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Research paper

Nicotine use and non-pathological alcohol use and their relationship to affective symptoms and sleep disturbances in bipolar disorder

Stine Holmstul Glastad [a,*], Sofie Ragnhild Aminoff [a,b], Roger Hagen [c,d,e], Margrethe Collier Høegh [a], Camilla Bakkalia Büchmann [a], Elizabeth Ann Barrett [a,b], Ingrid Melle [a], Bruno Etain [f,g,h,i], Trine Vik Lagerberg [a]

[a] NORMENT, Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, University of Oslo and Oslo University Hospital, Oslo, Norway
[b] Early Intervention in Psychosis Advisory Unit for South East Norway, Division of Mental Health and Addiction, Oslo University Hospital, Oslo, Norway
[c] Department of Psychology, University of Oslo, Oslo, Norway
[d] Department of Psychology, Norwegian University of Science and Technology, Trondheim, Norway
[e] Research institute, Modum Bad, Vikersund, Norway
[f] INSERM U1144, Optimisation Thérapeutique en Neuropsychopharmacologie, Paris, France
[g] Département de Psychiatrie et de Médecine Addictologique, Hôpital Fernand Widal, Assistance Publique des Hôpitaux de Paris (APHP), Paris, France
[h] Université Paris Cité, Paris, France
[i] Fondation FondaMental, Créteil, France

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ABSTRACT

Background: The use of alcohol and nicotine can negatively impact the course of bipolar disorder (BD), but there is limited knowledge about how symptoms and sleep disturbances are related to concurrent nicotine use and non-pathological use of alcohol.
Methods: We investigated how nicotine use and non-pathological use of alcohol relates to affective symptoms and sleep disturbances in 453 participants with BD without substance use disorders. Manic symptoms were assessed with the Young Mania Rating Scale, and depressive symptoms with The Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C). Sleep-related questions from IDS-C were used to create proxy variables for sleep disturbances, including Insomnia and Hypersomnia. Multinomial regression analysis was conducted to investigate the associations between nicotine use and sleep disturbances, controlling for possible confounders such as current use of illicit drugs and psychopharmacological treatment.
Results: Depressive and manic symptoms were not associated with the concurrent level of alcohol or nicotine use. Individuals with medium and high levels of daily nicotine use had higher risk of insomnia than those without. Non-pathological alcohol use was not associated with sleep disturbances.
Limitations: Sleep disturbances were based on items from the IDS-C questionnaire.
Conclusion: We found an elevated risk for insomnia in individuals with BD and medium or high levels of daily nicotine use. We found no association between the level of affective symptoms and the level of use of alcohol or nicotine. The direction of the relationship between nicotine use and insomnia needs clarification, as it is highly relevant for treatment planning.

1. Introduction

Individuals with bipolar disorder (BD) often misuse substances, most commonly alcohol and tobacco (Blanco et al., 2017). Meta-analyses have reported a lifetime prevalence of 30 % for alcohol use disorders (AUD) and 46 % for tobacco use disorder (TUD)/nicotine dependence in individuals with BD (Fornaro et al., 2022; Hunt et al., 2016). Comorbid AUD and TUD appear to have a negative impact on the course of the disorder. Although findings are mixed, studies indicate that comorbid AUD is associated with an increased risk of rapid cycling, mood episode recurrence, and affective lability (Lagerberg et al., 2017; Rakofsky and Dunlop, 2013). In addition, a higher risk for rapid cycling and suicide

* Corresponding author at: CoE NORMENT, Norwegian Centre for Mental Disorders Research, Division of Mental Health and Addiction, Institute of Clinical Medicine, Bygg 49, Ullevål Sykehus, PO Box 4956 Nydalen, 0424 Oslo, Norway.
E-mail address: s.h.olsen@ous-research.no (S.H. Glastad).

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attempts are reported in both men and women with higher levels of alcohol consumption. Also, higher alcohol consumption outside of AUD is associated with higher rates of depressive and manic episodes and additional psychiatric comorbidities in women (Gordon-Smith et al., 2020). Thus, pathological use of alcohol appears to have a negative impact on the BD course.

Less is known about the relationship between "normal" or non-pathological alcohol use, i.e. alcohol use that does not meet the criteria for a use/misuse disorder, and concurrent BD symptoms. Such knowledge is clinically relevant as it may indicate potentially harmful effects of "normal" alcohol use, and/or mood symptoms as possible drivers of alcohol use as self-medication. The impact of alcohol use below the level of AUD is also a concern often raised by individuals with BD as well as physicians. To our knowledge, the relationship between non-pathological alcohol use and current affective symptoms in BD has only been investigated in one previous study (Gross et al., 2020), where no relationships between alcohol use, defined as regular consumption of at least one unit per day, and depressive or manic symptoms were found. However, participants had to be euthymic without having experienced a mood episode during the last three months to be included in this study. The symptom levels in the investigated sample were thus low, restricting the possibility of finding significant associations (Gross et al., 2020).

TUD in individuals with BD has been associated with longer periods of untreated illness (Medeiros et al., 2018), more lifetime mood episodes (Gross et al., 2020), and recurrent suicide attempts (Icick et al., 2019). Findings diverge when it comes to the relationship between concurrent tobacco smoking and BD symptoms. In one study, smokers had more severe manic symptoms compared to non-smokers (Medeiros et al., 2018). Another study found associations between TUD and greater severity of both depressive and manic symptoms (Waxmonsky et al., 2005). However, in the euthymic sample reported by Gross et al. (2020), no associations between tobacco use and concurrent depressive or manic symptoms were found (Gross et al., 2020). To our knowledge, no studies have investigated the relationship between the use of "*snus*", a type of legal smokeless tobacco that is common in Scandinavian countries, and the symptoms of BD. Snus use has increased in Norway in recent years (Tjora et al., 2020), and there appear to be differences between people in the general population who use snus versus smoke cigarettes with regard to personality traits, gender, and age (Sæther et al., 2021). Consequently, the type of tobacco used may interact with different characteristics of individuals with BD, and tobacco type is thus of interest when investigating symptom levels and clinical profiles. Clarifying the relationship between nicotine use and BD symptoms is important, particularly as, unlike the general population, individuals with BD have not reduced their nicotine use significantly over the last decades (Rødevand et al., 2019). Of note, investigating putative differences between pathological (i.e. meeting diagnostic criteria for a use disorder) and more low-level use is problematic as nicotine is a highly addictive substance where use often escalates to addiction.

One clinical aspect of the affective syndromes of BD that is particularly likely to be associated with alcohol and nicotine use is sleep disturbances. Sleep disturbances are commonly present in both depressive and manic episodes and are part of the diagnostic criteria of mood episodes, regardless of the polarity (American Psychiatric Association, 2013; World Health Organization, 2016). They are also commonly present in euthymic periods of BD (Ng et al., 2015). In the general population, individuals with insomnia frequently report that they self-medicate their sleep disturbances with alcohol or non-prescribed medications (Ancoli-Israel and Roth, 1999). Sleep disturbances also appear to be a risk factor for early substance use onset and misuse in the general population (Roehrs et al., 2021). While there is an increasing focus on sleep and other circadian rhythm disturbances in BD (Gonzalez et al., 2014; McCarthy et al., 2021), few studies have investigated the relationship between sleep disturbances and current nicotine use or non-pathological alcohol use in BD. In one recent study, nicotine use was associated with an increase in sleep onset latency, reduced sleep efficiency and total sleep time (Gordon, 2019), while another study found no association between sleep disturbances and the use of nicotine or alcohol in euthymic patients. They did, however, not focus specifically on non-pathological use (De la Fuente-Tomás et al., 2018). With regards to non-pathological alcohol use, Gross et al. (2020) found a negative correlation between average daily consumption of alcohol and sleep duration in euthymic individuals with BD.

We have previously investigated clinical correlates of sleep disturbances in a mixed diagnostic sample of individuals with severe mental illnesses. We found that individuals with recent use of alcohol were more likely to present with insomnia than those without recent alcohol use (Laskemoen et al., 2019). BD was, however, not explicitly investigated, and the relationship between nicotine use and sleep disturbances was not explored.

Thus, the current study aims to investigate whether 1) the levels of manic and depressive symptoms and 2) the prevalence of current sleep disturbances in individuals with BD are related to the level of recent alcohol and nicotine use in a sample without lifetime substance use disorders while controlling for several possible confounders of the relationship including current use of illicit drugs and psychopharmacological treatment. We hypothesize that the levels of recent alcohol and/or nicotine use will be associated with current depressive and manic symptom levels and that the levels of nicotine and alcohol use will be higher in individuals with sleep disturbances than in those without.

2. Materials and methods

2.1. Participants

This study is part of the ongoing TOP study (Thematically Organized Psychosis Research) at CoE NORMENT (Norwegian Centre for Mental Health Research) in Oslo, Norway. Participants are recruited through their clinician at inpatient or outpatient clinics, their general practitioners, or by their own initiative. Inclusion criteria are a DSM-IV diagnosis of BD type I, II, or NOS (not otherwise specified) and age between 17 and 65 years. Exclusion criteria are pronounced intellectual deficit (IQ < 70), brain damage, defined as a head injury with hospitalization, and lack of understanding of a Scandinavian language. As we aimed to investigate "normal" use of nicotine and alcohol, we excluded participants with any lifetime or current SCID-I-verified substance use disorder (alcohol or illicit substances) from the total sample ($n = 582$). The final sample comprised 453 individuals: 284 participants with BD type I, 144 participants with BD type II, and 25 participants with BD NOS. The TOP study is conducted in accordance with the Declaration of Helsinki and has been approved by the Regional Committee for Medical Research Ethics (no. 2009/2485) and the Norwegian Data Inspectorate.

2.2. Clinical assessments

The diagnosis of BD was established by a medical doctor, psychiatrist, or clinical psychologist through the use of the Structured Clinical Interview for DSM-IV axis I disorders modules A-E (SCID-I). Diagnostic reliability is assessed with regular intervals in the TOP study and is very good with Cohen's kappa for diagnosis in the range between 0.92 and 0.99 across different assessment teams (Høegh et al., 2020). The Young Mania Rating Scale (YMRS) was used, which is an 11-item scale to measure manic symptoms over the last 48 h (Young et al., 1978). The Cronbach alpha of YMRS for this study was found acceptable at 0.706. The Inventory of Depressive Symptomatology, Clinician-Rated (IDS-C), a 30-item scale, was used to evaluate depressive symptom severity over the last seven days (Rush et al., 1996). The Cronbach alpha coefficient of IDS-C was found to be good at 0.883. Two items from the general subscale of the Positive and Negative Syndrome Scale (PANSS) was used as measures for current anxiety- and depressive symptoms (Kay et al., 1987). The depressive item (G6) is measured by an initial question of "How has your mood been in the past week: mostly good, mostly bad?".

This question is followed up by up to 11 questions, focusing on the degree of depression and its behavioral consequences such as appetite and participation in social activities. Anxiety (G2) is measured by an initial question of "Have you been feeling worried or nervous in the past week?", with up to six follow up questions evaluating the degree of anxiety. Both items G2 and G6 are scored on a Likert scale of 1–7, with a higher score indicating a higher degree of severity. Age at onset of BD was defined as the age at the participants' first SCID-verified mood episode, independent of polarity. The duration of illness was calculated by subtracting the age at onset from the age at inclusion. Information about medication use was collected by asking the participants about their current use of psychopharmacological agents.

2.3. Sleep assessments

Sleep disturbances were operationalized by using the four sleep items in IDS-C; Item 1: difficulty falling asleep (Sleep Onset Insomnia), Item 2: difficulty maintaining sleep (Mid-Nocturnal Insomnia), Item 3: early morning awakening (Early Morning Insomnia), and Item 4: hypersomnia (Rush et al., 1996). The score on each item goes from 0 to 3, with a higher score indicating higher severity. The IDS-C sleep items have been used as proxy measures for sleep disturbances in several previous studies (Laskemoen et al., 2019; Steinan et al., 2016a; Steinan et al., 2016b), and was operationalized as follows:

1. Insomnia was considered present if the participants had the following scores: Sleep Onset Insomnia $\geq$2 (takes at least 30 min to fall asleep, more than half the time), or Mid-Nocturnal Insomnia = 3 (awakens more than once a night and stays awake for 20 min or more, more than half the time), or Early Morning Insomnia $\geq$1 (more than half the time, awakens >30 min before need be), in addition to scoring 0 on the Hypersomnia item (sleeps no longer than 7–8 h/night, without naps).
2. Hypersomnia was considered present if the participant had a score of $\geq$1 on the Hypersomnia item (sleeps no longer than 10 h in a 24-h period, including naps).
3. No sleep disturbances were considered present if the participant did not fulfill the criteria of Insomnia or Hypersomnia.

2.4. Substance use assessments

The Alcohol Use Disorders Identification Test (AUDIT) and the Drug Use Disorders Identification Test (DUDIT) were used to investigate the level of problematic use of alcohol and illicit substances, respectively over the last year before the study inclusion (Berman et al., 2005; Saunders et al., 1993). Semi-structured interviews were used to assess the recent use of nicotine, alcohol, and illicit substances. Participants were asked whether they currently used any nicotine, and if this was confirmed, how many cigarettes and/or snus they used on average per day. Regarding alcohol use, participants were asked to indicate how many units of alcohol they had consumed in total in the last two weeks and the average number of units per week for the last six months. If participants had used any illicit drugs, they were asked to indicate the number of episodes they had used drugs during the last two weeks and six months and which drugs they had used.

2.5. Statistical analyses

All statistical analyses were conducted with the IBM Statistical Package for Social Sciences version 28. Continuous variables are described as means with standard deviations or medians with interquartile ranges. Bivariate analyses were conducted with Chi-square-, Kruskal-Wallis, Mann-Whitney *U* tests, Spearman's rank, or Pearson's correlations, as applicable. All tests were two-tailed. The significance level was set at $\leq$0.05.

The IDS-C total score, the YMRS total score and Sleep disturbance categories (Insomnia, Hypersomnia, No Sleep Disturbances), were tested against 1) the average number of units of nicotine used per day, both separately for cigarette and snus use and total nicotine use (cigarettes + snus) and 2) the average number of alcohol units used during a) the last two weeks and b) the last six months. The nicotine variable was highly skewed and therefore categorized into three groups for the multivariate analyses; no nicotine use (0), medium nicotine use (0.1–11.4 units per day), and heavy nicotine use (> 11.5 units per day) based on the median.

We conducted multivariate analyses of the relationships between the symptom-related variables (depressive symptoms, manic symptoms and sleep problems) and alcohol and nicotine use. The relationships between depressive or manic symptoms and the use of nicotine and alcohol were investigated in two separate logistic regression analyses. Both the IDS-C and YMRS scores were highly skewed and attempts to transform the data into normalized distributions were not successful. Thus, for depressive symptoms, the sample was divided into two groups; those with none or mild symptoms (IDS-C score 0–25, n = 344), and those with moderate to severe symptoms (IDS-C score 26–84, n = 81) (Rush et al., 2008). For manic symptoms the sample was also divided into two groups; those with no symptoms/normal scores (YMRS score 0–7, n = 376) and those with mild to severe symptoms (YMRS score 8–60, n = 59) (Tohen et al., 2009). No participants had a score that indicated severe or very severe manic symptoms. For the putative relationships between depressive or manic symptoms and alcohol and nicotine use, the following covariates were taken into account if significantly associated ($p \leq .05$) with the dependent variable: age, sex, BD type, current anxiety symptoms, recent use of any illicit drugs, recent use of cannabis, and medication use. Due to missing data for one or more variables, the final analysis with depressive symptoms comprised of 408 participants, and the final analysis with manic symptoms of 414 participants.

We investigated the relationship between sleep disturbances (Insomnia, Hypersomnia, No Sleep Disturbances) and nicotine use (categorized into three use levels) with a multinomial logistic regression analysis, with 'No Sleep Disturbances' as the reference group. Based on previous literature and a priori hypotheses, we considered the following variables as possible confounders of the relationship between sleep problems and alcohol or nicotine use: age, sex, BD type, current manic symptoms, current depressive symptoms, current anxiety symptoms, recent use of any illicit drugs, recent use of cannabis, and medication use. Medication use comprised three separate variables covering the use of antipsychotics, lithium, and antiepileptics (use vs. no use). In the final analysis, 32 cases were not included because of missing data for one or more variables (n = 421).

In addition to the independent variables of interest (alcohol and nicotine use), variables that were significantly associated ($p \leq .05$) with the outcome variable in bivariate analyses were entered as covariates in all models. Although sex was not found to be significantly associated with all the dependent variables in bivariate analyses, we chose to include it in the multivariate analyses since previous literature has repeatedly demonstrated that substance use is more prevalent in males than in females (Messer et al., 2017) and that sleep disturbances are more prevalent in females compared to males (Zhang and Wing, 2006). As the BD NOS group was small, it was merged with the BD II group for all multivariate analyses.

3. Results

3.1. Demographic and clinical characteristics

The demographic and clinical characteristics of the sample including affective symptom levels, the prevalence of sleep disturbances, and levels of recent nicotine and alcohol use, are presented in Table 1. The frequency and the number of units used is reported only for the participants who have used the specific substance.

Table 1
Demographic and clinical characteristics of the sample (N = 453).

Characteristics	Total
Female sex, *n* (%)	292 (64.5)
Age, years, median (IQR)	31.0 (18)
Education, years, median (IQR)	14 (3)
Age at onset, median (IQR)	19.0 (10)
Duration of illness, years, median (IQR)	10.0 (15)
BD-subtype, *n* (%)	
BD I	284 (62.7)
BD II	144 (31.8)
BD NOS	25 (5.5)
Current use of medication, *n* (%)	375 (84.3)
Antipsychotics	225 (49.7)
Antiepileptics	172 (38.0)
Lithium	91 (20.1)
YMRS total, median (IQR)	2 (4)
IDS-C total, median (IQR)	14 (17)
Depression PANSS item G6, median (IQR)	3 (3)
Anxiety PANSS item G2, median (IQR)	3 (2)
Sleep problems, *n* (%)	300 (66.2)
Insomnia	141 (31.1)
Hypersomnia	159 (35.1)
No sleep problems	153 (33.8)
AUDIT, median (IQR)[a]	5 (7)
Range	0–26
DUDIT, median (IQR)[b]	0 (0)
Range	0–23
Score > 0, *n* (%)	70 (21.1)
Nicotine use, *n* (%)	204 (45.7)
Cigarette use, *n* (%)	148 (34.3)
Snus use, *n* (%)	65 (15)
Cigarette and snus use, *n* (%)	9 (2)
No. of units of nicotine per day, median (IQR)	11.5 (12.0)
No. of cigarette per day, median (IQR)	12 (15)
No. of snus units per day, median (IQR)	8.0 (7)
Any use of alcohol last 2 weeks, *n* (%)	275 (62.6)
Median no. of units per week (IQR)	3 (5.5)
Any use of alcohol 6 months, *n* (%)	370 (85.5)
Median no. of units per week (IQR)	2.25 (5.2)
Any drug use[c] last 2 weeks, *n* (%)	25 (5.7)
Median no. of units per week (IQR)	1 (2.5)
Any drug use[c] last 6 months, *n* (%)	70 (17)
Median no. of units per week (IQR)	0.12 (0.5)
Any cannabis use last 2 weeks, *n* (%)	22 (5)
Any cannabis use last 6 months, *n* (%)	72 (16.5)

BD = Bipolar Disorder, *YMRS* = Young Mania Rating Scale, *IDS-C* = Inventory of Depressive Symptomatology Clinician Rated, *AUDIT* = Alcohol Use Disorders Identification Test, *DUDIT* = Drug Use Disorders Identification Test, *PANSS* = Positive and Negative Syndrome Scale, *IQR* = Interquartile Range (range from first to third quartile).
The median for different substances only includes participants who have used the substance.
[a] n = 318.
[b] n = 332.
[c] Includes cannabis use.

3.2. Bivariate analyses of the relationship between depressive and manic symptom levels and alcohol and nicotine use

We found no significant association between manic symptom levels and the level of alcohol consumption the last two weeks ($p = .546$) or the last six months ($p = .951$). Similarly, there was no relationship between manic symptom levels and levels of current nicotine use, neither for cigarettes ($p = .177$), snus ($p = .505$), nor any tobacco use ($p = .583$). Also, for depressive symptoms, no significant relationships were found for the level of alcohol consumption the last two weeks ($p = .860$), or the last six months ($p = .833$). Similarly, there was no relationship between depressive symptom levels and levels of current nicotine use, either for cigarettes ($p = .594$), snus ($p = .722$), or any tobacco use ($p = .851$).

3.3. Logistic regression analyses of the relationships between depressive or manic symptom levels and alcohol and nicotine use

In the first logistic regression, we investigated whether alcohol and/or nicotine use was associated with having no/mild versus moderate/severe depressive symptoms when the following covariates were included in the model; age, sex, BD-type, and current anxiety symptoms. Here, having BD type II or NOS as opposed to BD type I ($p < .05$) and anxiety symptoms ($p < .001$) were statistically significantly associated with having moderate/severe depressive symptoms. Alcohol or nicotine use was still not associated with depressive symptom level. The model was significant (χ^2 (7, N = 408) = 69.90, $p < .001$) (Table 2).

In the second logistic regression, we investigated whether alcohol and/or nicotine use was associated with the level of manic symptoms when the following covariates were included in the model: sex, current anxiety symptoms, and use of antipsychotics, lithium, and antiepileptics (use vs. no use for each medication type). Here, none of the variables were significantly associated with manic symptoms, and the model was not significant (χ^2(8, N = 414) = 6.84, $p = .554$) (Table 3).

3.4. Bivariate analyses of the relationship between sleep disturbances and alcohol and nicotine use

Alcohol and nicotine use as well as other characteristics across the sleep disturbance groups (Insomnia, Hypersomnia or No Sleep Disturbances) are presented in Table 4. We found no significant differences between the sleep disturbance groups in alcohol consumption the last two weeks ($p = .392$), or the last six months ($p = .539$).

Statistically significant differences were found across the sleep disturbance groups in the level of nicotine use ($p = .037$), with post-hoc analyses yielding a significant difference between Insomnia and No Sleep Disturbances ($p = .011$) but not between Hypersomnia and No Sleep disturbances ($p = .121$) or between Hypersomnia and Insomnia ($p = .286$) (Table 4).

3.5. Multinomial logistic regression analysis of the relationship between sleep disturbances and alcohol and nicotine use

As indicated in Table 5, the Insomnia versus No sleep disturbances

Table 2
Logistic regression predicting likelihood of reporting depressive symptoms.

	B	Std. error	Wald	*p*-Value	OR exp (B)	95 % CI
Age	−0.007	0.013	0.264	0.608	0.994	0.969–1.018
Sex, female	0.613	0.324	3.571	0.059	1.846	0.977–3.486
Diagnostic group, BD II + NOS	0.714	0.281	6.443	0.011	2.041	1.177–3.542
Anxiety PANSS item G2	0.760	0.123	38.153	<0.001	2.139	1.680–2.723
Alcohol use last 6 months	0.001	0.001	0.748	0.387	1.001	0.999–1.002
No nicotine use			0.128	0.938		
Medium nicotine use	0.127	0.355	0.128	0.721	1.135	0.566–2.275
High nicotine use	0.038	0.346	0.012	0.913	1.038	0.527–2.046
Constant	−4.541	0.707	41.239	<0.001	0.011	

BD = Bipolar Disorder, *PANSS* = Positive and Negative Syndrome Scale.
The model includes 408 participants due to missing data.
R2 = 0.16 (Cox and Snell), 0.25 (Nagelkerke).
Reference group: Male for the sex variable, BD I for the diagnostic group, No Nicotine Use for the nicotine variable.

Table 3
Logistic regression predicting likelihood of reporting manic symptoms.

	B	Std. error	Wald	*p*-Value	OR exp (B)	95 % CI
Sex, female	0.133	0.314	0.179	0.672	1.142	0.617–2.115
Medication antipsychotics	0.386	0.297	1.689	0.194	1.471	0.822–2.633
Medication lithium	0.120	0.365	0.108	0.742	1.128	0.551–2.306
Medication antiepileptics	0.250	0.300	0.695	0.405	1.284	0.713–2.312
Anxiety PANSS item G2	0.210	0.113	3.425	0.064	1.233	0.988–1.540
Alcohol use last 6 months	0.000	0.001	0.249	0.618	1.000	0.999–1.002
No nicotine use			1.037	0.595		
Medium nicotine use	−0.274	0.382	0.514	0.474	0.760	0.359–1.608
High nicotine use	−0.330	0.371	0.792	0.374	0.719	0.348–1.487
Constant	−2.799	0.504	30.809	0.000	0.061	

PANSS = Positive and Negative Syndrome Scale.
The model includes 414 participants due to missing data.
R2 = 0.02 (Cox and Snell), 0.03 (Nagelkerke).
Reference groups: Male for the sex variable, No Nicotine Use for the Nicotine variable, No use of Antipsychotics for the Medication Antipsychotics variable, No use of Lithium for the Medication Lithium variable, No use of Antiepileptics for the Medication Antiepileptic variable.

Table 4
Comparison of clinical and demographic characteristics across sleep profile groups.

	Insomnia N = 141	Hypersomnia N = 159	No sleep disturbance N = 153	Chi-square, Kruskal-Wallis χ2	*p*	Post-hoc
Age, mean (SD)	35.35 (12.3)	31.69 (11.3)	34.74 (11.7)	χ2 = 9.132	0.010	INS, NSD > HYPS
Female sex, n (%)	94 (66.7)	105 (66.0)	93 (60.8)	χ2 = 1.375	0.503	
BD type, n (%)				χ2 = 15.075	0.005	
BD I	70 (49.7)	110 (69.2)	104 (68.0)			
BD II	61 (43.3)	42 (26.4)	41 (26.8)			
BD NOS	10 (7.1)	7 (4.4)	8 (5.2)			
YMRS, median (IQR)	2 (6)	0 (2)	1 (4)[a]	χ2 = 34.285	<0.001	INS > HYPS, NSD
IDS-C, median (IQR)	20 (16)	16.5 (15)	7.5 (10)[b]	χ2 = 97.508	0.000	NSD < INS, HYPS
PANSS, median (IQR)						
Depression, item G6	3 (2)	3 (3)	2 (2)	χ2 = 23.142	<0.001	NSD < HYPS, INS
Anxiety, item G2	3 (1)	3 (1)	3 (2)	χ2 = 26.031	<0.001	INS > HYPS, NSD
Medication, n (%)	122 (87.8)	139 (87.4)	114 (77.6)	χ2 = 7.482	0.024	HYPS > INS
Antipsychotics	56 (39.7)	100 (62.9)	69 (45.1)	χ2 = 17.988	<0.001	
Lithium	22 (15.6)	39 (24.5)	30 (19.6)	χ2 = 3.742	0.154	HYPS > NSD
Antiepileptics	64 (45.4)	54 (34.0)	54 (35.3)	χ2 = 4.846	0.089	
Units of alcohol used per week last 2 weeks, median (IQR)	1.5 (5)	1 (3.8)	1.5 (4.3)	χ2 = 1.875	0.392	
Units of alcohol used per week last 6 months, median (IQR)	1.5 (4.6)	1.4 (4.8)	2 (4.9)	χ2 = 1.235	0.539	
Units of drugs used per week last 2 weeks, median (IQR)	0 (0)	0 (0)	0 (0)	χ2 = 1.102	0.576	
Units of drugs used per week last 6 months, median (IQR)	0 (0)	0 (0)	0 (0)	χ2 = 0.302	0.860	
Any cannabis use last 2 weeks, n (%)	10 (7.2)	6 (3.8)	6 (4.3)	χ2 = 2.097	0.350	
Any cannabis use last 6 months, n (%)	24 (17.4)	26 (16.4)	22 (15.7)	χ2 = 0.145	0.930	
Nicotine use, n (%)	73 (52.1)	75 (47.2)	56 (38.1)	χ2 = 5.905	0.052	
No. of units of nicotine per day, median (IQR)	3.5 (14)	0 (10)	0 (7)	χ2 = 6.607	0.037	INS > NSD

INS = Insomnia, *HYPS* = Hypersomnia, *NSD* = No Sleep Disturbances, *BD* = Bipolar Disorder, *YMRS* = Young Mania Rating Scale, *PANSS* = Positive and Negative Syndrome Scale.
[a] n = 136.
[b] n = 132.

regression model showed that participants with both medium ($p < .05$) and high levels of nicotine use ($p < .01$) had a significantly increased risk for insomnia compared to those who did not use nicotine, independently from potential confounders. The risk for insomnia was significantly and independently higher for participants with BDII + NOS than for participants with BD I ($p < .05$). The Insomnia group also had higher levels of anxiety symptoms ($p = .01$) and depressive symptoms ($p < .01$). The Hypersomnia vs. No Sleep Disturbances regression model showed no significant differences in the level of nicotine use between the groups. The Hypersomnia group had more depressive symptoms ($p < .01$) and was more likely to use antipsychotic medication ($p < .01$) compared to the No Sleep Disturbances group. The full model was significant ($\chi^2(22) = 101.07$, $p < .001$) with R2 = 0.21 (Cox and Snell) and 0.24 (Nagelkerke) (Table 5).

Although the levels of recent alcohol and drug use were not significantly different across the sleep disturbance groups (No sleep problems, Hypersomnia, Insomnia), we re-ran the full multinomial regression analysis with measures of alcohol and drug use during the last six months included in the model, as nicotine use usually is highly correlated with use of other substances (Waxmonsky et al., 2005). This model included all possible covariates that were taken into consideration, except for cannabis use, which was not included due to collinearity with

Table 5
Multinomial logistic regression analysis on the relationship between sleep disturbances and nicotine use.

	B	Std. error	Wald	*p*-Value	OR exp (B)	95 % CI
Insomnia						
Intercept	−0.956	0.815	1.376	0.241		
Age	0.012	0.011	1.068	0.301	1.012	0.990–1.034
Sex, male	−0.140	0.277	0.257	0.612	0.869	0.505–1.495
Medication antipsychotics	−0.019	0.287	0.004	0.947	0.981	0.559–1.721
Medication lithium	0.058	0.360	0.026	0.872	1.060	0.523–2.146
Medication antiepileptics	−0.285	0.275	1.076	0.300	0.752	0.439–1.288
YMRS	0.055	0.028	3.673	0.055	1.056	0.999–1.117
Anxiety PANSS item G2	0.286	0.112	6.571	0.010	1.331	1.070–1.657
Depression PANSS item G6	0.318	0.103	9.494	0.002	1.375	1.123–1.683
Diagnostic group, BD I	−0.669	0.297	5.070	0.024	0.512	0.286–0.917
No nicotine use	−0.979	0.333	8.626	0.003	0.376	0.195–0.722
Medium nicotine use	−0.887	0.407	4.742	0.029	0.412	0.185–0.915
Hypersomnia						
Intercept	1.057	0.767	1.899	0.168		
Age	−0.020	0.011	3.394	0.065	0.980	0.959–1.001
Sex, male	−0.218	0.265	0.676	0.411	0.804	0.478–1.353
Medication antipsychotics	−0.908	0.270	11.292	<0.001	0.403	0.238–0.685
Medication lithium	−0.282	0.324	0.755	0.385	0.754	0.400–1.424
Medication antiepileptics	0.038	0.270	0.019	0.890	1.038	0.611–1.764
YMRS	−0.064	0.034	3.497	0.061	0.938	0.877–1.003
Anxiety PANSS item G2	0.040	0.108	0.137	0.711	1.041	0.842–1.287
Depression PANSS item G6	0.304	0.100	9.315	0.002	1.356	1.115–1.648
Diagnostic group, BD I	−0.114	0.295	0.149	0.699	0.892	0.500–1.592
No nicotine use	−0.332	0.337	0.970	0.325	0.717	0.370–1.390
Medium nicotine use	0.045	0.392	0.013	0.908	1.046	0.485–2.257

BD = Bipolar Disorder, *YMRS* = Young Mania Rating Scale, *PANSS* = Positive and Negative Syndrome Scale.
The model includes 421 participants due to missing data.
R2 = 0.21 (Cox and Snell), 0.24 (Nagelkerke).
The reference group for the multinomial regression is "No Sleep Disturbances". Reference groups: BD II + BD NOS for the diagnostic group, High Nicotine Use for the nicotine variable, Female for the sex variable, Use of Antipsychotics for the Medication Antipsychotics variable, Use of Lithium for the Medication Lithium variable, Use of Antiepileptics for the Medication Antiepileptic variable.

illicit drug use. Here, as in the bivariate analyses, neither alcohol nor drug use were significantly associated with sleep disturbances. Nicotine use was still associated with a higher risk for insomnia, both for participants with medium ($p < .05$) and high levels of nicotine use ($p < .01$). The full model was significant ($\chi^2(26) = 102.64$, $p < .001$) with R2 = 0.23 (Cox and Snell) and 0.25 (Nagelkerke). (Results are presented in Supplementary Table 1).

4. Discussion

In this study we investigated the relationship between manic and depressive symptoms and levels of nicotine and alcohol use in BD without comorbid substance use disorders, with a specific focus on sleep disturbances. We found a significant independent association between nicotine use and sleep disturbances, where participants with both medium and high use levels had higher risk of insomnia compared to participants with no nicotine use. We did not find an association between non-pathological alcohol use and sleep disturbances. Furthermore, no significant relationships were found between manic or depressive symptoms and alcohol or nicotine use. These results were further supported by multivariate analyses taking covariates into account.

The relationship between nicotine use and insomnia was independent from possible confounders such as medication use and affective symptoms. A relationship between cigarette smoking and insomnia and shorter sleep duration has also been demonstrated in the general population (Nuñez et al., 2021; Patterson et al., 2016). The direction of the relationship is, however, not fully understood, and there may be disorder specific mechanisms behind the association in BD. Although the cross-sectional design of the current study precludes any causal inferences, one may speculate that while nicotine appears to cause disturbed sleep (McNamara et al., 2014) and lower sleep efficiency due to its stimulating properties (Spadola et al., 2019), individuals with BD may be particularly vulnerable to these effects due to unstable circadian rhythms (McCarthy et al., 2021). Insomnia might also be a symptom of nicotine withdrawal, as blood nicotine levels decrease during sleep (Zhang et al., 2006). Yet another possibility is that participants with insomnia use more nicotine than those without insomnia during the time they are involuntary awake. The proportion of participants with daily nicotine use in our sample was 45.7 %, which is considerably higher than in the general population of Norway (Rødevand et al., 2019). The increased risk of insomnia adds to the significant burden of health adversities associated with nicotine use.

Our finding that the level of daily nicotine consumption was not associated with depressive or manic symptom levels is in contrast to some previous reports (Medeiros et al., 2018; Waxmonsky et al., 2005) but in line with others (Gross et al., 2020). The mixed results could be explained by different levels of nicotine use in the study populations. For instance, in the study by Waxmonsky et al. (2005), the mean number of cigarettes used per day was 20, while the mean in Gross` study (Gross et al., 2020) was 13, which is more similar to the current median of 11.5.

The lack of significant relationships between current depressive or manic symptom levels and the levels of recent use of alcohol was contrary to our expectations, but in line with the results reported by Gross et al. (2020). Based on the findings of this study and our own, which to our knowledge are the only studies to date investigating the relationship between affective symptoms, and "normal" use of alcohol in BD, it appears that low to moderate levels of alcohol use (a median of 3 units per weeks in the current study and 2.2 units per day in Gross et al.'s study) do not increase the level of affective symptoms in BD. Conversely, individuals with BD do not appear to self-medicate low to moderate levels of manic and depressive symptoms with alcohol. However, the median number of alcohol units consumed was relatively low in our sample. Based on these findings, one may speculate that participants with BD

who self-medicate affective symptoms with alcohol commonly proceed to develop an alcohol use disorder, i.e. are excluded from the current study. Further studies are needed to clarify which levels of alcohol use that are harmful with regards to BD symptoms.

We did not confirm our hypothesis that alcohol use would be higher in individuals with sleep disturbances than those without. This contrasts with the findings of Gross et al. (2020) of a significant negative correlation between the level of alcohol consumption and sleep duration. The actigraphy-based sleep estimation used in the Gross et al. (2020) study may give more precise measures of sleep duration compared to the interview-based sleep disturbance proxies used in the current study. However, previous studies have found that BD individuals' subjective reports of sleep are relatively reliable (Ihler et al., 2020). The diverging findings may also be explained by the higher levels of alcohol use in the Gross et al. (2020) study, which also included participants with a past history of alcohol use disorder.

4.1. Strengths and limitations

Limitations: Sleep disturbances were assessed using items from the IDS-C and should be considered as proxies for sleep disturbances rather than diagnostic entities of sleep disorders. However, high reliability and validity of this method has been demonstrated in previous research (Soehner et al., 2014; Steinan et al., 2016a; Steinan et al., 2016b; Sylvia et al., 2012). Also, we did not use objective estimates of sleep such as actigraphy.

Strengths: The study comprises a large and representative catchment-area-based sample and a comprehensive clinical assessment including several measures of substance use. This also enabled adjustment for several possible confounders in the analyses.

5. Conclusion

The risk of insomnia is increased in BD individuals with moderate and high levels of nicotine use. The direction of this relationship should be clarified through future studies since such knowledge would be of substantial value for better prevention and treatment of two burdensome conditions in BD. Longitudinal and simultaneous digital monitoring of affective symptoms, sleep patterns and alcohol and nicotine use appear as a promising avenue to disentangle these complex interplays.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jad.2023.02.003.

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CRediT authorship contribution statement

SHG, TVL, SRA and RH designed the study and contributed with revising the manuscript. SHG conducted the data analyses and drafted the manuscript. TVL and BE contributed with the data analyses and interpretation. IM initiated the project. SHG, TVL, SRA, MCH, CBB and EAB collected data for the study. All authors were involved in critically reviewing the manuscript before approving the final version.

Conflict of interest

The authors report no conflicts of interest.

Data availability

The data that support the findings of this study will be made available upon reasonable request.

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