (category fluency and letter fluency), attention and processing speed (symbol coding), and executive function (the Tower of London test). For each subtest, we calculated a *z*-score using means and standard deviations in a sample of healthy controls ($N = 60$) from another study by our group. Age, sex, and socioeconomic status were thus not matched to the participants in the present study. We calculated composite scores by averaging all *z*-scores of the six subscale measures.

Trial participants were tested in person by research staff, who had been trained on the administration and scoring of the BACS. We used version A of the BACS for all visits since no other validated version was available in Danish at the time of the study. Testing took place prior to daily administration of benzodiazepine dosage or at least 2 h after taking the last dose.

Subjective well-being and psychosocial functioning

The importance of including patient-reported outcomes, such as measures of quality of life or subjective well-being, in clinical trials is increasingly being stressed, e.g., by the FDA and EMA [22, 23]. We therefore included a generic scale, the WHO-Five Well-being Index [24], and a disease-specific scale, the Subjective Well-being under Neuroleptic treatment scale (SWN, short version) [25]. The SWN has been evaluated as an independent outcome measure and as a quick assessment of subjective side effects with relevance to compliance. To assess psychosocial functioning, we used the Personal and Social Performance scale (PSP), which is a psychometrically validated measure of patients' personal and social functioning [26].

Extrapyramidal side effects and psychopathology

Benzodiazepines are sometimes prescribed to ameliorate extrapyramidal side effects from antipsychotic drug treatment. We therefore used a short version of the Udvalget for Kliniske Undersoegelser (UKU) side effect-rating scale to assess adverse drug effects at baseline and 24 weeks. The short version comprises four to five selected items in each of the four subscales (psychic, neurologic, autonomic, and other) from the full version of the UKU [27].

The Positive and Negative Syndrome Scale (PANSS) [28] was applied at baseline and endpoint to assess participants' mental states and symptomatology during benzodiazepine withdrawal.

Statistical analysis

We used SPSS version 22 for statistical analyses. We assessed the effect of prolonged-release melatonin and benzodiazepine dose reduction on BACS composite score using the mixed model with repeated measures (MMRM). Factors in the model were group, time, and group × time interaction. Prior to the analysis, we examined whether the distribution of the outcome defined by intervention and time approximated a normal distribution. Since there were few timed measurements, we applied an unstructured covariance matrix to the analyses. To assess the efficacy of melatonin we examined the group × time interaction and to assess the effect of benzodiazepine dose reduction, we examined the main effect of time. Likewise, to assess the effect of benzodiazepine dose reduction on BACS subscales, WHO, SWN, and PSP total scores, we evaluated the main effect of time in the MMRM analysis. We used the MMRM because it minimizes the effect of missing data as long as the data are missing at random. For all MMRM analyses, significance was set at $p < 0.005$ after Bonferroni correction for multiple comparisons (10 tests).

UKU and PANSS ratings in the two treatment groups at endpoint were evaluated using an independent samples *t* test. Differences between baseline and endpoint for the whole sample were assessed using a paired t test.

Results

Table 1 shows the demographic and clinical characteristics of 80 patients (40 in each intervention group) participating in cognitive testing at baseline. The intervention groups were similar except for a higher rate of anticholinergic drug use in the placebo group ($p = 0.04$). Theoretically, this may

Table 1 Baseline demographic and clinical characteristics

	Melatonin $N = 40$		Placebo $N = 40$	
	N	%	*N*	%
Sex				
Men	21	52.5	24	60.0
Women	19	47.5	16	40.0
Diagnosis				
Paranoid schizophrenia	29	72.5	33	82.5
Non-paranoid schizophrenia	2	5.0	4	10.0
Schizoaffective disorder	3	7.5	0	0
Bipolar affective disorder	6	15.0	3	7.5
Benzodiazepine treatment				
One drug	29	72.5	33	82.5
Two drugs	11	27.5	7	17.5
Clonazepam	25	62.5	22	55.0
Oxazepam	11	27.5	8	20.0
Other benzodiazepines or Z-drugs	4	10.0	10	25.0
Antipsychotic drug treatment				
One drug	26	65.0	18	45.0
Two drugs	12	30.0	17	42.5
≥Three drugs	2	5.0	5	12.5
Antidepressant drug treatment				
≥One drug	24	60.0	22	55.0
Mood stabilizer drug treatment				
≥One drug	17	42.5	10	25.0
Anticholinergic drug treatment	3	7.5	11	27.5
	Mean	SD	Mean	SD
Age, years	47.4	8.6	49.0	12.1
Duration of illness, years	21.5	10.9	20.9	9.1
PANSS total score	64.3	16.2	64.2	11.7
PSP score	45.1	10.5	41.6	10.0
WHO score	49.0	24.1	51.4	23.8
SWN total score	82.2	19.3	84.5	16.4
Benzodiazepine treatment duration, years	10.6	7.8	10.5	7.1
Benzodiazepine daily dosage, mg diazepam equivalents	25.1	20.4	23.2	13.9
Antipsychotic daily dosage, mg olanzapine equivalents	21.5	19.5	27.1	22.2

PANSS Positive and Negative Syndrome Scale, *PSP* Personal and Social Performance Scale, *WHO-5* WHO-5 scale, *SWN-S* Subjective Well-being under Neuroleptic treatment scale (short version)

The intervention groups were similar except for a higher rate of anticholinergic drug use in the placebo group ($p = 0.04$)

confer a benefit on the melatonin group when evaluating differential changes in BACS scores between the groups because anticholinergic drugs are known to impair cognitive performance. More than half of the patients were men, mean age was just below 50 years, and the majority of participants in both groups were diagnosed with paranoid schizophrenia. Most patients were treated with one benzodiazepine, most frequently clonazepam. In Denmark, clonazepam is widely used as an anxiolytic and sedating agent outside its licensed use as an antiepileptic drug.

Table 2 shows raw scores and z-scores for each intervention group and time point. The BACS composite score was approximately normally distributed for both treatment groups at each visit, as assessed by visual inspection of their histograms and the Shapiro–Wilk's test ($p > 0.05$). Table 3 shows results of the tests of type III effects in the MMRM

Table 2 BACS raw scores and z-scores at baseline and after 8, 16, and 24 weeks of gradual benzodiazepine dose reduction

BACS[a]	Baseline				8-week follow-up				16-week follow-up				24-week follow-up			
	PRM group ($n = 40$)		Placebo group ($n = 40$)		PRM group ($n = 29$)		Placebo group ($n = 30$)		PRM group ($n = 24$)		Placebo group ($n = 29$)		Placebo group ($n = 30$)		Placebo group ($n = 31$)	
	Raw score	Z-score	Raw score	Z-score	Raw score	Z-score	Raw score	Z-score	Raw score	Z-score	Raw score	Z-score	Raw score	Z-score	Raw score	Z-score
Verbal memory[a]	35.93 (10.90)	−2.36 (1.37)	34.78 (10.02)	−2.50 (1.26)	40.79 (12.60)	−1.75 (1.58)	41.40 (11.38)	−1.67 (1.43)	44.79 (11.73)	−1.24 (1.47)	42.24 (10.49)	−1.56 (1.31)	48.47 (12.33)	−0.78 (1.55)	43.52 (10.90)	−1.40 (1.37)
Digit sequencing task[a]	15.69 (4.82)	−1.90 (1.30)	15.83 (3.86)	−1.86 (1.04)	16.17 (4.43)	−1.77 (1.19)	17.13 (4.46)	−1.51 (1.21)	17.09 (4.24)	−1.51 (1.14)	16.77 (4.81)	−1.61 (1.30)	17.21 (3.86)	−1.49 (1.04)	17.48 (4.43)	−1.41 (1.19)
Token motor task[a]	52.24 (14.40)	−2.13 (1.22)	52.39 (12.08)	−2.12 (1.02)	56.04 (13.36)	−1.82 (1.13)	56.00 (15.96)	−1.82 (1.36)	54.25 (16.62)	−1.96 (1.41)	53.21 (13.95)	−2.05 (1.18)	55.23 (16.57)	−1.88 (1.40)	60.53 (17.42)	−1.43 (1.48)
Verbal fluency[a]	43.03 (12.83)	−1.52 (0.91)	43.30 (13.00)	−1.50 (0.92)	46.07 (14.98)	−1.31 (1.06)	44.60 (17.04)	−1.41 (1.20)	49.96 (18.51)	−1.03 (1.31)	45.40 (14.11)	−1.35 (1.00)	51.77 (17.41)	−0.91 (1.23)	46.88 (17.80)	−1.25 (1.26)
Symbol coding[a]	34.49 (9.54)	−2.91 (0.89)	33.88 (10.11)	−2.97 (0.94)	39.81 (10.32)	−2.42 (0.96)	36.27 (12.96)	−2.75 1.21	39.75 (12.04)	−2.42 (1.12)	35.77 (9.75)	−2.80 (0.91)	42.86 (9.52)	−2.13 (0.89)	39.82 (12.48)	−2.42 (1.16)
Tower of London[a]	14.03 (6.07)	−2.82 (3.07)	13.08 (4.85)	−3.30 (2.45)	16.46 (3.69)	−1.59 (1.87)	16.23 (3.33)	−1.70 (1.68)	15.82 (4.28)	−1.91 (2.17)	16.66 (3.12)	−1.49 (1.58)	16.33 (4.00)	−1.65 (2.03)	16.29 (3.75)	−1.68 (1.90)
Composite score[a]	–	−2.21 (1.05)	–	−2.37 (0.94)	–	−1.65 (0.90)	–	−1.82 (0.94)	–	−1.61 (0.84)	–	−1.80 (0.79	–	−1.44 (1.00)	–	−1.50 (0.94)

[a] Values are mean (standard deviation)

Table 3 MMRM analyses of BACS composite and subscales (type III fixed effects)

BACS	Main effect of intervention			Main effect of time			Intervention × time		
	F	Numerator *df*	*p*	*F*	Numerator *df*	*p*	*F*	Numerator *df*	*p*
Composite score	0.115	1	0.735	25.138	3	**<0.0005**	1.635	3	0.193
Verbal memory	0.282	1	0.597	32.455	3	**<0.0005**	3.044	3	0.036
Digit sequencing	0.515	1	0.475	5.238	3	**0.003**	0.505	3	0.681
Verbal fluency	0.199	1	0.657	8.285	3	**<0.0005**	1.343	3	0.269
Token motor	0.046	1	0.831	2.766	3	0.050	1.442	3	0.240
Symbol coding	1.455	1	0.231	20.426	3	**<0.0005**	3.150	3	0.031
Tower of London	0.001	1	0.976	8.012	3	**<0.0005**	1.783	3	0.161

Bold statistically significant after Bonferroni correction ($p < 0.005$)

Table 4 Characterization of benzodiazepine dose reduction

	Baseline		8 weeks		16 weeks		24 weeks	
	Melatonin ($N = 40$)	Placebo ($N = 40$)	Melatonin ($N = 40$)	Placebo ($N = 40$)	Melatonin ($N = 40$)	Placebo ($N = 40$)	Melatonin ($N = 40$)	Placebo ($N = 40$)
Mg diazepam equivalents, mean (SD)	25.1 (20.4)	23.2 (13.9)	13.7 (11.7)	13.2 (9.6)	10.5 (10.9)	8.8 (8.7)	8.6 (10.5)	5.9 (8.2)
Cessation of benzodiazepine use, *N* (%)			4 (10.0)	0	9 (22.5)	8 (20.0)	15 (37.5)	19 (47.5)
Relative dose compared with baseline, mean (SD)			0.54 (0.28)	0.53 (0.19)	0.40 (0.31)	0.35 (0.25)	0.35 (0.38)	0.22 (0.27)

Table 5 MMRM analyses of WHO, SWN total score, and PSP (type III fixed effects)

	Main effect of intervention			Main effect of time			Intervention × time		
	F	Numerator *df*	*p*	*F*	Numerator *df*	*p*	*F*	Numerator *df*	*p*
WHO	0.041	1	0.841	1.029	3	0.386	1.649	3	0.187
SWN total	<0.001	1	0.998	1.704	3	0.175	0.976	3	0.410
PSP	2.131	1	0.148	2.226	3	0.093	0.505	3	0.680

analysis. There was a strong main effect of time, i.e., benzodiazepine dose reduction, but no group × time interaction, i.e., no effect of prolonged-release melatonin compared with placebo on the time course of the BACS composite score.

BACS subscores were approximately normally distributed for both treatment groups at each visit, as assessed by visual inspection of their histograms and the Shapiro–Wilk's test ($p > 0.05$). However, in the melatonin group, digit sequencing at visit two and Tower of London at visit one and three were not normally distributed. Thus, these results should be interpreted cautiously. For BACS subscales, there was a strong effect of time (i.e., benzodiazepine dose reduction) on all subscales, except for the token motor test. There was no significant group × time effect after Bonferroni correction (Table 3). Since there was no effect of melatonin on any cognitive measure, it was not relevant to perform a sensitivity analysis to investigate a possible contribution of anticholinergic drug use frequencies in the two intervention groups (as shown in Table 1). To estimate the size of the change in the composite cognitive score from baseline to endpoint, we supplemented the analyses with a paired t test of the whole sample showing a mean increase in *z*-score of 0.692 (95 % CI −0.865 to −0.520). Table 4 shows the results of tapering. By visit 2 (after 8 weeks), benzodiazepine mean total daily dose had already halved in both intervention groups.

PSP and WHO scores were approximately normally distributed for both treatment groups at each visit, as assessed by visual inspection of their histograms and the Shapiro–Wilk's test ($p > 0.05$). SWN total scores were moderately negatively skewed for visit two and four in the melatonin group. Therefore, these results should be interpreted with some caution. Table 5 shows results of the tests of type III effects in the MMRM analysis. WHO, SWN total, and PSP scores were all stable across time and between intervention groups, i.e., no effect of time and no effect of the interaction term.

Presence and intensity of antipsychotic side effects as measured with a short version of the UKU significantly improved from baseline (mean 10.37; SD 4.91) to endpoint (mean 7.31; SD 4.80) in the whole sample ($p < 0.001$). Furthermore, there was no difference between the two intervention groups in change scores ($p = 0.07$). Likewise, the PANSS total score significantly improved from baseline (mean 63.48; SD 12.99) to endpoint (mean 60.70; SD 16.30) as assessed in the whole sample ($p = 0.025$). Again, there was no difference in change scores between intervention groups ($p = 0.07$).

Discussion

In this study, we investigated the effects of prolonged-release melatonin and benzodiazepine dose reduction on cognitive functioning in patients with schizophrenia or bipolar disorder withdrawing from chronic benzodiazepine use. We found that across 24 weeks benzodiazepine dose reduction/discontinuation was associated with marked improvements in cognitive functioning across all domains except for motor speed. There was no additional improvement in neurocognitive performance elicited by melatonin add-on compared with placebo. Neither benzodiazepine withdrawal nor melatonin affected subjective well-being or psychosocial functioning, which remained stable across the study period.

The strong antioxidant effects of melatonin coupled with the emerging evidence for an increased inflammatory response in schizophrenia and bipolar mood disorder provide the rationale for further exploration of melatonin as a cognitive enhancer [17]. Compared with other possible antioxidants (e.g., vitamins C and E), melatonin has the advantage of being highly lipid soluble and as such readily cross the blood–brain barrier [29]. This is the first clinical trial to investigate melatonin as a cognitive enhancer in severe mental illness. Previous studies have examined this indication for melatonin in other patient populations, particularly patients with dementia. Preclinical studies indicate that melatonin might slow down the progression of cognitive impairment in people with Alzheimer's disease [30]. However, as yet no clinical research has indicated that melatonin ameliorates the cognitive sequelae of dementia [31]. As such, our finding that there is no additional improvement in cognition following melatonin add-on during benzodiazepine tapering is in line with previous clinical findings, albeit within a different clinical condition. It is possible that the dose of melatonin applied in the current study was too low to be sufficiently neuroprotective and produce a pro-cognitive effect. However, the doses required for melatonin to exert its different potential therapeutic effects have not yet been sufficiently investigated.

The effect of benzodiazepine tapering on cognitive performance in schizophrenia patients was recently examined in a Japanese study of 30 patients with schizophrenia [32]. They controlled for practice effects using a comparison group of 10 patients with schizophrenia who did not undergo benzodiazepine discontinuation. Their results showed significant improvements with benzodiazepine dose reduction or discontinuation in verbal memory, working memory, and composite scores. While our results are consistent with the Japanese study, we did not include a control group and so cannot directly distinguish between the effects of benzodiazepine discontinuation and retest effects. Furthermore, our participants still had marked cognitive impairments at the study endpoint compared with normative data. Their cognitive deficits on composite scores remained in line with previously reported scores in patients with schizophrenia. This is consistent with the results of Barker et al. [10] who reported cognitive improvements after benzodiazepine withdrawal in non-psychiatric populations, but with significant impairments remaining compared with normative data.

It has been claimed in the literature that benzodiazepines might have a beneficial effect on schizophrenia symptoms [33]. However, a recent meta-analysis could not find any evidence for therapeutic efficacy of benzodiazepine treatment to improve overall schizophrenia symptoms in trials of up to 8-week duration [34]. In the current study, we observed a statistically significant reduction in PANSS total score from baseline to endpoint of less than 5 %. We believe this indicates that psychopathology did not worsen as a consequence of benzodiazepine withdrawal. Likewise, we found no indication from this study that antipsychotic side effects increased after benzodiazepine dose reduction/discontinuation.

The main limitation of this study is the lack of a control patient group who did not taper off usual benzodiazepine treatment. We did not include a treatment-as-usual control arm in the study because the main aim was to investigate the effects of melatonin. The lack of a control patient group makes it difficult to separate the effect of time from the effect of benzodiazepine dose reduction. It is well established that subjects who are repeatedly tested for cognitive functioning show some improvements due to practice. Observed practice effect sizes vary between studies, but differences up to 0.45 standard deviations are reported in chronic schizophrenia patients [35, 36]. Thus, the effect size observed in this study (an improvement of 0.69 standard deviations from baseline to endpoint for the composite score) was larger than most previous studies reporting cognitive changes over time in patients with schizophrenia or bipolar disorder. However, participants were repeatedly tested with the same verbal memory list, and improvements in the composite score were largely due to improvements

in this domain. Our design does not allow us to distinguish between the effects of benzodiazepine discontinuation and retest effects. However, it is highly likely that improvements in cognitive performance resulting from retest effects may also have been facilitated by the benzodiazepine tapering. We did include a healthy control group to obtain normative data. The mean age of the healthy controls included as references to calculate *z*-scores was approximately 24 years. This may have inflated the *z*-scores since an age-related decline has been demonstrated in the cognitive functions tested in the current study [37]. However, while the effect size of cognitive deficits may be inflated, the relative improvement should be unaffected by this bias. Nonetheless, our results seem to indicate that cognitive abilities at least do not worsen following benzodiazepine tapering. This might be reassuring for clinicians and patients who are reluctant to taper chronic benzodiazepine use because they fear destabilization of symptoms and reduced level of functioning.

Another limitation of the study is the heterogeneity of the study population, which might limit the external validity of our results. The assessment of external validity would also have been facilitated by a more detailed description of the study population than provided here.

This study supports current clinical guidelines emphasizing the need to restrict benzodiazepine prescriptions to short-term use only. Patients with schizophrenia or bipolar disorder whose chronic benzodiazepine treatment is tapered experience improvements in their cognitive performance. This may be a result of practice while maintaining stable levels of subjective well-being, psychosocial functioning, antipsychotic side effects, and psychopathology.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards This 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) and was registered at ClinicalTrials.gov (NCT01431092). The authors confirm that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All participants provided written informed consent.

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