

## Research paper

# Prediction of outcome of bright light treatment in patients with seasonal affective disorder: Discarding the early response, confirming a higher atypical balance, and uncovering a higher body mass index at baseline as predictors of endpoint outcome



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## ABSTRACT

**Background:** We tested the hypothesis that the early improvement in mood after the first hour of bright light treatment compared to control dim-red light would predict the outcome at six weeks of bright light treatment for depressed mood in patients with Seasonal Affective Disorder (SAD). We also analyzed the value of Body Mass Index (BMI) and atypical symptoms of depression at baseline in predicting treatment outcome.

**Methods:** Seventy-eight adult participants were enrolled. The first treatment was controlled crossover, with randomized order, and included one hour of active bright light treatment and one hour of control dim-red light, with one-hour washout. Depression was measured on the Structured Interview Guide for the Hamilton Rating Scale for Depression-SAD version (SIGH-SAD). The predictive association of depression scores changes after the first session. BMI and atypical score balance with treatment outcomes at endpoint were assessed using multi-variable linear and logistic regressions.

**Results:** No significant prediction by changes in depression scores after the first session was found. However, higher atypical balance scores and BMI positively predicted treatment outcome.

**Limitations:** Absence of a control intervention for the six-weeks of treatment (only the first session in the laboratory was controlled). Exclusion of patients with comorbid substance abuse, suicidality and bipolar I disorder, and patients on antidepressant medications, reducing the generalizability of the study.

**Conclusion:** Prediction of outcome by early response to light treatment was not replicated, and the previously reported prediction of baseline atypical balance was confirmed. BMI, a parameter routinely calculated in primary care, was identified as a novel predictor, and calls for replication and then exploration of possible mediating mechanisms.

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## 1. Introduction

Seasonal affective disorder, winter type (SAD), consists of recurrent Major Depressive episodes that occur primarily in the fall and winter and remit spontaneously in spring and summer (Magnusson, 2000; Rosenthal et al., 1984). It presents predominantly with “atypical” symptoms of increased sleepiness and appetite, carbohydrate craving, weight gain, and decreased energy. Bright light treatment is a safe and effective treatment for SAD (Eastman et al., 1998; Lewy et al., 1998; Rosenthal et al., 1984; Terman et al., 1998), although there is disagreement regarding its effect size, ranging from small-moderate (Martensson et al., 2015) to large (Golden et al., 2005). For instance, a pooled analysis revealed that nearly half (47%) of all patients with SAD, and 57% of those with moderate to severe symptoms, did not fully remit (Terman et al., 1998). In addition, as we have reported, for a sizable proportion of patients, response to light is incomplete compared with the degree of spontaneous improvement in the summer (Postolache et al., 1998).

SAD appears to be an expression of a dual vulnerability, first for chronobiological dysregulation, and second for mood dysregulation (Lam et al., 2001b; Young et al., 1991). The evidence for chronobiological vulnerabilities in SAD patients includes circadian and photoperiodic dysregulation (Lewy et al., 1998, 1987b; Roeklein et al., 2009; Wehr et al., 2001; Zhang et al., 2015). Consistent with addressing this chronobiologic vulnerability, light treatment shifts the circadian rhythms (Lewy et al., 1987a) and utilizes the machinery of the circadian system to decrease the duration of nocturnal melatonin (Wehr, 2001). Evidence for mood dysregulation vulnerabilities includes an increased seasonal variation in serotonin transporter binding in patients with SAD (Mc Mahon et al., 2016) returning to baseline following light treatment (Tyrer et al., 2016a, 2016b), and the reversal of tryptophan (i.e. serotonin) and catecholamine depletion by the successful antidepressant effect of light in SAD (Neumeister et al., 1998). Furthermore, light treatment has demonstrated an antidepressant effect not only in seasonal, but also in non-seasonal depression (Lam et al., 2016), and has a rapid onset of improvement in the depression scores, perhaps from the first light session (Virk et al., 2009). Thus, light treatment effects are very likely mediated not only by chronobiological mechanisms.

There are certain similarities between seasonal behavioral and physiological changes, particularly concerning metabolic regulation/dysregulation, between patients with SAD and seasonal animals. For instance, many animals show marked seasonal changes in adiposity (Bartness et al., 2002). Similarly, patients with SAD manifest considerable seasonal variation in their body weight (Cizza et al., 2005). As well, timed exposure to light in photoperiodic mammals can alter their seasonal adiposity (Bartness et al., 2002), which is comparable to the decreased appetite and weight-loss that is often associated with bright light treatment (Rosenthal et al., 1987b) and appears to consistently reduce appetite independent of the seasonal changes in mood (Danilenko et al., 2013). Light treatment also improves the control of eating in patients with comorbid bulimia (Lam et al., 2001a), and Night Eating Syndrome (Friedman et al., 2006; McCune and Lundgren, 2015). Conversely, certain atypical symptoms of depression such as hyperphagia and hypersomnia, predict the response to light (Lam, 1994; Nagayama et al., 1991; Terman et al., 1996).

We had previously reported that improvement of atypical depressive symptoms after one hour of bright light treatment correlated with improvements after two weeks of therapy (Sher et al., 2001). However, the study limitations included such taking place with subjects in a Positron Emission Tomography (PET) scanner, lack of controls, short duration (of only two weeks), and a small sample size.

The primary hypothesis was that changes in depression scores after first bright light treatment session, which we previously reported to significantly improve mood (Reeves et al., 2012), and changes in depression scores with a full course of daily bright light treatment will be

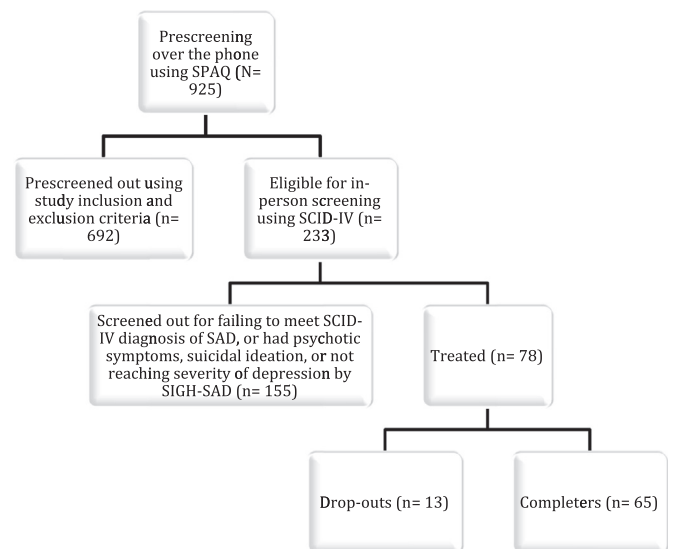


Fig. 1. Flow chart showing number of participants from the beginning to the end of study. SPAQ: Seasonal pattern assessment questionnaire; N: Total sample at beginning of study; n: Population sample at various stages after initial screening; SCID-IV: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-IV; SAD: Seasonal Affective Disorder; SIGH-SAD: Structured Interview Guide for the Hamilton rating scale-Seasonal Affective Disorder version.

positively correlated. Given the metabolic issues implicated in SAD, we also hypothesized that atypical depression symptoms and BMI at baseline would predict treatment outcome.

## 2. Methods

### 2.1. Participants

The participants were 18–64 years of age with mean age (SD) of 44.5 (10.3) years, with 33 women (42%) and 45 men (58%), who met criteria for current diagnosis of SAD, winter type and the necessary severity of depression criteria by Structured Interview Guide for Hamilton Depression Rating Scale-Seasonal Affective Disorder Version (SIGH-SAD, Williams et al., 1994). Fig. 1 is a flow chart showing the number of participants involved from the initial telephone screening to the end of the study.

We excluded individuals with psychotic disorders or bipolar I disorder, current suicidal ideation or history of suicidal behavior, vision problems not correctable by refraction, somatic conditions that had increased sensitivity to light, alcohol or substance abuse in the past year, overnight work shift schedule, patients with developmental disabilities and gross impairment in cognitive function, as well as those treated with antidepressant medication, mood stabilizer, or antipsychotic medication in the past 30 days. Women who were pregnant, nursing, or intended to become pregnant were excluded as well. The study took place from the fall equinox to the spring equinox, i.e. during the astronomical fall and winter. The actual start of the study depended on the depression severity criteria, as described in the methods. The recruitment in the end portion of the winter took into account that the six-weeks duration does not overlap with the spring equinox. Thus, last days of potential start of the study was on February 6. After a full explanation of the study, the participants signed informed consent after demonstrating understanding of risks, benefits, and alternatives to participating in the study on a semi-structured interview. This study was approved by the University of Maryland Institutional Review Board.

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