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BIPOLAR DISORDERS (R HIRSCHFELD, SECTION EDITOR)

Use of "Lights" for Bipolar Depression

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Abstract

Purpose In this review, we will review the background and diagnosis of bipolar disorder (BD); describe the efficacy data and potential circadian and neural mechanisms underlying the effects of bright light for bipolar depression; and discuss the implementation of light therapy in clinical practice.

Recent Findings To date, morning bright light is the most widely tested form of light therapy for all mood disorders. Clinical trial reports suggest that midday or morning bright light treatment and novel chronotherapeutic interventions are effective for bipolar depression. Mechanisms of response may relate to effects on the circadian system and other changes in neural functioning.

Summary Using bright light to manage depressive symptoms in BD is reasonable but also requires concurrent antimanic treatment and careful clinical monitoring for response, safety, and mood polarity switch.

Keywords Bipolar disorder · Depression · Light therapy · Clinical trials · Chronotherapeutics

Introduction

Bipolar disorder (BD) is a major mood disorder that is characterized by interruptions with depressive, manic, and hypomanic mood episodes from a baseline level of euthymia. Recurrent depression is twice as common as recurrent mania (35% vs 14%) [1]. Having bipolar depression is frequently complicated by episodic and chronic illness, impaired psychosocial functioning, poor general health, reduced quality of life, and increased suicide risk [2, 3]. The indicated treatments for bipolar depression provide low rates of response in only 38% of patients who receive antimanic drugs and 32.4% who receive antimanic drugs with antidepressants [4].

Light therapy (LT) is a natural, low-risk intervention delivered with commercially available and inexpensive boxes for use at home or in the office setting (cet.org). LT provides a rapid, robust, and sustained antidepressant effect for seasonal affective disorder (SAD) [5, 6], non-seasonal major depression [7••], and depression in pregnancy [8]. Seasonal mood worsening and atypical mood symptoms which are frequently described in bipolar illness are highly predictive of a positive response to light therapy [9]. Given the limitations and complexity of drug therapies in BD, bright light and chronotherapeutic protocols are promising non-drug somatic options which target symptoms and enhance outcomes for bipolar depression. In this paper, we will review the background and diagnosis of BD; describe the efficacy data and potential circadian and neural mechanisms underlying the effects of bright light for bipolar depression; and discuss the implementation of light therapy in a clinical practice.

Bipolar Disorder: Background and Diagnosis The lifetime prevalence of BD is 1–2% and bipolar spectrum disorders, 3.7–6.4% [10]. Patients have persistent symptoms up to 47% of the time [11] and are at high risk for relapse with rates of 40% at 1 year [3] and 87% at 5 years [12]. The cumulative effects from loss of functioning are substantial, and the annual cost to society is as high as 24 billion dollars for persons with

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BD [13]. The defining feature of BD is mania or hypomania. Mania is an abnormally euphoric, expansive, or irritable mood state for a minimum of 1 week, with symptoms of grandiosity, agitation, excessive energy, racing thoughts, pressured speech, impulsive behaviors, distractibility, poor judgment, and impaired functioning. Hypomania is defined by 4 or more days of increased creativity, productivity, and sociability, or heightened irritability that is noticeable to family or coworkers. During major depressive episodes, patients have low mood or anhedonia, sleep disturbances (particularly delayed sleep phase), psychomotor agitation or slowing, difficulty with making decisions, inappropriate guilt or self-blame, atypical symptoms of increased appetite, weight gain, low energy, and hypersomnia, and with severe episodes, suicidal thoughts or plans, delusional beliefs, and hallucinations.

Episodes of major depression interspersed with episodes of mania or hypomania are most characteristic of BD-type I which affects women and men equally. The sub-types of BD including type II (major depressive episodes and hypomania), mixed episodes (concurrent manic and depressive symptoms), and rapid cycling (4 or more episodes of opposite polarity in 1 year) are more frequent in women than men. Patients with BD can endorse winter seasonal depression or SAD, which typically onsets in the autumn or winter, spontaneously resolves by springtime, and is classified with the DSM-5 specifier "With Seasonal Pattern." SAD and bipolar illness associate with an increased sensitivity to environmental cues that alter circadian rhythms and trigger relapse. Patients do not necessarily have an increased risk for seasonal mood variations [14] but may still derive an increased response to circadian modulators such as bright light, which can serve to regulate circadian rhythms and improve mood symptoms through this mechanism or another thymoleptic effect.

Why Consider Light Therapy?

Efficacy Data. Review of Past and Recent Publications (Table 1) Since the original reports of LT for SAD from three decades ago, a large evidence base has accrued to support its efficacy [15, 16]. The evidence base is grounded by the publications of three seminal studies that implicated the superiority of response to morning bright light presented with fluorescent bright white light boxes as a stand-alone intervention over plausible placebos [5, 6], and combined with fluoxetine [17]. Patients with manic depressive illness also displayed the classical phenomenology of SAD [18]. The patients showed a rapid, full response to bright light within 3–4 days of treatment [18, 19] and demonstrated an increased degree of melatonin suppression compared to normal subjects [20]. The impressive responses to morning bright light were not significantly different between bipolar and unipolar patients with winter depression [21]. The antidepressant effects quickly dissipated after withdrawal of the bright light or crossover to the non-active unit [18].

A parallel interest in LT for non-seasonal MDD has evolved [16, 22]. One hour daily of bright white light improved non-seasonal depressive symptoms significantly more than placebo units in early pilot studies [23]. Full-spectrum bright light (which is no longer used for safety concerns) was equally effective for non-seasonal and seasonal major depression [24]. Studies with larger samples and credible placebo comparisons showed LT was efficacious as a sole intervention and as adjunctive treatment [7••, 25]. Patients with non-seasonal major depression responded to daily treatment with 60 min of 10,000 lx bright white light at a higher frequency compared to 30 min of 50 lx placebo red light (67% vs 41%) [25]. Bright light therapy produced a significantly larger effect (Cohen's $d = 0.53$; 95% CI 0.18 to 0.89) compared to placebo in a meta-analysis of outcomes of non-seasonal depressed patients [16]. The largest, multi-site randomized clinical trial (RCT) confirmed that the mood improvement (measured by change in depression scores) from 10,000 lx bright white light from 7 to 8 AM [7••] was superior to placebo after 4, 6, and 8 weeks of treatment and similar to the changes from an antidepressant drug response [26]. Bright white light (Cohen's $d = 0.80$, 95% CI 0.28 to 1.31), and bright white light plus fluoxetine (Cohen's $d = 1.11$, 95% CI 0.54 to 1.64) produced large and significant treatment effects compared to placebo (presented in the form of a placebo pill and inactivated unit) [7••].

To date, morning bright light is the most widely tested form of light therapy for all mood disorders. The pilot studies on bipolar depression were promising and suggested high levels of responsivity to morning or midday bright light [19, 23, 24, 27–30]. Surprisingly, morning LT has been compared against placebo units for bipolar depressive episodes in only three RCTs [29–31]. In a 2-week placebo-controlled trial of morning LT for 1 h daily, the response (≥ 50% reduction on the Hamilton Rating Scale for Depression, HRS-D) to 5000 lx white LED light was significantly greater than dim (< 100 lx) red light (78%, 26/33 vs 43%, 13/30; $p < 0.01$) and corresponded with lower HRS-D depression scores (8.6 ± 3.4 vs 10.5 ± 3.2, $p = 0.03$, respectively) [29]. Another study examined 8 weeks of morning treatment for 60 min/day with 7000 lx white light compared to low-density negative ionization and did not find significant differences on measures of response (≥ 50% reduction on the Structured Interview Guide for the Hamilton Depression Scale with Atypical Depression Supplement, SIGH-ADS; bright light = 50% vs low density = 55.6%) and percentage reduction on the SIGH-ADS depression scores (bright light = 52% vs low density = 47%) [30]. In the third study, 2 weeks of morning treatment for 30 min/day with 10,000 lx morning light provided significantly higher rates of response (≥ 50% reduction on the Montgomery–Asberg Depression Rating scale, MADRS; 81% vs 19%,

Table 1 Studies on Light Therapy for Bipolar Depression: Study Design, Eligibility Criteria, Intervention and Mood Polarity Switch

Studies	Year	Design	Groups (N)	Diagnosis and Eligibility Criteria.	Intervention	Duration of intervention	Mood Switch Potential	Comments
Light Therapy for Bipolar Depression								
Light therapy for bipolar disorder: a case series in women. Sit et al, Bipolar Disorders, 2007. (Reference #45)	2007	Dose ranging, prelimi-nary safety and efficacy study with pbo lead-in.	dim red light n=9, morning light n=4, midday light n=5.	Women with BD type I or II (SCID interview), current major depression and moderate or severe episode (SIGH-ADS ≥ 20), no current mania (MRS ≤ 4), stable antimanic therapy, stable antidep drug therapy, no rapid cycling, no psychosis, no OCD, no active SI, no alcohol or substance use d/o, no photosensitizing drugs.	Placebo lead-in (50 lux red light) for 30 min/d for 2 wks, followed by 7,000 lux, 4,000 Kelvin, UV filtered bright light for 15 min/d, increase by 15 min q 2 wks, target dose of 45 min/d.	8 weeks acute phase, 16 wks continuat phase	MRS: morning light induced mixed episodes in 3 of 4 within 2 wks of initiating treatment. NO polarity switch with midday light.	Seasonality: acceptable to have both seasonal and non-seasonal patterns.
Adjunctive bright light therapy for bipolar depression: a randomized double blind pbo controlled trial. Sit et al, Am J Psychiatry, 2018. (Reference #44)	2017	RCT	bright white N=23, dim red light N=23.	BD Type I or II (SCID interview), current major depression and moderate or severe episode (SIGH-ADS ≥ 20), no current mania (MRS ≤ 4), stable dose antimanic therapy, stable dose antidep drug therapy, no change in psychotherapy, no rapid cycling, no photosensitizing drugs, no eye disorders, no psychosis, no OCD, no active SI, no alcohol or substance use disorder.	Bright white light (7,000 lux, 4,000 Kelvin) vs dim red light (50 lux), identical external appearance. Midday exposure (NOON and 2:30 PM) for 15 min/d for one week, increase by 15 min each week, to reach a final target dose of 60 min/d by week 4 or until remission. Continue midday light for 60 min/d (or at remission dose) until week 6.	6 weeks	Weekly MRS scores; no mood polarity switch	Seasonality: BLT and dim red light groups both endorsed a high frequency of seasonal episodes (82.6% vs 82.6%) and a moderate degree of seasonality on the Personal Inventory of Depression and SAD (PIDS) subscale (11.0, sd 4.4 vs 11.3, sd 7.0).
Clinical efficacy, onset time and safety of bright light therapy in acute bipolar depression as an adjunctive therapy: A randomized controlled trial. Zhou et al, J Affective Disorders, 2018. (Reference #29)	2018	Single Blind Trial	bright light N=33, vs dim red light N=30.	"Clinical criteria for bipolar disorder, depressed phase," verified on medical record, stable "psychotropic medication" for 2 weeks, no antidepressant therapy, baseline HAMD>17, YMRS<12, no concurrent ECT/TMS, no substance abuse, healthy vision, not pregnant or	Morning light for 1 hours daily. "BLT" device: 180 watt LED, 5,000 lux and 10,000 K. Dim red light: <100 lux. Note: white LED typically emit 4,000 to 6,400 K. Limitation: description of the study LED bulbs is improbable. Anything that emits 10,000 K would produce something akin to an	2 weeks	No hypomania. BLT, YMRS increased by 10 in one patient. Dim red light, 8 point increase in the YMRS in one patient.	No evaluation of seasonality.

Table 1 (continued)

Studies	Year	Design	Groups (N)	Diagnosis and Eligibility Criteria.	Intervention	Duration of intervention	Mood Switch Potential	Comments
				lactating, no photosensitizing drugs.	outdoor sky effect (unlikely that any device or LED can produce this level of effect).			
Efficacy of bright light therapy in bipolar depression. Kupeli et al, Psychiatry Research, 2018. (Reference #31)	2018	Single Blind Trial	bright light N=16, red light N=16.	DSM-IV BD type I or II, HAMD >17, stable "maintenance dose" for one month, no psychosis, suicide risk, chronic or serious medical condition, eye and neurological disorders.	Morning light, 2 fluorescent 72 watt bulbs emitting 10,000 lx for 30 min/d. Red Light: 500 lx.	2 weeks	NO assessment	Seasonality: no specific measure used; 25% assigned to BLT endorsed a seasonal pattern. Did not inquire seasonality in the red light group.
Light therapy and fluvoxamine in the treatment of bipolar psychotic depression: a pilot study. Franchini L et al, Clinical Neuropsychiatry, 2009. (Reference #35)	2009	Open Label Trial	fluvoxamine n=10, fluvoxamine plus light n=16	BD-I, severe depression with psychotic features, no other Axis I, no alcohol or substance use disorder, no epilepsy, no major medical diseases, no MAOI, no IM antipsychotic agents.	FVX: 100 mg daily on days 1-3, 100 mg bid days 4-7, 150 mg bid thereafter PLUS lithium (11 pts) and flurazepam 45 mg daily. Sessions: 30 min/d of 10,000 lux light between 4:45 AM and 8:45 AM.	6 weeks	FVX plus LT: 1 manic switch, FVS only: no switch	No evaluation of seasonality.
Effect of adjunctive LT on ameliorating breakthrough dep in adolescent onset BD. Papatheodorou and Kutcher, 1994. (Reference #32)	1994	Open Label Trial	Single group, n=7	Ages 16 to 22 years with DSM-III-R BD and persistent depression >3 weeks, confirmed on the KIDDIE-SADS. Lifetime Diagnoses: 2-rapid cycling, 2-affective psychosis, 6-clear manic episodes, 1-early onset mood swings and psychotic depression.	BLT: 10,000 lux cool-white, UV filtered, fluorescent unit for 45-60 min/d between 0700 and 0900 every morning AND between 1900 and 2100 every evening.	1-week in the hospital and take home light box prn.	none, hospitalized and rec'd close monitoring, but did not use a rating scale.	No evaluation of seasonality.
Non-Seasonal Bipolar Depression								
Sham controlled randomized trial of adjunctive light for non-seasonal depression. Chojnacka et al, J Affective Disord, 2016. (Reference #36)	2016	RCT	Bright white N=52, sham control N=43.	Adults "with... unipolar or bipolar depression," current major depressive episode, antidepressants in sufficient doses for at least 4 weeks, mood stabilizers or antipsychotics OK; no alcohol or substance dependence, no SAD, no	Bright white light (10,000 lux) or sham device for 30 min/d between 8 and 9 AM. Sham: "created from converted computer equipment" which "looked like a true ion generator, but it had no therapeutic... efficacy and no ions were emitted".	2 weeks	NO assessment	Exclusion: SAD per Seasonal Health Questionnaire (Thompson et al, 2001).

Table 1 (continued)

Studies	Year	Design	Groups (N)	Diagnosis and Eligibility Criteria.	Intervention	Duration of intervention	Mood Switch Potential	Comments
				severe physical disease, no eye disease, not pregnant or breastfeeding. BD=50, unipolar=45.	Note: Missing descriptions of the randomized procedure and protection of the blind.			
Augmentation of light therapy in difficult to treat depressed pts. Camardese et al, Neuropsych Dis and Treatment, 2015. (Reference #34)	2015	Open Label Trial	Single group, n=31	HAMD-21 ≥ 15 (mild episode per Zimmerman et al, 2013) and "difficult to treat" according to Rush criteria, no non-affective psychosis, no substance use disorders, no recent suicide attempt, no ocular disease, no dementia or cognitive disorder. unipolar-16, bip-15.	Bright light (10,000 lux) for 30 min/d between 5:45 AM and 8:15 AM. If none or partial response after one week, increase to 45 min/ for weeks 2 to 3.	3 weeks	Young Mania Rating Scale; mania ratings increased across 5 weeks but the change in score was not significantly different between groups.	Seasonality: response rates were not affected by the interaction of dx by season.
Controlled trial of safety and efficacy of BLT vs negative air ions in patients with bip dep. Dauphinais et al, 2012. (Reference #30)	2012	RCT	bright light n=18, vs low density negative ions, n=20	BD type I or II (MINI interview), depressed phase, no manic episode, stable-dosed medications required, NO SAD per DSM-IV criteria for seasonal pattern, no other medical disorder, no other Axis I as a principal diagnosis, no spontaneous decrease of depressive symptoms (reduction of baseline SIGHADS ≥ 25%), no suicide risk, no change in psychotherapy, no use of illicit drugs, no ocular disease, no photosensitizing drugs.BD type I or II (MINI interview), depressed phase, no manic episode, stable-dosed medications required, NO SAD per DSM-IV criteria for	Screening and stabilization (0-31 days). Treatment (8 weeks). Follow-up (8 weeks). BLT: 7,000 lux for 7.5 min/d upon morning rising for 3 days, then 15 min/d, each week, increase dose by 15 min (7.5 min increments), target maximum of 45 min/d by Week 4 or after.	8 weeks	Irritability (Low) and hypomania (BLT and Low) which resolved by Week 8 and did not result in polarity switch.	Global Seasonality Scale assessed at baseline. No season by time interaction for the MADRS from Light tx in the winter vs other seasons.

Table 1 (continued)

Studies	Year	Design	Groups (N)	Diagnosis and Eligibility Criteria.	Intervention	Duration of intervention	Mood Switch Potential	Comments
				seasonal pattern, no other medical disorder, no other Axis I as a principal diagnosis, no spontaneous decrease of depressive symptoms (reduction of baseline SIGHADS ≥ 25%), no suicide risk, no change in psychotherapy, no use of illicit drugs, no ocular disease, no photosensitizing drugs.				
Summertime bright light treatment of bipolar major depressive episodes. Bauer, 1993. (Reference #33)	1993	case reports, open treatment	Single group, n=3	DSM-III-R Bipolar Disorder and current major depressive episode.	LT with 2,500 lux cool white fluorescent light, for 2 hours/d between 6 AM and 8 AM. Small sample size.	6 weeks	1 (of 3) developed manic symptoms and light was discontinued after the trial.	non-seasonal episode (3 cases rec'd summertime light)
Controlled trial of bright light for nonseasonal major depressive disorders. Kripke et al, 1992. (Reference #23)	1992	RCT	bright white n=25, dim red n=26.	MDD n=42, BD n=11. Diagnoses: unipolar recurrent n=27, unipolar single episode n=12, dysthymic disorder n=13, atypical bipolar n=6, bipolar depressed n=4, bipolar manic n=1, and cyclothymic disorder n=1.	Evening BLT (2000-3000 lux) from 8 to 11 PM n=20 vs Dim Red Light from 7-10 PM n=19. (Initially 7-dim red and 5 BLT used 2 hours of light 5-6 AM AND 9-10 PM without significant effect before changing protocol). Limitation: small number of bip pts.	1 week	BLT: 2 - agitated (per report, not manic but per dsm5, maybe so), 2 - mildly hypomanic.	Post-protocol, tx withdrawal resulted in rapid relapse within 2 days in the BLT group. NONE had SAD per Dr. Rosenthal's scoring of the SAD-GLAD scale.
Phototherapy in nonseasonal depression. Mackert et al, 1991. (Reference #40)	1991	RCT	white light n=22, red light n=20.	DSM-III-R, non-seasonal MDD or BD. NO ophthal disorders, alcohol or substance abuse, brain injury, neurological disorders, acute suicidality. MDD=18, BD=6.	2500 lux full spectrum for 2 hrs/d from 7:20 AM to 9:20 AM vs 50 lux dim red light. Medication OK: 3-no mood stabilizer, 2-perazine (mid potency typical antipsychotic), 1-clomipramine. Limitation: small number of bip pts.	1 week	not assessed	Excluded SAD patients
Effects of phototherapy on non-seasonal unipolar and bipolar depressive spectrum disorders.	1991	RCT	2,500 lux vs 400 lux. Missing numbers per group.	Enrolled patients from November to February without seasonal pattern, no psychotropic or	LT: 2 hr/d for 7 consecutive mornings between 8 AM and 11 AM, within 1 hr of normal wake time, "to	1 week	HIGH-SAD - no switches	"pts had... past dep episodes... in summer as well as winter, without a predilection for episodes

Table 1 (continued)

Studies	Year	Design	Groups (N)	Diagnosis and Eligibility Criteria.	Intervention	Duration of intervention	Mood Switch Potential	Comments
Deltito et al, 1991. (Reference #27)				hypnotic medications, no past "full blown manic episodes". Unip=11, BDII=6.	avoid phase advancing." Limitation: small number of bip pts.			during only one season…"
Morning light treatment hastens the antidepr effect of citalopram. Benedetti et al, 2003. (Reference #41)	2003	RCT	Green light n=18 (BD=6), pbo deactiv unit n=12 (BD=3).	DSM-IV MDD or BD, without seasonal pattern. Recruitment during the winter months, no other Axis I, no alcohol or substance abuse, no suicidality, no depot injections, no epilepsy, no tx with MAOI, no pregnancy. unipolar=21, BD=9.	400 lx green light at 6:00 AM for 30 min/d + citalopram 40 mg daily vs drug + deactivated neg ion generator at 7:45 AM for 2 weeks. Timing of light designed to induce phase advance. Limitation: small # of BD.	2 weeks	not assessed	Excluded pts with a "seasonal pattern".
Seasonal Bipolar Depression								
Circadian time of morning light administration and therapeutic response in winter depression. Terman JS et al, 2001. (Reference #37)	2001	Cross-over design.	M=morning, E=evening. Two groups: M1E2 n=21, vs E1M2 n=21.	DSM-III-R MDD OR BD NOS, winter seasonal depression, no suicide risk, comorbid Axis I disorder. uni=29 bip=13.	BLT: 10,000 lux 2,700 K, 28 x 61 cm units. Morning LT, 30 min/d at awakening ~6:30 AM and evening ~ 2 hrs bef bedtime. Two week baseline interval to confirm diagnosis, then randomized to M1E2 or E1M2 and 10-14 days for each time-period (M/E) for 20-28 days of tx. Limitations: effects from second exposure contaminated by first exposure, small number of bip pts.	Morning - 2 wks, PM - 2 weeks	not assessed	Examined groups based on median circadian time (CT) of 9.53 hours after DLMO (or estimated DLMO per baseline mid-point sleep) and separated into 2 groups with earlier vs later median CT. Pts with an earlier CT showed higher remission rates from M light (16/20=80% vs 8/21= 38.1%) compared to later CT, and still some response to E light (12/39=30.1%).
Controlled trial of timed bright light and neg air ionization for tratment of winter depression. Terman M et al, 1998. (Reference #6)	1998	Cross-over design.	Bright Light, High vs Low Density ion generating devices. 6 Groups (n=19 to 27/grp): ME, EM, MM and EE, high-high and low-low ion devices.	DSM-III-R MDD OR BD NOS, winter seasonal depression, no suicide risk, comorbid Axis I disorder. Also "abstained from psychotropic medication", no alcohol, no recreational drugs, no other Axis I, no suicide attempts in 3 yrs, no	Bright light: 10,000 lux, 30 min/d, high density ions: 4.5 X 1013 ions/sec, low density ions: 1.0 X 1011 ions/sec for 30 min/d. Two week baseline, study period for 20-28 days, withdrawal phase for 1-3 weeks.	2 consecut tx, each 10-14 days	not assessed	Insufficient N of bip pts.

Table 1 (continued)

Studies	Year	Design	Groups (N)	Diagnosis and Eligibility Criteria.	Intervention	Duration of intervention	Mood Switch Potential	Comments
				habitual late sleep onset after 1 AM or awakening after 9 AM. MDD=89, BD NOS=29, BD=6.				
Bright Light Treatment of Winter Depression. Eastman et al, 1998. (Reference #5)	1998	RCT	Morning 6,000 lux Light n=33, Evening 6,000 lux Light n=32, Pbo sham neg ions n=31	"Usual criteria for SAD" and atypical symptoms. Did not explicitly exclude patients with BD.	BLT: 6,000 lux versus pbo: sham neg ion generators for 1.5 hours daily. Limitation: missing numbers of pts with BD vs MDD.	4 weeks	not assessed	Insufficient N of bip pts.
Mood and behavioral effects of four-week light treatment in winter depressives and controls. Bauer MS et al, 1994. (Reference #38)	1994	open trial	2,500 lux LT for winter dep n=12 vs LT for controls n=12 vs quiet activity for controls n=12	Winter dep: MDD-9, hyperthymic-1, BD-2, no substance dependence, no medical illness, no psychotropic medications. Controls: "free of any current or past psychopathology", no family history of Axis I, no medical problems, no medications.	LT: 2,500 lux light between 0600 and 0800 hours for winter depressives vs controls, and 2 hours quiet activity at 0600 for controls.	4 weeks	YMRS ratings. 1 "depressive" switched into hypomania at BL, "dropped from study", 4 dep developed clinically sig hypomania; symptoms remitted after LT halted or decreased to 1 hour daily."Pts were symptom free with shorter durations of light exposure."	Insufficient N of bip pts.
Changes in norepinephrine output following light therapy for fall/winter seasonal depression. Anderson JL et al, 1992. (Reference #39)	1992	open trial	"morning" bright light versus bright light "at varying times each day" (missing n/group)	DSM-III-R recurrent MDD or BD NOS with seasonal pattern, n=9.	2,500 lux morning LT 1 hr/d OR LT for 1 hr "at varying times each day". Limitation: missing # of BD vs MDD.	2 weeks	not assessed	Insufficient N of bip pts.
Seasonal Affective Disorder: a description of the syndrome and preliminary findings with light therapy. Rosenthal NE et al, 1984. (Reference #18)	1984	Crossover study.	2,500 lux full spectrum, versus 100 lux dim yellow light.	Major affective disorder per Research Diagnostic Criteria and at least 2 consecutive years of maj dep episodes which recurred in the fall/winter and remitted the following spring or summer, BD-II=22, BD-I=5, unipolar=2.	Two separate kinds of light were used: bright, white full-spectrum fluorescent light (2,500 lux at 90 cm), and dim yellow fluorescent light (100 lux at 90 cm). Asked to sit in front of the lights for 3 hours before dawn and 3 hours after dusk for 2 weeks.	2 weeks	see results	93% of SAD pts enrolled with BD II or I.

respectively, $p < 0.0001$) and remission (MADRS < 9; 44% vs 12.5%, respectively, $p = 0.05$) compared to 500 lx red light [31]. In two of the studies, mania/hypomania from morning bright light were absent or rare events [29, 30]; the third study lacked a standard mania measure [31]. The 8-week trial of morning bright light compared with low-density negative ionization produced similar and rather robust response and remission rates of 50% and 55.6%, respectively [30]. Their findings implicated the intriguing but unanticipated effects from the comparator unit or the pre-trial stabilization phase that was designed to ensure participant safety [30]. Many of the publications were limited by the small numbers of cases, lack of controls [32–35], brief duration of treatment and follow-up (only 2 weeks) [29, 31], and insufficient description of their study design [36]. Others examined bipolar and unipolar patients together without a breakdown of outcomes per group [5, 25, 36–39], did not indicate the numbers of unipolar vs bipolar patients [5, 39], and oversampled for unipolar patients [23, 27, 37, 38, 40, 41] which can result in misattributions of the positive response and raise questions about the generalizability of the reports. Not assessing for emergent mania/hypomania especially in patients with bipolar illness presents the added concern for detection bias [42–44] and provides no information into the tolerability of LT.

Given the limited treatment options, our group explored the effects of light therapy in a dose-ranging, preliminary safety and efficacy trial for non-rapid cycling, mood-stabilized, currently depressed patients with DSM-IV BD I or II [45]. Participants were assigned morning light starting with 50 lx red light for 30 min/day for 2 weeks, then transitioned to 7000 lx white light for 30 min/day. Every 2 weeks, the light dose was increased by 15 min to reach a target of 45–60 min/day. With morning bright light, one patient experienced full response but three developed mixed states (Fig. 1) and two ceased the light treatment immediately. The mixed symptoms emerged shortly after initiating and experiencing the brief euthymic effects of morning light.

Because of the unexpected and rapid induction of mixed mania from morning light, our group re-examined the literature and discovered that others including Leibenluft et al. [28] also found destabilizing effects of morning light in patients with rapid cycling bipolar illness. With morning light, one patient developed worsening depression; in another, ultra-rapid cycling ensued; and in the third case, the patient cycled from depression to hypomania then back into major depression [28]. In contrast, midday light successfully restored euthymia in two rapid cycling patients with depression [28]. Their evidence corresponds with the hypothesis that bright light can produce an enlargement of the amplitude of melatonin secretion and, consequently, a more robust and stable endogenous circadian rhythm [46]. Moreover, midday light possibly curtails the induction of a large circadian phase advance which is commonly attributed to the therapeutic effect from morning light exposure. Inducing circadian rhythm stabilization plus an antidepressant response using properly timed light (at midday) would be a real advantage for patients with rapid cycling or treatment refractory illness who often cannot tolerate the activating effects of antidepressant drug or device-based treatments.

Given the promising, albeit preliminary findings from others, we adjusted the timing of light to midday, i.e., between noon and 2:30 PM. With midday light, three patients experienced full response and one who responded partially experienced full response to morning light [45]. The depression score reduction was large and significant (mean SIGH-ADS −13.1, 95% CI = −7.8 and −18.4; $p = 0.0006$) and patients did not show any intolerable adverse effects or mood polarity switch from 6 weeks of midday light (Fig. 2). The induction of mania/mixed episodes from morning light [45] was not so unusual and also described in reports of morning bright light in rapid cycling [28], non-seasonal, seasonal, and even antenatal depression [23, 33, 38, 47]. In the next study, we examined 7000 lx bright white light at midday as adjunctive treatment for moderate or severe bipolar depression in a randomized, double-blind, placebo-controlled clinical trial [44••]. The group randomized to bright white light showed a significantly higher rate of remission (68.2% vs 22.2%; adjusted odds ratio = 12.6, $p = 0.004$; Fig. 3) compared with dim red light. No hypomania, mood polarity switch, or serious adverse effects were observed. Patients who received midday bright white light vs dim red light had significantly lower depression scores, better global functioning, less excessive sleep, and less trouble concentrating.

Chronotherapeutics: a Novel Approach Chronotherapeutics or "triple chronotherapy" is another promising, novel, and rapidly acting intervention [48, 49]. Integration of the three component modalities provides the most robust response: [1] sleep deprivation is intended to provoke a rapid antidepressant effect, [2] phase-advanced sleep schedule corrects the phase-delayed activity/sleep pattern; and [3] morning bright light is implemented to reverse the depressogenic effects of recovery sleep after sleep deprivation, and sometimes, bright light is added at midnight to promote alertness during the epochs of sleep deprivation [50]. Because of the protocol design, it is difficult to attribute the antidepressant effects solely to bright light when another potent competing or complementary modality is being used at the same time [44••]. To address this difficulty, investigators have incorporated ingenious, modalities for comparison e.g. implementation of non-phase advancing sleep, carefully timed partial night sleep deprivation, and exposure to bright light at midday, all of which minimize the circadian effects and produce an acceptable comparator. Preliminary reports on dysphoric premenstrual women [51], depressed pregnant women [52], and bipolar depressed adults [53] suggest that this strategy is feasible but studies with sufficient numbers are still needed.

Pathophysiology and Putative Mechanisms of Bright Light: Circadian Effects Human behavior and physiology such as sleep-wake cycles, physical activity, core body temperature, cortisol, and melatonin release vary according to diurnal or circadian rhythms [54, 55] and are highly responsive to light. Light from the environment is integrated by the suprachiasmatic nuclei (SCN) which is embedded within the anterior hypothalamus. The SCN provides the intrinsic drive and genetic machinery to regulate circadian rhythms [56–58]. In humans, melatonin is secreted in a nightly pattern, suppressed by light exposure, and virtually undetectable during the daytime. The timing of nocturnal melatonin secretion serves as one reliable marker of the central circadian clock [55, 59].

Phase Shift Model The mechanism by which light therapy exerts an antidepressant effect is not fully known. The most prominent hypothesis is the phase shift model, which proposes that some mood disorders and more specifically SAD, involves a mismatch between the sleep–wake cycles and the circadian pacemaker in the SCN [60–62]. In SAD patients, the characteristic delayed sleep/wake pattern represents a form of circadian phase delay which is not in synchrony with the internal time clock [60] but is readily corrected with properly timed exposure to morning bright light to produce a circadian phase advance. The efficacy of morning bright light is likely tied to the induction of circadian sleep phase advance [46]. The extent to which morning light advanced circadian rhythms correlated with the degree of SAD symptom reduction [37]. However, others did not replicate the findings [63]. Certain aspects of circadian dysregulation may be present in non-SAD episodes and contribute to depressive mood symptoms [62, 64–66]. Hence, circadian phase advancement strategies are beneficial for not only SAD but possibly for non-seasonal depression and instances of SAD episodes without major circadian phase delay [37]. For this reason, bright light and some antidepressant drugs and mood stabilizers, e.g., lithium may derive at least some of their efficacy from their phase-advancing effects on the circadian clock [67]. Bright light in the morning can also produce enlargement of the circadian amplitude which imparts stabilizing effects on the circadian clock's rhythmicity and timing, and thereby preventing extremes in circadian phase shifts, increasing the resistance to further shifts and possibly reducing depressive symptoms [46].

Why midday light? Responsivity to light is typically taken as evidence of involvement of the circadian system in mood disorders. However, the response to light therapy may be independent of the time of day or circadian system [68]. The antidepressant effects of midday and evening bright light are plausible and described in seasonal, non-seasonal, bipolar-depressed, and rapid-cycling patients [6, 28, 44••, 68]. The gradual emergence of response to midday bright light in bipolar-depressed patients [44••] was similar to the response to morning exposure in non-seasonal- and perinatal-depressed patients [7••, 8] but contrasted with the ultra-rapid response in SAD patients [20, 69]. Midday bright light improved sleep parameters in some patients [70] and induced small advances in circadian phase [70] and small increases in the amplitude of nocturnal melatonin production in healthy subjects [66] and elderly patients with insomnia [70]. However, correlations between mood improvement and the subtle changes in circadian phase and amplitude from midday light have not been established yet and require further study. Together, midday light may produce a less potent effect on circadian rhythms, but still target a separate depression neural pathway to improve affective symptoms.

Pathophysiology and Putative Mechanisms of Bright Light: Neurotransmission and Light There is a growing focus on the impact of bright light on neural functioning and the photic effects on serotonin neurotransmission [71]. Broad-spectrum light therapy enhanced serotonergic transmission in healthy volunteers and patients with SAD [72, 73•]. In contrast, depletion of the serotonin and dopamine precursors (tryptophan and catecholamine) quickly reversed the antidepressant effects of light therapy and induced relapse, low mood, and anhedonia in remitted patients with recent SAD [74, 75]. Winter-time treatment with bright light significantly increased serotonin activity in the anterior cingulate cortex [73•] but produced no effect in the autumn [72]. The serotonergic effects of bright light were also observed in the prefrontal cortex, and to a lesser degree in the midbrain [73•]. The serotonergic system also distributes projections from the midbrain raphe to the SCN and provides regulatory input to the circadian pacemaker [76]. Activation of the serotonin 1A receptors produced large circadian phase shifts and inhibition of serotonin 1A activity (from an extended light pulse) associated with circadian inertness [77]. Although bright light enhances serotonergic transmission, the non-responders to bright light combined with sleep deprivation showed much lower pre-treatment levels of serotonin compared to responders [78]. Therefore, in patients with severe deficits in serotonin, some chronotherapeutics may not provide a sufficient response and other treatment modalities might be indicated.

Variations of the serotonin transporter (SERT) gene correlated with differences in serotonin signaling, risk for mood disorder, and response to treatment. The short (S) allele variant associates with reduced serotonin signaling [79] and increased risks for SAD [80] and atypical depression [81], compared to the long (L) allele. In patients with BD, the carrier of the L-allele was markedly predictive of response to bright light [41]. Asymptomatic S-allele carriers also showed corticolimbic changes associated with mood improvement with reductions in amygdala and medial prefrontal cortex (mPFC) activity during negative stimuli, after 3 weeks of daily bright light exposure [82]. Together, the compelling pilot data findings implicate the SERT gene variant as a moderator of light

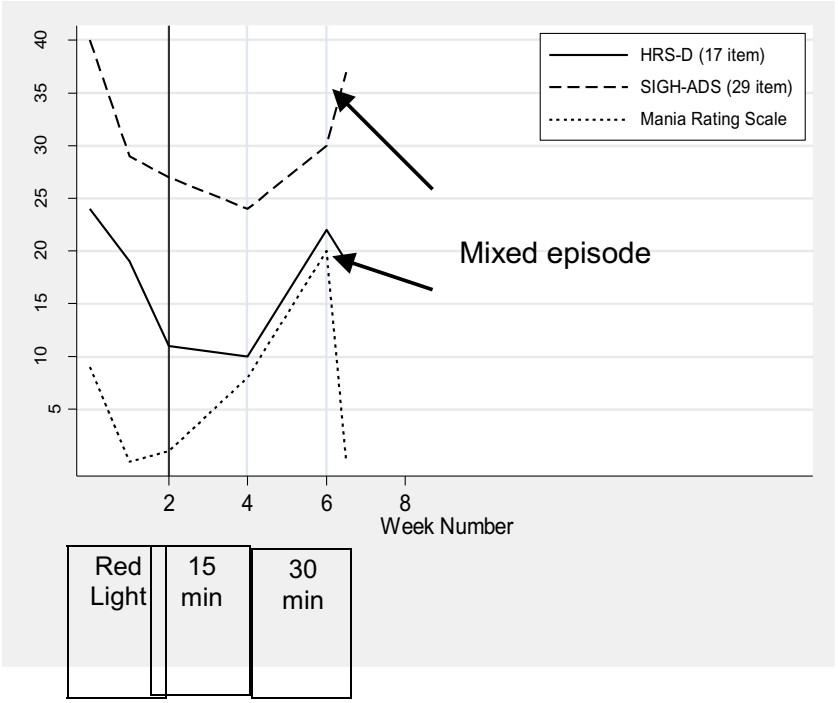


Fig. 1 Response to morning light

treatment response but require further study to replicate and validate the findings.

Impact of Light Therapy on Neural Function To understand the neural effects of light therapy, the majority of studies examined the changes in cortical blood flow [72, 73•] and functional activity. Studies of functional activity indicated significant improvements in cortical functioning mainly in the frontal and limbic areas and some changes in the pituitary volumes. Using measures with functional magnetic resonance imaging (fMRI) bright light induced increased brain responses and enhanced coupling between the prefrontal cortex and the amygdala in healthy men [82]. The effects of bright light also improved functioning in the brainstem and subcortical regions of healthy patients [83]. The severity of winter depressive symptoms was positively correlated with the volume of the pituitary gland

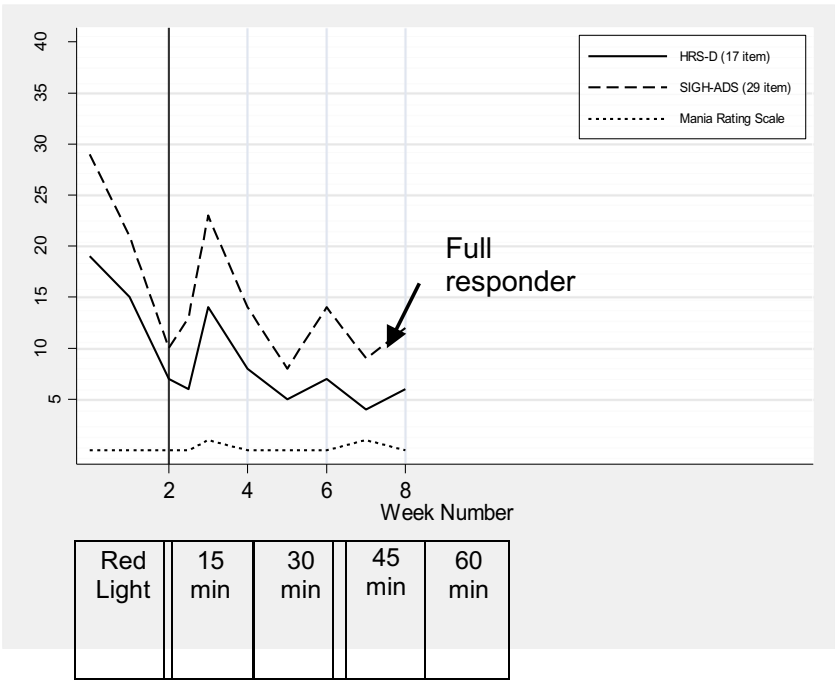
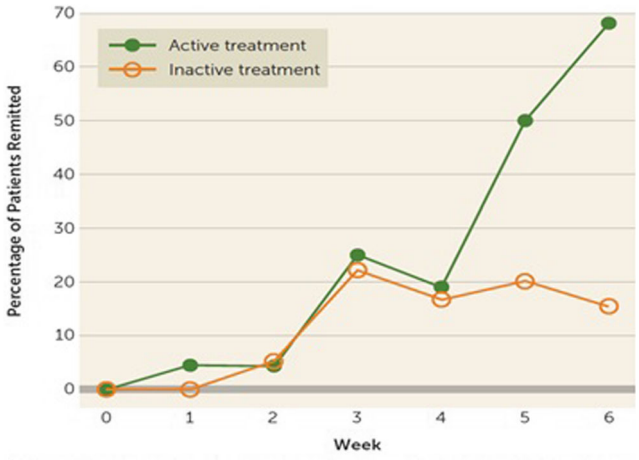


Fig. 2 Response to midday light



[a] Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio=7.50, 95% CI=1.80, 31.28, p=0.003; adjusted odds ratio=12.64, 95% CI=2.16, 74.08, p=0.004).

Fig. 3 Remission rates across study weeks for bipolar-depressed patients randomized to bright white light compared with dim red light. Significant difference in remission rates between the active treatment group (68.2%) and the inactive treatment group (22.2%) (odds ratio = 7.50, 95% CI = 1.80, 31.28, $p = 0.003$; adjusted odds ratio = 12.64, 95% CI = 2.16, 74.08, $p = 0.004$). From Sit DK et al. [44••]. Copyrighted by the American Journal of Psychiatry, 2018. Used With Permission from the American Psychiatric Association Publishing

[84] but not necessarily with symptom reduction from light therapy. Patients who were susceptible to the negative effects of sleep-loss showed improvements in fMRI signals from blue compared to green light, in the ventrolateral prefrontal cortex (PFC), dorsolateral PFC, and intraparietal sulcus [85]. Blue light particularly enhanced the responses to emotional stimuli in the temporal cortex and in hippocampus which were not affected by green light [85]. Improvements in mood symptoms pointed to changes in neural functioning produced by bright light [86] but replication is needed to confirm their findings.

Neural functioning studies are starting to discriminate between patients who respond to light therapy compared to those who do not. Responders showed increased cortical blood flow in the frontal cingulate and thalamus from measures with positron emission tomography (PET) [87] and increased connectivity among the PFC, anterior cingulate cortex, and insula, which was related to symptom reduction to combined light therapy and sleep deprivation treatment [88]. Those who did not respond to treatment showed lower connectivity measures at baseline and after treatment [88]. Depressed individuals who responded to light therapy and sleep deprivation showed greater increases in neural excitability than those who did not respond from measures of electroencephalography (EEG) with transcranial magnetic stimulation (TMS) [89]. EEG signals such as alpha, theta, and delta power improved in the responders to light therapy over those who were non-responders [90]. Responders to the combination treatment with sleep deprivation and morning bright light also showed increased blood flow in PFC, anterior cingulate, and subcallosal gyrus, but reduced blood flow in medial PFC and frontal pole at baseline [48, 49]. Together, bright light likely imparts effects on the depression neural pathways. The data provide hints at differential responses in neural functioning which may be predictive of treatment response but further study is needed to confirm the potential role for uses in treatment planning.

How to Implement Light Therapy (Table 2)

Important determinants of the efficacy and side effects of bright light are closely tied to the timing [91, 92], intensity [64, 66, 92], duration [93], wavelength [67, 93, 94], and distance from the light box. Most light sources provide 10,000 lx (illuminance) at a distance of 12–13 in. Although treatment recommendations for SAD [15] suggest a starting dose of 10,000 lx of morning light for 30 min daily, the earlier literature did not provide specific guidelines for BD other than the need for antimanic drug coverage. Small pilot studies have used 2500 lx for 2 h every morning [27], 400 lx daily for 2 h [27], 400 lx green light plus sleep deprivation [50], and 10,000 lx for 45–60 min twice daily [32] to improve depressive symptoms of BD. Recent studies implicated response with 7000 lx broad-spectrum light for 30–60 min at midday [44••, 45]. Although optimal efficacy may be attributed to the blue wavelength [57, 58], broad-spectrum white light units are preferable because they are most available for purchase by patients and have an established record of ophthalmic safety [95]. Patients are advised to receive antimanic therapy before starting light therapy and to have regular monitoring and guidance from a trained clinician during their treatment with bright light. The suggested device is the broad-spectrum light box unit which emits 7000 lx, 4000 K of blue enriched bright white light and conforms to high standards for design and production (www.cet.org). The preferred unit measures 12 in. by 14 in. and provides illumination of a broad visual field, lighting from above to avoid glare and maximal ultraviolet filtration. The optimal placement of the unit is on a desk stand at a distance of 12 in. from the eyes, with the patient asked to face the light box without directly staring at it (to minimize discomfort) during the daily sessions of light therapy. Patients are recommended to use the light box treatment daily at home or work. Treatment begins with 15-min/day of light therapy between 12:00 PM and 2:30 PM; every week, the duration increases by 15 min to reach a target dose of 60 min/day or until the mood symptoms have fully remitted. Increasing the light dose depends on the tolerability, side effects, and any hypomanic/mixed symptoms. Early remission (minimal to no symptoms and normal functioning) is expected by 4–6 weeks of treatment [44••]. For patients with partial or minimal response with midday bright

light, the next step is to move the timing of LT to the morning and titrate to a dose of 45–60 min/day [44••].

Adverse Effects of Light Therapy The standard 7000–10,000 lx, ultraviolet-blocked, white fluorescent light box presents minimal risk of adverse outcomes [21, 67]. Light is a uniquely flexible treatment, and the rapid onset and offset of effect can be harnessed to clinical effect. Adverse effects usually subside quickly after reducing the light dose [63]. Side effects may include headache [23, 31, 67], eye strain [23, 36, 67], agitation [36, 67], nausea [67], and insomnia [23, 28, 29, 31] and in women, reports of menstrual disturbances [96] and dysfunctional uterine bleeding [45]. No ocular effects were observed after a 5-year period [95]. During treatment with bright light, patients who experience worsening depression, suicidal ideation, or emergent hypomania are to contact their clinician for immediate and appropriate clinical management. Suicidal ideation may emerge within 2 weeks of starting light treatment [97] and is more likely in patients with inadequate antimanic treatment [21], a history of rapid cycling, and before the full antidepressant effect is experienced [67]. Although we expect ongoing improvement after 6 weeks, there is no published evidence yet on the durability of response and how long patients should continue using the light box. Given that patients with bipolar depression who discontinued maintenance treatment relapsed twice as often as patients who continued treatment after 1 year (70% vs 36%) [98], the patients who experienced remission with bright light treatment may preferentially continue bright light at the same dosage to prevent recurrence, and consider increasing the light dose or transitioning from midday to morning bright light to enhance their response.

Conclusion

Investigation of a potent, somatic intervention that is *visible* presents major challenges to light therapy researchers [5]. For this reason, successfully completed studies and published reports are potentially very important contributions to the literature. Using bright light to manage depressive symptoms in BD is reasonable but requires concurrent antimanic treatment and careful clinical monitoring for response, safety, and mood polarity switch. Individualized planning and judicious decisions will need to be made regarding whether to continue using bright light throughout the year to prevent relapse (for which we have no data yet), or to discontinue treatment for individuals at risk for manic induction.

Compliance with Ethical Standards

Conflict of Interest Dorothy Sit and Sarah Haigh each declare no potential conflicts of interest.

Table 2 Guideline for Implementing Light Therapy for Patients with Bipolar Depression

Eligibility Criteria.

- Maintenance therapy with anti-manic drug therapy for at least 4 weeks is imperative.
- Continuing stable dosed antidepressant with anti-manic drug therapy is acceptable.
- Patients must receive regular monitoring and guidance on treatment from a trained clinician.
- Manic, hypomanic, mixed symptoms or rapid cycling illness are contraindications.

Selection and Proper Positioning of the Bright Light Box Unit.

- Select a broad-spectrum, bright white light that provides ultraviolet filtration and emits 7,000 to 10,000 lux at a distance of 12-13 inches.
- The preferred unit should measure 12 by 14 inches, illuminate a broad visual field, incorporate a diffusion screen and provide illumination from above to minimize glare and ensure proper illumination.
- The optimal placement of the unit is on a desk stand at a distance of 12 inches from the eyes.
- The patient is asked to face the light box but avoid directly staring at it to minimize discomfort.
- Patients are asked to use the light every day at home or work to experience a full response.

Note. Although the optimal efficacy may be attributed to the blue wavelength, the broad spectrum white light unit is preferable, most widely available, and confirmed to have an established record of ophthalmic safety.

Timing and Dosing Schedule.

- Begin with a light dose of 15 minutes/day at midday (between 12:00 PM and 2:30 PM) for the first week. Every week, increase the light dose by 15 minutes until the patient reaches the target dose of 45-60 minutes/day (by week 4) OR until the mood symptoms have fully remitted.
- Proceed with increasing the light dose as long as the patient finds it tolerable, without major side effects or hypomanic/mixed symptoms.
- Expect early remission with minimal to no symptoms and normal functioning, by four to six weeks of treatment.
- For non-responders to midday light, move the timing of light to the morning, minutes after awakening, and increase the light dose to 45-60 minutes/day.

Adverse Effects.

- With standard bright white light, the risk of adverse effects is minimal and side effects usually subside quickly after reducing the light dose.
- Side effects may include headache, eye strain, agitation, nausea, insomnia, and in women, reports of menstrual disturbances and dysfunctional uterine bleeding.
- No ocular effects were observed after a five year period.
- Rarely, patients can have worsening depression, suicidal ideation, or emergent hypomania and are asked to contact their clinician or the emergency room for immediate management.

Safety Concerns.

- Suicidal ideation is rare, and may emerge within two weeks of starting light treatment. The likelihood is increased with inadequate antimanic treatment, rapid cycling, and prior to experience of the full antidepressant effect.

Maintenance Treatment.

- We would expect ongoing improvement even after 6 weeks given the positive dose response relationship (Fig. 3). However, there is still no

Table 2 (continued)

data to indicate the durability of response and how long patients should continue using the light box.
• Knowing that patients who discontinued maintenance treatment relapsed twice as often as patients who continued treatment after one year (70% vs 36%), the patients who remit with bright light may prefer to continue treatment at the same dosage to prevent recurrence.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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