Appetitive Symptoms Differentially Predict Treatment Response to Fluoxetine, Light, and Placebo in Nonseasonal Major Depression

Robert D. Levitan, MD, MSc[a,b,*]; Anthony J. Levitt, MBBS[b,d]; Erin E. Michalak, PhD[c]; Rachel Morehouse, MD[e]; Rajamannar Ramasubbu, MD[f]; Lakshmi N. Yatham, MBBS, MBA[c]; Edwin M. Tam, MDCM[c]; and Raymond W. Lam, MD[c]

ABSTRACT

Objective: We previously reported that morning bright light therapy is efficacious in adults with nonseasonal major depressive disorder (MDD), both on its own and in combination with fluoxetine. Given that appetitive symptoms predict response to bright light therapy in seasonal depression, we examined, in this secondary analysis, whether the same held true in these nonseasonal MDD patients.

Methods: Data were collected from October 7, 2009, to March 11, 2014. One hundred twenty-two patients who met *DSM-IV-TR* criteria for MDD without a seasonal pattern were randomly assigned to light monotherapy, fluoxetine, combination light and fluoxetine, or double-placebo (inactivated negative ion generator plus placebo pill). Multiple regression assessed the percentage change in Montgomery-Asberg Depression Rating Scale (MADRS) scores based on treatment condition, appetitive symptom score at baseline (sum of 4 items on the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version), and the condition-by–appetitive score interaction. Sex was considered as a possible moderator of these effects.

Results: The overall regression model predicting treatment response was highly significant ($P < .001$), and the treatment condition–by–appetitive score interaction was a strong predictor of MADRS change scores ($t = 2.65$, $P = .009$). For individuals in the placebo group, more appetitive symptoms at baseline predicted less decrease in MADRS scores at 8 weeks ($r = –0.37$; large effect size). In contrast, for individuals in the active treatment groups, more appetitive symptoms at baseline predicted more of a decrease in depression scores at 8 weeks (fluoxetine group $r = +0.23$, medium effect size; light therapy group $r = +0.11$, small effect size; combination group $r = +0.32$, medium to large effect size). No moderation effect of sex was found.

Conclusions: More severe appetitive symptoms at baseline predicted treatment response differentially across the 4 treatment groups. Contrary to prior findings in seasonal depression, this association was not robust for MDD patients receiving light therapy alone, although it was stronger in patients receiving fluoxetine with or without light. As the group sample sizes were modest, the current findings should be considered as preliminary only.

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[a]Mood and Anxiety Disorders Program, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

[b]Department of Psychiatry, University of Toronto, Toronto, Ontario, Canada

[c]Department of Psychiatry, University of British Columbia; Mood Disorders Centre, Djavad Mowafaghian Centre for Brain Health, Vancouver, British Columbia, Canada

[d]Mood Disorders Program, Sunnybrook and Women's College Health Sciences Centre, Toronto, Ontario, Canada

[e]Department of Psychiatry, Dalhousie University, Saint John, New Brunswick, Canada

[f]Department of Psychiatry, University of Calgary, Calgary, Alberta, Canada

**Corresponding author:* Robert D. Levitan, MD, MSc, Centre for Addiction and Mental Health, 100 Stokes Street, Toronto, Ontario, M6J 1H4 Canada (robert.levitan@camh.ca).

Identifying reliable predictors of treatment response that can guide clinical decision-making is a fundamental goal of individualized medicine. Matching treatment choice to particular patient needs takes on added significance for disorders with marked heterogeneity such as major depressive disorder (MDD). One strategy to individualize treatment in MDD has been to differentiate individuals based on neurovegetative symptom profiles, ie, classic (loss of appetite, insomnia) versus atypical/reversed (increased appetite, hypersomnia). Indeed, the initial description of atypical depression was motivated by the observation that patients who lacked classic melancholic features were less likely to respond to tricyclics.[1] Subsequent work suggested that patients with atypical features responded best to monoamine oxidase inhibitors.[2] There has been some attempt to examine whether atypical vegetative symptoms predict treatment response to newer agents such as selective serotonin reuptake inhibitors[3,4]; however, the scope of this work remains limited at the current time.

Seasonal affective disorder (SAD) is a form of depression defined by predictable onset and offset at particular times of the year.[5] Of note, the vast majority of patients with winter SAD have reversed vegetative symptoms, which are often the first to arise in the short days of fall.[6] Several early studies of light therapy for SAD[7–11] focused on whether the atypical and classic vegetative symptom clusters were predictive of response. Taken as a whole, this research demonstrates that reversed appetitive symptoms predict a positive response to light therapy in SAD while classic melancholic symptoms, including appetite loss, are less reliable in this regard.

In a study of 122 adults with nonseasonal MDD, we recently reported[12] that both light monotherapy and the combination of light and fluoxetine had significant benefits compared to a double-placebo condition. To optimize the translational value of this work, the goal of the current study was to determine which subset of these patients with MDD most benefitted from

Clinical Points

- In patients with seasonal affective disorder, increased appetite and overeating predict a robust response to light therapy.
- The current study in patients with nonseasonal major depressive disorder (MDD) found no significant association between appetitive symptoms and light therapy response.
- Our initial findings suggest that fluoxetine with or without light therapy may be a good treatment for patients with nonseasonal MDD and more severe appetitive symptoms.

active treatment. We were particularly interested in whether appetitive symptoms predict response to light therapy in patients with nonseasonal MDD, akin to what has been observed in SAD.[7–11] On the basis of these prior results in SAD, we hypothesized that more severe appetitive symptoms would predict a positive treatment outcome in patients with nonseasonal MDD receiving bright light therapy. We report here on this secondary analysis of our initial data.

METHODS

Methods have previously been described in detail[12] but are briefly summarized here. The randomized, double-blind study was mainly conducted in 3 psychiatric outpatient clinics in Vancouver and Toronto. The study was approved by institutional review boards (IRBs) at each center. Data were collected from October 7, 2009, to March 11, 2014, and the study was registered at www.clinicaltrials.gov as NCT00958204. Inclusion criteria for patients included age of 19–60 years, diagnosis of MDD[13] as confirmed with the Mini-International Neuropsychiatric Interview (MINI),[14] psychotropic medication–free status for at least 2 weeks, and 17-item Hamilton Depression Rating Scale (HDRS)[15] score ≥ 20 at screening and baseline. Exclusion criteria included *DSM-IV-TR* diagnoses of MDD with a seasonal pattern, any bipolar or psychotic disorder, and substance abuse/dependence within the past year; unstable medical illnesses; retinal disease; pregnancy or breast-feeding; prior use of fluoxetine or light therapy; treatment-resistant depression defined as lacking response to 2 or more antidepressants at therapeutic doses for > 6 weeks; use of other concurrent treatments for depression, including psychotherapy; and serious suicidal risk.

The study used a "double dummy" 2 × 2 design in which patients both used a treatment device and took a pill each day. Patients were randomized to receive active light therapy with a light box (Carex Day-Light Classic [Carex Health Brands], emitting 4,000-Kelvin fluorescent white light with an ultraviolet filter, rated at 10,000 lux at 14 inches from screen to cornea) or a sham condition with a deactivated negative ion generator (Sphere FreshAIR, Sphere One Inc). Similarly, patients were randomized to receive fluoxetine 20 mg/d or an identical placebo pill. This resulted in 4 treatment conditions: active light plus fluoxetine, active light plus placebo pill, fluoxetine plus sham device, and a "double placebo" condition with placebo pill plus sham device (placebo-sham). To ensure plausibility of the sham condition, deception was used (with approval from the IRBs) to mask the objectives of the study. Patients were informed that half of the devices would be inactivated, but were not told that all the light devices were active while all the ion generators were inactive. There were no significant differences in expectation ratings for both devices at baseline, confirming the success of the deception.

Both treatment devices were used at home for 30 minutes daily, as soon as possible after awakening between 7:00 and 8:00 AM. Patients were encouraged to sleep only between 10:00 PM and 8:00 AM when possible and to avoid spending an excessive or unusual amount of time outdoors during the study period. Patients were assessed at baseline (week 0) and at weeks 1, 2, 4, 6, and 8. The primary study outcome was change in the Montgomery-Asberg Depression Rating Scale (MADRS)[16] score from week 0 to week 8, as assessed using trained telephone raters blind to treatment condition.

Current Statistical Approach

Baseline assessment. As part of the baseline assessment, a trained research assistant administered the Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version (SIGH-SAD),[17] which includes 4 variables to assess appetitive symptoms. The variables with corresponding score items are as follows: "Appetite Increase" (0 = no increase, 1 = wants to eat a little more than normal, 2 = wants to eat somewhat more than normal, 3 = wants to eat much more than normal); "Increased Eating" (0 = is not eating more than normal, 1 = is eating a little more than normal, 2 = is eating somewhat more than normal, 3 = is eating much more than normal); "Carbohydrate Craving" (0 = no change in food preference or consumption, 1 = craving or eating starches or sugars somewhat more than before, 2 = craving or eating starches or sugars much more than before, 3 = irresistible craving or eating of sweets and sugars); and "Weight Gain" (0 = no weight gain, 1 = probable weight gain due to current depression, 2 = definite weight gain due to current depression). The maximum appetitive symptom score summed across these 4 variables was thus 3 + 3 + 3 + 2 = 11. Of note for the current hypothesis, the MADRS does not assess appetitive symptoms and is thus distinct from the SIGH-SAD in this regard. This difference in the 2 scales enabled us to test the current hypothesis without the potential confound of appetitive symptoms' being used as both a predictor and an outcome.

Primary analysis. To assess whether appetitive symptoms at baseline were associated with treatment outcome based on the MADRS, we first plotted the relationship between appetitive symptoms at baseline and the percentage change in MADRS scores, generating a separate regression line for each of the 4 treatment groups. Next, we used multiple regression to predict the percentage change in MADRS scores using treatment condition, the total appetitive symptom score, and the condition-by–appetitive score interaction term. Sex was considered as a possible moderator for our primary analysis,

Table 1. Participant Characteristics[a]

Variable	Placebo (n = 30)	Fluoxetine (n = 31)	Light (n = 32)	Combination (n = 29)	Complete Sample (N = 122)
Female, n (%)	22 (73.3)	22 (71.0)	17 (53.1)	15 (51.7)	76 (62.3)
Age, y	36.2 (11.5)	37.3 (11.2)	35.1 (9.6)	38.9 (12.6)	36.8 (11.2)
BMI, kg/m^2	27.5 (8.1)	26.7 (9.1)	27.7 (7.1)	27.0 (6.3)	27.2 (7.7)
Duration of current episode, wk	45.0 (50.9)	88.9 (162.5)	79.5 (90.2)	90.0 (130.3)	75.6 (115.0)
No. of past episodes (excluding current episode)	2.5 (2.3)	1.3 (1.3)	2.0 (2.0)	1.3 (1.7)	1.8 (1.9)
MADRS score at baseline (week 0)	25.8 (4.5)	26.6 (4.7)	27.0 (5.8)	26.9 (4.1)	26.6 (4.8)
CGI-S score at baseline (week 0)	4.3 (1.0)	4.5 (0.6)	4.5 (0.6)	4.4 (0.7)	4.5 (0.7)
Sum of 4 appetitive symptoms on the SIGH-SAD at baseline (week 0)	3.7 (3.8)	2.2 (2.9)	2.8 (2.6)	2.1 (2.3)	2.7 (3.0)

[a]Values shown as mean (SD) unless otherwise noted. No significant differences were found between treatments on any of these variables (all $P > .09$).
Abbreviations: BMI = body mass index, CGI-S = Clinical Global Impressions–Severity of Illness scale, MADRS = Montgomery-Asberg Depression Rating Scale, SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version.

and both age and body mass index (BMI) at baseline were considered as possible covariates. Pending a significant condition-by–appetitive score interaction, the next step would be to perform pairwise comparisons of the strength of this association using the same statistical approach as was used in the primary analysis but limited to 2 groups at a time. Finally, we compared this same association in the double placebo group versus all active treatment groups combined. All analyses were done using SPSS version 22.[18]

RESULTS

Review of Prior Findings

As reported previously,[12] our initial main study finding was that light treatment alone and the combination of light and fluoxetine were more effective than placebo in treating patients with nonseasonal MDD, while fluoxetine was not more effective than placebo. Post hoc Tukey tests found that the combination was also superior to fluoxetine.

Current Results

Baseline characteristics. Baseline demographics and clinical measures by study group are summarized in Table 1. A preliminary analysis of variance showed no significant difference in baseline depression scores, appetitive symptom scores, or BMI across the 4 study groups. None of the other measures were significantly different across the 4 treatment conditions.

Primary analysis. The relationship between appetitive symptoms on the SIGH-SAD at baseline and the percentage decrease in MADRS scores with treatment is plotted in Figure 1 for each of the 4 study groups considered separately. As shown, for individuals in the placebo group, having more appetitive symptoms at baseline predicted less of a decrease in depression scores at 8 weeks ($r = -0.37$; large effect size). In contrast, for individuals in the active treatment groups, having more appetitive symptoms at baseline predicted more of a decrease in depression scores at 8 weeks (fluoxetine group $r = +0.23$, medium effect size; light therapy group $r = +0.11$, small effect size; combination group $r = +0.32$, medium to large effect size). Thus, in contrast to established work in seasonal depression,[7–11] the group that received light therapy alone did not show a strong relationship between appetitive symptoms and treatment outcome. Across all study subjects considered together, there was no significant correlation between appetitive symptoms and treatment response ($r = -0.05$) or between baseline BMI and treatment response ($r = -0.02$).

The multiple regression predicting MADRS change scores with treatment condition, the appetitive score at baseline, and the treatment condition–by–appetitive score interaction was highly significant ($F_{3,118} = 10.09$, $P < .001$). Of greatest interest for the current hypothesis, the treatment condition–by–appetitive score interaction was a strong predictor of MADRS change scores ($t = 2.65$, $P = .009$). Sex was not a significant moderator of this association, and neither age nor BMI at baseline was a significant covariate. These 3 variables were thus excluded from subsequent analyses.

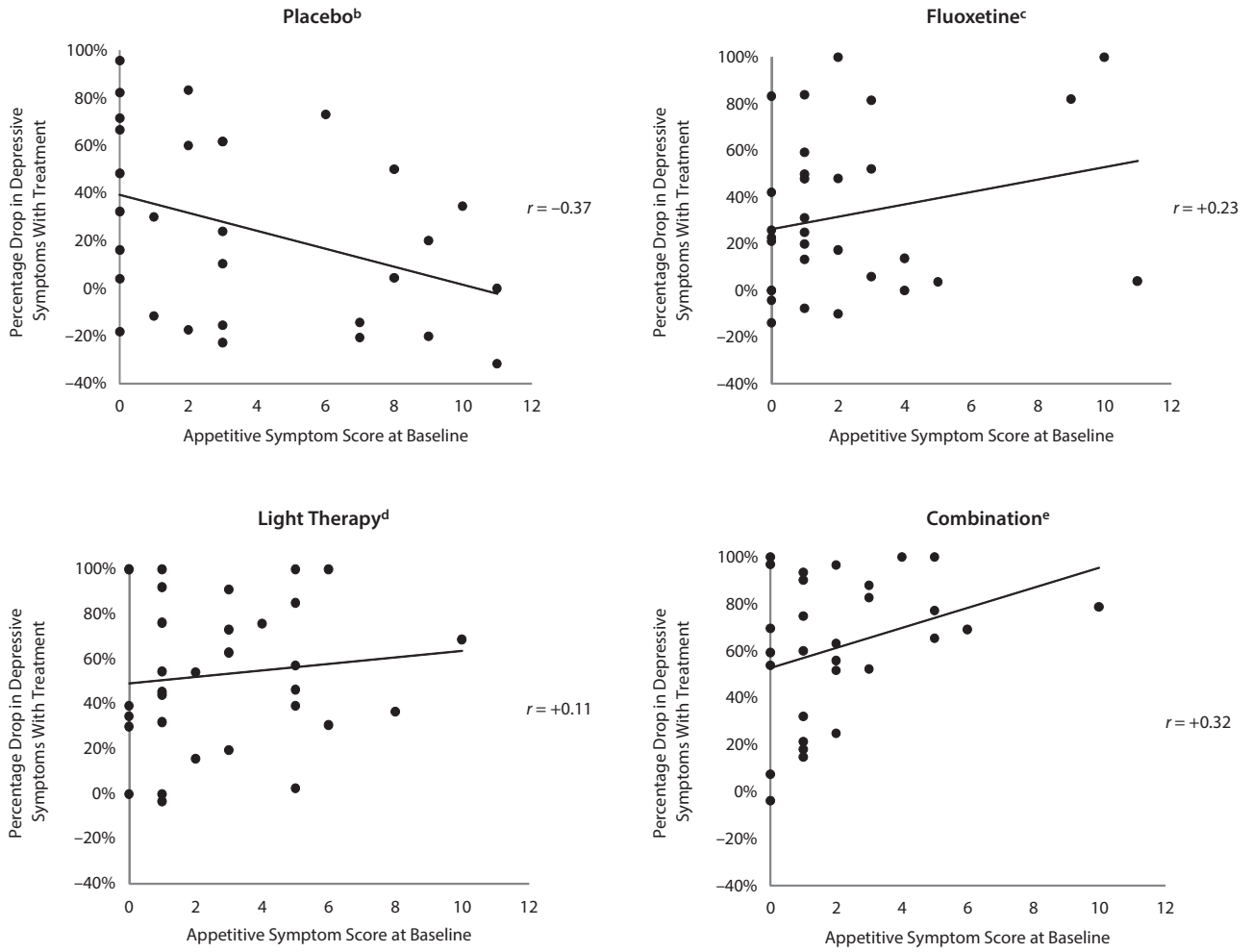
When pairwise group comparisons of the association between appetitive scores and MADRS change scores were performed, the sham-placebo group was found to differ significantly from both the combination treatment group ($\beta = 2.68$; 95% confidence interval [CI], 0.58 to 4.79; $t_{3,55} = 2.55$, $P = .013$) and the fluoxetine-only group ($\beta = 6.45$; 95% CI, 0.89 to 12.0; $t_{3,57} = 2.32$, $P = .024$) and at a trend level of significance relative to the light therapy–only group ($\beta = 2.62$; 95% CI, −0.33 to 5.57; $t_{3,58} = 1.78$, $P = .08$). No significant pairwise group differences were found among the 3 active treatment groups.

When the same analysis was done after combining the 3 treatment groups into a single "any active treatment" group, there was a significant difference in the slope of the regression line relative to the sham-placebo group ($\beta = 3.93$; 95% CI, 1.35 to 6.50; $t_{3,118} = 3.02$, $P = .003$).

DISCUSSION

The current study demonstrated significant group differences in the association between appetitive symptoms at baseline and treatment response in 122 patients with nonseasonal MDD. Appetitive symptoms predicted a positive treatment outcome in patients receiving fluoxetine

Figure 1. Relationship Between the Appetitive Symptom Score at Baseline (based on the SIGH-SAD) and the Percentage Drop in Depression Score With Treatment (based on the MADRS) in Each of the 4 Treatment Groups[a]



[a]Negative values for percentage decreases in depression scores are consistent with a worsening of depression over time.
[b]Two subjects in the placebo group had an appetitive score of 3 and a 61.5% drop in depression score.
[c]Two subjects in the fluoxetine group had an appetitive score of 0 and a 0.0% drop in depression score.
[d]Two subjects in the light therapy group had an appetitive score of 0 and a 100% drop in depression score.
[e]Combination = light therapy plus fluoxetine.
Abbreviations: MADRS = Montgomery-Asberg Depression Rating Scale, *r* = correlation coefficient, SIGH-SAD = Structured Interview Guide for the Hamilton Depression Rating Scale, Seasonal Affective Disorders version.

with or without light therapy and a poor outcome in the sham-placebo group. Contrary to our working hypothesis, appetitive symptoms were not a strong predictor of response to light therapy alone.

In trying to explain the lack of a strong association between appetitive symptoms and light therapy response in nonseasonal MDD, it should be noted that appetitive symptoms occur in most patients with SAD,[5] but only a minority of other patients diagnosed with MDD.[19,20] Consistent with this observation, the mean for the 4-item SIGH-SAD appetitive total score from our prior study of SAD[21] was significantly greater than in the current study (mean ± SD = 5.4 ± 3.2 vs 2.7 ± 3.0, $t_{216} = 6.41$, $P < .001$). This difference, and the fact that appetitive symptoms are often the first to emerge during the short days of fall in patients with SAD,[6] suggests that increased eating plays a more fundamental role in the pathophysiology of SAD than it does in nonseasonal MDD. Indeed, several authors[22–24] have suggested that appetitive symptoms in SAD reflect an evolutionary adaptive mechanism to conserve energy in the face of harsh environmental conditions. Genetic data further support the concept of a "seasonal thrifty phenotype."[25] On the other hand, eating-related symptoms in nonseasonal MDD are more heterogenous in nature, in many cases constituting an affect regulation strategy in individuals who have experienced some form of early life adversity.[26–28] While early life adversity was not assessed in the primary study that was the basis for the current secondary analysis, including that variable would be an interesting extension of this work going forward.

Given our main research focus on light therapy in MDD, and use of fluoxetine as a comparative control condition in

the current protocol, we did not predict a priori that appetitive symptoms would be associated with either a positive or a negative response to fluoxetine. In the current study, appetitive symptoms did ultimately predict a good response to fluoxetine with or without light. Some prior studies have found a positive response to fluoxetine in patients with atypical features,[29–31] although negative studies have also been reported.[32,33] Unlike the current analyses, prior studies did not have a specific focus on appetitive symptoms per se, limiting comparisons to the current results. A separate line of work[34,35] has demonstrated that high-dose fluoxetine is efficacious for bulimia and binge-eating disorder.

Limitations

Figure 1 suggests that, compared to the other 3 groups, the placebo group included more individuals with severe appetitive symptoms at baseline. In support of this finding, when we considered the 3 active treatment groups together, there was a trend for appetitive symptom scores to be higher in the placebo group than in the active treatment groups combined ($P = .079$). Furthermore, this study was not well powered to study subgroup effects given its moderate sample size overall (calculated power to predict MADRS change scores based on 2 variables for the current analysis = 0.53 vs a target of 0.80). With these factors taken into consideration, the current findings should be considered as preliminary only.

Clinical Implications

While our initial publication based on this sample[12] showed that fluoxetine-only was not significantly better than sham-placebo for the overall treatment of nonseasonal MDD, the current findings suggest that fluoxetine used alone or combined with light therapy may be helpful for the subgroup of patients with more appetitive symptoms. On the other hand, in contrast to studies in SAD,[7–11] the current results do not support a clear benefit of light therapy alone in patients with nonseasonal MDD and more appetitive symptoms. Given the aforementioned limitations, however, much larger studies of nonseasonal MDD patients with increased appetitive symptoms are needed to confirm these initial results.

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