



Light therapy for depression in adolescent outpatients: A pilot study

Procedure Manual

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Abstract: Depressive disorders in adolescence are common and impairing conditions that require treatment. Psychotherapies and medications have been shown to be effective to treat depression but have limitations that create barriers to uptake. Non-medication treatments for adolescent depression have not been well studied in adolescents. Bright Light Therapy (BLT) is an established and effective treatment for adult depression, seasonal affective disorder, and bipolar disorder. Investigation into BLT with adolescents has been encouraging despite the limited context of use in the inpatient hospitalization samples. Feasibility and acceptability of the treatment, optimal dose, and optimal timing of BLT requires further investigation in an outpatient population. We propose a pragmatic investigation of BLT in partnership with primary care physicians who most often identify adolescents in need of treatment for depressive disorders. The primary objective of this study is to conduct an 8-week dose-finding open-trial of BLT with 16 adolescents referred from primary care settings. Additionally, our team will survey local pediatricians to learning about knowledge and acceptability of referring to BLT. Outcomes from this study will inform recommendations for future trials of BLT in primary care.

Background and significance: Adolescent depression is a major health concern, affecting up to 5% of the population.¹ Depression is a significant risk factor for suicide and later life social and educational impairment, and untreated adolescent depression leads to significant societal costs.² Psychotherapies and medication treatment, primarily Selective Serotonin Reuptake Inhibitors (SSRI), have been shown to be effective in the treatment of adolescent depression, with combination treatment (psychotherapy and medication management) considered the optimal treatment approach.³ Barriers to this treatment include lack of available therapy and psychiatric providers, hesitancy in prescribing SSRIs among primary care clinicians, and limited acceptance of SSRIs by patients and families. Additionally, up to 40% of adolescents with depression may not improve with adequate combined treatment.⁴

Bright Light Therapy, a non-pharmacologic treatment that can be delivered immediately in the home setting, may be an acceptable treatment option for outpatient adolescents with depression. BLT is effective in the treatment of seasonal affective disorder,⁵ non-seasonal depression,⁶ and bipolar depression in adults.⁷ Geoffroy et al. identified BLT monotherapy as similar in effectiveness to antidepressant medications, and indicated that BLT may augment antidepressants when used in combination.⁸ In adolescents, the only trials of BLT for depression have been conducted among inpatients, where duration of and adherence to treatment can be closely monitored.⁹⁻¹²

Up to 14% of adolescents screen positive for depression in the primary care setting.¹³ Given our pragmatic approach to acceptability of BLT for adolescents with depression, we will partner with primary care providers to identify strategies to optimally enroll and monitor our pilot sample of patients.

We propose a dose-finding feasibility and acceptability study of BLT treatment for adolescents in an outpatient practice setting. In conjunction with the Bright Light trial we will conduct a brief survey of pediatric primary care clinicians to evaluate their knowledge of and interest in prescribing and managing bright light therapy in their adolescent outpatients with depression.

Feasibility and acceptability of use of a BLT for any duration has not been established in adolescent outpatients who will have to modify behavior patterns to build light box therapy into their

day. To date, studies of BLT for depression have included a range of light intensity and treatment duration. Dose-finding studies such as that conducted by Sit el al¹⁴ for adults with bipolar depression have not been carried out among adolescent patients, and the minimum daily light exposure time to achieve symptom response has not been established in this group.

Study element Hypotheses and anticipated outcomes

Hypotheses (pediatric clinician survey)

1. Pediatric clinicians will endorse interest in bright light therapy as a treatment option for their adolescent patients with depression.
2. Pediatric clinicians will prefer an online seminar as a means to learn about prescribing bright light therapy

Outcomes (pediatric clinician survey)

1. Response rate
2. Rate of survey responders with interest in prescribing BLT.

Hypotheses (light therapy pilot)

1. Adolescent outpatients with major depression will use their assigned bright light box to achieve at least 80% of prescribed minutes per week.
2. Adolescent outpatients with major depression will tolerate bright light therapy with minimal side effects.
3. Adolescent outpatients with major depression will achieve a decrease in Short Mood and Feelings Questionnaire (SMFQ) (Parent OR Child-Rated) total scores from baseline to week 8 of the intervention at one of the assigned light therapy doses (in minutes).
4. Adolescent outpatients with major depression will achieve a decrease in CGI-S total scores from baseline to week 8 of the intervention at one of the assigned light therapy doses (in minutes).

Outcomes (light therapy pilot):

1. Adherence: Percentage of prescribed minutes that light box is used
2. Tolerability: Side effects as measured by SAFTEE -20 item
3. Tolerability: sleep/wake cycle changes as measured by actigraphy (or sleep diary if actigraphy is not tolerated)
4. Efficacy at each dose: scores of 8 or less on the SMFQ (Parent- and/or Child-Rated) or least a one standard deviation ($SD = 5.1$) decrease in score between weeks 0 and 8
5. Efficacy at each dose: Scores of 2 or less on the CGI-I

Study Procedure: Pediatric Clinician Survey

An 8- item survey will be distributed to pediatric clinicians (pediatricians and pediatric nurse practitioners) who are members of the Mood, Anxiety and ADHD Collaborative Care program (MAACC). The survey will be sent by email using the Google Docs survey platform. The survey will include demographic questions about the respondent's professional degree and years in practice followed by questions about knowledge of BLT, interest in use of BLT, and preferences as to potentially learning more about BLT. Reminder emails will be sent at 1 and 2 weeks to non-respondents. Data analysis will include calculation of response rate and percentages of respondents' Likert scores for each item.

Study Procedure: BLT pilot

A pilot sample of 16 youth will be recruited for a dose-finding trial. Partnering community providers will refer potential subjects with depression and elevated scores on youth screening measures, Patient Health Questionnaire-9 (PHQ-9) (≥ 9) or PHQ-2 (≥ 3), without endorsed suicidality.

Inclusion Criteria:

- Subject must be 12 to 18 years old at the point of consent.
- An English primary caregiver who is legally able to provide consent and who can contribute weekly mood ratings
- Primary Diagnostic and Statistical Manual, 5th Edition (DSM-5) diagnosis of Major Depression Disorder (MDD) as determined by structured interview with study clinician.
- Clinical Global Impression Severity (CGI-S) rating of depression ≥ 4
- Baseline SMFQ score $> = 11$

Exclusion Criteria:

- Patients with bipolar disorder, Attention Deficit Hyperactivity Disorder, moderate to severe autism, schizophrenia, or schizoaffective disorder, intellectual disability
- Patients with a major medical illness or ocular condition (e.g. glaucoma, retinal disease, macular degeneration) that would interfere with participation in the study
- Patients who pose a significant and imminent risk to self or to others.
- Patients with concurrent or recent (< 4 months) medication or new (< 3 months) psychotherapy treatment for depression.
- Patients taking psychostimulant medication, melatonin, beta-blockers, chloroquine, or regular non-steroidal anti-inflammatory agents, or St. John's Wort.

Data Analysis Plan:

(Feasibility and acceptability) We will track subject recruitment and retention as well as engagement with light boxes and with the assessments.

(Dose-finding) Within subject two-tailed t-tests will be used to assess outcome variable of SMFQ score and CGI-S at week 0 and at 1-week intervals through the 8 weeks of the study (*see table 3 for list of measures with abbreviations*). Correlations between treatment and moderator variables will be calculated. Missing data will be replaced with the Last-Observation Carried Forward (LOCF).

Dr. Sit will provide training on BLT to primary care providers in a preferred format as determined by survey. Referred patients and their caregiver will complete a phone screening and consent to participate in the study with a research coordinator. Consented patients will be scheduled for an eligibility assessment. Patient and parent will complete the MINI-KID and baseline measures online via REDCap prior to the eligibility evaluation (Table 1). Eligibility evaluation will be completed with a licensed psychologist or psychiatrist. Patients who consent to participate will receive a 10,000 lux bright light device and an actigraphy device which will track sleep and light exposure. Trained light box staff will demonstrate proper use of the light unit and subjects will review the provided take-home print materials on proper use of the light unit (Appendix – “Positioning of the Light Box”).

Table 1

Construct	Measure	Admin	Baseline [#Q's]	Weekly	Q 2 weeks	6 wks post
SCREENING						
Depression	Patient Health Questionnaire-9 or -2	Youth (Y)				
ELIGIBILITY						
Major Depression	MINI-KID	Parent (P)/Y	X			
Seasonality	Seasonal Pattern Assessment Questionnaire	Y	X [24]			
PRIMARY OUTCOMES						
Depression	Mood and Feelings Questionnaire 13 (MFQ)	P/Y	X [13]	X [13]		X
Suicide	Columbia Suicide Scale (CSS)	Y	X [2]	X [2]		X
Severity	Clinical Global Impressions –Severity and -Improvement (CGI-S,I)	Clinician	X		X	X
Mania	Brief Child Mania Rating Scale (CMRS)	P	X		X [10]	X
Side effects	Systematic Assessment for Treatment Emergent Effects (SAFTEE, modified, 26-items)	Y	X [20]	X [20]		X
COVARIATES						
Sleep	Medical Outcomes Study Sleep Scale	Y	X [8]		X [8]	X
Chronotype	Morningness-Eveningness Questionnaire	Y	X [19]			
Process	Expectations/perceived effectiveness of treatment	Y	X [2]			X
Process	Adherence data from light box	device			X	
Process	Sleep-Wake Diary			X		
Sleep, activity	Actigraphy data from watch	device			X	

In the first 2 weeks of the study, a sham (placebo) light will be dosed for 15 minutes per day upon awakening. At the 2-week device check, the research coordinator will examine the light boxes and convert them to 10000 lux. The light dose time will continue at 15 minutes for another 2 weeks. Every 2 weeks, participants will advance the dosing by 15 min increments up to 45 min/d depending on their weekly depression scores and ratings of side effects, tolerability and acceptability (Table 2). The efficacy of LT is usually observed by 4-6 weeks in general populations. Our 8-week trial is a reasonable time frame that will allow detection of a treatment effect.

Table 2: Light Therapy Use.

Weeks	Light type	Minutes/day
0-2	Sham/placebo	15
2-4	10000 lux	15
4-6	10000 lux	30
6-8	10000 lux	45

Adherence. Subjects will record their daily use of the light box. From our experience, daily report of usage data effectively tracks adherence to light therapy. Subjects will be prompted to provide a daily

record of their light box use to the study research coordinator via the subject's preferred means of communication. This may include email, voice, or text message. All messages will be sent from and received to a password-protected device operated by the study coordinator at Lurie Children's Hospital and will be deleted after reading/listening. The research staff will call subjects weekly to monitor any problems with adherence or using the box during the acute phase. Daily use of the unit will be reviewed at each visit. As longer durations of use (45 min daily) could be burdensome, we will encourage subjects to take a 2-3 minute break in the middle to stand up, stretch, or use the bathroom.

Table 3: Study Visit Schedule.

Week	Study Visit location & Type	Duration	REDCap Measures	Reimbursement Youth/ Guardian
-1	Telemedicine coordinator visit	30 minutes	Informed Consent & Measures	40/20
0	Telemedicine clinician visit	60 minutes		20/10
0	In person light/watch	45 minutes		Pick up light box & watch and learn how to use them
1			Measures	
2	Telemedicine clinician visit	20 minutes	Measures	20/10
2	In person light/watch	10 minutes	yes	
3			Measures	
4	Telemedicine clinician visit	20 minutes	Measures	20/10
4	In person light/watch	10 minutes	yes	yes
5			Measures	
6	Telemedicine clinician visit	20 minutes	Measures	20/10
6	In person light/watch	10 minutes	yes	

Safety and Side Effects (Contingency Plan). Every 2 weeks, subjects will be assessed for safety, side effects and treatment emergent hypomania or mixed symptoms. Assessments will take place via telemedicine visits with one of the co-investigators. In addition, patient- and parent-reported symptoms

and side effects (obtained via REDCap and the forms listed in Table 1) will be reviewed weekly. Participants who have worsening depression (MFQ score increase of 5 points or more), suicidal ideation (CSR score of 2 or more), emergent mania (CMRS ≥ 10) or thoughts of harming others will be evaluated by a PI (RB/JP/DS) and referred immediately to emergency psychiatric services for clinical management if indicated. There is no evidence that light at the intensity proposed in this design has any major adverse effects on general or ocular health.¹⁵ Headache, eye strain, agitation, nausea, and insomnia may occur and are usually mitigated by a reduction in light dose by 15 minutes. Side effects will be carefully monitored using the SAFTEE (26-item). Individuals who have side effects will have their dose reduced by 15-minutes, which is an effective approach to manage emergent side effects.¹⁶ If a participant wishes to withdraw from the study, the study physician will advise a weaning plan or taper schedule to allow the participant to gradually lower and stop the light therapy dose. She or he will reduce the light dose by 10 minutes every 1-2 days (from an initial dose of 30-45 min/d) and aim to completely stop within 5-6 days. The study team also will help them develop an alternative treatment plan.

Subjects desiring further treatment coordination and recommendations for their depression will receive this after 8 weeks of light therapy. Subjects whose depression responds to light therapy will be given the light box to keep at the end of the study. Subjects may disengage from the study at any point and receive referral and coordination to therapy and/or medication management treatment as is clinically indicated.

Non-responders will be advised to taper off treatment (or weaned from therapy) by reducing the dose of light by 15 minutes every 3 days and stop by day 7.

For responders, they will be given a bright light box to keep, so they can continue the treatment at home.

At the final visit, the team will meet with the participant and parent to reveal and discuss the participant's outcomes of treatment. A consultation letter will also be sent to the participant, parent and referring clinician. In the letter and team discussion, we will detail what bright light therapy involves, the participant's level of response, experience of side effects or adverse outcomes, and the recommended light dose based their individual response. We will provide some guidance on how long to continue treatment to maintain response and prevent relapse by extrapolating from literature on antidepressant maintenance trials (given the limited availability of maintenance trials in light therapy). For non-responders, the discussion will encompass options for pharmacological and non-pharmacological therapies depending on their preferences.

Device maintenance and monitoring: The active light box is a white fluorescent 4000 Kelvin unit that emits 10000 lux and measures 33cm x 40cm. The placebo box that emits 50 lux dim red light will appear identical to the active unit. Subjects will position themselves 30-36 cm from the box with their faces fully exposed to the light. Prior to assigning light boxes to participants, the light box manager will open each carton, check for malfunctions, insert bulbs and panels appropriate for the active or placebo conditions, perform a photometry check, affix a 13-inch ribbon which the subject will use to set head distance, affix a battery-operated kitchen timer with which to time treatment sessions, tape a code number on each box and carton, and seal the carton. Standard braces for the light box will secure the photometer that

will be used to ensure each measurement of illuminance will be exactly the same, as small differences in angular tilt can cause marked differences.

Light therapy can affect sleep/wake cycles, and sleep/wake cycles can affect mood. We will be collecting information on sleeping and waking through actigraphy watches that track movement and activity levels. The actigraphy device is a Phillips Spectrum Plus Actigraphy watch which weighs 31 grams, is rugged and water resistant. The watch collects activity level and sleep information along with multiple light measurements and wearer adherence.

<https://www.usa.philips.com/healthcare/product/HCNOCTN445/actiwatch-spectrum-plus-get-the-actiwatch-advantage>

Participants or their parent/guardian will be asked to bring the light box and actigraphy device to a Lakeforest Pediatrics office or Lurie Children's clinic for a quality check during weeks 2, 4, and 6. The research coordinator will conduct these checks which will involve making sure the devices are functioning properly and downloading usage data. At the 2-week visit, the research coordinator will reconfigure the light box unit from the sham to the active light configuration.

Data Safety and Monitoring Plan (DSMP). The research team is ethically responsible for monitoring patient safety and appropriately responding to clinical information obtained in this study. Patient safety monitoring will be the primary responsibility of the study investigators (RB, LG, JP and DS). For urgent clinical situations or adverse events investigators will evaluate and provide first line recommendations of management. Safety will be evaluated at several levels: 1) the individual patient, 2) the group of patients as the study data accrue through review of the adverse events and patterns of outcomes and 3) the integrity of the data and data monitoring procedures. In weekly meetings, the investigators and RC will evaluate patient safety, study progress as well as recruitment, data integrity and confidentiality. Quarterly, the team will conduct a comprehensive evaluation of the progress. In this review, the team will examine data quality and timeliness; accrual and retention; overall risks versus benefits from enrollment; withdrawal and patient removals; and external factors, such as scientific or therapeutic developments that could change patient safety or the ethics of continuing the study. Study flow (responders compared to non-responders), treatment tolerability and side effect (SE) frequency, severity and management will be thoroughly examined. Serious adverse events, patient hospitalization or suicide attempt will be reviewed within 48 hours and reported to the IRB. The DSMP report will be submitted for the annual IRB review.

Compensation

Payment for Taking Part in this Study:

For completing every study visit, the adolescent will receive a total of \$200.00 and the guardian will receive a total of \$90. If a participant withdraws from the study prior to completion, they will be compensated for the visits completed. Table 3 describes the compensation schedule and the plan for reimbursement. Patients that withdraw before or between the two reimbursement time points (after week 4 and after week 14) will be compensated for the number of completed sessions.

All compensation will be made using an e-gift card program, reward genius, that is used for other Lurie Children's studies. The parent and youth will be sent the e-gift card to a preferred email. Participants have the opportunity to select an Amazon or Target gift card. The gift card does not expire.

Youth and caregiver compensation schedule is described in Table 3. Planned compensation for youth and that complete the study will be given out in 2 gift cards distributed after the 4- and 14-week visits in the amount of \$100.00 at each time period. Caregivers will receive \$50.00 after week 4 and \$40.00 after week 14.

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