Sleep disturbances in schizophrenia spectrum and bipolar disorders – a transdiagnostic perspective

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ABSTRACT

Background: Sleep disturbances are prevalent in severe mental disorders but their type and frequency across diagnostic categories has not been investigated in large scale studies.
Methods: Participants with Schizophrenia spectrum disorders (SCZ, (N = 617)), Bipolar disorders (BD, (N = 440)), and Healthy Controls (HC, (N = 173)) were included in the study. Sleep disturbances (insomnia, hypersomnia and delayed sleep phase) were identified based on items from the Inventory of Depressive Symptoms – Clinician rated scale. Clinical symptoms were assessed with the Positive and Negative Syndrome scale and level of functioning with the Global assessment of Functioning scale.
Results: The rate of any sleep disturbance was 78% in SZ, 69% in BD and 39% in HC. Insomnia was the most frequently reported sleep disturbance across all groups. Both diagnostic groups reported significantly more of any sleep disturbances than HC (P < 0.001). Having a sleep disturbance was associated with more severe negative and depressive symptoms and with lower functioning across diagnostic groups (P < 0.001, $\eta^2 = 0.0071$). Hypersomnia was the only sleep disturbance associated with previous treatment history.
Conclusion: Sleep disturbances, including insomnia, hypersomnia and delayed sleep phase, are frequent in SCZ and BD, and associated with more severe clinical symptomatology across diagnostic groups. This suggests that sleep disturbance is a clinically relevant transdiagnostic phenomenon.
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1. Introduction

Sleep disturbances are frequent across a wide range of mental disorders [1]. Not only are sleep disturbances a distressing symptom in itself, but has been suggested as a putative mechanism for causing and maintaining symptoms and functional difficulties [2]. However, the type and frequency of sleep disturbances have not been investigated across the main diagnostic categories of severe mental disorders, Schizophrenia Spectrum Disorders (SCZ) and Bipolar Disorders (BD). Thus, there is a need for large scale studies investigating whether sleep disturbance is a transdiagnostic phenomenon in psychotic disorders.

There are several types of sleep disturbances, but descriptive studies mainly focus on insomnia. Insomnia is the most common sleep disturbance and one of the most prevalent health disorder in the general

population, with prevalence rates varying from 4%–48% [3]. Different types of insomnia, including problems falling asleep and staying asleep, are also the most commonly reported sleep disturbances in severe mental disorders [4,5]. Far less attention has been given to hypersomnia; a sleep disturbance characterized by prolonged nocturnal sleep, excessive daytime sleepiness and unrefreshing naps [6]. Systematic prevalence studies are lacking, but hypersomnia is estimated to be present in 0.02–0.07% of the general population [7], in contrast to around 30% in studies of SCZ and BD populations [8,9].

Hypersomnia may be related to abnormalities in the circadian organization of the sleep-wake cycle. Delayed sleep phase (DSP) is, however, the most commonly occurring circadian misalignment. DSP consists of a phase delay in relation the desired time for sleep, accompanied by trouble falling asleep or waking at the time of desire, whilst sleep itself is reported to be normal [10]. The prevalence of DSP in the general population is not well known; however one population-based study found a prevalence of 0.17% [11]. The comorbidity between DSP and severe mental disorders is high, especially for mood disorders, and of considerable theoretical interest since circadian dysregulation has been proposed as one of the mechanism underlying BD [12,13]. They are also the most recognized early symptoms of mania [14]. As sleep

disturbances also often appear in the prodromal phase of psychotic disorders, they are suggested to be involved in the pathophysiology of psychosis [15] and in exacerbation of psychotic symptoms [16]. Sleep disturbances in severe mental disorders have also been linked to lower quality of life, suicide attempts and poorer clinical and cognitive functioning, as well as higher relapse rates of mood episodes [4,17–21]. Despite the potentially wide-ranging negative effects of sleep disturbances in severe mental disorders, the use of formal sleep assessments and evidence-based treatment is rare [22,23]. Increased awareness of the frequency and magnitude of sleep disturbances among people with severe mental disorders might aid professionals to recognize the importance of sleep disturbance as a specific treatment target.

Many factors may influence sleep quality. Insomnia is more common in women and increases with age [3], whilst hypersomnia and DSP are more prevalent in the young [6,10]. Comorbid alcohol and drug abuse may influence both sleep quality and symptoms [4]. Antipsychotics, anxiolytics, hypnotics or sedatives also have effects that may both improve sleep quality, influence sleep architecture or cause disruption of the sleep wake cycle [24]. These effects are more likely to occur after long-term use; emphasizing the importance of studying sleep at different stages of treatment [17]. Weight gain, a frequent and problematic side effect of many medications, is also associated with sleep disturbances [25] and may increase the susceptibility for additional sleep disturbances such as obstructive sleep apnea. We lack studies of how these factors can mediate or moderate sleep disturbances in severe mental disorders due to small sample sizes in previous studies.

1.1. Aims of the study

We thus aim to determine the type and frequency of self-reported sleep disturbances in patients with schizophrenia spectrum disorders and bipolar disorders compared to healthy controls, and between previously treated and first-treatment patient groups. We also aim to explore the relationship between sleep disturbances, clinical symptoms and functioning, with adjustment for the possible influence of age, gender, recent alcohol and drug use, history of alcohol or drug dependency, use of medications with sedative effects and weight.

2. Materials and methods

2.1. Participants

One thousand and fifty-seven participants with severe mental disorders (SCZ n = 617, BD n = 440) and 173 healthy controls (HC) were recruited from the larger 'Thematically Organized Psychosis (TOP) Research Study' at the Norwegian Centre for Mental Disorders Research (NORMENT) in Oslo, Norway. To be included in the current study all participants had to have data on sleep disturbances. Patients were recruited from 2003 to 2018 and healthy controls from 2017 to 2018. In the SCZ group, 352 had a diagnosis of schizophrenia, 90 were diagnosed with schizoaffective disorder, 43 with schizophreniform and 132 had other psychotic disorders. In the BD group, 283 had bipolar I disorder, 130 had bipolar II disorder and 27 had bipolar NOS. Participants with less than one year of adequate treatment at study baseline were classified as first-treatment participants, 278 with SCZ and 153 with BD. Adequate treatment is part of the inclusion criteria and is defined as a) mood stabilizers or antipsychotic medication in adequate dosage for >12 weeks or b) admission to a psychiatric ward designed for treatment of psychotic disorders. The remaining participants (339 with SCZ and 287 with BD) were classified as previously treated. Exclusion criteria for all participants included history of hospitalized head injury, neurological disorder, obstructive sleep apnea, restless legs syndrome, IQ below 70 and age outside the range of 18–60 years. Exclusion criteria were assessed as part of a thorough physical examination by a physician including history of somatic health, height and weight (BMI), which both clinical participants and healthy controls underwent. Healthy controls were drawn from the population register in Oslo and Akershus. They were an screened with interview about severe mental illness symptoms and the Primary Care Evaluation of Mental Disorders [26] and excluded if they or their first degree relatives had a lifetime history of severe psychiatric disorders (DSM-IV axis 1 disorder), or if they met criteria for alcohol or drug abuse/dependency during the last 6 months. SCZ and BD participants were not excluded because of alcohol or drug abuse/dependency to ensure a representative clinical sample. All participants gave written informed consent. The study was approved by 'The Regional Committee for Research Ethics' and 'The Norwegian Data Inspectorate'.

2.2. Demographics and clinical characteristics

All clinical assessment was completed by trained medical doctors, psychiatrists or clinical psychologists. Clinical participants were diagnosed with the Structural Clinical Interview for DSM-IV (SCID-I) [27]. Symptoms were measured with the Positive and Negative Syndrome Scale (PANSS) using Wallwork's five factor model [28]. High score on the PANSS is indicative of more severe current symptoms. The current level of depressive symptoms was measured by the PANSS depressive factor (Wallwork) including the following items; G2 Anxiety, G3 Guilt Feelings, and G6 Depression Posturing. Global functioning was measured with Global Assessment of Functioning Scale-Split version – function score (GAF-F) [29]. Based on clinical interview and medical charts, information about current alcohol or drug use (the number of units of alcohol and use of illegal drugs past two weeks) and current use of psychotropic medication (type of medication(s) and dose of antipsychotics, antidepressants, antiepileptics and/or lithium) and was obtained. We defined the following as "medication with potential sedative effects", based on their mechanisms of action and reports of having sedation as a main effect or as a major side-effect: 1) All substances marked as sedatives. 2) Antipsychotics, antidepressants and mood stabilizers where sedation is marked as a major side effect in their description of action (based on information given in The Norwegian Pharmaceutical Product Compendium) [30]. 3) By checking their known moods of action on neurotransmitters involved in promoting sleepiness (histaminergic/muscarinergic) such as e.g. quetiapine and olanzapine. Lifetime history of alcohol or drug abuse or dependency was based on DSM-IV substance related diagnoses.

2.3. Sleep disturbances

Sleep disturbances in both clinical groups and HC were obtained as part of the clinical assessment using the Inventory of Depressive Symptoms – Clinician rated scale (IDS-C) [31]. IDS-C comprises four sleep items; difficulty falling asleep (item 1), difficulty maintaining sleep (item 2), early awakening (item 3) and hypersomnia (item 4). All items are scored from 0 to 3 with higher scores indicating higher level of disturbance. IDS-C has been used in several studies to identify different subtypes of sleep disturbances; the items have been validated as measures of insomnia and hypersomnia severity and have shown predictive value in clinical diagnoses of sleep disorders [19,32–35]. Based on the sleep items from IDS-C we use the following definitions of sleep disturbances [8,13], pinpointing that our definitions of the different sleep disturbances are to be regarded as symptoms of sleep disturbances and not diagnostic categories.

1. **Insomnia** was considered present if participants had a score of: Sleep Onset Insomnia ≥2 (more than half of the time it takes minimum 30 min to fall asleep), Mid-Nocturnal Insomnia = 3 (more than half the time, one wakes up more than once a night and stays awake for 20 min or more), or Early Morning Insomnia ≥1 (more than half the time, one wakes up >30 before one needs to get up)

as well as scoring zero on the Hypersomnia item (0 = sleeps no >7–8 h a night, without naps).

2. **Hypersomnia** was considered present if participants had a score of ≥1 on the Hypersomnia item (sleeping up to 10 h per day) with no evidence of Insomnia.

3. **Delayed sleep phase** (**DSP**): DSP was operationalized as Sleep Onset Insomnia ≥3 (more than half the time, it takes >60 min to fall asleep), and Hypersomnia ≥1.

4. **Any sleep disturbance**: Was considered present if participants scored over cut-off on any of the sleep disturbances described.

2.4. Statistical analyses

We used the statistical package for the Social Sciences (SPSS Inc., Chicago, IL version 24). Chi-square statistics and logistic regression analyses were used to examine the influence of diagnostic categories on the likelihood of specific sleep disturbances (any sleep disturbance, insomnia, hypersomnia or DSP). The risk for sleep disturbances after adjustments for the two diagnostic groups (SCZ and BD) are reported using odds ratios (OR) with 95% confidence intervals (CI). As none of the HCs reported DSP, only diagnostic groups were analyzed for DSP. We explored the possible association between sleep disturbances and demographic/clinical factors (age, gender, medication with sedative effects, recent intake of alcohol and drugs, a history of alcohol or drug dependency, and BMI) that could influence sleep patterns using *t*-tests or chi-square statistics. Most of the demographic and clinical variables were illness specific and therefore not entered as covariates in analyses containing HC. However, their impact on the risk of sleep disturbances in SCZ and BD was investigated in follow-up analyses using multivariate binary logistic regression. Binary logistic regression analyses were also used to examine the influence of treatment history (first-treatment vs. previously treated) and diagnosis on the likelihood of sleep disturbances.

To avoid the risk of type I errors when exploring the relationship between sleep disturbances, clinical symptoms and functioning, the effect of having any sleep disturbance on clinical symptoms and functioning was first investigated by multivariate analysis of variance (MANOVA). Based on a significant MANOVA, the analysis was continued with a series of ANCOVAs with clinical symptoms (Wallwork's five-factor model) and functioning (GAF-F) as dependent variables and "any sleep disturbance" as the main factor. Diagnostic group and demographic and clinical characteristics that were associated with both the sleep disturbance and the dependents in bivariate associations were entered as co-variates. Effect size was calculated by η^2. Unless otherwise stated, a significance level of P < 0.05 (two-tailed tests) was employed.

3. Results

3.1. Demographics and clinical characteristics

As shown in Table 1, the SCZ group was significantly younger, included more males and had lower level of education compared to BD and to HC. The SCZ group also reported more drug dependency, used more antipsychotic medication and less mood stabilizers than BD. There was, however, no difference in BMI, alcohol use or use of medication with sedative effects.

3.2. Sleep disturbances in diagnostic groups compared to healthy controls

As illustrated in Table 2, 78% of participants in the SCZ group, 69% in the BD group and 39% of the HC group reported at least one type of sleep disturbance. The frequency of reporting any sleep disturbance was significantly higher in SCZ than BD. For all three groups, the most frequently reported sleep disturbance was one or more types of insomnia. This was experienced in around 1/2 of participants in both diagnostic groups and 1/3 of the HC group, with no difference in the overall insomnia rate between SCZ and BD. Both sleep onset insomnia and mid nocturnal insomnia was also significantly more frequent in the two clinical groups compared to HC. Early morning insomnia was nominally, but not statistically significantly, more frequent in the HC group compared to clinical groups. The most prominent difference between clinical groups and HC was found for hypersomnia (in 3% of HC and

Table 1
Demographic and clinical characteristics of the sample.

	SCZ Spectrum N = 617	BD N = 440	HC N = 173	ANOVA/ Chi-square		
				F/x^2	P	Post hoc
Demographics						
Age, mean ± SD[a]	30.7 ± 9.8	34.0 ± 12.0	34.8 ± 10.1	F = 15.25	<0.001	HC, BD > SCZ | SCZ < HC,BD
Female sex, n (%)	264 (42.8)	262 (59.5)	49 (45.0)	χ^2 = 29.77	<0.001	HC, SCZ ˉBD
Education in years, mean ± SD[b]	12.3 ± 2.6	13.5 ± 2.4	14.9 ± 2.2	F = 61.39	<0.001	HC > SCZ,BD | SCZ < HC,BD
Clinical variables						
Alcohol units last two weeks, mean ± SD[c]	7.0 ± 21.1	9.7 ± 20.1	–	F = 4.35	0.04	
Drug use last two weeks, yes (%)	56 (9.0)	45 (11.2)	–	χ^2 = 0.39	0.53	
Lifetime alcohol dependency, Yes (%)	86 (13.8)	61 (13.8)	–	χ^2 = ˉ0.01	0.97	
Lifetime drug dependency, Yes (%)						
First-treatment, n (%)	124 (20.1)	57 (13.2)	–	χ^2 = 9.23	0.002	
	278 (45.0)	153 (34.8)	–	χ^2 = 11.25	<0.001	
Medication & somatic variables						
BMI, mean ± SD[d]	26.2 ± 5.2	25.8 ± 4.6	–	F = 1.80	0.18	
Antipsychotics (%)	524 (84.9)	226 (51.5)	–	χ^2 = 140.39	<0.001	
≥2 agents (%)	130 (21.3)	27 (6.1)	–	χ^2 = 45.29	<0.001	
Mood stabilizers (%)	87 (14.0)	237 (53.7)	–	χ^2 = 191.04	<0.001	
≥2 Mood stabilizers (%)	10 (1.6)	26 (5.9)	–	χ^2 = 14.36	<0.001	
Antidepressants (%)	192 (30.9)	149 (33.8)	–	χ^2 = 0.89	0.35	
Anxiolytics/hypnotics (%)	69 (11.3)	39 (8.8)	–	χ^2 = 1.51	0.22	
Medication with sedative effects (%)	343 (55.4)	196 (44.6)	–	χ^2 = 12.54	<0.001	

Mood stabilizer refers to lithium or antiepileptics. SCZ spectrum = schizophrenia spectrum; BD spectrum = bipolar disorder s; HC = healthy controls. BMI=Body Mass Index. [a] 99.7% (n = 1054) of the clinical participants had data on age. [b] 90.0% (n = 951) of the clinical participants completed data on years of education. [c] 98.4 (n = 1040) of the clinical participants had data on alcohol use during the last two weeks. [d] 93.9% (n = 992) of the clinical participants had data on BMI. 63.0% (n = 109) of the HC group had data on age, sex, BMI, and years of education.

Table 2
Frequency and characteristics of sleep disturbances across groups.

Sleep variables	Whole sample (N = 1230)	HC (n = 173) vs. diagnostic groups (N = 1057)				BD (N = 440) vs. SCZ (N = 617)			
		HC	Patients	x^2	P	BD	SCZ	x^2	P
Any sleep disturbance N (%)	857 (69.4)	68 (39.3)	785 (74.4)	85.49	<0.001	302 (68.6)	483 (78.3)	12.50	<0.001
Insomnia (any type) N (%)	556 (45.1)	63 (36.4)	491 (46.5)	6.01	<0.05	200 (45.5)	291 (47.1)	0.30	0.58
–Sleep onset insomnia, N (%)	378 (30.6)	19 (11.0)	358 (33.9)	36.6	<0.001	134 (30.4)	224 (36.3)	3.92	0.05
–Mid nocturnal insomnia, N (%)	142 (11.5)	9 (5.2)	132 (12.5)	7.78	<0.01	59 (13.4)	73 (11.8)	0.59	0.44
–Early morning insomnia, N (%)	294 (23.8)	49 (28.3)	245 (23.2)	2.16	0.141	117 (26.6)	128 (20.7)	4.93	<0.05
Hypersomnia, N (%)	299 (24.2)	5 (2.9)	294 (27.8)	50.19	<0.001	102 (23.2)	192 (31.1)	8.06	<0.01
Delayed sleep phase, N (%)	83 (6.7)	0 (0)	83 (7.9)	14.57	<0.001	17 (3.9)	66 (10.6)	16.57	<0.001

BD = bipolar disorder; SCZ = Schizophrenia; HC = Healthy controls.

28% of clinical groups). Hypersomnia was also significantly more frequent in SCZ compared to BD. No HC reported DSP, but DSP was almost 3 times more common in SCZ compared to BD.

Any type of sleep disturbance, hypersomnia and DSP were associated with younger age. Recent drug use was associated with less hypersomnia, DSP and lower frequency of any sleep disturbance whilst participants with a history of drug dependency had higher frequency of any sleep disturbance. Recent use of alcohol and a history of alcohol dependency was only associated with more insomnia. Use of medication with sedative effects was associated with higher frequency of any sleep disturbance and hypersomnia. There were no associations between gender or BMI and any sleep disturbances. Follow-up analyses showed that the differences between SCZ and BD for any sleep disturbance, hypersomnia and DSP remained significant also when controlling for age, drug use and medication with sedative effects.

3.3. Sleep disturbances and treatment history

Hypersomnia was the only sleep disturbance related to differences in treatment history (Table 3). There was also a significant interaction effect between treatment history and diagnostic group on the risk of hypersomnia, with higher frequency in previously treated SCZ and in first-treatment BD (Fig. 1). Previously treated SCZ participants also used significantly higher doses of antipsychotic medication and mood stabilizers (antipsychotics: 91.2% vs 77.2%, mood stabilizers: 19.7% vs 7.2%) and had higher BMI (BMI: 26.9 vs 25.3) than first-treatment SCZ participants. The previously treated BD group, however, used significantly less antipsychotics and medication with sedative effects compared to first-treatment participants (45.7% vs 62.5%, 38.8 vs 55.3%). Follow-up analyses showed that the interaction between treatment history and diagnostic group on hypersomnia was significantly influenced by medication with sedative effects. However, the main effect of diagnosis x treatment history remained significant after controlling for medication with sedative effects, in addition to age and recent drug use.

3.4. Relationship between sleep disturbance and clinical symptoms/functioning

Patients reporting any sleep disturbance had overall more symptoms and poorer functioning than patients without sleep disturbance (MANOVA: F = 13.18, $p<0.001$, $\eta^2 = 0.0071$). Follow-up univariate ANCOVAs showed that clinical participants with any sleep disturbance had significantly poorer GAF scores and poorer PANSS negative and depressive factor scores than participants without any sleep disturbance. Of the clinical and demographic factors previously found to be associated with sleep disturbances, younger age was associated with all PANSS symptoms meaures except depression. Having a history of drug dependency was associated with more positive, disorganized and excited symptoms as well as functioning, whilst a history of alcohol dependency was associated with more excited symptoms. The use of medication with sedative effects was associated with more negative symptoms and with poorer functioning.

To rule out potential confounding or mediating effects, diagnostic group, age, medication with sedative effects and history of drug dependency were entered as covariates in the analyses of the association between sleep disturbances and clinical symptoms/functioning across diagnostic groups (Table 4). More severe symptomatology and poorer functioning in patients with any sleep disturbance were still observed after adjusting for covariates.

4. Discussion

To the best of our knowledge, this is one of the largest studies of sleep disturbances across severe mental disorders. We found that the risk of having any sleep disturbance in SCZ or BD was almost twice as high as that reported in HC. This underlines the need to focus on sleep disturbances in severe mental disorders. The most frequently reported sleep disturbance across all groups was insomnia, whilst hypersomnia and DSP were considerably more frequent in both clinical groups
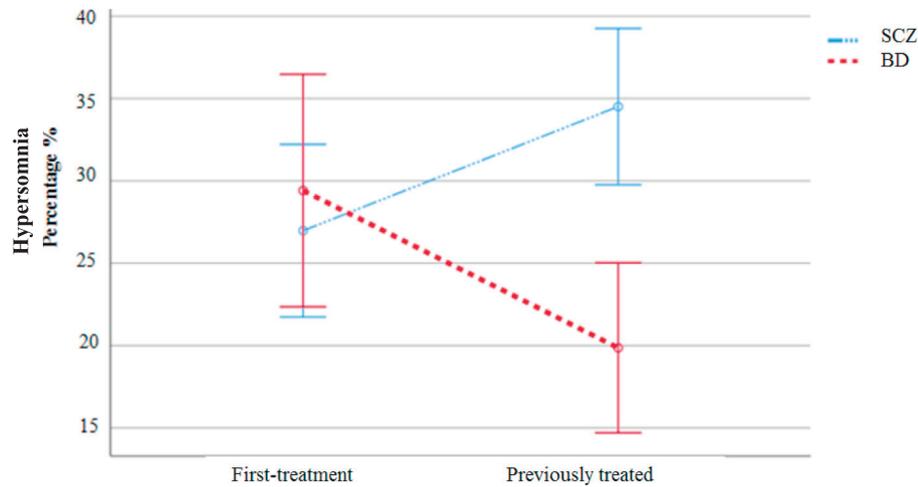
Table 3
Sleep disturbances across treatment history.

	Any sleep disturbance			Insomnia			Hypersomnia			Delayed sleep phase		
	OD	CI	P	OD	CI	P	OD	CI	P-value	OD	CI	P
FT vs PT	0.91	0.60–1.39	0.67	1.36	0.93–2.07	0.12	0.60	0.38–0.94	<0.05	1.29	0.45–3.74	0.64
BD vs. SCZ	1.33	0.85–2.06	0.21	1.36	0.92–2.02	0.13	0.89	0.57–1.37	0.59	3.58	1.36–9.43	<0.05
FT/PT* BD/SCZ	1.50	0.82–2.61	0.19	0.66	0.40–1.11	0.12	2.40	1.36–4.24	<0.01	0.76	0.23–2.48	0.65

FT = First-treatment; PT = previously treated. BD = bipolar disorder, SCZ = schizophrenia disorder; OD = Odds ratio; CI = confidence interval. Table three includes patients only.

Fig. 1. Interaction between diagnostic groups and treatment history on hypersomnia.

compared to HC. Hypersomnia and DSP were also more common in SCZ compared to BD.

Sleep disturbances were not found to differ in frequency across treatment history, with the exception of hypersomnia, which was more frequent in those with previously treated SCZ and in first-treatment BD. Our study further shows that having a sleep disturbance is associated with more negative and depressive symptoms, and with poorer functioning across SCZ and BD. Age, drug dependency and medication with sedative effects were related to having any sleep disturbance and hypersomnia. Medication with sedative effects influenced the interaction between diagnosis and treatment history in the frequency of hypersomnia, but did not fully mediate the association.

Our findings shows that sleep disturbances are a potential core feature of severe mental illness and supports that sleep disturbances are a transdiagnostic phenomenon. A transdiagnostic perspective implies transfer of knowledge across diagnostic categories and may have important clinical implications, such as tailoring treatment specifically targeting sleep disturbances [36].

The high prevalence of insomnia is of particular importance. Insomnia that is initially occurring secondary to another condition often becomes an independent problem, sharing a reciprocal relationship with the primary disorder [37]. A recent review also suggests that insomnia is associated with increased risk of cardiovascular disease, diabetes, the metabolic syndrome, significant morbidity and increased risk of premature mortality [38]. Although no association to BMI was found in the current study, comorbid insomnia may have additional downstream adverse health consequences in these already vulnerable and exposed diagnostic groups. It is also of interest that half of the HC group reported insomnia, reflecting how frequent the subjective experience of

insomnia is in the general population today. Interestingly, several studies indicate that the prevalence rates of insomnia in the general population seem to be rising [39].

Only a handful of previous studies have investigated hypersomnia in BD and SCZ; however, none of them have directly compared the two diagnostic groups to a HC group, or investigated the role of age, medication with sedative effects or drug use in this context. Given the relatively high prevalence of hypersomnia in both SCZ (30.9%) and BD (23.1%), contrasted to the low prevalence in HC (2.9%), it is important to increase clinical awareness of this phenomenon. The finding that hypersomnia is associated with younger age fits well with prevalence studies of hypersomnia in the general population. The hypersomnia is partly, but not entirely, explained by the use of medication with sedative effects. Since around half of the participants in both clinical groups were using this type of medication, a change to other types could be a clinically relevant and potentially effective way of reducing hypersomnia rates.

We only found a small subgroup experiencing DSP in SCZ (10%) and BD (4%), with no occurrence in the HC group. Although the interest in circadian rhythms in patients with SCZ is increasing, there is scarce information concerning the prevalence of DSP. Our study therefore adds valuable descriptive information to the field. The subgroups reporting DSP were younger. A recent review of Alloy, Ng [40] indicates that irregular social rhythms contribute to circadian dysregulation. Individuals with BD are found to exhibit greater social rhythm irregularity compared to HC [41], and may also be hypersensitive to life event-induced social rhythm disruption [42]. These findings, coupled with the frequent shift toward an evening circadian preference often seen in adolescents due to biological changes

Table 4
Sleep disturbances and clinical features across diagnostic groups.

Clinical variables	Any sleep disturbance	No sleep disturbance	ANCOVA		
	Mean ± SD	Mean ± SD	F	P	Partial η^2
PANSS positive	8.5 ± 4.3	7.2 ± 3.6	1.23	0.27	0.001
PANSS negative	11.7 ± 5.5	9.6 ± 4.7	19.33	<0.001	0.02
PANSS disorganized	6.5 ± 2.6	6.1 ± 2.3	0.13	0.72	˜0.001
PANSS excited	5.6 ± 2.1	5.4 ± 2.0	0.19	0.66	˜0.001
PANSS depressed	8.3 ± 3.2	6.9 ± 2.9	40.16	<0.001	0.037
GAF functioning	47.4 ± 12.7	53.3 ± 14.5	6.36	<0.01	0.006

GAF = Global Assessment of Functioning scale; PANSS = Positive and Negative Syndrome Scale. PANSS was organized after Wallwork's five-factor model (Wallwork et al., 2012). Demographic and clinical characteristics that were associated with both the sleep disturbance and the dependent variable were entered as covariates in the model. *PANSS Negative* was corrected for: age, diagnosis and use of medication with sedative effects (Yes/no). *PANSS Positive, PANSS Disorganized and PANSS excited* were adjusted for age, diagnosis and drug dependency. *PANSS Depressed* was corrected for diagnosis only. GAF-F was corrected for: diagnosis, use of medication with sedative effects (Yes/no), and drug dependency. Table four includes patients only.

during puberty [43], underlines the need of more awareness of potential circadian rhythm dysregulation in young people with severe mental disorders.

To this date the majority of research on sleep disturbances in severe mental disorders has been done in older patients with multiple illness episodes. The frequency of sleep disturbances in our study sample does not seem to differ substantially in first-treatment versus previously treated participants, suggesting that sleep disturbances are key disease characteristic independent of treatment history. This finding implies that sleep disturbances are evident early in disease development, and may also indicate that they are not treated adequately at this point. Our finding that medication with sedative effects was significantly higher in first-treatment BD compared to first-treatment SCZ was unexpected. This finding is of clinical importance, suggesting that we need better tailoring of drug treatment in the early phases of bipolar disorder.

One of the main findings of the current study was that clinical participants with severe mental disorders experiencing sleep disturbances had more severe negative- and depressive symptoms, followed by significantly lower functioning compared to clinical participants without sleep disturbances. This is in line with smaller studies (N < 100), which found symptoms of insomnia in SCZ to be associated with poorer social and functional outcomes [44] and more severe psychopathology [32,45]. By contrast, better sleep in SCZ has been found to be linked to healthier coping strategies and greater quality of life [44]. Studies of BD patients show that decreased sleep is associated with more severe mood symptoms, poorer daytime functioning and lower life satisfaction compared to those with longer sleep [32]. Our study adds to these findings by showing that the association between sleep disturbances and clinical symptoms are not confounded by clinical diagnosis, age, alcohol or drug use, medication with sedative effects or BMI. Due to the cross sectional nature of our study, we are not able to investigate causality in the relationship between sleep disturbances, severe mental disorders and clinical symptoms. It is thus equally plausible that symptom severity is influencing the quality of sleep, as the other way round. There is however growing evidence indicating that sleep disturbances, particularly insomnia, seem to be causally related to symptoms of severe mental disorders [22,46–48].

Several limitations should be mentioned. The present study relies on definitions of sleep disturbances which categorize them from ratings on an established symptom scale typically used to assess sleep disturbance in symptomatic and remitted depression, rather than the use of formal diagnostic criteria. Our definition of hypersomnia did for example not include daytime sleepiness assessment. Thus, our groups are more precisely regarded as symptoms of sleep disturbances rather than diagnostic categories. This may contribute to higher frequency of reported sleep disturbances. However, compared to other methods of sleep assessment (actigraphy, polysomnography and diagnostic interview for sleep assessment), high levels of reliability and validity of these sleep profiles have been demonstrated in other clinical studies using similar definitions [13,19,32–35,49–54], and are shown to be sufficiently representative of the underlying diagnostic categories [34,55]. Moreover, descriptive studies of sleep disturbances in severe mental disorders are predominantly based on objective sleep measures (e.g. actigraphy, polysomnography). Such methods fail to capture the subjective experience of sleep quality, which is important both in the diagnostic assessment of the sleep disturbances relevant in this study, but also vital for designing better treatment interventions for these diagnostic groups. The time frame used to assess sleep disturbances is 7 days, which may lead to assessment of a more acute rather than chronic sleep disturbance. However, sleep disturbances were found in both first-treatment- and previously treated participants, indicating sleep disturbances as an underlying problem.

No specific screening tool for primary sleep disturbances were given in the assessment of exclusion criteria, therefore we cannot rule out that people with an undiagnosed primary sleep disorder are included in the study. A thorough physical examination in addition to questions about history of somatic health would however most likely pick up on symptoms compatible with OSA and restless legs syndrome, be noted, and the participant thereby excluded. The Bipolar Disorder group is not divided into different phases of illness (manic, euthymic or depressed), although sleep disturbances may vary depending on this. Being one of the main aims, the relationship between sleep disturbances and symptomatology was however measured continuously because this made more sense considering that affective episodes are more common in bipolar disorder and psychotic episodes are more common in schizophrenia spectrum disorders. Moreover, although manic symptoms are not included among the continuous symptoms we investigated, the PANSS excitement factor includes the following items; P4 Excitement, P7 Hostility P7, G8 Uncooperativeness, G14 Poor impulse control. We therefore argue that the PANSS excitement factor can be viewed as a proxy for symptoms of mania.

A considerable strength of this study is the large sample consisting of schizophrenia spectrum disorders, bipolar disorders and HC, assessed with the same protocol across diagnostic groups. The large sample also makes it possible to explore the effects of potentially mediating and moderating factors on sleep disturbances. Moreover, the thorough assessment of medication with sedative effects is a major strength. Few other studies, especially in BD, classify and address the influence of medication with sedative effects on different types of sleep disturbances. Exclusion of patients with alcohol or drug use has constrained representability of clinical samples in previous studies. The differentiation between having a history of alcohol or drug dependency and recent use in our study adds valuable information to the field by showing that recent drug use is associated with less sleep disturbances, whilst having a history of drug dependency is associated with more sleep disturbances. This is of clinical importance because ongoing drug use may partly mask sleep disturbances and be part of an attempt to deal with them.

There are several implications of the present findings. Firstly, that sleep disturbances should be assessed routinely in severe mental disorders. DSM 5 recommends that sleep disturbances no longer should be classified as primary or secondary. This implies that treatment should be tailored, directly targeting the specific sleep disturbance also in severe mental disorders. An important aspect is that sleep and circadian systems are adapted to be responsive to unconditioned environmental stimuli, particularly light, eating and social activities. The neurobiology of sleep/circadian function can thus be modulated non-pharmacologically, such as behavioral and/or light manipulations for sleep and circadian function [36]. Moreover, knowledge about the subjective experience of sleep disturbances in these patient groups show that many patients believe that sleep disturbances are intrinsic to their illness [56,57]. There is a great potential for raising awareness about sleep hygiene; i.e. the importance of physical activity, social rhythms and reduction of caffeine and electronic devices with blue light. Furthermore, several studies on the effectiveness on cognitive behavioral therapy are on the rise, showing that Cognitive-Behavioral Therapy for Insomnia (CBT-I) may be particularly helpful for addressing cognitive and behavioral factors that maintain and exacerbate insomnia [48,58,59].

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References

[1] Wulff K, Dijk DJ, Middleton B, Foster RG, Joyce EM. Sleep and circadian rhythm disruption in schizophrenia. Br J Psychiatry 2012;200:308–16.
[2] Allison G, Harvey PD. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry 2008;165:820–9.
[3] Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. Sleep Med Rev 2002;6:97–111.
[4] Benson KL. Sleep in schizophrenia: pathology and treatment. Sleep Med Clin 2015; 10:49–55.
[5] Harvey AG, Soehner AM, Buysse D. Bipolar disorder. In: Kryger MH, Roth T, editors. Principles and practice of sleep medicine. 6. ed. Philadelphia, PA: Elsevier; 2017. p. 1363–9.
[6] Carbonell LP-, Leschziner G. Clinical update on central hypersomnias. J Thorac Dis. 2017:S112-S23.
[7] Ohayon MM. Prevalence and comorbidity of sleep disorders in general population. Rev Prat 2007;57:1521–8.
[8] Steinan MK, Scott J, Lagerberg TV, Melle I, Andreassen OA, Vaaler AE, et al. Sleep problems in bipolar disorders: more than just insomnia. Acta Psychiatr Scand 2016;133:368–77.
[9] Sharma P, Dikshit R, Shah N, Karia S, De Sousa A. Excessive Daytime Sleepiness in Schizophrenia: A Naturalistic Clinical Study. Journal of clinical and diagnostic research: JCDR. 2016;10:Vc06-vc8.
[10] Nesbitt AD. Delayed sleep-wake phase disorder. J Thorac Dis 2018;10:S103–s11.
[11] Schrader H, Bovim G, Sand T. The prevalence of delayed and advanced sleep phase syndromes. J Sleep Res 1993;2:51–5.
[12] Harvey AG. Sleep and circadian rhythms in bipolar disorder: seeking synchrony, harmony, and regulation. Am J Psychiatry 2008;165:820–9.
[13] Steinan MK, Morken G, Lagerberg TV, Melle I, Andreassen OA, Vaaler AE, et al. Delayed sleep phase: an important circadian subtype of sleep disturbance in bipolar disorders. J Affect Disord 2016;191:156–63.
[14] Jackson A, Cavanagh J, Scott J. A systematic review of manic and depressive prodromes. J Affect Disord 2003;74:209–17.
[15] Zanini M, Castro J, Coelho FM, Bittencourt L, Bressan RA, Tufik S, et al. Do sleep abnormalities and misaligned sleep/circadian rhythm patterns represent early clinical characteristics for developing psychosis in high risk populations? Neurosci Biobehav Rev 2013;37:2631–7.
[16] Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E, et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinal study in North America. Arch Gen Psychiatry 2008;65:28–37.
[17] Davies G, Haddock G, Yung AR, Mulligan LD, Kyle SD. A systematic review of the nature and correlates of sleep disturbance in early psychosis. Sleep Med Rev 2017;31:25–38.
[18] Ritsner M, Kurs R, Ponizovsky A, Hadjez J. Perceived quality of life in schizophrenia: relationships to sleep quality. Qual Life Res 2004;13:783–91.
[19] Sylvia LG, Dupuy JM, Ostacher MJ, Cowperthwait CM, Hay AC, Sachs GS, et al. Sleep disturbance in euthymic bipolar patients. Journal of psychopharmacology (Oxford, England). 2012;26:1108–12.
[20] Russo M, Mahon K, Shanahan M, Ramjas E, Solon C, Purcell SM, et al. The relationship between sleep quality and neurocognition in bipolar disorder. J Affect Disord 2015;187:156–62.
[21] Kanady JC, Soehner AM, Klein AB, Harvey AG. The association between insomnia-related sleep disruptions and cognitive dysfunction during the inter-episode phase of bipolar disorder. J Psychiatr Res 2017;88:80–8.
[22] Reeve S, Sheaves B, Freeman D. Sleep disorders in early psychosis: incidence, severity, and association with clinical symptoms. Schizophr Bull 2018. https://doi.org/10.1093/schbul/sby129 (Epub ahead of print).
[23] Rehman A, Waite F, Sheaves B, Biello S, Freeman D, Gumley A. Clinician perceptions of sleep problems, and their treatment, in patients with non-affective psychosis. Psychosis 2017;9:129–39.
[24] Kamath J, Virdi S, Winokur A. Sleep disturbances in schizophrenia. Psychiatr Clin North Am 2015;38:777–92.
[25] Hung CC, Liao CC, Wu PL, Lee SD, Lane HY. Metabolic Abnormality and Sleep Disturbance are Associated with Clinical Severity of Patients with Schizophrenia. Biomedicine (Taipei). 2014;4:6.
[26] Spitzer RL, Williams JB, Kroenke K. Linzer M, deGruy FV, Hahn SR, et al. JAMA 1994; 272:1749.
[27] First MB, Spitzer RL, Gibbon M, Williams JBW. Structured clinical interview for DSM-IV axis I disorders: patient edition (SCID-P), version 21995.
[28] Wallwork RS, Fortgang R, Hashimoto R, Weinberger DR, Dickinson D. Searching for a consensus five-factor model of the positive and negative syndrome scale for schizophrenia. Schizophr Res 2012;137:246–50.
[29] Pedersen G, Karterud S. The symptom and function dimensions of the Global Assessment of Functioning (GAF) scale. Compr Psychiatry 2012;53:292–8.
[30] Felleskatalogen AS. Felleskatalogen. Oslo, Norway2018.
[31] Rush AJ, Gullion CM, Basco MR, Jarrett RB, Trivedi MH. The inventory of depressive symptomatology (IDS): psychometric properties. Psychol Med 1996;26: 477–86.
[32] Gruber J, Harvey AG, Wang PW, Brooks 3rd JO, Thase ME, Sachs GS, et al. Sleep functioning in relation to mood, function, and quality of life at entry to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). J Affect Disord 2009;114:41–9.
[33] Kaplan KA, Gruber J, Eidelman P, Talbot LS, Harvey AG. Hypersomnia in inter-episode bipolar disorder: does it have prognostic significance? J Affect Disord 2011;132:438–44.
[34] Soehner AM, Kaplan KA, Harvey AG. Prevalence and clinical correlates of co-occurring insomnia and hypersomnia symptoms in depression. J Affect Disord 2014;167:93–7.
[35] Steinan MK, Krane-Gartiser K, Morken G, Scott J. Sleep problems in euthymic bipolar disorders: a review of clinical studies. Curr Psychiatr Rev 2015;11:235–43.
[36] Harvey AG, Murray G, Chandler RA, Soehner A. Sleep disturbance as transdiagnostic: consideration of neurobiological mechanisms. Clin Psychol Rev 2011;31:225–35.
[37] McCrae CS, Lichstein KL. Secondary insomnia: diagnostic challenges and intervention opportunities. Sleep Med Rev 2001;5:47–61.
[38] Jackson CL, Redline S, Emmons KM. Sleep as a potential fundamental contributor to disparities in cardiovascular health. Annu Rev Public Health 2015;36:417–40.
[39] Pallesen S, Sivertsen B, Nordhus IH, Bjorvatn B. A 10-year trend of insomnia prevalence in the adult Norwegian population. Sleep Med 2014;15:173–9.
[40] Alloy LB, Ng TH, Titone MK, Boland EM. Circadian rhythm dysregulation in bipolar spectrum disorders. Curr Psychiatry Rep 2017;19:21.
[41] Shen GH, Alloy LB, Abramson LY, Sylvia LG. Social rhythm regularity and the onset of affective episodes in bipolar spectrum individuals. Bipolar Disord 2008;10:520–9.
[42] Boland EM, Bender RE, Alloy LB, Conner BT, Labelle DR, Abramson LY. Life events and social rhythms in bipolar spectrum disorders: an examination of social rhythm sensitivity. J Affect Disord 2012;139:264–72.
[43] Dolsen MR, Wyatt JK, Harvey AG. Sleep, circadian rhythms, and risk across health domains in adolescents with an evening circadian preference. J Clin Child Adolesc Psychol 2018:1–11.
[44] Hofstetter JR, Lysaker PH, Mayeda AR. Quality of sleep in patients with schizophrenia is associated with quality of life and coping. BMC Psychiatry 2005;5:13.
[45] Waters F, Sinclair C, Rock D, Jablensky A, Foster RG, Wulff K. Daily variations in sleep-wake patterns and severity of psychopathology: a pilot study in community-dwelling individuals with chronic schizophrenia. Psychiatry Res 2011;187:304–6.
[46] Freeman D, Sheaves B, Goodwin GM, Yu LM, Nickless A, Harrison PJ, et al. The effects of improving sleep on mental health (OASIS): a randomised controlled trial with mediation analysis. Lancet Psychiatry 2017;4:749–58.
[47] Harvey AG, Kaplan KA, Soehner A. Interventions for sleep disturbance in bipolar disorder. Sleep Med Clin 2015;10:101–5.
[48] Harvey AG, Soehner AM, Kaplan KA, Hein K, Lee J, Kanady J, et al. Treating insomnia improves mood state, sleep, and functioning in bipolar disorder: a pilot randomized controlled trial. J Consult Clin Psychol 2015;83:564–77.
[49] Gonzalez R, Tamminga C, Tohen M, Suppes T. Comparison of objective and subjective assessments of sleep time in subjects with bipolar disorder. J Affect Disord 2013;149:363–6.
[50] Boudebesse C, Geoffroy PA, Bellivier F, Henry C, Folkard S, Leboyer M, et al. Correlations between objective and subjective sleep and circadian markers in remitted patients with bipolar disorder. Chronobiol Int 2014;31:698–704.
[51] Geoffroy PA, Boudebesse C, Bellivier F, Lajnef M, Henry C, Leboyer M, et al. Sleep in remitted bipolar disorder: a naturalistic case-control study using actigraphy. J Affect Disord 2014;158:1–7.
[52] Geoffroy PA, Scott J, Boudebesse C, Lajnef M, Henry C, Leboyer M, et al. Sleep in patients with remitted bipolar disorders: a meta-analysis of actigraphy studies. Acta Psychiatr Scand 2015;131:89–99.
[53] Kaplan KA, Talbot LS, Gruber J, Harvey AG. Evaluating sleep in bipolar disorder: comparison between actigraphy, polysomnography, and sleep diary. Bipolar Disord 2012;14:870–9.
[54] Manber R, Blasey C, Arnow B, Markowitz JC, Thase ME, Rush AJ, et al. Assessing insomnia severity in depression: comparison of depression rating scales and sleep diaries. J Psychiatr Res 2005;39:481–8.
[55] Harvey AG, Talbot LS, Gershon A. Sleep disturbance in bipolar disorder across the lifespan. Clin Psychol (New York) 2009;16:256–77.
[56] Chiu VW, Harvey RH, Sloan NB, Ree M, Lin A, Janca A, et al. Cognitive and behavioral factors associated with insomnia in inpatients with schizophrenia and related psychoses. J Nerv Ment Dis 2015;203:798–803.
[57] Chiu VW, Ree M, Janca A, Waters F. Sleep in schizophrenia: exploring subjective experiences of sleep problems, and implications for treatment. Psychiatry Q 2016;87: 633–48.
[58] Freeman D, Waite F, Startup H, Myers E, Lister R, McInerney J, et al. Efficacy of cognitive behavioural therapy for sleep improvement in patients with persistent delusions and hallucinations (BEST): a prospective, assessor-blind, randomised controlled pilot trial. Lancet Psychiatry 2015;2:975–83.
[59] Sheaves B, Freeman D, Isham L, McInerney J, Nickless A, Yu LM, et al. Stabilising sleep for patients admitted at acute crisis to a psychiatric hospital (OWLS): an assessor-blind pilot randomised controlled trial. Psychol Med 2017:1–11.