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ORIGINAL ARTICLE

The Influence of Predominant Polarity and Chronotype on Lithium Response in Bipolar Disorder

Bipolar Bozuklukta Lityum Tepkisi Üzerindeki Predominant Polarite ve Kronotipin Etkisi

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ABSTRACT

Aim: This study investigates the prevalence and clinical correlates of predominant polarity (PP), depressive predominant polarity (DPP), and manic predominant polarity (MPP) in patients with bipolar disorder type 1 (BD-1), as well as their association with chronotype and lithium response.
Method: The present study with a cross-sectional design was conducted on 80 BD-1 patients in remission between 18-65 years of age. Data collection involved sociodemographic questionnaires and assessments using the Young Mania Rating Scale (YMRS), Hamilton Depression Rating Scale (HDRS), Biological Rhythms Interview of Assessment in Neuropsychiatry, (BRIAN) Morningness-Eveningness Questionnaire (MEQ), and the Alda Scale. DPP and MPP were defined as a lifetime ratio of ≥2:1 of either hypomanic/manic episodes or depressive episodes, respectively.
Results: Participants (mean age 35.32 ± 11.39 years; 61.25% female) showed two dominant polarities: DPP (46.25%) and MPP (53.75%). No significant differences were found in treatment, illness duration, or episode number (p>0.05). However, the MPP group had significantly earlier onset age (p=0.009) and higher scores on the BRIAN, MEQ, and Alda scales (all p<0.001). Manic episodes correlated positively with BRIAN and strongly with MEQ (rs1=-0.355, rs2=-0.373). The Alda scale showed strong positive correlations with BRIAN and MEQ, and strong negative correlations with depressive episodes (rs1=-0.355, rs2=-0.373, rs3=-0.274).
Conclusion: The present study demonstrates that PP and chronotype significantly influence lithium response in individuals with BD-I. The MPP group was found to have an earlier onset of the disorder and exhibit more pronounced evening characteristics. Additionally, the MPP group showed a stronger response to lithium.

Keywords: Bipolar disorder, chronotype, depression, lithium, mania, predominant polarity,

ÖZ

Amaç: Bu çalışmada, bipolar bozukluk (BD) tip 1 (BD-1) hastalarında baskın polarite (PP) - depresif baskın polarite (DPP) ve manik baskın polarite (MPP) - yaygınlığı ve klinik korelasyonları ile bunların kronotip ve lityum yanıtıyla ilişkisi araştırılmıştır.
Yöntem: 18-65 yaş aralığında, remisyondaki 80 BD-1 hastasında kesitsel bir çalışma yürütülmüştür. Veri toplama, sosyodemografik anketler ve Young Mani Derecelendirme Ölçeği (YMRS), Hamilton Depresyon Derecelendirme Ölçeği (HDRS), Nöropsikiyatride Değerlendirmenin Biyolojik Ritim Görüşmesi, (BRIAN) Sabah-Akşam Anketi (MEQ) ve Alda Ölçeği kullanılarak yapılan değerlendirmeleri içermektedir. DPP ve MPP, sırasıyla hipomanik/manik epizotların veya depresif epizotların yaşam boyu oranı ≥2:1 olarak tanımlanmıştır.
Bulgular: Katılımcılar (ortalama yaş 35,32 ± 11,39 yıl; %61,25 kadın) iki baskın kutupluluk gösterdi: DPP (%46,25) ve MPP (%53,75). Tedavi, hastalık süresi veya bölüm sayısında anlamlı bir fark bulunmadı (p>0,05). Ancak, MPP grubunun başlangıç yaşı önemli ölçüde daha erkendi (p=0,009) ve BRIAN, MEQ ve Alda ölçeklerinde daha yüksek puanlar vardı (hepsi p<0,001). Manik bölümler BRIAN ile pozitif ve MEQ ile güçlü bir şekilde ilişkiliydi (rs1=-0,355, rs2=-0,373). Alda ölçeği BRIAN ve MEQ ile güçlü pozitif korelasyonlar ve depresif bölümlerle güçlü negatif korelasyonlar gösterdi (rs1=-0,355, rs2=-0,373, rs3=-0,274).
Sonuç: Bu çalışma, PP ve kronotipin BD-I'li bireylerde lityum yanıtını önemli ölçüde etkilediğini göstermektedir. MPP grubunun bozukluğun daha erken başladığı ve daha belirgin akşam özellikleri sergilediği bulunmuştur. Ek olarak, MPP grubunun lityuma daha güçlü bir yanıt gösterdiği görülmüştür.

Anahtar Kelimeler: Baskın polarite, bipolar bozukluk, depresyon, kronotip, lityum, mani

Introduction

Bipolar disorder (BD) is a chronic and debilitating mental illness affecting approximately 2% of the global general population worldwide with large inter-individual variability (1). Typically emerging during adolescence or early adulthood, BD is characterized by recurrent episodes of depression, mania, or hypomania, in addition to subthreshold symptoms occurring between these mood episodes (2). Notably, around 50% of patients experience a predominance of depressive episodes, while the other half tend to have more manic episodes (3). Despite common epidemiological assumptions suggesting that individuals with BD spend a greater duration in depression compared to mania, the clinical trajectories of BD can be quite heterogeneous (4).

To better understand this heterogeneity, researchers have advocated for a more nuanced classification of BD accounting for predominant polarity (PP), a concept

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introduced by Jules Angst in a study of 95 individuals with BD (5). This classification distinguishes between two main types: depressive (DPP), for patients primarily experiencing major depressive episodes, and manic (MPP), for those with a predominance of (hypo)manic episodes (6).

Research has established strong correlations between PP and various clinical variables. MPP is typically associated with male gender, BP type 1 (BD-1), psychotic features, early age of onset, and manic onset, while DPP correlates with depressive onset, a higher frequency of mood episodes, and a history of suicide attempts (7, 8). Additionally, a study exploring the influence of affective temperament found links between cyclothymic and hyperthymic temperaments and MPP, indicating that temperament may shape the clinical presentation across different PP groups (9).

Identifying an individual's PP may enhance personalized management strategies for BD. Evidence suggests that patients with MPP or DPP may demonstrate varied responses to both acute and long-term treatments, as well as differential effectiveness of psychopharmacological agents during stabilization phases (8, 10). Previous reviews have posited that MPP and DPP could affect nearly half of all individuals with BD, potentially correlating with distinct individual characteristics (11). However, despite the growing interest in this area, systematic analyses comparing rates and individual characteristics of MPP versus DPP remain absent.

Chronotype, defined as an individual's circadian preference, reflects the physiological organization of the circadian system (12). Several cross-sectional studies suggest that individuals with BD are more likely to identify as evening types compared to control populations, indicating this may be an underexamined factor associated with a more adverse course of illness(13). However, to date, no studies have investigated the relationship between PP and chronotype.

This study aims to address this gap by identifying the prevalence and clinical correlates—specifically focusing on lithium response—of different mood predominance types in BD, as well as assessing their association with chronotype.

Methods

This cross-sectional study included 80 patients (initially 89, but nine were excluded due to missing data of PP) with BB-1 in remission, aged 18–65, and regularly followed up in the outpatient clinic of the XXX clinic in the Department of Psychiatry at XXX University.

The patients included in the study had already been diagnosed with BD under the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) and were symptomatically in remission. At the time of the study, to exclude the presence of manic and depressive episodes Young Mania Rating Scale (YMRS) (14) and Hamilton Depression Rating Scale-17 (HAM-D) (15) were administered to all patients. Individuals with dementia, mild cognitive impairment, intellectual disabilities, shift work employment, and comorbid diagnoses of alcohol and substance abuse were excluded.

Initially, the demographic and clinical variables of the patients were recorded. This study used Colom's definition of PP to categorize patients (16). Based on this, MPP and DPP are defined as a lifetime ratio ≥2:1 of either hypomanic/manic episodes or depressive episodes, respectively. This restrictive definition splits patients into three categories (MPP, DPP, and undetermined PP). As no participants were classified as having undetermined PP, analyses were conducted only on participants with MPP or DPP.

The chronotypes of both groups were evaluated according to the Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN) (17) and the Morningness-Eveningness Questionnaire (MEQ) (18). The patients' response to lithium treatment was determined according to the Lithium Treatment Response Scale (the Alda scale) (19). Briefly, the scale measures the degree of improvement in the course of treatment (Criterion A) weighted against clinical factors considered relevant for determining whether or not the observed improvement is due to the treatment (Criteria B1–B5). The total score is calculated by subtracting the total B score from the A score. The degree of response for each patient is quantified with a score from 0 to 10 (total score). Patients with a total score equal to 7≥ are considered lithium responders, while patients with a total score e lower than 7 are considered non-responders.

This study was granted ethical approval by the Local Ethics Committee of XXX (Decision Number: 2024/685). It was conducted under the Declaration of Helsinki and the International Conference on Harmonization/Good Clinical Practice guidelines. Before participating in the study, written informed consent was obtained from all

participants after the nature of the procedures had been fully explained, and the local ethics committee approved the study.

Statistical Analysis

The data from the study were entered using the Statistical Package for the Social Sciences (SPSS) version 22. The Kolmogorov-Smirnov test was performed to determine whether the parameters followed a normal distribution. The Chi-square test was used to compare categorical variables, while the independent samples t-test was used to compare numerical variables between groups. Pearson correlation analysis was employed to assess the correlation between numerical variables. Statistical significance was defined as $p < 0.05$.

Results

The study was completed with 80 BB-1 patients. The mean age of the patients was 35.32 ± 11.39 years, with 61.25% being female (n=49). The PPs were 46.25% (n=37) DPP and 53.75% (n=43) MPP. No statistically significant difference was detected between the DPP and MPP groups in terms of gender, marital status, use of alcohol and smoking status, and other demographic parameters (p>0.05).

Also, no significant differences were found between DPP and MPP groups regarding types of pharmacotherapies, total duration of illness, or total episode count (p>0.05); however, the age of onset was 21.5 ± 6.6 years in the MPD group and significantly earlier in this group (p=0.009) Table 2 shows the demographic and clinical characteristics of groups.

Table 1. Comparison of demographic and clinical features under predominant polarity

Mean±SD/n (%)	DPP (n=37)	MPP (n=43)	χ2/t	p
Age (y)§	38.5±11.3	32.6±10.9	2.139	0.03
Gender/Female‡	23 (62)	26 (60)	0.034	0.85
Marital Status/Married‡	22 (59)	21 (48)	4.63	0.98
Education/University‡	11 (29)	15 (34)	1.20	0.75
Employment Status/Employed‡	16 (43)	21 (44)	0.03	0.95
Smoker/Yes‡	7 (18)	10 (23)	0.02	0.53
Alcohol use/Yes‡	1 (3)	2 (4)	0.03	0.95
Presence of Comorbid Medical Condition/Yes‡	7 (19)	5 (12)	0.98	0.25
Age of Onset (y)§	27.4±7.1	20.5±6.6	2.70	**0.04**
Duration of BPD(y)§	12.6±8.5	10.5±8.3	0.98	0.32
Number of Total Episodes§	6.2±4.7	4.9±5.2	1.13	0.26
Mania / Hypomania	2.2±1.9	3.6±3.1	-2.35	**0.02**
Depression	4.0±3.6	1.4±1.3	3.42	**0.01**
Number of Hospitalization§	6.2±3.7	5.1±3.2	1.23	0.31
Types OF Treatment‡	37 (100)	43 (100)	7.02	0.71
Lithium Monotherapy	12 (32)	6 (14)		
Lithium+AP	15 (40)	25 (58)		
Lithium+VLP+AP	3 (8)	6 (14)		
Others	7 (20)	6 (14)		
Psychotic Features/Yes‡	17 (46)	25 (58)	1.47	0.22
Family History for Psychiatric Disorders‡d	20 (54)	25 (58)	0.01	0.54

§= t-test; ‡= χ2 Test; SD=Standard deviation, P values in boldface indicate statistical significance, MPP: Manic predominant polarity, DPP: Depressive predominant polarity, AP: Antipsychotic, VLP: Valproic acid

When comparing two groups based on chronotype scale scores and Alda scale scores, the MPP group showed significantly higher scores on the BRIAN, MEQ, and Alda scales (t=-7.183, p=0.00; t=-3.968, p=0.00; t=-6.971, p=0.00, respectively) (Table 3).

Table 2. Comparison of psychometric properties under predominant polarity

Mean±SD/n (%)	DPP (n=37)	MPP (n=43)	χ2 / t	p
BRIAN	5.46±1.19	7.63±1.24	-7.18	**0.00**
MEQ	52.01±6.17	58.13±6.07	-3.968	**0.00**
ALDA	4.70±1.17	6.97±1.42	-6.971	**0.00**

§= t-test; ‡= χ2 Test; SD=Standard Deviation, P values in boldface indicate statistical significance, MPP: Manic Predominant Polarity, DPP: Depressive Predominant Polarity, BRIAN: Biological Rhythms Interview of Assessment in Neuropsychiatry, MEQ: Morningness-Eveningness Questionnaire, ALDA: Alda Lithium Response Scale

A weak positive correlation was found between manic episodes and BRIAN, while a strong positive correlation was observed with MEQ (respectively rs1=-0.355, rs2=-0.373). Additionally, strong positive correlations were noted between the Alda Scale and both BRIAN and MEQ, alongside strong negative correlations with the total number of depressive episodes (respectively rs1=-0.355, rs2=-0.373, rs4=-0.274) (Table 4)

Table 3. Pearson's product-moments correlation coefficients

	1	2	3	4	5	6	7
1. TDD	1.00						
2. NTE	**0.730****	1.00					
3. NM	**0.642****	**0.766****	1.00				
4. ND	**0.572****	**0.868****	**0.351****	1.00			
5. BRAIN	0.008	0.27	0.312*	-0.207	1.00		
6. MEQ	**0.323****	0,147	**0.357****	-0.500	**0.344****	1.00	
8. ALDA	-0.064	-0.159	0.178	**-0.352****	**0.324****	**0,429****	1.00

Note. * p <.05, ** p <.01, *** p <.001. TDD: Total Duration of Disease, NTE: Number of Total Episodes, NM: Number of mania/hypomania episodes, ND: Number of depression episodes, BRIAN: Biological rhythms interview of assessment in

neuropsychiatry, MEQ: Morningness-Eveningness Questionnaire, ALDA: Alda Lithium Response ScaleDiscussion

This study is the first to investigate the relationship between PP, chronotype, and lithium response in BD patients, thereby contributing to the existing literature by exploring the intricate associations among these variables. This cross-sectional study demonstrated a relatively balanced distribution between the DPP and MPP groups (46.25% vs. 53.75%), consistent with existing literature indicating considerable individual variability in the presentation of mood episodes. The absence of statistically significant differences between the groups concerning demographic factors such as marital status, education, and employment suggests that these variables do not effectively differentiate between DPP and MPP. A review of the literature reveals inconsistent data regarding the relationship between PP and demographic variables (20). Similarly, there were no statistically significant differences between groups for several clinical variables, including type of pharmacotherapy, total duration of illness, and total episode count. Although the literature presents conflicting evidence on this topic, some findings indicate a higher episode count in the MPP group and differences in the types of treatments utilized between the two groups. However, the small sample size may have contributed to these findings (21).

A notable difference emerged in the age of onset, which was significantly earlier in the MPP group (p=0.009). This finding aligns with prior research indicating an association between earlier onset and MPP, thereby reinforcing the consistency of our results with existing theories (7, 22). A meta-analysis conducted in 2024, which included 13 studies comprising 2,494 individuals with BD, provided strong evidence that individuals with MPP have an earlier onset of the disorder compared to those with DPP (10).

The most striking finding relates to the chronotype assessment. The MPP group exhibited significantly higher scores on both the BRIAN and MEQ scales, suggesting a greater inclination toward eveningness. This observation implies a potential connection between circadian rhythm preferences and PP in BD. Furthermore, the observed stronger correlation between the number of manic episodes and the eveningness scores supports the notion of a mechanistic relationship between circadian disruption and the expression of manic symptoms. Eveningness is associated with manic symptoms in BD (23) though null findings are more common (24). Additionally, based on social rhythm theory, it has been proposed that evening individuals experience greater disruptions in social rhythms and more sleep disturbances, correlating with increased manic episodes (25, 26).

The significant difference in lithium response, as indicated by the Alda scale, between the two groups is also critical. The MPP group exhibited substantially higher Alda scores, which suggests a potentially improved response to lithium treatment. Notably, the negative correlation between the Alda scale and the total number of depressive episodes, along with the positive correlation between the Alda scale and the total number of manic episodes, indicates that a higher frequency of manic episodes and a lower frequency of depressive episodes may be linked to a stronger lithium response. This finding, while not entirely surprising due to lithium's greater efficacy in managing manic episodes compared to depressive symptoms (27), warrants further investigation. Also, Scott et al. (2020) conducted a study involving 900 individuals diagnosed with BD-1, in which they identified MPP as a strong indicator of lithium response (28). Clinically, this finding is significant as it implies that PP could serve as a valuable predictor of treatment response, potentially informing personalized treatment strategies. Moreover, the strong positive correlations between the Alda scale and both BRIAN and MEQ scores further support the hypothesis that chronotype influences the effectiveness of lithium. Previous studies suggested a possible association between lithium response and chronotype in patients with BD (29), however, the predominance of cross-sectional studies limited causal inferences (23, 30, 31). Therefore, experimental studies are needed to establish causality in this field. Considering all these findings and evidence, it can be inferred that lithium has a stronger effect on individuals with MPP and evening chronotype. Further research with larger sample sizes is crucial to confirm this hypothesis.

While the study offers valuable insights, several limitations must be acknowledged. The cross-sectional design restricts the ability to establish causal relationships. The relatively small sample size, limited to BD-I patients in remission from a single clinic in Turkey, may affect the generalizability of the findings. Additionally, relying on self-report measures for chronotype assessment using BRIAN and MEQ may introduce potential biases. Furthermore, the study did not evaluate the possible effects of other pharmacotherapies on circadian rhythms.

Future research should focus on the following points:

1) Longitudinal studies to determine the temporal relationships between PP, chronotype, and lithium response.

2) Larger, more diverse samples (including BD-II and varied populations) to enhance generalizability.

3) Exploration of biological markers (e.g., genetic variations influencing circadian rhythms or lithium metabolism) to elucidate underlying mechanisms.

4) Mechanistic studies to investigate why MPP is associated with a better lithium response and earlier onset, potentially involving genetic and neurobiological examinations of circadian rhythms and mood regulation.

Conclusion

This cross-sectional study has demonstrated that PP and chronotype significantly influence lithium response in individuals with BD-I. It was found that individuals in the MPP group experience an earlier onset of the disorder and exhibit more pronounced characteristics of the evening chronotype. Additionally, the MPP group showed a stronger response to lithium, providing significant insights for personalizing treatment responses. These findings suggest that lithium has a greater effect on individuals with MPP and evening chronotype while emphasizing the need for validation in larger sample sizes and longitudinal studies. Overall, the results indicate that PP and chronotype are important factors in predicting treatment response, highlighting the necessity for further research in future studies.

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