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Relationship between Polygenic Risk Score and the Hypnotics in Bipolar I Disorder

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Objective: Bipolar disorder (BD) is marked by significant change in mood and energy levels with sleep disturbance a common feature, resulting in diminished quality of life and impaired daily functioning. This study assessed the association between BD-polygenic risk scores (PRS) and hypnotics in bipolar I disorder (BD-I) patients.
Methods: Large-sample data were collected from the genome-wide association study of a multicenter Bipolar Genomic Study, and 1,394 BD-I patients with available medication information were divided into two groups depending on whether they used hypnotics or not. The Diagnostic Interview for Genetic Studies (DIGS) score was used to assess the clinical manifestations and function of the participants and the association between the use of hypnotics and genetic risk was analyzed.
Results: Of the 1,394 total participants, 556 (40%) patients received hypnotics, mostly benzodiazepines, administered singly or in combination with other sleeping agents such as, Z-drugs, melatonin-related drugs, and trazodone. The DIGS score was significantly higher for negative categories in the group prescribed hypnotics as was the BD-PRS score, according to the four p value thresholds (p = 0.3, 0.2, 0.1, and 0.05). Logistic regression analysis confirmed a statistically significant association between the BD-PRS and hypnotic use.
Conclusion: Our results suggest an association between hypnotic use and genetic susceptibility to BD. Sleep disturbances in participants were based on the prescription status of hypnotics supporting the hypothesis that sleep disturbances may be associated with genetic aspects of BD-I. Further genetic studies on genetic overlaps between BD and specific phenotypes or medication responses are required.

KEY WORDS: Bipolar disorder; Polygenic risk score; Hypnotics; Sleep disturbance.

INTRODUCTION

Bipolar disorder (BD) is a recurrent and chronic mental disorder characterized by wide range of fluctuations in mood state and energy levels [1,2]. In the 'Global Burden of Disease' study of the World Health Organization, BD was listed as one of the top 10 primary causes of disability worldwide [3]. Interestingly, sleep disturbances and circadian rhythm dysfunction are thought to be essential features of this condition [4-6]. In BD, sleep disturbances tend to aggravate before the onset of an episode, exacerbate during the episode, and sometimes persist even after pharmacological intervention [7-9]. Even in euthymic mood states, patients experience sleep disturbances, subsequent functional impairment, reduced sleep efficiency, and a fear of inadequate sleep [10]. It negatively affects the course and prognosis of BD, eventually leading to impairment of daily functioning and diminished quality of individual's life [11]. Additionally, BD patients with sleep disturbances show deficits in cognitive performance, including working memory and processing speed, when compared to those without sleep disturbances [12].

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Notably, sleep disturbances may moderate treatment response to BD. There is some evidence of a relatively low probability of a maintenance response to pharmacological treatment in BD patients with sleep disturbances [13]. Further, circadian rhythm dysfunction, disrupted sleep–wake patterns, and abnormal melatonin secretion are well documented in BD [5].

The causes of BD have been less researched than those of unipolar depression or schizophrenia (SPR), and its pathogenesis remains unclear. Nevertheless, its genetic components and heritability are considered stronger than those in unipolar depression [14]. Revealing how certain endophenotypes or responses to treatments in BD are related to the intrinsic genetic properties of BD is crucial for personalized treatment. Genetic studies have identified an association between circadian rhythm-related clock genes and sleep disturbances in BD. For example, single nucleotide polymorphism (SNP) CLOCK 3111C/T seems to be associated with mood disorder recurrence [15]. Glycogen synthase kinase 3-beta (GSK3-β) is involved in the phosphorylation of circadian clock genes and is recognized as a gene related to BD [16]. The results of genome-wide association study (GWAS), which identified the Meis Homeobox 1 loci associated with insomnia as a susceptible gene for mood disorders, including BD, provide a biological underpinning for sleep disturbances in BD [17,18]. In other studies, some evidence suggests genetic polymorphisms related to the circadian mechanism, such as the CLOCK gene, have been linked to depressive relapse. In theory, a mismatch between the external environment and the internal circadian phase through polymorphisms can contribute to higher risk of depression in BD [19].

Polygenic risk score (PRS) is a numerical value for the polygenic risk of multi-factorial disorders. The PRS is calculated after conducting a GWAS on a large-scale reference sample and analyzing SNPs weighted by their effect sizes for various p value thresholds to estimate certain diseases or phenotypes in an individual sample [20]. Beyond the limitations of the two-dimensional linear regression method that aligns and compares genome sequences in GWAS, PRS analyzes the risk of certain diseases by calculating the weighted sum of the effects and influences using a three-dimensional combination of various SNPs [20]. Thus, PRS is a useful technique for studying genetic overlap between different diseases, as well as polygenic overlap between certain diseases and phenotypes.

PRS analyses have been successfully applied to various multifactorial diseases in medicine, such as coronary artery disease, type II diabetes, and inflammatory bowel disease [21]. Studies have also reported the association of SPR-PRS with antipsychotic responses to clozapine and lurasidone [22,23] and the association of major depressive disorder (MDD)-PRS and neuroticism-PRS with selective serotonin re-uptake inhibitor response [24]. An international consortium genetics study confirmed an inverse association between SPR-PRS and lithium response in BD patients [25], as well as an inverse association between MDD-PRS and lithium response [26]. A study of BD genetic risk and circadian rhythm analyzing the association between each chronotype and BD-PRS found an association between the evening type and BD risk in a sample of Native Americans and Mexican Americans [27]. In a study on the correlation between PRS for each type of sleep disturbances and subtypes of BD (BD-I vs. BD-II), it was reported that the genetic liability for sleep disorders varies depending on the type of BD. They identified that higher insomnia PRS was linked to BD-II, and higher sleep-duration PRS was linked to BD-I [28].

Reportedly, few studies have examined the association between BD-PRS and the use of certain psychotropic medications, particularly hypnotic/sedative agents, in BD patients. As BD is a complex genetic disease rather than a single-gene disorder [29], we believe that the PRS can be used for diagnosis, prognosis, and treatment prediction, and eventually for personalized medicine [30,31]. This study aimed to assess the correlation between BD-PRS and the use of hypnotics (sedatives or sleep medication) in BD. Finally, we aimed to explore the potential of utilizing the BD-PRS to assess the necessity for hypnotics in individual patients with BD.

METHODS

Data Extraction and Participants

A large sample dataset of all SNPs and prescription data was collected from GWAS in a multicenter Bipolar Genomic Study (BiGS) by the Bipolar Disorder Genetic Association Information Network and Translational Genomic Institute. The BiGS is a large-scale collection of data from multi-institutional research conducted in the United States [32].

Dr. Kelsoe, a member of BiGS, obtained the dataset for data extraction. All the participants provided informed consent prior to the initiation of study. Among these participants, 1,394 BD-I patients with available medication information were selected from this cohort. The Diagnostic Interview for Genetic Studies (DIGS) score, a semi-structured clinical interview designed for genetic studies to assess clinical outcomes of mood and psychotic disorders, was used to assess the clinical manifestations and life functioning of participants [33,34]. It consists of six items which are considered clinically significant outcomes in BD, such as "chronicity," "psychotic features," "mixed symptoms," "suicidality," "general impact of illness on life functioning," and "substance abuse." The detailed contents of the DIGS scores are presented in Table 1.

Genotyping and Quality Control

Genotyping was conducted on the BiGS samples using the Affymetrix Genome-Wide Human SNP Array 6.0. Initially, the sample included 2,200 BD patients and 1,436 controls with 703,012 SNPs. For racial homogeneity of the participants, European ancestry patients with available prescription data alone were included. Quality control excluded patients with $>$ 10% missing data and poor SNP quality (such as poor allele clustering, minor allele frequencies [MAFs] $<$ 0.01, duplicate errors, Hardy–Weinberg equilibrium $< 10^{-6}$), as indicated by principal component analysis, and the final sample included 1,394 BD-I patients.

In this study, the term "hypnotics" refers to benzodiazepines (BZDs), Z-drugs (such as zolpidem, eszopiclone, zaleplon), melatonin-related drugs (such as melatonin, ramelteon), and trazodone, which are used to treat sleep disturbances in patients. The term did not represent the main therapeutic agents which were mood stabilizers, antipsychotic agents, and antidepressants among the prescription data.

Polygenic Risk Score

We derived BD-PRSs from reference data provided by the Psychiatric Genomics Consortium, which comprised 7,481 BD patients and 9,250 controls. Each individual's PRS was calculated using PLINK software [35]. The selection of SNPs was based on certain criteria, such as imputation MAF $<$ 0.2, linkage disequilibrium ($r^2 < 0.25$ within 500 kb), and INFO score $<$ 0.9. Multiple p value thresholds (p = 0.3, 0.2, 0.1, 0.05, 0.01, 0.001, and 0.0001) were used to derive the PRS for the target sample. The PRS was then standardized with a mean value of 0 and a standard deviation of 1.

Statistical Analysis

The participants were divided into two groups depending on the use of hypnotics. We examined demographic variables such as age at onset, age at the time of assessment, sex, and DIGS' score representing the severity of certain clinical manifestations. Independent sample t and chi-square tests were performed to compare the clinical outcomes and demographic variables between the two groups. Additionally, we conducted a t test to compare BD-PRS scores between the two groups according to various p value thresholds (p = 0.3, 0.2, 0.1, 0.05, 0.01, 0.001, and 0.0001). We performed the same analysis for specific types of hypnotics such as BZDs and Z-drugs. Binary logistic regression analyses for the use of hypnotics were performed to confirm the association of BD-PRS while controlling for potentially confounding variables such as sex, age, and several clinical outcomes. In addition, the backward elimination method was used to remove less significant variables from these models. All stat-

Table 1. Scoring of Diagnostic Interview for Genetic Studies (DIGS) according to clinical outcomes

Score	Chronicity	Psychotic features	Mixed symptoms	Suicidality	General impact of illness on life functioning	Substance misuse
0	Never	Never	Never	Never	None	Never
1	$<$ 2 yr	Fleeting	Mixed symptoms	Passive death wishes	Employment	No dependence
2	$\geq$2 yr	1 episode	$\geq$ A mixed episode	Thought about suicide	Employment but not disabled	Brief usage
3	Frequent symptoms	$\geq$ 2 episodes		Acted on ambivalently	Disabled but living independently	Relapsing
4		All episodes		Acted on seriously	Disabled & not living independently	Chronic usage
5		Chronic psychosis				

istical analyses were performed using the SPSS (version 29.0.1.0; IBM Co.).

RESULTS

A total of 556 (40%) of the 1,394 BD-I patients were prescribed hypnotics. BZDs (n = 427) were the most prescribed hypnotics, administered as monotherapy or in combination with other hypnotics (including Z-drugs [n = 97], melatonin [such as melatonin, ramelteon; n = 6], and trazodone [n = 129]). The proportions of BZDs, non-BZDs, and their combinations are summarized in Figure 1.

From the results of independent sample *t* test, DIGS scores of "mixed symptoms," "suicidality," and "general impact of illness on life functioning" were significantly higher in the group prescribed with hypnotics (Fig. 2, Table 2-1). When each type of hypnotic was analyzed, the same results were observed in the BZDs group (Table

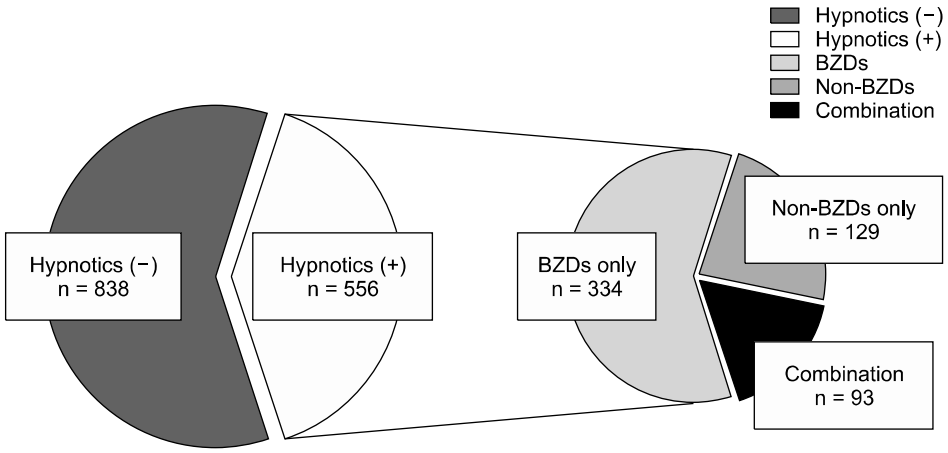

Fig. 1. Number of participants prescribed with and without hypnotics. BZDs, benzodiazepines.

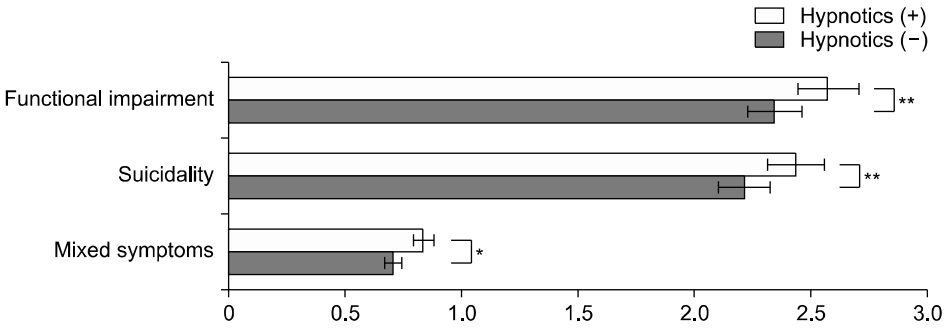

Fig. 2. Differences in clinical outcomes based on whether hypnotics were prescribed or not.
*$p < 0.05$, **$p < 0.01$.

Table 2-1. Comparison in psychopathology between groups prescribed with and without hypnotics

Variables	Hypnotics (−)	Hypnotics (+)	χ^2, *t*	*p* value
AAO (yr)	19.07 ± 9.75	18.89 ± 9.21	0.341	0.733
Age at assessment (yr)	43.61 ± 13.50	45.53 ± 11.41	−2.865	0.004**
Sex (female/male)	498/340	388/168	15.479	< 0.001**
DIGS score				
Chronicity	2.76 ± 1.54	2.78 ± 1.44	−0.306	0.759
Psychotic symptoms	1.64 ± 1.16	1.70 ± 1.23	−0.794	0.427
Mixed symptoms	0.71 ± 0.87	0.84 ± 0.89	−2.508	0.012*
Suicidality	2.22 ± 1.45	2.44 ± 1.43	−2.662	0.008**
General impact of illness on life functioning	2.35 ± 0.90	2.58 ± 0.86	−4.588	< 0.001**
Substance misuse	2.09 ± 1.15	2.15 ± 1.15	−0.900	0.368

AAO, age at onset; DIGS, Diagnostic Interview for Genetic Studies.
*$p < 0.05$, **$p < 0.01$.

2-2). However, the prescription of Z-drugs was not associated with any notable variance in DIGS scores (Table 2-3). Across all groups, the prescription of hypnotics was more prevalent among females than males.

The BD-PRS score was significantly higher in the hypnotics group according to the four p value thresholds (p= 0.3, 0.2, 0.1, and 0.05) (Fig. 3, Table 3-1). This was the case even when each type of hypnotic (BZDs and Z-drugs) was analyzed independently (Tables 3-2, 3-3).

By the results of binary logistic regression analysis of the use of hypnotics in patients BD-I patients, BD-PRS was significantly increased according to the four p value thresholds (p = 0.3, 0.2, 0.1, and 0.05) in the group prescribed hypnotics, independent of other variables. Also, functional impairment and female sex were associated with the use of hypnotics in BD-I, independent of other variables. Table 4 shows the statistical associations at a p value threshold of 0.3. The same pattern is observed at thresholds of 0.2, 0.1, and 0.05.

DISCUSSION

We conducted a genetic study using several endophenotypes that have the most significant impact on the prognosis of BD. We identified a statistically significant association between an increased hypnotic use and a higher BD-PRS. The use of hypnotics was also associated with a

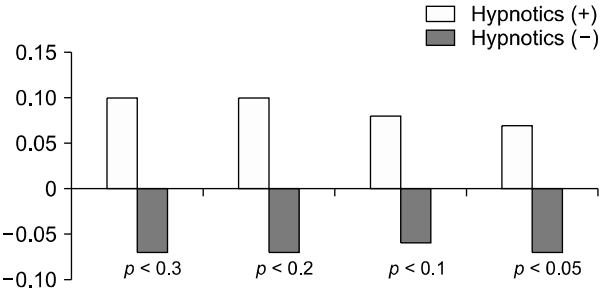

Fig. 3. Differences in polygenic risk scores (PRSs) based on whether hypnotics were prescribed or not.

Table 2-2. Comparison in psychopathology between groups prescribed with and without Benzodiazepines

Variables	BZDs (−)	BZDs (+)	χ^2, t	p value
AAO (yr)	19.05 ± 9.69	18.87 ± 9.20	0.321	0.748
Age at assessment (yr)	44.09 ± 13.35	45.02 ± 11.25	−1.344	0.179
Sex (female/male)	589/378	297/130	9.558	0.002**
DIGS score				
Chronicity	2.76 ± 1.52	2.80 ± 1.44	−0.439	0.661
Psychotic symptoms	1.64 ± 1.17	1.72 ± 1.23	−1.025	0.305
Mixed symptoms	0.72 ± 0.87	0.87 ± 0.89	−2.801	0.005**
Suicidality	2.26 ± 1.46	2.43 ± 1.41	−1.994	0.046*
General impact of illness on life functioning	2.38 ± 0.89	2.58 ± 0.87	−3.667	< 0.001**
Substance misuse	2.09 ± 1.15	2.16 ± 1.14	−0.968	0.333

BZDs, benzodiazepines; DIGS, Diagnostic Interview for Genetic Studies.
*p < 0.05, **p < 0.01.

Table 2-3. Comparison in psychopathology between groups prescribed with and without Z-drugs

Variables	Z-drug (−)	Z-drug (+)	χ^2, t	p value
AAO (yr)	19.09 ± 9.65	17.72 ± 1.16	1.366	0.172
Age at assessment (yr)	44.17 ± 12.88	47.04 ± 10.44	−2.563	0.012*
Sex (female/male)	814/483	72/25	5.123	0.024*
DIGS score				
Chronicity	2.78 ± 1.51	2.67 ± 1.29	0.666	0.506
Psychotic symptoms	1.67 ± 1.18	1.62 ± 1.25	0.362	0.717
Mixed symptoms	0.76 ± 0.88	0.84 ± 0.91	−0.785	0.433
Suicidality	2.31 ± 1.44	2.34 ± 1.56	−0.224	0.823
General impact of illness on life functioning	2.44 ± 0.89	2.48 ± 0.83	−0.417	0.677
Substance misuse	2.10 ± 1.14	2.28 ± 1.20	−1.430	0.153

AAO, age at onset; DIGS, Diagnostic Interview for Genetic Studies.
*p < 0.05, **p < 0.01.

Table 3-1. Comparison in polygenic risk scores between groups prescribed with and without hypnotics according to four p value thresholds

PRS (thresholds)	Hypnotics (−)	Hypnotics (+)	t	p value
PRS ($p < 0.3$)	−0.07 ± 1.026	0.10 ± 0.950	−3.125	0.002**
PRS ($p < 0.2$)	−0.07 ± 1.026	0.10 ± 0.951	−3.221	0.001**
PRS ($p < 0.1$)	−0.06 ± 1.022	0.08 ± 0.959	−2.714	0.007**
PRS ($p < 0.05$)	−0.07 ± 1.030	0.07 ± 0.929	−2.546	0.011*
PRS ($p < 0.01$)	−0.02 ± 1.016	0.02 ± 0.968	−0.686	0.493
PRS ($p < 0.001$)	0.31 ± 0.993	0.36 ± 1.011	−0.864	0.388
PRS ($p < 0.0001$)	0.88 ± 1.004	0.89 ± 0.971	−0.195	0.846

PRS, polygenic risk scores.
*$p < 0.05$, **$p < 0.01$.

Table 3-2. Comparison in polygenic risk scores between groups prescribed with and without benzodiazepines according to four p value thresholds

PRS (thresholds)	BZDs (−)	BZDs (+)	t	p value
PRS ($p < 0.3$)	−0.04 ± 1.026	0.10 ± 0.932	−2.459	0.014*
PRS ($p < 0.2$)	−0.05 ± 1.028	0.11 ± 0.925	−2.795	0.005**
PRS ($p < 0.1$)	−0.04 ± 1.028	0.08 ± 0.928	−2.296	0.022*
PRS ($p < 0.05$)	−0.05 ± 1.031	0.07 ± 0.896	−2.286	0.022*
PRS ($p < 0.01$)	−0.03 ± 1.011	0.06 ± 0.962	−1.549	0.122
PRS ($p < 0.001$)	0.31 ± 0.987	0.39 ± 1.027	−1.431	0.153
PRS ($p < 0.0001$)	0.88 ± 0.997	0.88 ± 0.978	−0.030	0.976

PRS, polygenic risk scores; BZDs, benzodiazepines.
*$p < 0.05$, **$p < 0.01$.

Table 3-3. Comparison in polygenic risk scores between groups prescribed with and without Z-drugs according to four p value thresholds

PRS (thresholds)	Z-drug (−)	Z-drug (+)	t	p value
PRS ($p < 0.3$)	−0.01 ± 1.008	0.23 ± 0.849	−2.653	0.009**
PRS ($p < 0.2$)	−0.01 ± 1.007	0.20 ± 0.881	−2.026	0.043*
PRS ($p < 0.1$)	−0.02 ± 1.008	0.21 ± 0.851	−2.568	0.011*
PRS ($p < 0.05$)	−0.03 ± 1.001	0.19 ± 0.855	−2.045	0.041*
PRS ($p < 0.01$)	−0.02 ± 1.003	0.13 ± 0.904	−1.367	0.172
PRS ($p < 0.001$)	0.33 ± 1.011	0.33 ± 0.843	0.011	0.991
PRS ($p < 0.0001$)	0.89 ± 0.995	0.78 ± 0.928	1.074	0.283

PRS, polygenic risk scores.
*$p < 0.05$, **$p < 0.01$.

Table 4. Logistic regression analysis for the absence or presence of hypnotics associated with clinical variables and BD-PRS ($p < 0.3$)

Variables	B	Standard error	Wald	p value	Odds ratio	95% confidence interval	
						Lower limit	Upper limit
Age (yr)	0.010	0.005	3.536	0.060	1.010	1.000	1.020
Sex	−0.469	0.138	11.540	< 0.001**	0.626	0.478	0.820
DIGS score							
Mixed symptoms	0.135	0.074	3.319	0.068	1.144	0.990	1.323
Suicidality	−0.021	0.047	0.200	0.655	0.979	0.892	1.074
Functional impairment	0.325	0.078	17.505	< 0.001**	1.384	1.189	1.612
Substance misuse	0.017	0.058	0.090	0.765	1.018	0.908	1.140
BD-PRS (p value threshold < 0.3)	0.224	0.066	11.662	< 0.001**	1.252	1.100	1.424

BD-PRS, bipolar disorder polygenic risk score; DIGS: Diagnostic Interview for Genetic Studies.
*$p < 0.05$, **$p < 0.01$.

higher severity of certain clinical aspects, such as suicidal thoughts and/or behavior, more frequent mixed episodes, and a more severe impact on one's living and functional impairment. Regression analysis revealed that a higher BD-PRS had a significant correlation with hypnotics use, regardless of other factors like age, sex, and the severity of several clinical symptoms. Apart from the BD-PRS, another variable that independently correlated with the use of hypnotics was the general impact of illness on life functions. We emphasize the importance of not overlooking the clinical impact of sleep disturbances on the prognosis of the illness, and the need for appropriate sleep interventions in BD. Previous studies have suggested that difficulties in mood regulation during the daytime and disturbances in night-time sleep/circadian rhythms negatively influence each other, resulting in a vicious cycle [11]. In line with our results, some analytical studies suggest that sleep disturbances in BD are associated with psychotic symptoms and a higher number of suicide attempts [36]. In another study, using PRS analysis, a statistical association between genetic susceptibility in BD and adverse childhood experiences was observed, suggesting an interaction between genes and the environment during the illness [37]. Classical genetic association studies have revealed genetic susceptibility between mood spectrum disorders (BD, recurrent depressive disorder, seasonal affective disorder) and certain circadian genes (such as CLOCK, ARNTL1, PER1, PER2, PER3, NPAS2, and NR1D1) [38,39]. Interestingly, another study provides genetic evidence for the association between the therapeutic effects of Lithium on BD and the modulation of circadian rhythmicity. GSK3-β gene, playing a critical role in regulating the suprachiasmatic nucleus (SCN)–the master pacemaker of circadian rhythms–is known to have its phosphorylation activity inhibited by Lithium [40]. Such genetic susceptibility in BD individuals could imply a reduced ability to adequately adapt to the 24-hour circadian rhythm, making them prone to sleep disturbances.

Interestingly, no significant association was identified between the prescription of hypnotics and the severity of substance abuse. This suggests that prescribing hypnotics to treat sleep disturbances in patients with BD-I does not necessarily increase the risk of drug dependence or misuse. Instead, we believe that the therapeutic benefits of pharmacological sleep interventions with appropriate dosage and tolerability would outweigh the risk of recurrent mood episodes.

In a review regarding personalized medicine for BD, the importance of sleep changes in predicting imminent affective instability was emphasized, highlighting the potential significance of chronotherapeutic targets that regulate biological rhythms, such as pharmacologic interventions targeting melatonin receptors, light therapy, and blue light blocking [41]. Compared to SPR, there have been fewer genetic studies using different phenotypes in BD. However, we can accumulate objective data for personalized medicine of BD if further studies can be conducted on endophenotypes such as circadian rhythmicity, sleep deprivation, and drug responsiveness.

This study had a few limitations. Given its cross-sectional design, this study might not adequately establish the causality between the variables studied as only the associations could be identified. Second, the confounding impact of sedative effects from other medications which were not defined as "hypnotics" (such as mood stabilizers, antipsychotics, and antidepressants) were not considered. Finally, the analysis was conducted exclusively on BD-I patients without a control group, limiting the generalizability of the findings.

Conclusions

Using large-scale data of BD-I patients and their PRS, we found a significant association between the use of hypnotics and a higher BD-PRS. There was also a significant association between hypnotic use and impaired functioning of the patients' lives. However, the correlation with drug/substance misuse was not statistically significant. This study not only provides suggestions for the genetic association of sleep disturbances in BD but may also elucidate the objective basis for personalized medicine specific to each individual. Further studies should be conducted on endophenotypes, such as circadian rhythmicity, sleep deprivation, and drug responsiveness. Ultimately, these attempts could accumulate data for the future of personalized medicine for complex genetic disorders, such as BD.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Young-Min Park, John R. Kelsoe, Bun-Hee Lee. Formal analysis: Hyeon Woo Lee. Methodology: Young-Min Park, Bun-Hee Lee, Tatyana Shekhtman. Software: Hyeon Woo Lee. Writing–original draft: Hyeon Woo Lee. Writing–review & editing: Young-Min Park.

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