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Comparison of Venlafaxine Alone Versus Venlafaxine Plus Bright Light Therapy Combination for Severe Major Depressive Disorder

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ABSTRACT

Objective: Phototherapy, ie, bright light therapy, is an effective and safe treatment of major depressive disorder (MDD). It exerts rapid mood-elevating activity, similar to antidepressant medications, most likely mediated through both monoaminergic and circadian system melatonergic mechanisms. We assessed the efficiency of bright light therapy as an adjuvant treatment to antidepressant pharmacotherapy in patients with severe MDD randomized by Hamilton Depression Rating Scale (HDRS) score to either (1) 150 mg venlafaxine hydrochloride daily at 7:00 AM or (2) 150 mg venlafaxine plus 60-minute light of 7000 lux the initial week of clinical management (venlafaxine + bright light therapy) daily at 7:00 AM.

Method: 50 inpatients with severe MDD at the Psychiatry Clinic of Yüzüncü Yıl University Training and Education Hospital participated. The study, which was conducted from January 2013 through June 2014, entailed patients diagnosed with severe MDD based on *DSM-IV-TR* for the first time. Mood states were assessed by the HDRS, Profile of Mood States (POMS), and Beck Depression Inventory (BDI) before treatment and at 1, 2, 4, and 8 weeks of treatment.

Results: On the basis of the HDRS score as the primary outcome variable, both strategies significantly improved depression and negative mood states already at the first treatment week ($P < .001$). Differences in therapeutic effects by treatment strategy were remarkable at the second and fourth weeks of clinical management ($P = .018$ and $P = .011$, respectively), with beneficial effects continuing until trial conclusion. Those treated with venlafaxine + bright light therapy evidenced significantly lower HDRS depression scores ($P < .05$) as well as BDI scores ($P < .05$) and POMS negative mood states scores (depression-dejection, tension-anxiety, anger-hostility, fatigue-inertia, and confusion-bewilderment subscales; all $P < .05$) after the second week. At week 4 of the trial, 19 (76%) of the 25 venlafaxine + bright light therapy patients versus just 11 (44%) of the 25 venlafaxine patients ($P < .05$) attained the target goal of treatment, a HDRS score ≤ 13, indicative of mild depression, and, although not statistically significant in our small sample study ($P = .36$), at week 8, 76% of venlafaxine + bright light therapy patients (n = 19) versus just 64% of the venlafaxine patients (n = 16) experienced complete remission of depression (HDRS score ≤ 7).

Conclusions: Both venlafaxine and venlafaxine + bright light therapy treatment strategies significantly reversed the depressive mood of patients with severe MDD; however, the latter induced significantly stronger and more rapid beneficial effects. Future longer-term studies with large sample sizes, nonetheless, are required to confirm and generalize these results to patients of diverse ethnicities and cultures with both severe and mild MDD.

Trial Registration: ANZCTR.org.au registration number: ACTRN12614001061628

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The World Health Organization currently ranks depression, a highly debilitating condition, as the fourth leading cause of disability worldwide, and projects it will become the second leading one by 2020. Effective treatment strategies for major depressive disorder (MDD) include psychotherapy, sleep deprivation/wake therapy, antidepressant pharmacotherapy, or combinations of these and other therapies.[1] Clinical studies indicate phototherapy, ie, bright light therapy, is a safe and effective means of managing several primary and secondary affective illnesses, eg, antenatal and postpartum depression, bipolar and certain eating disorders, chronic fatigue syndrome,[2,3] non-seasonal depression,[4,5] and adolescent and adult attention-deficit/hyperactivity disorder.[6,7] Moreover, recent MDD studies suggest bright light therapy when utilized as an adjuvant to antidepressant medication is more beneficial than medication alone.[7,8] Both animal model and patient studies of MDD and other affective disorders in which depressed mood is characteristic report disrupted circadian organization, manifesting as dampened circadian rhythm amplitude and/or altered circadian phasing, of the sleep-wake, hormonal, and other rhythms, perhaps the consequence of abnormalities of biological clock or associated time-keeping genes.[9–14] bright light therapy is believed to exert mood-elevating effects not only through monoaminergic but also through circadian system–associated melatonergic mechanisms, as demonstrated, for example, by shift-work, jet-lag, and circadian rhythm sleep disorder bright light therapy studies.[15] This may explain the observed enhancement of the beneficial effects of antidepressant medication when bright light therapy is used as adjuvant therapy.[2,16,17]

A growing body of evidence indicates bright light therapy constitutes a valid and well-tolerated, biologically oriented, nonpharmacologic antidepressant treatment modality.[17] A meta-analysis by Golden et al[16] found bright light therapy to be effective as antidepressant medications for both seasonal and non-seasonal depression. Furthermore, a large seasonal affective disorder (SAD) trial[18] found bright light therapy, in comparison to fluoxetine treatment, produced clinically equivalent reduction of depression level and symptoms, and with earlier favorable response and fewer adverse effects.

The findings of early investigations of the effectiveness of bright light therapy were compromised by absence

Clinical Points

- Effectiveness of adjuvant bright light therapy plus selective serotonin reuptake inhibitor in seasonal affective disorder (SAD) is well-established in the literature, but potential advantage of adjuvant bright light therapy plus serotonin-norepinephrine reuptake inhibitor (SNRI) treatment in severe non-SAD patients deserves clinical evaluation.
- SNRI antidepressant venlafaxine drug therapy in combination with bright light therapy 60 minutes in the morning, even when limited to just the initial week of clinical management, significantly enhanced the speed of remission of severe major depressive disorder compared to venlafaxine alone and also was associated with improved clinical outcomes.

of the incorporation of a placebo-control group in the research design.[2] In the Eastman et al[19] placebo-controlled study of bright light therapy in MDD, patients specifically administered morning light displayed significantly better improvement in symptom relief relative than those provided placebo treatment. The finding of the study conducted by Terman et al[20] was similar: morning light resulted in better outcomes than evening light and placebo. Even et al[17] extensively reviewed the outcomes of investigations entailing bright light therapy used alone or as an adjuvant treatment for patients with SAD versus those without SAD. They concluded bright light therapy is more effective for SAD than non-SAD applications. Moreover, although the authors stated investigations with bright light therapy when used alone for patients without SAD were inconclusive, they reported the majority of non-SAD studies supported greater efficiency of adjuvant bright light therapy when combined with SSRI pharmacotherapy compared to placebo or control groups.

Most past MDD bright light therapy trials were conducted in cohorts of mildly to moderately depressed outpatients. To our knowledge, the clinical relevance of bright light therapy as a useful adjuvant treatment to manage severe MDD patients has yet to be explored and reported. Thus, the aim of our current study was to assess the efficiency of bright light therapy as an adjuvant treatment to venlafaxine for severe MDD. We compared mood states and depression scores obtained at regular intervals before and during the course of treatment of 2 groups of hospitalized patients randomized according to the Hamilton Depression Rating Scale (HDRS) score either to venlafaxine alone or to venlafaxine + bright light therapy in combination.

MATERIALS AND METHODS

Participants

The trial involved 50 first-time–diagnosed patients with severe MDD hospitalized in the psychiatry clinic of Yüzüncü Yıl University Training and Education Hospital. Patients were included into the study after being thoroughly informed about the research protocol and providing consent for participation. Inclusion criteria were voluntary agreement of participation, first-time diagnosis of severe MDD (*DSM-IV-TR*; Structured Clinical Interview for *DSM-IV* Axis I disorders, [SCID-I]), age > 18 and < 65 years, no current or past history of bipolar disorders, no history of drug abuse or addiction, and satisfaction of eligibility requirements for bright light therapy.

Patient Forms and Assessment Instruments

MDD was diagnosed using the Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID-I),[21] plus Hamilton Depression Rating Scale (HDRS).[22,23] A demographic form, the Profile of Mood States Scale (POMS),[24] and the Beck Depression Inventory (BDI)[25,26] were additionally completed by participants.

Treatment Randomization

Patients were structurally randomized utilizing the HDRS score of each participant determined at baseline, before commencement of the therapeutic trial, to 1 of 2 treatment groups: (1) venlafaxine alone or (2) venlafaxine + bright light therapy in combination so as to minimize group difference in mean HDRS score. The study required nearly 1.5 years to complete, since the aim of the investigation was to include only patients diagnosed for the first time with severe MDD.

Treatment Protocols

Venlafaxine treatment. Venlafaxine, a potent serotonin-norepinephrine reuptake inhibitor (SNRI), was started at a dose of 75 mg/d, always in the morning at 7 AM, for the first week of the trial and thereafter, from the second to the eighth week of the trial, provided at a dose of 150 mg/d.

Bright light therapy. A special light unit (Day Light; Uplift Technologies, Model DL930EU), designed and marketed for medical use, was positioned at eye level 60 cm from the patient to deliver a light dose of 7,000 lux bright light therapy, according to the specifications provided by the manufacturer of the light device, for 60 minutes daily at 7 AM, immediately following venlafaxine ingestion. The findings of previously conducted clinical trials led to the recommendation that bright light therapy be scheduled in the morning, shortly after awakening.[2,27] To optimize treatment response, we initiated bright light therapy no later than 8.5 hours after the presumed onset of melatonin secretion given the sleep (~10:00 PM)/wake (6:30 AM) and related dark/light cycle regimen of the hospital ward. Patients were instructed not to gaze directly into the light, and they were supervised to ensure their eyes remained open throughout each bright light therapy session. As it is well-known that light therapy for a prolonged duration can cause contrast sensitivity and ocular conditions, we performed bright light therapy in conjunction with venlafaxine pharmacotherapy only during the first week of the treatment regimen. The study was conducted from January 2013 through June 2014.

Outcome Variables

The validated Turkish version of the HDRS,[22] to assess the severity of depression symptoms, contains 17 questions. The highest possible score is 53, with a score of > 14 indicating

moderate depression and a score of >19 indicating severe depression; the higher the score attained, the more severe the depression. The primary outcome variables were (1) change from baseline in the HDRS scale score as a function of week of treatment during the 8-week protocol, and (2) proportion of patients achieving a HDRS score of ≤13 indicative of remission of severe depression. The proportion of patients achieving complete recovery, signified by a HDRS score ≤7, which indicates absence of depression, was also assessed. Additionally, changes in patient self-rating scores of the POMS and its subscales plus BDI were evaluated as secondary response variables. The HDRS, POMS, and BDI instruments were completed at baseline and again after 1, 2, 4, and 8 weeks of the trial to objectively assess the speed and extent of patient response to the respective treatment strategies. The screening tools were administered by experienced psychiatrists who had a clinical background of managing psychiatric patients for at least 5 years.

Study Ethics

The study was conducted according to the Declaration of Helsinki; all investigative procedures were reviewed and approved by the Clinical Ethics and Research Committee of the Yüzüncü Yıl University, Faculty of Medicine. The study was registered in ANZCTR.org.au with the registration code of ACTRN12614001061628. Individuals were invited to volunteer to participate in the clinical trial following diagnosis of severe MDD plus confirmation of satisfying all inclusion and exclusion criteria. All participants signed a consent form declaring that they had been fully informed of the purposes, procedures, and conduct of the study. They were not paid for their participation.

Data Analysis

Descriptive sample statistics were derived for the demographic variables, and sample characteristics were compared between the 2 treatment groups using *F* and χ^2 test statistics. Repeated-measures analysis of variance (rANOVA) models were run to evaluate change on scale and subscale instrument scores obtained over the 8-week course of therapy. In addition, mean scale scores of these assessment instruments obtained at each of 5 time points, ie, baseline and after 1, 2, 4, and 8 weeks of venlafaxine or venlafaxine + bright light therapy, were compared by one-way ANOVA to assess potential differences in the speed of therapeutic response. The threshold for statistical significance was always $P < .05$.

RESULTS

Patient Demographics

All 50 patients completed the trial; 25 patients received venlafaxine only and 25 patients received venlafaxine + bright light therapy. The mean age of the sample of 50 patients was 35.76 (SD ± 10.31) years. Some 54% of the participants (n = 27) were female, 78% (n = 39) were married, and 32% (n = 16) reported psychopathology in first-degree family members. As shown in Table 1, the mean age and years of education plus number of participants that were male and female, married and unmarried, and having family members with history of psychopathology did not differ according to treatment group (ANOVA and χ^2 square tests).

Table 1. Comparisons of Patient Demographic Variables of the Venlafaxine (n = 25) and Venlafaxine + Bright Light Therapy (n = 25) Treatment Groups

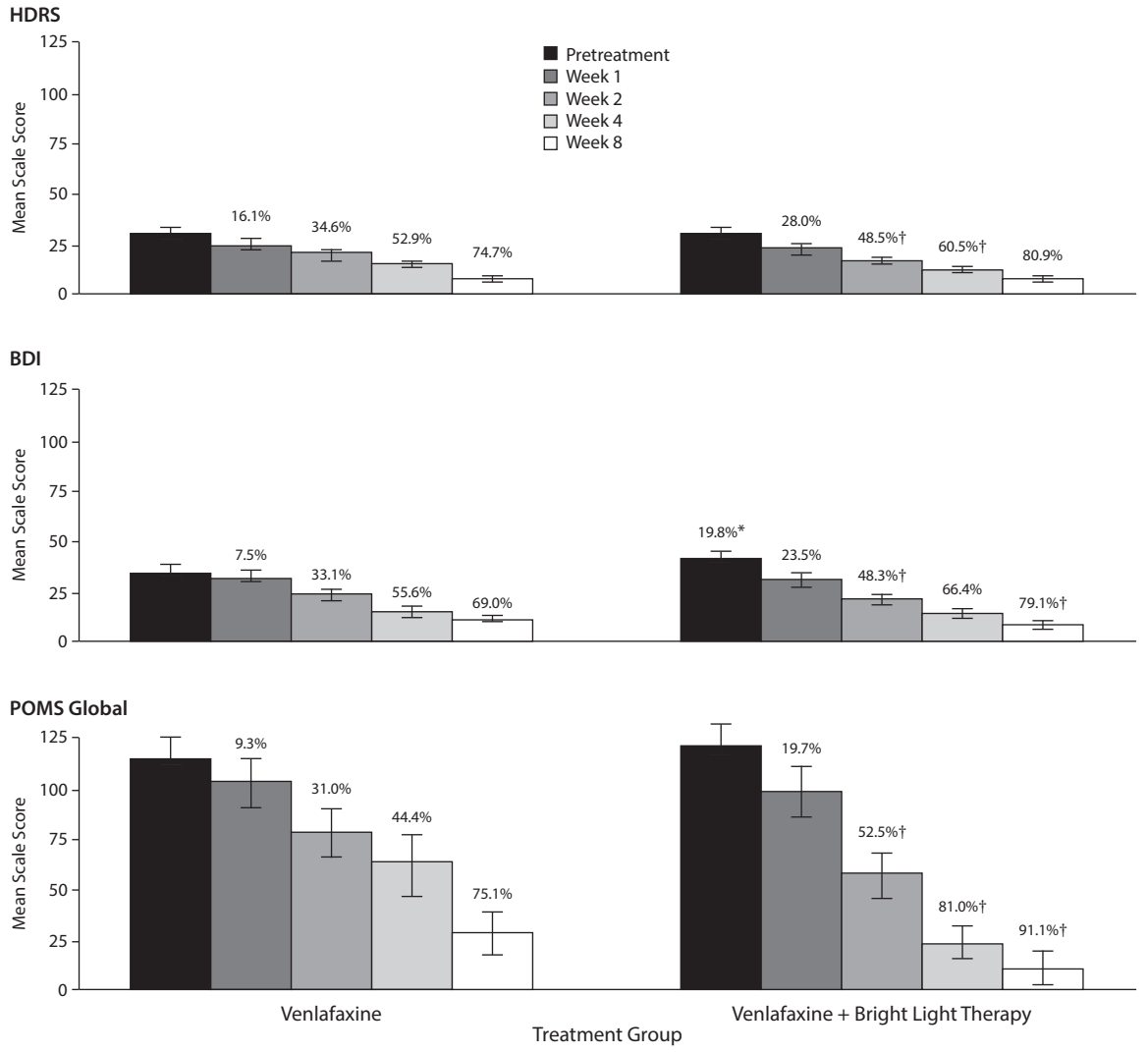
	Venlafaxine		Venlafaxine + Bright Light Therapy			
Variable	Mean	SD	Mean	SD	t_{48}	*P*
Age, y	38.36	11.84	33.16	7.94	1.824	.074
Education, y	9.68	4.28	8.60	3.97	0.925	.359
	n	%	n	%	χ^2_1	*P*
Sex					0.081	.777
Male	12	48.0	11	44.0		
Female	13	52.0	14	56.0		
Marital status					0.117	.733
Single	5	20.0	6	24.0		
Married	20	80.0	19	76.0		
Family psychopathology	6	24.0	10	40.0	1.471	.225

Treatment Outcomes

Patients in the 2 treatment groups, venlafaxine only and venlafaxine + bright light therapy, were assessed at specific intervals by the HDRS, BDI, and POMS instruments during the 8-week course of therapy to compare the speed and extent of regression of their depression. The findings are reported for the primary HDRS and secondary BDI and POMS outcome variables.

HDRS primary outcome variable. As shown in Figure 1 and Table 2, the mean HDRS depression score of both treatment groups declined significantly (1-way ANOVA) during the 8-week protocol. The HDRS-assessed depression level decreased significantly ($P < .01$) in patients in both treatment groups after the second week of therapy, and it continued to decline thereafter, with the effects sustained until the conclusion of the trial. As shown in Table 2, the mean HDRS score at each time point of assessment was better reduced from baseline, significantly so after 2 and 4 weeks of therapy, by venlafaxine + BRT than venlafaxine. Thus, as also verified by the results of additional ANOVA shown in Table 3, the speed of reduction in the HDRS score was significantly more rapid by the combined venlafaxine + BRT than by only venlafaxine treatment. Finally, the proportion of patients attaining remission differed according to treatment strategy. The target goal of treatment, a HDRS score ≤13 (indicative of mild depression), was attained at the fourth week of the trial by 19 (76%) of the 25 venlafaxine + bright light therapy–treated patients, but just 11 (44%) of the 25 venlafaxine-treated patients ($Z = 2.31$; $P < .05$). The enhanced therapeutic effect of the combination venlafaxine + bright light therapy versus venlafaxine monotherapy was sustained to the end of the trial. The same proportion, 76% (n = 19), of the venlafaxine + bright light therapy–treated patients who at the fourth week of treatment evidenced rapid reduction in depression (target HDRS score ≤13) also achieved complete

Figure 1. Bar Graph of Mean HDRS, BDI, and POMS Global Score Per Treatment Group at Each of the 5 Assessment Time Points (baseline and after 1, 2, 4, and 8 weeks of therapy)[a]



[a]Actual HDRS, BDI, and POMS global units are shown on the y-axis, and percent change from baseline (set = 100%) values are shown above each successive time point of reassessment during treatment depicted by a differently shaded bar.
*Significant difference ($P < .05$) between groups for the baseline scores (the mean BDI score of the venlafaxine + bright light therapy group was 19.8% higher than the mean BDI score of the venlafaxine treatment group).
†Significant difference ($P < .05$) between groups for the designated week of treatment based on ANOVA of actual HDRS and POMS global score units and on ANCOVA of actual BDI score units.
Abbreviations: ANCOVA = analysis of covariance, ANOVA = analysis of variance, BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, POMS = Profile of Mood States.

remission (HDRS score ≤ 7) at the eighth week of treatment versus just 64% (n = 16) of the venlafaxine-treated patients, although the difference in the proportion of recovered patients between the venlafaxine + bright light therapy and venlafaxine treatment strategies at week 8 was not statistically significant ($Z = 0.93$ $P = .36$). The HDRS score data reported in Tables 2 and 3 and represented in Figure 1 thus indicate the combined venlafaxine + bright light therapy, relative to the venlafaxine only, treatment strategy more quickly and more strongly resolved patient depression.

Secondary outcome variables. Tables 2 and 3 report the mean baseline and follow-up BDI scores of the 2 treatment groups. The mean baseline BDI score was statistically significantly greater (more severe depression level) in the venlafaxine + bright light therapy than venlafaxine group; thus, we compared the mean BDI scores of the 2 treatment groups by one-way ANCOVA, with the baseline BDI score of each patient utilized as the covariate. Accordingly, over the 8-week course of therapy, reduction of the BDI score was statistically comparable to that of the HDRS. The score on the BDI also declined after the first week of therapy, more so and more rapidly until the conclusion of the trial in the venlafaxine + bright light therapy than venlafaxine group, as reported in Table 2 and shown Figure 1.

Tables 2 and 3 and Figure 2 present changes from baseline in the mean global POMS scale and also subscales according

Table 2. Comparisons of Mean HDRS, BDI, and POMS Scale Scores Between Venlafaxine (n = 25) and Venlafaxine + Bright Light Therapy (n = 25) Treatment Groups at 5 Time Points Scheduled at Baseline and During the 8-Week Study Protocol[a]

	Venlafaxine		Venlafaxine + Bright Light Therapy					
Measure	Mean	SD	Mean	SD	*F*	*df*	*P*	η^2
Hamilton Depression Rating Scale								
Baseline	29.28	6.93	29.88	6.17	0.104	1, 48	.748	.002
Week 1	24.56	6.53	21.52	6.41	2.761	1, 48	.103	.054
Week 2	19.16	6.17	15.40	4.56	6.002	1, 48	**.018**	.111
Week 4	13.80	3.69	11.08	3.53	7.093	1, 48	**.011**	.129
Week 8	7.40	5.08	5.72	2.99	2.028	1, 48	.161	.041
Beck Depression Inventory[b]								
Baseline	33.40	9.38	40.00	8.93	6.495	1, 48	**.014**	.119
Week 1	30.88	8.47	30.60	9.34	3.509	1, 47	.067	.069
Week 2	22.36	7.96	20.68	6.13	4.277	1, 47	**.044**	.083
Week 4	14.84	7.62	13.44	5.69	3.480	1, 47	.068	.069
Week 8	10.36	5.75	8.36	4.43	4.403	1, 47	**.041**	.086
POMS								
Depression-dejection								
Baseline	37.16	11.36	41.36	11.50	1.687	1, 48	.200	.034
Week 1	32.92	9.32	31.84	18.07	0.071	1, 48	.792	.001
Week 2	26.48	10.11	19.00	8.02	8.405	1, 48	**.006**	.149
Week 4	23.24	12.35	9.28	6.49	25.040	1, 48	**<.001**	.343
Week 8	11.12	9.11	5.28	6.15	7.057	1, 48	**.011**	.128
Tension-anxiety								
Baseline	23.68	4.88	23.24	4.03	0.121	1, 48	.730	.003
Week 1	21.12	5.53	17.72	4.62	5.568	1, 48	**.022**	.104
Week 2	16.92	4.84	13.44	4.76	6.570	1, 48	**.014**	.120
Week 4	15.40	6.74	8.16	2.84	24.506	1, 48	**<.001**	.338
Week 8	9.60	3.93	6.72	3.85	6.864	1, 48	**.012**	.125
Anger-hostility								
Baseline	27.40	8.19	30.96	8.15	2.376	1, 48	.130	.047
Week 1	25.08	8.48	25.72	14.57	0.036	1, 48	.850	.001
Week 2	21.60	8.80	15.60	7.65	6.614	1, 48	**.013**	.121
Week 4	15.80	9.29	7.56	6.10	13.734	1, 48	**.001**	.222
Week 8	8.68	7.13	4.40	5.58	5.581	1, 48	**.022**	.104
Confusion-bewilderment								
Baseline	14.84	4.75	14.60	3.06	0.045	1, 48	.833	.001
Week 1	14.20	4.75	12.08	4.06	2.875	1, 48	.096	.057
Week 2	12.64	4.72	9.32	2.46	9.737	1, 48	**.003**	.169
Week 4	11.00	4.95	6.88	3.03	12.595	1, 48	**.001**	.208
Week 8	7.60	3.43	5.88	3.22	3.345	1, 48	.074	.065
Fatigue-inertia								
Baseline	17.96	4.51	19.60	8.35	0.747	1, 48	.392	.015
Week 1	15.68	4.82	14.04	4.88	1.430	1, 48	.238	.029
Week 2	12.40	4.32	9.68	4.94	4.295	1, 48	**.044**	.082
Week 4	10.36	5.99	4.84	3.08	16.817	1, 48	**<.001**	.259
Week 8	4.56	4.41	2.96	3.19	2.160	1, 48	.148	.043
Vigor-activity								
Baseline	9.28	4.69	9.88	4.33	0.221	1, 48	.640	.005
Week 1	10.00	4.29	10.36	3.81	0.098	1, 48	.755	.002
Week 2	12.92	3.97	10.08	3.04	8.070	1, 48	**.007**	.144
Week 4	13.64	4.91	13.92	3.49	0.054	1, 48	.817	.001
Week 8	13.68	4.66	14.52	4.45	0.424	1, 48	.518	.009
POMS Global								
Baseline	111.76	31.04	119.88	24.64	1.049	1, 48	.311	.021
Week 1	101.32	28.10	96.28	32.57	0.343	1, 48	.561	.007
Week 2	77.12	29.60	56.96	26.85	6.361	1, 48	**.015**	.117
Week 4	62.16	35.59	22.80	19.55	23.487	1, 48	**<.001**	.329
Week 8	27.88	26.80	10.72	19.33	6.743	1, 48	**.012**	.123

[a]Statistical tests conducted by analysis of variance. *P* values in boldface indicate statistical significance.
[b]Baseline depression score used as covariate in ANCOVA models to compare group difference in BDI score at weeks 1, 2, 4, and 8.
Abbreviation: POMS = Profile of Mood States.
Symbol: η^2 = measure of effect size, ie, amount of variance explained by group difference.

Table 3. Comparison of Changes From Baseline in the Mean BDI, HDRS, and POMS Global and Subscale Scores Over the 8 Weeks of Venlafaxine (n = 25) Versus VH + BLT (n = 25) Treatment

	Course of the Treatment												
	T1		T2		T3		T4		T5				
Measure	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	$F_{4,96}$[a]	η^2	Post Hoc[b]
HDRS													
Venlafaxine	29.28	6.93	24.56	6.53	19.16	6.17	13.80	3.69	7.40	5.08	125.480	.839	T1 > T2 > T3 > T4 > T5
Venlafaxine + bright light therapy	29.88	6.17	21.52	6.41	15.40	4.56	11.08	3.53	5.72	2.99	212.558	.899	T1 > T2 > T3 > T4 > T5
BDI													
Venlafaxine	33.40	9.38	30.88	8.47	22.36	7.96	14.84	7.62	10.36	5.75	68.962	.742	T1 = T2 > T3 > T4 > T5
Venlafaxine + bright light therapy	40.00	8.93	30.60	9.34	20.68	6.13	13.44	5.69	8.36	4.43	155.854	.867	T1 > T2 > T3 > T4 > T5
POMS													
Depression-dejection													
Venlafaxine	37.16	11.36	32.92	9.32	26.48	10.11	23.24	12.35	11.12	9.11	42.884	.641	T1 > T2 > T3 > T4 > T5
Venlafaxine + bright light therapy	41.36	11.50	31.84	18.07	19.00	8.02	9.28	6.49	5.28	6.15	64.371	.728	T1 > T2 > T3 > T4 > T5
Tension-anxiety													
Venlafaxine	23.68	4.88	21.12	5.53	16.92	4.84	15.40	6.74	9.60	3.93	75.266	.758	T1 > T2 > T3 > T4 > T5
Venlafaxine + bright light therapy	23.24	4.03	17.72	4.62	13.44	4.76	8.16	2.84	6.72	3.85	114.770	.827	T1 > T2 > T3 > T4 = T5
Anger-hostility													
Venlafaxine	27.40	8.19	25.08	8.49	21.60	8.80	15.80	9.29	8.68	7.13	46.147	.658	T1 = T2 > T3 > T4 > T5
Venlafaxine + bright light therapy	30.96	8.15	25.72	14.57	15.60	7.65	7.56	6.10	4.40	5.58	72.263	.751	T1 = T2 > T3 > T4 = T5
Confusion-bewilderment													
Venlafaxine	14.84	4.75	14.20	4.75	12.64	4.72	11.00	4.95	7.60	3.43	23.502	.495	T1 = T2 = T3 > T4 > T5
Venlafaxine + bright light therapy	14.60	3.06	12.08	4.06	9.32	2.46	6.88	3.03	5.88	3.22	43.238	.643	T1 > T2 > T3 > T4 = T5
Fatigue-inertia													
Venlafaxine	17.96	4.51	15.68	4.82	12.40	4.32	10.36	5.99	4.56	4.41	53.128	.689	T1 > T2 > T3 > T4 = T5
Venlafaxine + bright light therapy	19.60	8.35	14.04	4.88	9.68	4.94	4.84	3.08	2.96	3.19	77.411	.763	T1 > T2 > T3 > T4 = T5
Vigor-activity													
Venlafaxine	9.28	4.69	10.00	4.29	12.92	3.97	13.64	4.91	13.68	4.66	11.190	.318	T1 = T2 < T3 = T4 = T5
Venlafaxine + bright light therapy	9.88	4.33	10.36	3.81	10.08	3.04	13.92	3.49	14.52	4.45	9.334	.280	T1 = T2 = T3 < T4 = T5
POMS Global													
Venlafaxine	111.76	31.04	101.32	28.10	77.12	29.60	62.16	35.59	27.88	26.80	64.880	.730	T1 > T2 > T3 > T4 = T5
Venlafaxine + bright light therapy	119.88	24.64	96.28	32.57	56.96	26.85	22.80	19.55	10.72	19.33	172.801	.878	T1 > T2 > T3 > T4 = T5

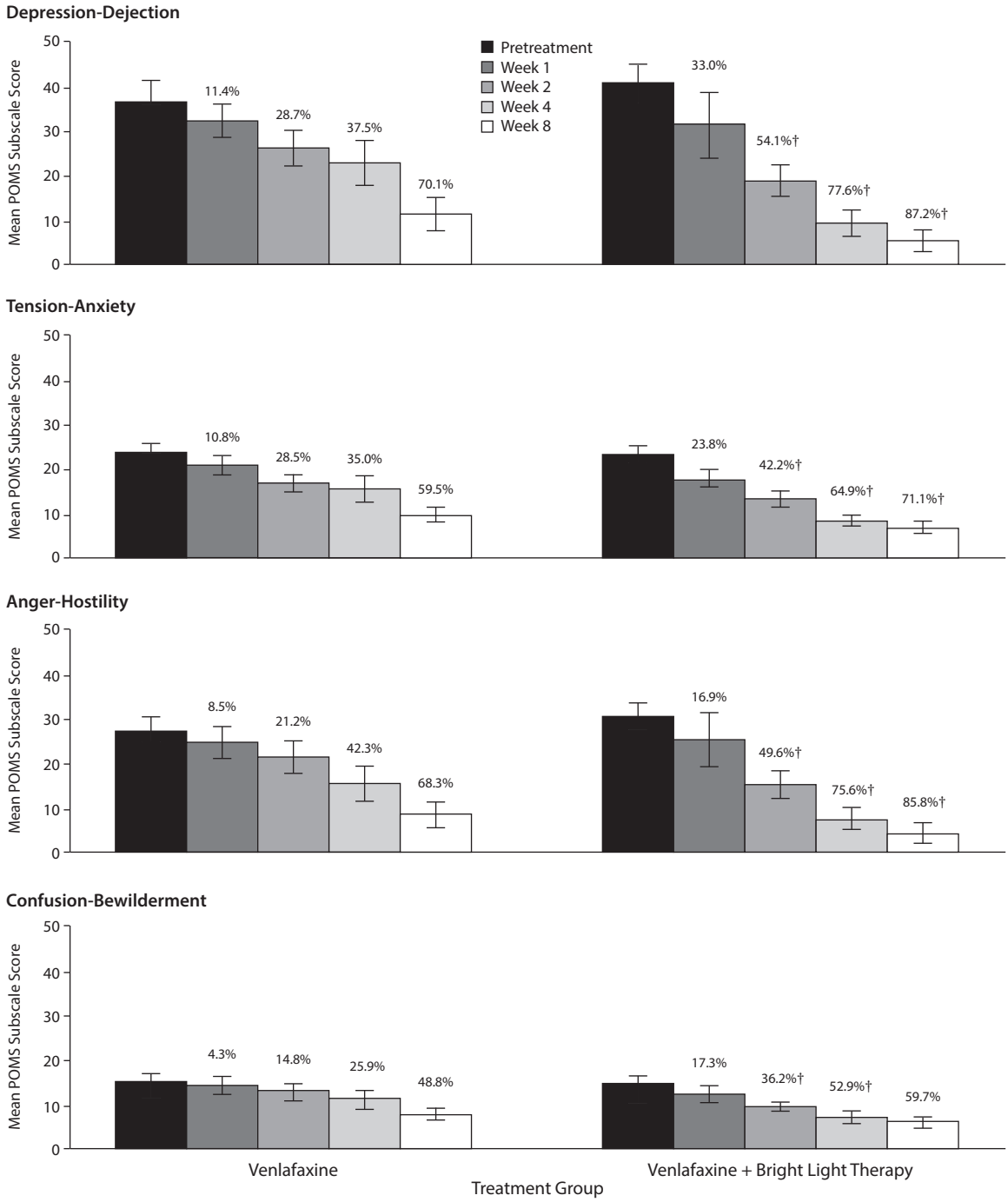
[a]All P values < .001.
[b]Post hoc comparisons conducted by the Bonferonni multiple comparison test.
Abbreviations: BDI = Beck Depression Inventory, HDRS = Hamilton Depression Rating Scale, POMS = Profile of Mood States, T1 = initial baseline assessment before treatment initiation, T2 = after 1 week of venlafaxine or venlafaxine + bright light therapy, T3 = after 2 weeks of clinical therapy, T4 = after 4 weeks of clinical therapy, T5 = after 8 weeks of clinical therapy.
Symbol: η^2 = measure of effect size, ie, amount of variance explained by group difference.

to treatment strategy over the 8-week trial. The greater and more rapid beneficial effect of venlafaxine + bright light therapy relative to venlafaxine alone is confirmed by the POMS global and subscale scores. In particular, the mean scores on the depression-dejection, tension-anxiety, anger-hostility, confusion-bewilderment, and fatigue-inertia POMS subscales reveal the more favorable effects (P always < .025) of the combination therapy at the second week of treatment and, with the exception of the confusion-bewilderment (P = .074) and fatigue-inertia (P~.15) subscales, that was sustained to the conclusion of the trial. Although the mean score of the vigor-activity subscale of the POMS indicates more favorable effect of the venlafaxine + bright light therapy than venlafaxine therapy at the second week of the study, this differential treatment effect was not sustained. The greater rapidity and strength of antidepressant activity of the venlafaxine + bright light therapy versus venlafaxine treatment is especially evident from the POMS subscale time point means reported in Tables 2 and 3 and bar graphs of Figure 2.

DISCUSSION

The therapeutic response to antidepressant medications by MDD patients is often delayed for up to 4 to 6 weeks; thus, strategies to improve the speed and extent of therapeutic response are of major clinical interest.[28] The current study investigated whether an earlier, ie, more rapid, therapeutic effect is obtained in severe MDD patients requiring hospitalization when morning SNRI antidepressant venlafaxine drug therapy is administered in combination with morning bright light therapy during the initial week treatment than when venlafaxine antidepressant pharmacotherapy is administered alone in the morning, and whether this early therapeutic response is sustained throughout the course of treatment. The results of the study showed MDD inpatients who received venlafaxine + bright light therapy versus those

Figure 2. Bar Graph of Mean Depression-Dejection, Tension-Anxiety, Anger-Hostility, and Confusion-Bewilderment Subscale Scores of the POMS Per Treatment Group at Each of the 5 Assessment Time Points (baseline and after 1, 2, 4, and 8 weeks of therapy)[a]



[a]Actual units are shown on the y-axis, and percent change from baseline (set = 100%) values are shown above each successive time point of reassessment during treatment depicted by a differently shaded bar.
†Significant difference ($P < .05$) in actual POMS subscale score units between treatment groups per time point of assessment.
Abbreviation: POMS = Profile of Mood States.

who received venlafaxine experienced significantly earlier and stronger reduction of depression, based not only on the study's primary HDRS outcome measure, but also on the secondary BDI and POMS outcome measures, particularly the depression-dejection, tension-anxiety, anger-hostility, fatigue-inertia, and confusion-bewilderment subscales of the POMS. Moreover, adverse effects of bright light therapy, such as headache, nausea, eyestrain, irritability, fatigue, and insomnia,[16] were not reported to us by our patients.

In a seminal monograph, Rosenthal et al[29] emphasized the beneficial effect of bright light therapy for SAD. In a 5-year, 14-center longitudinal study entailing 332 adult SAD

outpatients, Terman et al[30] demonstrated that 2,500 lux bright light therapy administered twice daily for 1 week resulted in a significantly improved emotional state spectrum. Our results are in agreement with those of previous studies and point to the efficacy of bright light therapy in adult non-seasonal depression.[31–33] Recently published studies also verify the efficacy of bright light therapy as an adjuvant to antidepressant medication in the treatment of adolescent depression and ADHD.[7,8]

The most important finding of our study is that adjunctive bright light therapy, even when limited to the initial week of treatment, shortened the delay of the depression-remitting effect of venlafaxine; although significant decrease in the severity of depressive symptoms and negative mood states was observed after the second week in the venlafaxine group, much greater relief of depression and mood symptoms was observed earlier, after the first week of treatment, among our severe MDD inpatients managed with venlafaxine + bright light therapy. Indeed, the target effect of treatment, an HDRS score ≤ 13 (mild or no depression), at the fourth week of the trial was achieved in 19 (76%) of the 25 venlafaxine + bright light therapy patients compared to just 11 (44%) of the 25 venlafaxine patients. Of further clinical interest, even if not statistically significant, is the difference by treatment strategy in the complete remission of depression (HDRS score ≤ 7) at the conclusion of the 8-week protocol, 76% of the venlafaxine + bright light therapy versus 64% of venlafaxine patients. Overall, our findings are consistent with the literature, ie, that morning phototherapy exerts antidepressant activity, and, as hypothesized by others, most likely through more than a single mechanism. One of the speculated processes is through photoperiodic responsiveness, eloquently described by Hazlerigg,[34] which is an ancestral mechanism lying in a thyroid signaling pathway and functioning in concert with a light-sensing pathway that specifically includes the retinal photoreceptors, circadian clock, and melatonin. The circadian approach to depression based on studies of SAD is founded on the hypothesis that postulates such patients are abnormally phase delayed. Research has demonstrated that bright light therapy scheduled in the morning induces phase advance and that bright light therapy scheduled in the evening induces a phase delay in the circadian time structure.[35,36] Findings that are consistent with the hypothesis that bright light therapy exerts antidepressant effects through multiple mechanisms.

Despite the proven effectiveness of morning phototherapy in treating SAD, results of studies regarding patients without SAD are mixed. For example, Yamada et al[37] reported bright light therapy significantly reduces the severity of depression of patients without SAD, and Dietzel et al[38] reported it is effective in the treatment of MDD. In contrast, Mackert et al[39] concluded that phototherapy administered for 2 hours daily for 1 week is ineffective for non-seasonal depression; although a decline in depression scores was observed, findings were statistically unsubstantial probably due to the insufficient number of participants and underpowering of the study. Although Prasko et al[40] suggested bright light therapy alone is more effective than bright light therapy coadministered with imipramine, and thus not in itself a useful adjuvant therapy for patients without SAD, Even et al,[17] on the basis of a systematic review of 15 studies, disagreed and found that bright light therapy is an effective adjuvant treatment to antidepressant medications, particularly SSRIs. Moreover, they concluded that supportive evidence for the effectiveness of bright light therapy when used alone, without antidepressant pharmacotherapy, is inconsistent.

In our study, the emotional states of depression as measured by the POMS subscale scores of depression-dejection, tension-anxiety, and anger-hostility were decreased significantly more by the venlafaxine + bright light therapy than the venlafaxine strategy commencing at the second week and continuing thereafter until the conclusion of trial, at the eighth week of treatment, and for the POMS subscales of fatigue-inertia and confusion-bewilderment at both the second and fourth weeks of treatment. Wirz-Justice[41] reported, independent of specific patient diagnosis, that the severity of psychiatric symptoms increases and long-term outcomes worsen when circadian disturbances are present, reinforcing the crucial relationship between circadian rhythms, sleep, and emotional state. Preliminary evidence indicates that bright light therapy exerts positive influence on behavior, irritability, and attention,[6,42] and this may explain the greater benefit of venlafaxine when combined with bright light therapy in our study. In this regard, bright light therapy has been shown to stabilize and normalize the disorganized circadian system of shift workers, transmeridian travelers, and patients with circadian rhythm sleep disorders, with apparently an additional associated benefit of improved emotional state.

Adjuvant bright light therapy studies are crucial, and as discussed above the findings of most, but not all,[40] such past studies support the efficacy of bright light therapy when used in combination with antidepressant pharmacotherapy. However, comparison of the therapeutic effects of bright light therapy and antidepressant medications is difficult because of between-study differences in, eg, investigative procedure, preconceived patient expectations about treatment effects, protocol design, exact outcomes measures, and patient characteristics. Moreover, in many studies the number of patients per treatment groups was rather small, which might underpower statistical outcomes. Finally, a basement effect might undermine the ability to detect differences in treatment effects, since in some studies mean patient baseline depression scores were rather low, too close to those indicative of remission. Nonetheless, in general, the therapeutic efficiency of bright light therapy, particularly bright light therapy adjunctive to antidepressant pharmacotherapies, has been found to be a promising approach in treating depression and with favorable clinical outcomes.[43]

Our trial has several limitations. First, it was a single-center study, and the cohort sizes of the 2 treatment groups were relatively small; thus, our results should be interpreted with caution. Further studies involving larger patient

sample sizes are required to evaluate both the safety and more rapid (earlier) and stronger effect of the combination antidepressant medication plus bright light therapy treatment in comparison to traditional antidepressant pharmacotherapy only. Second, our study included neither a single nor a double-blind protocol; as a consequence, certain unknown and unintended biases may have affected the findings. Third, our study followed patients for 8 weeks, and although this was long enough to substantiate statistically significant differences in the immediate effects of the 2 treatments, it was an insufficient duration to assess long-term clinical outcomes. Fourth, we cannot rule out a placebo effect of bright light therapy, since we did not incorporate a placebo control for it in the venlafaxine-only group. Fifth, although we scheduled BRT early in the morning because we did not utilize sleep diaries to record the patient's bed and wake-up times, we cannot conclude with certainty if its timing was optimal relative to the melatonin/circadian system/light phase-response. Sixth, we assumed an eye-level light dose of 7,000 lux at 60 cm; however, we did not possess assessment devices to measure the actual light intensity received from the Day Light Model DL930EU by our patients. These limitations should be addressed in future studies involving patients of diverse cultures and ethnicities. Finally, future studies should explore bright light therapy as an adjuvant treatment for therapies applied to the broad spectrum of affective disorders for which antidepressant medications are commonly prescribed and also for other clinical antidepressant interventions such as sleep deprivation and phase advance.

CONCLUSION

The results of our study entailing cohorts of hospitalized patients with severe MDD indicate morning bright light therapy when incorporated as an adjuvant to traditional antidepressant venlafaxine pharmacotherapy exerts strong antidepressant effects. Moreover, compared to venlafaxine treatment alone, venlafaxine + bright light therapy combination treatment, even when limited only to the first week of management, hastens the beneficial effects of venlafaxine such that crucial improvement in mood occurs after the first week of therapy and with statistically significant improvement in mood occurring after the second week of therapy. We believe our study provides convincing evidence for the efficacy of bright light therapy as an adjuvant treatment to antidepressant pharmacotherapy for severe MDD.

Drug names: fluoxetine (Prozac and others), imipramine (Tofranil and others).

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