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ORIGINAL ARTICLE

Efficacy of light therapy on non-seasonal depression and inflammatory markers

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Abstract
Background and objectives: The evidence for efficacy of light therapy in non-seasonal depression remains controversial. The primary aim of this study was to investigate the efficacy of bright light therapy when it was combined with antidepressant treatment in the course of major depressive disorder without seasonal pattern. The secondary aim was to assess the inflammatory response to bright light therapy.
Methods: Patients who had a Hamilton Depression scale score of 17 or above, who were receiving antidepressant monotherapy for at least 4 weeks were included in the study ($n = 74$). Patients were assigned to either antidepressant monotherapy ($n = 40$) or combination of antidepressant and bright light therapy ($n = 34$). The severity of the depression and suicidal ideation was evaluated by Hamilton Depression Scale and The Beck Scale for suicide ideation. The effect of light therapy on inflammatory markers was investigated based on the neutrophil/lymphocyte ratio, platelet/lymphocyte ratio, platelet counts and mean platelet volume. Their clinical state was monitored at the baseline, 1 day and 2 weeks after treatment.
Results: Independent from treatment group, patients showed decreased depression and suicidal ideation scores after treatment. The results of statistical analysis of time × group interactions regarding depression and suicidal ideation scores also showed significant differences between groups over time. For inflammatory markers, only the lymphocyte count showed significant difference between groups over time. Except platelet/lymphocyte ratio, all inflammatory markers showed significant alterations with time independent from treatment arm.
Conclusion: Combining light therapy with oral antidepressants can be helpful in non-seasonal depression as well.

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Introduction

Depression is a common psychiatric disorder affecting over 300 million people around the world and by the year 2010, it is expected to be the second most common cause of disability following the cardiovascular diseases.[1,2] Despite a wide range of treatment options including antidepressants and psychotherapy, many patients are still resistant to treatment or they develop adverse effects causing treatment interruption.[3] Almost half of the patients do not respond to first-line treatments adequately, and after an 8-weeks of antidepressant treatment, only 35–40% of patients experience remission of symptoms.[4,5] Therefore, alternative treatment modalities are required for the management of depressive symptoms.

Bright light therapy (BLT) is a choice of treatment which is used mostly to treat seasonal affective disorder (SAD). It comprises exposure to artificial bright light for a given period of time particularly in the mornings.[6] Patients with non-seasonal depression also experience symptoms of irregular sleep–wake patterns, diurnal mood swings, altered circadian patterns of hormones and core body temperature problems which can be associated with circadian abnormalities. These abnormalities provide a rationale for the use of light therapy in non-seasonal depression.[7–9]

Previous studies have investigated the clinical potential of light therapy in patients with non-seasonal depressive disorders.[10–12] However, the results from these studies are contradictory. A new meta-analysis and systematic review resulted a beneficial effect of light therapy in non-seasonal depression but the overall quality of the evidence was poor due to high risk of bias and inconsistency. So, more studies are needed in order to address this significant gap.

There is increasing evidence from studies which support the role of inflammatory response and immune system in the pathophysiology of mood disorders.[13–15] Neutrophil to lymphocyte ratio (NLR) and platelet to lymphocyte ratio (PLR) are simple, relatively cheap and reproducible parameters which can easily be obtained from white blood cell essay.[16] A recent meta-analysis reported that patients with major depressive disorder (MDD) had higher NLR as compared to healthy controls and overall results supported the hypothesis that NLR and PLR might be useful to detect the inflammatory activation seen in mood disorders.[16] The relationship between major depression and increased platelet activity has also been previously reported by several studies. They found that increased mean platelet volume (MPV) is associated with the diagnosis of major depression.

The primary aim of this study was to investigate the efficacy of BLT when it was combined with antidepressant treatment in the management of patients with a current depressive episode in the course of MDD without seasonal pattern. The secondary aim was to assess the inflammatory response to BLT in these patients. So, treatment response was evaluated with both clinical outcomes (Hamilton Depression Scale and The Beck Scale for suicide ideation) and inflammatory markers (NLR, PLR, MPV).

Patients and methods

Patients

This study was approved by Çukurova University School of Medicine (ÇUSM) Ethics Committee. All patients signed written informed consent before participation into the study. Patients were recruited from the psychiatric inpatient clinics of Balcali Hospital, Adana, Turkey between March and October 2017. All patients were diagnosed with MDD based on Diagnostic and Statistical Manual of Mental Disorders (DSM)-5 diagnosis and classification system. Patients between 18 and 65 years of age, who had a Hamilton Depression Scale (HDS) score of 17 or above, who were receiving selective serotonin reuptake inhibitor (SSRI) or serotonin-norepinephrine reuptake inhibitor (SNRI) monotherapy for at least 4 weeks were included in the study. 86 patients who met the inclusion criteria went on with a clinical interview. Patients who had comorbid psychiatric disorders ($n = 3$), or who were using antipsychotics or receiving electroconvulsive therapy (ECT) ($n = 4$) were excluded from the study because the efficacy of light therapy and antidepressant drugs on depression could not be clearly understood in these patients. Patients who had chronic inflammatory disease ($n = 2$), who had a history of smoking or alcohol use disorder ($n = 3$) were also excluded because of the possible effects of these situations on inflammatory markers. Thus, final analysis included 74 depressive patients, 40 of whom received antidepressant (AD) monotherapy and 34 patients received combination of AD + BLT. The patients were randomized according to their admission order. All of the patients completed all of the assessments and no drop-out was occurred.

Procedure

Socio-demographical information was collected with a form which was created by the investigators. The severity of the depression was evaluated by HDS and suicidal ideation was evaluated by The Beck Scale for suicide ideation (BSSI).

Blood samples were drawn from the antecubital vein at 06.30 in the morning after 12 h fasting before the treatment. Follow up samples were collected with the same method just one day and two weeks after the light therapy. The effect of light therapy on inflammatory markers was investigated based on the neutrophil, lymphocyte, and platelet counts. NLR, PLR were calculated by using these values. The clinical scales and laboratory tests were performed before treatment, one day after treatment and two weeks after treatment.

BLT was applied in a sitting position at a distance of 40 cm from the patient and a 60-degree angle for 60 min for 14 days with a glance at the light every minute using a light intensity of 10,000 lx with a device designed for medical use (Klarstein, Model 10006251). Treatment protocol was determined based on instructions provided by the manufacturer of the light therapy device. We woke up all patients (both AD + BLT and AD monotherapy groups) at 06.30 am and the treatment was carried out every morning from 07:00 to 07:30, at least 30 min after patient's wake up.

Table 1 Socio-demographical and clinical characteristics of participants.

	Treatment group		*p*
	BLT + AD	AD monotherapy	
Gender			
Female	22 (64.71)	28 (70)	0.628[a]
Male	12 (35.29)	12 (30)	
Marital status			
Single	7 (20.59)	4 (10)	0.202[a]
Married	27 (79.41)	36 (90)	
Employment			
Employed	4 (11.76)	5 (12.5)	0.999[a]
Unemployed	30 (88.24)	35 (87.5)	
Medical disease			
Yes	9 (26.47)	9 (22.5)	0.692[a]
No	25 (73.53)	31 (77.5)	
Medication compliance			
Yes	34 (100)	35 (87.5)	0.058[a]
No	0 (0)	5 (12.5)	
Social support			
Yes	26 (76.47)	37 (92.5)	0.053[a]
No	8 (23.53)	3 (7.5)	
The Beck Scale for suicide ideation score (Pretreatment)	4 (2–16)	6.5 (4–9.5)	0.095[b]
Hamilton Depression Scale Score (Pretreatment)	21.38 ± 5.48	20.10 ± 2.64	0.219[c]

[a] Fisher Exact test. Descriptive statistics presented as number (percentage).
[b] Mann Whitney *U* test. Descriptive statistics presented as median (Q1 – Q3).
[c] Independent Samples *t*-test. Descriptive statistics presented as mean ± standard deviation.

During the BLT, the patients continued to take their antidepressants without any change in dosage or medication time. All the patients slept an average of 7–8 h/day and no sleep restriction has been applied to avoid any possible confounding situation. As all the patients were hospitalized at inpatient psychiatry clinics at the time of the study, we could strictly control their drug adherence and sleep durations. No medication that has the potential to alter inflammatory marker levels was given to the patients.

Statistical analysis

74 depressed patients were enrolled to the study. Fischer exact test, Mann–Whitney *U* test and independent samples of *t* test are used in order to compare the socio-demographical and clinical characteristics of two groups. The outcome parameters (inflammatory markers and BSSI and HAMD scale) were evaluated before treatment, after treatment and 2 weeks after treatment. Two-way repeated measures of analysis of variance (ANOVA) was used for comparison of time dependent alterations in outcome parameters between two groups. For outcome parameters that violated the ANOVA assumptions, an R package called npaRLD for non-parametric longitudinal data was used in the analysis. The limit for statistical significance was accepted as $p < 0.05$. SPSS Statistics, version 23.0 and R version 3.0 were used to perform the analyses.

Results

The socio-demographical and clinical characteristics of two groups are presented in Table 1. There were no significant differences between groups in terms of gender, marital status, employment status, history of ECT, medication compliance, social support and scores of HDS and BSSI before treatment ($p > 0.05$).

Time dependent alterations in HDS score, BSSI score and serum inflammatory marker levels are presented in Table 2. Independent from treatment group, patients showed decreased HDS and BSSI scores after treatment ($p < 0.001$). Independent from treatment group, serum levels of inflammatory markers also showed significant alterations after treatment. Neutrophil count increased one day after treatment and it decreased significantly 2 weeks after treatment ($p = 0.003$) whereas lymphocyte count increased gradually ($p < 0.001$); thus, NLR decreased as a result after treatment ($p < 0.001$). Two weeks after the treatment, MPV was found significantly decreased ($p < 0.001$) among all patients. Independent from treatment group, there was no significant difference in PLR over time ($p > 0.05$).

Table 2 Time dependent alterations of outcome parameters with time × group interaction results.

	All patients	*p*	Treatment group		*p*
			BLT + AD	AD monotherapy	
The Beck Scale for suicide ideation					
Pretreatment	5 (3–10)	**<0.001**	4 (2–16)	6.5 (4–9.5)	**<0.001**[a]
After treatment	5 (1–9)		1 (0–5)	6.5 (5–9)	
2 weeks after treatment	3.5 (0–7)		0 (0–4)	5 (3–7)	
Hamilton Depression Scale					
Pretreatment	20.69 ± 4.21	**<0.001**[b]	21.38 ± 5.48	20.1 ± 2.64	**<0.001**[b]
After treatment	16.69 ± 5.96		13.18 ± 6.69	19.68 ± 2.96	
2 weeks after treatment	15.14 ± 5.33		11.88 ± 5.95	17.9 ± 2.47	
Platelet/Lymphocyte ratio					
Pretreatment	118.61 ± 39.01	0.985[b]	111.38 ± 27.91	124.75 ± 45.88	0.785[b]
After treatment	118.16 ± 40.57		109.92 ± 38.62	125.17 ± 41.33	
2 weeks after treatment	117.96 ± 40.82		112.29 ± 42.04	122.78 ± 39.65	
Mean platelet volume					
Pretreatment	10.29 ± 0.98	**<0.001**[b]	10.4 ± 1.03	10.21 ± 0.94	0.141[b]
After treatment	9.7 ± 0.72		9.63 ± 0.64	9.76 ± 0.77	
2 weeks after treatment	9.81 ± 0.8		9.88 ± 0.84	9.76 ± 0.77	
Neutrophil count					
Pretreatment	5582.7 ± 1931.37	**0.003**[b]	5495.29 ± 1653.43	5657 ± 2157.91	0.751[b]
After treatment	5706.46 ± 1865.24		5633.24 ± 1555.18	5768.7 ± 2111.17	
2 weeks after treatment	5069.19 ± 2037.42		5122.35 ± 1886.24	5024 ± 2180.57	
Lymphocyte count					
Pretreatment	2597.7 ± 760.6	**<0.001**[b]	2596.18 ± 675.74	2599 ± 834.56	**<0.001**[b]
After treatment	2722.84 ± 776.85		2810.88 ± 661.08	2648 ± 864.48	
2 weeks after treatment	2897.57 ± 958.19		3239.71 ± 896.96	2606.75 ± 921.4	
Neutrophil/Lymphocyte ratio					
Pretreatment	2.31 ± 1.05	**<0.001**[b]	2.27 ± 0.95	2.35 ± 1.13	0.136[b]
After treatment	2.25 ± 0.96		2.11 ± 0.75	2.36 ± 1.11	
2 weeks after treatment	1.9 ± 0.9		1.65 ± 0.63	2.11 ± 1.04	

[a] An R software package npaRLD (Nonparametric Analysis of Longitudinal Data in Factorial Experiments).
[b] Two way repeated measures ANOVA.

The results of statistical analysis of time × group interactions are also presented in Table 2 and in Figs. 1–3. HDS and BSSI scores showed significant differences between groups over time ($p < 0.001$). BLT + AD combined therapy group showed more significant decreases in both scores compared to AD monotherapy group. For inflammatory markers, only the lymphocyte count showed significant difference between groups over time ($p < 0.001$). BLT + AD combined therapy group showed gradual increase in lymphocyte count over time whereas AD monotherapy group did not.

Table 3 presents the correlation between clinical scales and inflammatory markers. Pretreatment BSSI scores were found positively correlated with mean platelet volume ($r = 0.375$, $p < 0.001$). Pretreatment HDS scores were found negatively correlated with lymphocyte count ($r = -0.229$, $p < 0.05$).

Discussion

This study aimed to investigate the efficacy and safety of BLT in non-seasonal MDD. The primary outcome measurement was HDS score and secondary outcome measurements were BSSI scores and serum inflammatory markers. As a primary outcome, HDS scores decreased significantly one day after the treatment and continued to decrease two weeks after the treatment in both groups. It means that both AD monotherapy and BLT + AD combined therapy groups showed significant improvements in depression severity after treatment. This improvement was significantly more prominent in combined therapy group compared to AD monotherapy, indicating that BLT can be a helpful additional therapeutic intervention for non-seasonal depression. The mechanism of BLT is not fully understood yet, but major hypotheses in SAD involves resynchronizing circadian rhythms and restoring neurotransmitter dysfunction.[17–19] It is proposed that bright light has circadian phase–shifting effects in humans.[20] However, studies investigating light therapy in SAD have not consistently demonstrated the correlations of phase shift with clinical response.[18,21] Also, as the antidepressant effect of BLT can be seen in patients without delayed circadian rhythms, an additional mechanism of action may be in place.[22] Since it is known that rapidly depleting catecholamines particularly

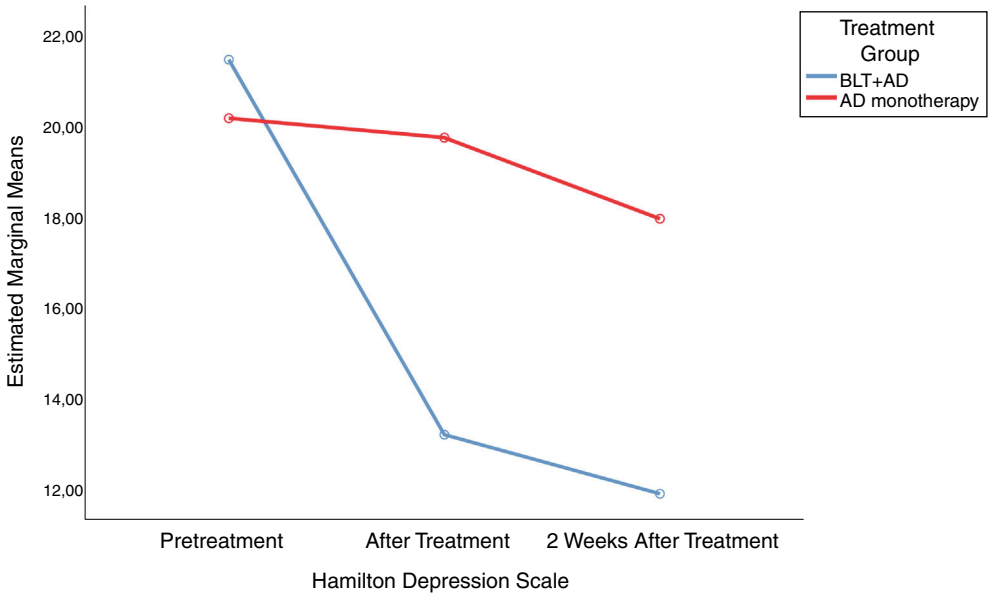

Figure 1 Change in Hamilton Depression Score in BLT + AD and AD monotherapy groups with time. BLT: bright light therapy. AD: antidepressants.

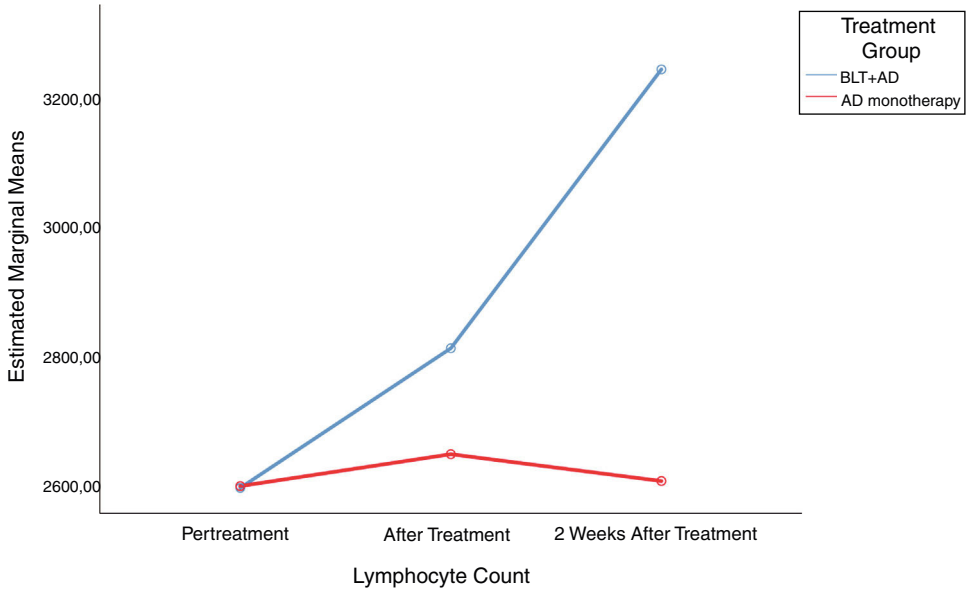

Figure 2 Change in lymphocyte count in BLT + AD and AD monotherapy groups with time.

serotonin can reverse the beneficial effects of light therapy in SAD,[23–25] it is also suggested that bright light may have direct monoaminergic effects which are similar to antidepressant effect.[26] Although there are observational and randomized controlled studies showing that BLT decreases suicidal ideation, several case reports[27,28] have presented a number of cases who attempted suicide after BLT. The present study assessed suicidal ideation before and after the treatment and found that suicidal ideas decreased significantly after treatment with both AD and AD + BLT. However, patients who received combined therapy showed more significant remission in suicidal ideation compared to patients receiving AD monotherapy. So, adjuvant BLT can also be used safely in depressive patients with suicidal ideation.

Except the PLR, all the inflammatory parameters changed significantly over time, meaning that both treatment options have an effect on inflammatory response in depressive patients. The neutrophil count decreased with two weeks of treatment whereas lymphocyte count increased gradually resulting in decreased NLR among all patients. NLR is a routinely used marker calculated from the neutrophil and lymphocyte counts in the complete blood count which clearly indicates the severity of systemic inflammation in diseases such as coronary artery disease, diabetes

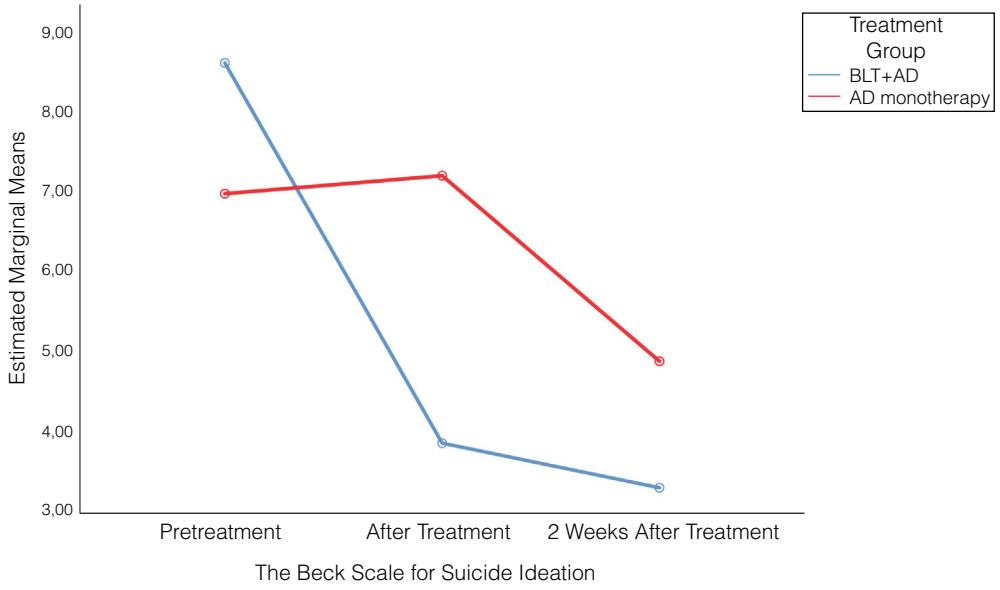

Figure 3 Change in Beck Scale for suicide ideation in BLT + AD and AD monotherapy groups with time.

Table 3 Correlation between clinical outcome parameters and inflammatory markers.

			Before treatment		After Treatment		2 weeks after treatment	
			r	*p*	*r*	*p*	*r*	*p*
BSSI	–	Platelet/Lymphocyte ratio	−0.184	0.117[b]	0.012	0.920[b]	−0.017	0.887[b]
BSSI	–	Mean platelet volume	0.375	**<0.001**[b]	−0.035	0.768[b]	0.021	0.862[b]
BSSI	–	Neutrophil count	−0.113	0.338[b]	0.043	0.717[b]	−0.146	0.215[b]
BSSI	–	Lymphocyte count	0.124	0.294[b]	0.124	0.292[b]	−0.165	0.161[b]
BSSI	–	Neutrophil/Lymphocyte ratio	−0.196	0.094[b]	−0.051	0.664[b]	0.017	0.888[b]
HAMD scale	–	Platelet/Lymphocyte ratio	0.188	0.110[a]	0.225	0.054[a]	0.108	0.362[a]
HAMD scale	–	Mean platelet volume	0.163	0.166[a]	0.009	0.937[a]	−0.005	0.965[a]
HAMD scale	–	Neutrophil count	−0.049	0.678[a]	0.023	0.843[a]	0.018	0.878[a]
HAMD scale	–	Lymphocyte count	−0.229	**0.049**[a]	−0.109	0.356[a]	−0.035	0.767[a]
HAMD scale	–	Neutrophil/Lymphocyte ratio	0.092	0.434[a]	0.119	0.313[a]	0.036	0.760[a]

[a] Pearson correlation coefficient.
[b] Spearman Rho correlation coefficient.

mellitus, Alzheimer's disease, ulcerative colitis, cirrhosis, and cancer.[29–32] NLR has prognostic value in cardiovascular diseases and various cancers independent of other factors.[33–35] MDD patients with higher HDS score were found to have higher NLR values.[36] It was reported that increase in NLR was associated with more severe depression.[36] Although our results showed a significant decrease in NLR with either treatments, we did not find a correlation between NLR and depression severity. Similar to NLR, PLR is also a novel inflammatory marker which can be used as a prognostic factor for cardiovascular diseases and cancer. A recent study[37] reported that the PLR were higher in patients with severe major depression with psychotic features than in other patients and this can be useful for assessing the prognosis of major depression. However, our study neither found a significant difference in PLR in response to both treatment options, nor a correlation between PLR and depression severity. MPV is an indicator of platelet activity, the relationship between MDD and increased platelet activity has been previously reported by several studies.[38,39] Patients with major depression were found to have increased MPV levels in comparison with participants without depression[39] and MPV was found significantly decreased after escitalopram treatment.[38] Consistent with these findings, our study showed that, independent from treatment arm, patients had decreased MPV two weeks after the treatment, but there was no significant correlation between depression severity and MPV.

The results of time × group interaction analysis showed no significant differences between groups apart from lymphocyte count. After 2 weeks of treatment, patients who were receiving AD monotherapy showed a negligible increase in lymphocyte count whereas patients receiving combined therapy showed a marked increase in lymphocyte number. This result shows that the effect of BLT is dissimilar to the effects of antidepressants on lymphocytes.

Bright light can affect the immune system by two separate mechanisms: skin mediated and eye-brain mediated. Wavelengths that are above 400 nanometer (nm) can penetrate into epidermal and dermal layers of the skin. Within these layers, light can directly interact with circulating lymphocytes which are responsible from the persistence of immune function. Another possible mechanism is an indirect way which involves transmission of light (400 nm or above) through retina to the brain. When it reaches to the brain, it stimulates specific brain areas such as the pituitary, hypothalamus, and the pineal glands in order to produce certain neurochemicals such as hormones, neurotransmitters and neuropeptides. These neurochemicals might directly cause alterations in immune function.[40] The skin-mediated response might be responsible for alterations seen in lymphocyte number in our combined therapy group which is not expected to be observed with antidepressant monotherapy. Finding of the negative correlation between lymphocyte number and severity of depression also supports the idea that lymphocyte count can be an important indicator of adjuvant BLT response in non-seasonal depression.

This study has several limitations. First, since the patients have been assigned to treatment alternatives by a non-randomized method, this can result in differences in baseline characteristics between two groups causing a risk of selection bias. These confounding factors can be either known or unknown factors. Although most of the known factors such as gender, employment status, medication compliance, social support and pretreatment depression severity were not significantly different between groups, it is impossible to control unknown factors without randomization. Second, since the patients were not blind to treatment alternatives, placebo effect cannot be ruled out in observed improvement of depressive symptoms with light therapy. Future randomized, sham controlled and double blinded clinical studies will provide higher level of evidences for the efficacy of BLT in non-seasonal depression.

Conclusion

In conclusion, studies examining the effect of BLT in non-seasonal depression are limited and inflammatory responses in these patients have not been studied yet. To the best of our knowledge, this study is the first which investigates the efficacy of BLT in non-seasonal depression with a focus on inflammatory markers. Present study indicated that combining BLT, as a well-tolerated treatment alternative, with classical antidepressant treatment modalities can be helpful in patients suffering from non-seasonal depressive disorder as well. Future randomized, sham controlled and double-blind clinical studies will provide higher level of evidences for the efficacy of BLT in non-seasonal depression.

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Conflict of interest

The authors have no conflict of interest to declare.

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