Psychiatria Danubina, 2025 Vol. 37, No. 3, pp 322-330 https://doi.org/10.24869/psyd.2025.322 *Original research*

Optical coherence tomography findings of patients on bipolar disorder treatment: What does OCT say about lithium? A cross-sectional study

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received: 15. 01. 2025; revised: 14. 03. 2025; accepted: 18. 06. 2025

Summary

Background: *The aim of this study is to determine the effects of the bipolar disorder (BD) pharmacotherapy on the parameters of spectral-domain optical coherence tomography (SD-OCT) including retinal nerve fiber layer (RNFL), ganglion cell layer (GCL), inner plexiform layer (IPL), and choroidal thickness (CT).*

Subjects and Methods: *The patient group was divided into three subgroups according to the regular use of lithium (Li), sodium valproate plus valproic acid combination (SV-VPA), and any of the antipsychotics (AP). The OCT parameters were measured using the SD-OCT device.*

Results: *There were 36 subjects on Li treatment, 36 on SV-VPA treatment and 28 on AP treatment. In both eyes, RNFL subsectors, GCL, IPL were decreased in the BD group compared to the HC group, while CT increased ($p<0.05$). In the comparison between the BD subgroups, it was shown that RNFL subsectors, GCL, and IPL were higher in the Li group than in the SV-VPA and AP groups ($p<0.05$), and CT was similar between the BD subgroups ($p>0.05$). It was reported that there was a difference between smokers and non-smokers in the BD group only in terms of RNFL subsectors ($p<0.05$). In the BD group, a significant positive correlation was detected between disease duration, duration of relevant medication use and age and various RNFL parameters ($p<0.05$), while no relationship was found between GCL, IPL and disorder parameters ($p>0.05$).*

Conclusions: *This study compared the OCT parameters of euthymic state BD type 1 subjects with the HC group and showed that RNFL, GCL and IPL were decreased in the BD group, while CT was increased. It has been suggested that the use of Li may play a more effective role in protecting the RNFL subsectors, GCL and IPL than the use of SV-VPA and AP alone.*

Keywords: *Bipolar disorder, lithium, optical coherence tomography, neuroprotective effect, valproic acid*

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INTRODUCTION

Optical coherence tomography (OCT), which was initially used in the evaluation and follow-up of macular disorders and glaucoma, was later used in the investigation of neurological and neuropsychiatric disorders (Kalenderoğlu et al., 2016; Silić et al., 2020). Schizophrenia was the first psychiatric disorder studied via OCT (Çelik et al., 2016). Studies reporting that retinal nerve fiber layer (RNFL) decreases in schizophrenia and that this decrease is related to the duration of the disorder and symptom severity have inspired studies examining OCT parameters in bipolar disorder (BD) (Kalenderoğlu et al., 2016). In their first study in the literature where they examined BD subjects with OCT, Mehraban et al. (2016) reported that peripapillary RNFL decreased in patients with BD and that this decrease was related to the duration of the disorder. In the second study conducted in this field, Kalenderoğlu et al. (2016) showed that RNFL and ganglion cell layer (GCL) levels of BD subjects in the euthymic period were lower than the control group, that there was a significant relationship between GCL and disorder parameters, and that GCL started to decrease earlier than RNFL in BD. Khalil et al. (2017) demonstrated in their study, regardless of the type of BD episode, that ganglion cell complex (GCC), which is the combination of the three inner retinal layers including RNFL, GCL, and inner plexiform layer (IPL) (Jeoung et al., 2013), decreased in patients, but that this decrease was not related to the disorder parameters. In the following years, Garcia-Martin et al. (2019) found in their study on euthymic BD subjects that RNFL, GCL, and IPL decreased in BD; Khalil et al. (2019) compared BD subjects with healthy controls, regardless of the episode type, and found that GCC decreased; Orduna-Hospital et al. (2021) found that RNFL and GCL decreased in BD subjects; Liu et al. (2021) found that RNFL decreased in euthymic BD; Alici et al. (2019) found that RNFL and GCL were decreased in euthymic BD subjects

and reported that GCL may be more useful in early disorder prediction; Gokcinar et al. (2020) reported that GCC decreased in BD subjects in any episode; Qarni Fadil et al. (2020) found that RNFL decreased in euthymic BD; Ayık et al. (2022) found that RNFL was not different compared to healthy controls, GCL and IPL decreased, and there was a negative relationship between GCL and IPL and disorder parameters; Kilicarslan et al. (2022) stated that the RNFL, choroidal thickness (CT) and GCL, IPL volumes of BD subjects were not different from healthy controls; Torun et al. (2023) reported that CT and GCL of BD subjects decreased, but RNFL did not change; Onur et al. (2023) reported that GCC of euthymic BD subjects were reduced.

In the first studies examining OCT parameters in BD, findings were examined without specifying the episode type. Cokunlu et al. (2022) compared BD subgroups including euthymic, manic and depressive states with healthy controls for the first time and found that the GCCs of all patient groups were thicker than the controls. Additionally, there was no significant difference in GCC between patient subgroups. Kurt et al. (2023) compared BD subgroups including euthymic, manic, and depressive states with healthy controls and reported that RNFL decreased in the BD group and GCL, CT did not change. There were no differences in OCT parameters between BD states. It was reported that the RNFLs of patients using sodium valproate plus valproic acid combination (SV-VPA) were lower than the control group and those using lithium (Li), and there was no difference in OCT parameters between the Li and control group.

Sánchez-Morla et al. (2021) approached the BD-OCT relationship from a different perspective, investigated whether artificial intelligence could be used in OCT examinations, and stated that IPL and GCL were the best markers in distinguishing BD from healthy controls.

As the number of BD-OCT studies in the literature increased, researchers examined data from case-control studies in meta-analyses. In a meta-analysis, Lizano et al. (2020) found that peripapillary RNFL, peripapillary GCL, and IPL were decreased in BD subjects compared to healthy controls. Prasannakumar et al. (2023) found in their meta-analysis that RNFL decreased in BD.

While all studies examining OCT parameters in BD were conducted cross-sectionally, Satue et al. (2022) shared their five-year follow-up findings. Accordingly (Satue et al., 2022), peripapillary RNFL thickness in BD subjects gradually decreased compared to the control group. Additionally, in the same study (Satue et al., 2022), a negative correlation was found between GCL thickness and disease duration.

The possible effects of drugs used in the treatment of BD on OCT parameters have been investigated in a limited number of studies. Gokcinar et al. (2020) showed that GCC was reduced in the BD group compared to healthy controls. In the study in which 42 subjects were on lithium and 28 subjects were on SV-VPA treatment, no difference was found in terms of OCT parameters between Li and SV-VPA subjects. However, the inclusion of subjects in any BD state in this study and the possible effect of BD state including euthymic, manic, depressive on the results is an important limitation. Altun et al. (2020) compared the RNFL of 46 euthymic BD subjects according to the medication they used and reported that the antipsychotic (AP) level could be a negative predictor for the RNFL subregions in BD, and the serum SV-VPA level could be a positive predictor for the RNFL subregions. Kurt et al. [18] found that the RNFL of 67 BD type 1 (manic episode 20, depressive episode 24, and euthymic 23) subjects, 26 of whom were on Li treatment, was lower than healthy controls. Kurt et al. (2023) reported that there was no difference in OCT parameters between BD states. According to the study of Kurt et al. (2023), the patients on SV-VPA had significantly lower RNFL thicknesses compared to the control and the Li groups, and all chorioretinal measurements were similar between the Li and the control groups. The most important limitation of Kurt et al. (2023)'s study is that they did not exclude the effect of different medication use in the same episode when comparing episode types, and the effect of different episodes on the same medication when comparing the effect of the medication. On the other hand, in all three studies, only the RNFL was examined, the GCL, IPL and CT layer were not examined. The aim of this study is to compare euthymic BD subjects on Li, SV-VPA and AP treatment with healthy controls. Our hypothesis is that the effect of treatment on OCT parameters may be different.

SUBJECTS AND METHODS

This was a cross-sectional study of patients at the Adiyaman Training and Research Hospital. Ethics approval was provided by the Adiyaman University Ethics Committee (Date: 20.03.2019, Number: 2019/2-14).

The patients who admitted to the Adiyaman Training and Research Hospital psychiatry outpatient clinic between 01.01.2016 – 31.12.2018 and met the diagnosis of BD type 1 (BD-1) according to the diagnostic and statistical manual of mental disorders, fifth edition (DSM-5) (American Psychiatric Association, 2013) were included. The healthy control (HC) group consisted of hospital staff who applied to the ophthalmology clinic once a year for health screening and had no ophthalmological problems.

The information received from patients is verified through the patient's relatives. In addition, the information received from patients and their relatives is subject to final verification via e-nabiz. *e-nabiz*, the national patient registration system, is a database where all medical histories of patients can be accessed.

Both groups consisted of subjects between the ages of 18-65. While there was no additional psychiatric disorder according to the structured clinical interview for DSM-5 in the patient group, there was no any psychiatric disorder in the HC group. There was no intellectual disability among the subjects. There were no subjects who had used alcohol or illegal substances for the last month, and one subject each with a history of alcohol or substance use disorder was not included in the groups. There was no BD subject with a history of electroconvulsive therapy. None of the subjects had a history of brain surgery or brain trauma, epilepsy or other neurological diseases.

There was no diagnosis of ophthalmological disease in either group. Systemic diseases that may affect the results, such as hypertension, diabetes mellitus, and inflammatory disease, were selected as exclusion criteria for both groups. Those with additional psychiatric disorders according to structured clinical interview for DSM-5 were excluded from the study. Subjects with BD diagnosis less than 5 years ago were not included in the study. Subjects diagnosed with BD and treated for more than 2 years were included in the study. BD subjects in manic and depressive episodes were excluded, and subjects in a euthymic state for more than 6 months were included. Subjects who used medications, including painkillers, antibiotics, and muscle relaxants, other than mood stabilizers and APs, in the last one month were not included in the study.

All patients had been using a fixed dose of medication for at least 3 months. Some of the patients were using Li at a dose of 900 mg/day and some at a dose of 1200 mg/day. The Li level of the subjects was between 0.8-1.1 mEq/L. SV-VPA doses of the subjects ranged between 750-1500 mg/day. The SV-VPA level of the subjects was between 70-90 mcg/mL.

Young Mania Rating Scale (YMRS) was used in this study. YMRS was developed in order to measure the severity of manic symptoms. It is a scale including 11 items, each containing five degrees of severity that is also valid and reliable in Turkey (Karadağ et al., 2002). Among the scores, <13 scores is accepted as normal, 13-19 scores is minimum severity, 20-26 scores is low, a score between 27 and 38 is evaluated moderate, and a score higher than 38 is accepted as severe.

IPL, GCL, CT, and RNFL sub-sectors (nasal (N), temporal (T), nasal-inferior (NI), nasal-superior (NS), temporal-inferior (TI), temporal-superior (TS), and global (mean)) were measured using the SD-OCT device (SpectralisTM OCT, Version 6.0, Heidelberg Engineering, Germany). Two independent researchers who had

Table 1 Sociodemographic and clinical parameters of subjects

Variables		BD-1 (n=100)	HC (n=50)	p value
Age (years)		39.92±1.02	38.17±1.98	0.452
Gender	**Female**	48 (48.0%)	32 (64.0%)	0.083
	Male	52 (52.0%)	18 (36.0%)	
Marital status	**Married**	58 (58.0%)	42 (84.0%)	0.005*
	Single	33 (33.0%)	6 (12.0%)	
	Widow	9 (9.0%)	2 (4.0%)	
Educational status	**No education**	6 (6.0%)	5 (5.0%)	0.010*
	Primary	38 (38.0%)	7 (7.0%)	
	Secondary	11 (11.0%)	14 (14.0%)	
	High	31 (31.0%)	16 (16.0%)	
	University	14 (14.0%)	8 (8.0%)	
Working status	**Actively working**	27 (27.0%)	33 (66.0%)	0.001*
	No working	73 (73.0%)	17 (34.0%)	
Smoking status	**Yes**	41 (41.0%)	8 (16.0%)	0.003*
	No	59 (59.0%)	42 (84.0%)	

*p<0.05; Independent samples t-test and Chi-square test was used in statistical analysis.
Abbreviations: BD-1=Bipolar disorder type 1, HC=Healthy control

no prior knowledge of the patient or the control participants examined the OCT measurements. OCT procedure was performed on both groups between 09.00 and 11.00 while they were fasting. All subjects took their last psychotropic dose at 21.00 and did not use any medication in the morning.

SPSS 21.0 package program was used for data analysis. The mean ± standard deviation and percentages were used as descriptive statistics. The Chi-square test was used to compare categorical variables. The normality of the data was tested using the Kolmogorov-Smirnov test. An independent samples t-test was used to compare two normally distributed variables, One-way ANOVA was used to compare normally distributed variables more than two, Mann-Whitney U test was used to compare two non-normally distributed variables, and Kruskal Wallis-H test was used to compare non-normally distributed variables more than two. A value of less than 0.05 (p-value) was considered statistically significant.

RESULTS

Sociodemographic and clinical variable were shown on Table 1 and Table 2.

OCT parameters of patient (n=100) and control (n=50) groups were compared (Table 3).

OCT parameters of patient subgroups were compared (Table 4).

The BD-1 group was compared within itself according to smoking status. In the BD-1 group, right T (p=0.003), TI (p=0.009), mean (p=0.031) subsectors and left T (p=0.012) subsector of RNFL were significantly lower in smokers than in non-smokers. In BD-1 group, the remaining OCT parameters were similar between smokers and nonsmokers. There was no difference in OCT parameters between smokers and non-smokers in the HC group (p>0.05).

OCT parameters of Li users were compared according to their smoking status. In the Li group, smokers' right T

Table 2 Features of patients diagnosed with BD

Parameters		**Li (n=36) % mean±SD**	**SV-VPA (n=36) % mean±SD**	**AP (n=28) % mean±SD**	**p value**
Gender	**Female**	19 (52.8%)	19 (52.8%)	10 (35.7%)	0.122
	Male	17 (47.2%)	17 (47.2%)	18 (64.3%)	
Marital status	**Married**	23 (63.9%)	21 (58.3%)	14 (50.0%)	0.072
	Single	10 (27.8%)	12 (33.3%)	11 (39.3%)	
	Widow	3 (8.3%)	3 (8.3%)	3 (10.7%)	
Educational status	**No education**	3 (8.3%)	2.(5.6%)	1 (3.6%)	0.178
	Primary	13 (36.1%)	15 (41.7%)	10 (35.7%)	
	Secondary	5 (13.9%)	3 (8.3%)	3 (10.7%)	
	High	12 (33.3%)	9 (25.0%)	10 (35.7%)	
	University	3 (8.3%)	7 (19.4%)	4 (14.3%)	
Smoking status	**Yes**	15 (41.7%)	15 (41.7%)	11 (39.3%)	0.023*
	No	21 (58.3%)	21 (58.3%)	17 (60.7%)	
Family BD history	**Yes**	16 (44.4%)	17 (47.2%)	16 (57.1%)	<0.001*
	No	20 (55.6%)	19 (52.8%)	12 (42.9%)	
Age (years)		39.72±1.92	40.88±1.61	38.92±1.74	0.859
Duration of medication use		8.91±5.18	7.36±3.09	6.14±2.85	0.028*
Number of episode		6.66±4.95	6.83±4.02	5.03±2.71	0.185
Duration of BD		17.05±11.93	16.94±8.80	15.64±9.88	0.890
Number of hospitalization		3.5±4.42	3.8±3.13	2.8±2.49	0.256
YMRS		9.97±4.31	13.00±5.77	10.03±4.00	0.056

*p<0.05; Chi-square test was used in statistical analysis. **Abbreviations:** Li=Lityum, SV-VPA=Sodium valproate plus valproic acid combination, AP=Antipsychotic, BD=Bipolar disorder, SD=Standard deviation, YMRS=Young Mania Rating Scale

Table 3 Comparison of OCT parameters of patient and control groups

Parameters	Right Eye			Left Eye		
	BD-1 (mean±SD)	HC (mean±SD)	p value	BD-1 (mean±SD)	HC (mean±SD)	p value
NS	111.37±22.79	114.70±20.44	0.385[a]	121.46±27.33	126.96±20.48	0.211[a]
N	79.40±16.58	83.46±14.6	0.063[b]	72.86±14.66	78.44±12.88	0.005[b*]
NI	117.41±27.41	128.71±24.94	0.010[a*]	117.08±29.04	125.12±25.42	0.049[a*]
TS	139.3±21.81	147.1±8.55	0.037[a*]	137.81±25.64	147.32±14.57	0.002[b*]
T	72.02±10.76	74.58±8.66	0.146[a]	71.74±13.45	72.12±9.22	0.648[b]
TI	147.02±21.04	153.26±17.48	0.073[a]	146.77±26.46	154.14±18.67	0,010[b*]
Mean	102.23±11.2	107.1±8.55	0.004[a*]	101.42±13.89	107.86±9.18	<0.001[b*]
CT	317.05±79.44	248.8±30.6	<0.001[b*]	313.32±86.37	249.16±31.67	<0.001[b*]
GCL	1.13±0.10	1.20±0.48	<0.001[b*]	1.13±0.08	1.20±0.04	<0.001[b*]
IPL	1.20±0.04	1.38±0.07	<0.001[b*]	0.93±0.06	0.96±0.05	0.029[a*]

*p<0.05; [a]Independent samples t-test and [b]Mann-Whitney U test was used in statistical analysis. **Abbreviations:** OCT=Optical coherence tomography, BD-1=Bipolar disorder type 1, HC=Healthy control, SD=Standard deviation, NS=Nasal-superior, N=Nasal, NI=Nasal-inferior, TS=Temporal-superior, T=Temporal, TI=Temporal-inferior, CT=Choroid thickness, GCL=Ganglion cell layer, IPL=Inner plexiform layer

Table 4 Comparison of OCT parameters according to drug subgroups of the patient group

Parameters	Right Eye				Left Eye			
	Li (mean±SD)	SV-VPA (mean±SD)	AP (mean±SD)	p value	Li (mean±SD)	SV-VPA (mean±SD)	AP (mean±SD)	p value
NS	115.11±24.69	110.19±22.81	108.07±20.18	0.473[a]	127.36±25.57	122.05±31.57	113.1±18.48	0.085[a]
N	82.80±18.71	78.75±15.73	75.85±14.30	0.276[b]	75.11±13.77	77.44±17.09	69.21±11.92	0.206[b]
NI	122.52±27.52	113.66±29.93	115.64±27.85	0.044[a*]	122.69±25.96	112.97±35.78	115.14±22.15	0.166[a]
TS	143.86±23.44	137.50±24.31	135.75±14.84	0.090[a]	139.61±18.07	135.83±36.44	138.03±16.0	0.464[b]
T	72.86±12.56	72.08±10.37	70.85±8.86	0.438[a]	72.16±15.51	73.52±14.27	68.89±8.61	0.627[b]
TI	154.75±21.27	141.91±21.38	143.64±17.86	0.008[a*]	152.11±23.14	143.88±34.04	143.6±17.65	0.093[b]
Mean	106.02±11.40	100.5±11.56	99.53±9.34	0.002[a*]	105.19±10.22	100.16±18.77	98.17±9.15	0.004[b*]
CT	317.42±80.05	307.72±80.54	328.5±78.56	0.610[b]	318.91±85.97	292.5±80.73	332.89±77.22	0.076[b]
GCL	1.17±0.07	1.11±0.12	1.10±0.08	0.002[b*]	1.17±0.07	1.12±0.08	1.10±0.08	0.005[b*]
IPL	0.98±0.19	0.90±0.18	0.91±0.05	0.009[b*]	0.96±0.07	0.91±0.06	0.91±0.05	<0.001[a*]

*p<0.05; [a]One-way ANOVA and [b]Kruskal Wallis test was used in statistical analysis. **Abbreviations:** OCT=Optical coherence tomography, Li=Lityum, SV-VPA=Sodium valproate plus valproic acid combination, AP=Antipsychotic, SD=Standard deviation, NS=Nasal-superior, N=Nasal, NI=Nasal-inferior, TS=Temporal-superior, T=Temporal, TI=Temporal-inferior, CT=Choroid thickness, GCL=Ganglion cell layer, IPL=Inner plexiform layer

(p=0.039) and mean (p=0.025) subsectors of RNFL were lower than non-smokers. In the Li group, smokers' left T (p=0.033) and mean (p=0.049) subsectors of RNFL were lower than non-smokers. The remaining parameters were similar between smokers and non-smokers (p>0.05).

OCT parameters of SV-VPA users were compared according to their smoking status. In the SV-VPA group, smokers' right T (p=0.019), TI (p=0.046) and mean (p=0.049) subsectors of RNFL were lower than non-smokers. In the SV-VPA group, smokers' left T (p=0.033) and mean (p=0.049) subsectors of RNFL were lower than non-smokers. In the SV-VPA group, smokers' left T (p=0.008) and TI (p=0.023) subsectors of RNFL were lower than non-smokers. In SV-VPA group, the remaining parameters were similar between smokers and non-smokers in both eyes (p>0.05).

OCT parameters of AP users were compared according to their smoking status. There was no significant

difference in OCT parameters between smokers and non-smokers in both eyes (p>0.05).

In the patient group (n=100), a significant relationship was found between age and right NS (r=0.305, p=0.002), TS (r=0.222, p=0.026) and mean (r=0.231, p=0.021) subsectors of RNFL, between disorder duration and right NS (r=0.204, p=0.042) subsector of RNFL, between the duration of relevant medication and the right NS (r=0.212, p=0.034), N (r=0.239, p=0.017), TI (r=0.203, p=0.043), and mean (r=0.243, p=0.015) subsectors of RNFL, while no significant difference was found between YMRS, number of episodes and OCT parameters.

In the right eye of the Li group, no significant difference was found between age, YMRS, number of episodes, duration of disorder, duration of relevant medication and OCT parameters. In the left eye of the Li group, a significant relationship was found between age and T subsector (r=0.347, p=0.038) of RNFL, between number of episode and CT (r=-0.379, p=0.023), between TS (r=0.463, p=0.004), T subsectors (r=0.368, p=0.027) of RNFL, while no significant difference was found between YMRS, duration of disorder, number of episodes and OCT parameters.

In the left eye of the SV-VPA group, a significant relationship was found between age and right NS subsector of RNFL (r=0.439, p=0.007), between duration of disorder and right NS subsector of RNFL (r=0.403, p=0.015).

In the right and left eye of the AP group, no significant difference was found between age, YMRS, number of episodes, duration of disorder, duration of relevant medication and OCT parameters.

DISCUSSION

There are many studies in the literature examining the level of RNFL in subjects diagnosed with BD. Starting from the study of Mehraban et al. (2016), which was the first study on this topic, dozens of studies conducted until today have reported that RNFL subsectors have decreased in BD. As the neural nerve structure leaving the brain loses its myelin sheath, it enters the retinal structure. Thus, it is considered that possible neurodegeneration in retinal nerves may develop faster than the substantia grisea of the brain. RNFL is structurally similar to the substantia grisea of the brain. Changes in the thickness of RNFL is caused by the axonal damage in the retinal nerve tissue. As a result of the damage occurred in minimum 50% of ganglion cells, changes in RNFL thickness may occur and it becomes observable (Celik et al., 2016). When the global subsector of RNFL in the present study was considered, it was found that there was a significant thinning in both eyes in the BD-1 group when compared to the HC group. Also, when the subsectors of RNFL were considered, it was observed that there was partial thinning in the BD-1 group when compared to the HC group, and such thinning was also significant in some subsectors. In addition, this decrease in RNFL in the BD-1 group was also found to be related to the duration of the disorder, but not to the severity of the disorder. The fact that the BD-1 group was selected from subjects in the euthymic state and the patients' disorder severities were low and similar may explain this finding.

Although there are exceptions (Kurt et al., 2023), there are many studies showing that GCL and IPL are also reduced in BD-1 (Garcia-Martin et al., 2019; Orduna-Hospital et al., 2021; Alici et al., 2019). According to the study of Kalenderoğlu et al. (2016), there was a significant relationship between GCL and disorder parameters, and that GCL started to decrease earlier than RNFL in BD. The study of Ayık et al. (2022) is also important as it shows that GCL and IPL are affected earlier than RNFL. Studies have also shown that GCL and IPL are associated with clinical features of BD. Ayık et al. (2022) found that there was a negative relationship between GCL and IPL and disorder parameters. In the present study, it was shown that GCL and IPL were reduced in BD-1, consistent with the majority of studies in the literature.

Choroid is one of the richest tissues in the human body in terms of vascularization and plays important roles in the oxygenation and nutrition of the outer retina, thermal regulation, positional state, removal of retinal residues, and in the secretion of growth factors (Parver, 1991; Jurišić et al., 2020). Thus, it can be easily affected by any systemic event that may affect the blood flow (Karadağ et al., 2018). In the present study, it was found that the CT measured in both eyes was significantly increased in the patients with BD without any systemic diseases that could impair the vascular structure or affect the blood flow. Recent studies have suggested that the mechanisms involved in the pathogenesis of mental disorders may be associated with neuroinflammation (Tsai et al., 2018). Evidences regarding the presence of the pathogenic role of microglia-induced neuroinflammation in psychiatric disorders increase every passing day. It is considered that the main reason for the increase in the CT may be caused by the inflammatory process in BD. As a matter of fact, it is a universal consent that the inflammatory process develops psychiatric disorders. Therefore, it is thought that when there is an active inflammation, it increases the blood flow in the tissue and causes the choroidal structure to thicken (Karadağ et al., 2018).

The changes in the dopamine and serotonin levels cause changes in intracellular signal generators such as glycogen synthase kinase-3 beta (GSK-3β) together with the changes in central nervous system. Recent studies on

BD conducted on genetically modified mice showed the differences in GSK-3β depending on the changes in the electroretinogram response of the rods, and such changes were also observed in high-risk mice offspring of the patients with BD. Thus, it is suggested that the changes in dopamine and serotonin levels may cause changes in the retinal layer in the patients with BD. Literature regarding the structural retinal analysis in the patients with BD is quite novel and there is limited number of studies showing axonal loss in the retina of such patients (Mehraban et al., 2016; Khalil et al., 2017; Chen et al., 2014).

The main purpose of this study was to examine the OCT parameters of treatment subgroups. The most striking finding of our study is that the retinal parameters of the patients using Li were relatively preserved compared to other treatment subgroups. In vitro and ex vivo studies have stated that Li has long-lasting neurotrophic effects, and some of the changes in the brains of the rodents and human neuronal cells are protective against cell death (Hellweg et al., 2002). It is also known that it has neuroprotective effects against various damages including glutamate-induced excitotoxicity, ischemia-induced neuron damage, radiation-induced brain damage, and neurodegenerative conditions (Chiu & Chuang, 2010). However, despite the underlying mechanisms of neuroprotective effects are not known yet, it is considered that this is mediated by multiple ways such as transcriptional regulation, inhibition of apoptosis, and the changes in neurogenesis. As an example, it is shown that lithium has a critical role in the neuroprotective, neurotrophic, anti-inflammatory, and neurogenic effects by increasing the activity of the transcription factor activator protein-1 and phosphorylated cyclic adenosine monophosphate response element binding protein-1 in cultured nerve cells and different parts of the brain, and by inhibiting glycogen synthase kinase-3 beta (Contestabile et al., 2013; Paratcha & Ledda, 2008; Kang et al., 2012). Also, it has been shown that it inhibits cell apoptosis by regulating proapoptotic p53, B-cell lymphoma 2, B-cell lymphoma 2-associated X-protein, caspase, heat shock protein 70, and cytochrome-c release (Zanni et al., 2015; Ren et al., 2003; Chen & Chuang, 1999).

In the literature, OCT parameters of Li users with a diagnosis of BD have been investigated in a limited number of studies. In the study of Gokcinar et al. (2020), GCC of Li and SV-VPA users was found to be similar. The fact that CT was not investigated and episode discrimination was not performed in this study is a serious limitation. In the study by Kurt et al. (2023) in which they examined only RNFL, drug groups were compared without distinguishing between episodes. The most important feature that distinguishes our study from other studies is that only subjects in the euthymic state were included in this study. Findings have been found to support studies showing that Li has neuroprotective properties. Li use was associated with lower reductions in RNFL subsectors, GCL, and IPL, but there were no differences in CT between medication subgroups.

The fact that only subjects in the euthymic state were included, that GCL, IPL and CT were examined in addition to RNFL, that the diagnosis of BD was made taking into account DSM-5, and that all subjects were stated to be BD type 1 are some of the strengths of our study.

The most important limitation of this study is its cross-sectional nature. Further prospective studies are required. The possible effect of medicines that can be used short-term during BD-1 treatment is not excluded. It is known that many of the patients using Li and SV-VPA also use AP. In our study, the APs used by the patients in addition to Li and SV-VPA were not presented. However, it should not be forgotten that this is a common limitation for all studies with similar designs in the literature. As a matter of fact, subjects of BD followed only by a mood stabilizer medication are quite rare. Since it is not possible to discontinue medications other than mood stabilizers while performing this study, it is not easy to overcome this limitation. A possible effect of smoking on the results could not be excluded.

CONCLUSION

This study shows that RNFL, GCL, IPL decreased and CT increased in BD-1 compared to the control group. Lithium use is associated with a lower reduction in RNFL, GCL, and IPL than use of SV-VPA and AP alone. Further studies are needed to show whether this situation is related to the neuroprotective properties of Li.

Ethical Considerations: Does this study include human subjects? YES

Conflict of Interest: No conflict of interest.

Funding Sources: The authors received no funding from an external source.

Authors Contribution: Dr. Aslı Egeli-Karataş served as lead for for conceptualization, formal analysis and writing, and contributed for investigation. Dr. Aysun Kalenderoğlu served as lead for conceptualization, methodology and investigation, and contributed to formal analysis and writing. Dr. Mehmet Hamdi Örüm served contributed to formal analysis and writing (initial draft & review). Dr. Ayşe Sevgi Karadağ contributed for formal analysis, supervision and writing.

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