Original Investigation

Efficacy of Bright Light Treatment, Fluoxetine, and the Combination in Patients With Nonseasonal Major Depressive Disorder
A Randomized Clinical Trial

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IMPORTANCE Bright light therapy is an evidence-based treatment for seasonal depression, but there is limited evidence for its efficacy in nonseasonal major depressive disorder (MDD).

OBJECTIVE To determine the efficacy of light treatment, in monotherapy and in combination with fluoxetine hydrochloride, compared with a sham-placebo condition in adults with nonseasonal MDD.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo- and sham-controlled, 8-week trial in adults (aged 19-60 years) with MDD of at least moderate severity in outpatient psychiatry clinics in academic medical centers. Data were collected from October 7, 2009, to March 11, 2014. Analysis was based on modified intent to treat (randomized patients with ≥1 follow-up rating).

INTERVENTIONS Patients were randomly assigned to (1) light monotherapy (active 10 000-lux fluorescent white light box for 30 min/d in the early morning plus placebo pill); (2) antidepressant monotherapy (inactive negative ion generator for 30 min/d plus fluoxetine hydrochloride, 20 mg/d); (3) combination light and antidepressant; or (4) placebo (inactive negative ion generator plus placebo pill).

MAIN OUTCOMES AND MEASURES Change score on the Montgomery-Åsberg Depression Rating Scale (MADRS) from baseline to the 8-week end point. Secondary outcomes included response (≥50% reduction in MADRS score) and remission (MADRS score ≤10 at end point).

RESULTS A total of 122 patients were randomized (light monotherapy, 32; fluoxetine monotherapy, 31; combination therapy, 29; placebo, 30). The mean (SD) changes in MADRS score for the light, fluoxetine, combination, and placebo groups were 13.4 (7.5), 8.8 (9.9), 16.9 (9.2), and 6.5 (9.6), respectively. The combination (effect size [*d*] = 1.11; 95% CI, 0.54 to 1.64) and light monotherapy (*d* = 0.80; 95% CI, 0.28 to 1.31) were significantly superior to placebo in the MADRS change score, but fluoxetine monotherapy (*d* = 0.24; 95% CI, −0.27 to 0.74) was not superior to placebo. For the respective placebo, fluoxetine, light, and combination groups at the end point, response was achieved by 10 (33.3%), 9 (29.0%), 16 (50.0%), and 22 (75.9%) and remission was achieved by 9 (30.0%), 6 (19.4%), 14 (43.8%), and 17 (58.6%). Combination therapy was superior to placebo in MADRS response (β = 1.70; *df* = 1; *P* = .005) and remission (β = 1.33; *df* = 1; *P* = .02), with numbers needed to treat of 2.4 (95% CI, 1.6 to 5.8) and 3.5 (95% CI, 2.0 to 29.9), respectively. All treatments were generally well tolerated, with few significant differences in treatment-emergent adverse events.

CONCLUSIONS AND RELEVANCE Bright light treatment, both as monotherapy and in combination with fluoxetine, was efficacious and well tolerated in the treatment of adults with nonseasonal MDD. The combination treatment had the most consistent effects.

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Major depressive disorder (MDD) affects at least 5% of the population, with a lifetime prevalence estimated at 14%.[1] It is the second-ranked cause of disability worldwide[2] and is associated with impairment in quality of life,[3] increased risk of mortality,[4] and societal burden.[5] Treatments for MDD include psychotherapies and antidepressants,[6,7] but remission rates remain low despite adequate treatment[8] and more therapeutic options are needed.

Light therapy, an effective treatment for seasonal affective disorder (SAD),[9] may also be appropriate for MDD. Bright light is a safe, well-tolerated, nonpharmacological treatment that can be used alone or combined with medications.[10] Light can correct disturbed circadian rhythms, which have been implicated in the pathophysiology of MDD.[11] Previous meta-analyses of light therapy for nonseasonal MDD, however, have yielded only equivocal and conflicting evidence for efficacy.[12,13] Two more recent systematic reviews both concluded that the quality and methods of the identified studies were too heterogeneous to conduct a meta-analysis.[14,15] They each found insufficient evidence for efficacy of bright light monotherapy, although 1 review found low-quality evidence for bright light as adjuvant treatment to antidepressants.[15]

In summary, these systematic reviews indicate that the evidence for benefits of bright light therapy for nonseasonal MDD is inconclusive and well-designed studies are required to resolve this issue. Hence, we conducted a placebo-controlled study to investigate the efficacy of light therapy, an antidepressant (fluoxetine hydrochloride), and the combination for the treatment of outpatients with nonseasonal MDD. We hypothesized that light monotherapy and the combination treatment would be more efficacious in reducing depressive symptoms than a placebo condition.

Methods

Setting

This randomized, double-blind study was mainly conducted in 3 psychiatric outpatient clinics (1 clinic in Vancouver, British Columbia, Canada, and 2 clinics in Toronto, Ontario, Canada); because of slow recruitment, the study was halted in 2 other sites (only 5 patients were entered over 2 years). Data were collected between October 7, 2009, and March 11, 2014, and the analysis was conducted from March 16, 2015, to May 9, 2015. The study was approved by institutional review boards at the University of British Columbia and the University of Toronto.

Participants

Participants were recruited by referral and advertisements and provided written informed consent. eTable 1 in Supplement 1 lists eligibility criteria. In summary, patients were aged 19 to 60 years ; had a *DSM-IV-TR*[16] diagnosis of MDD as assessed by board-certified psychiatrists and confirmed with the Mini International Neuropsychiatric Interview (MINI)[17] and a score of 20 or higher on the Hamilton Depression Rating Scale (HAM-D)[18] at screening and baseline; and were psychotropic medication free for at least 2 weeks prior to the baseline visit. Patients were excluded for seasonal pattern, bipolar and psychotic disorders, substance abuse or dependence within the past year, or serious suicidal risk as judged by the clinician. Comorbid anxiety and other psychiatric disorders were allowed if they were not the primary diagnosis. Patients were also excluded if they had unstable medical illnesses, had retinal disease, were pregnant or breastfeeding, or had previously used fluoxetine or light therapy. Patients were also excluded for treatment resistance during the current episode (lack of response to ≥2 antidepressants at therapeutic doses for >6 weeks) or for using other concurrent treatments for depression, including psychotherapy.

Protocol and Randomization

The full trial protocol is available in Supplement 2. Eligible patients after the screening visit (week −1) entered a 1-week phase without treatment to regulate their sleep-wake schedule as much as possible (eg, patients were encouraged to sleep only between 22:00 and 08:00) and to identify spontaneous responders. Patients who significantly improved in this week (defined as ≥25% improvement in HAM-D scores) were withdrawn. Otherwise, participants were randomly allocated 1:1:1:1 to 1 of 4 treatment conditions for 8 weeks: (1) light monotherapy using a fluorescent light box plus a placebo pill; (2) fluoxetine monotherapy using an inactive ion generator with fluoxetine hydrochloride, 20 mg/d; (3) placebo treatment with an inactive ion generator plus a placebo pill; or (4) combined treatment using a light box plus fluoxetine hydrochloride, 20 mg/d. Randomization codes were computer generated centrally and stratified by site in random blocks of 4 or 8. Allocation concealment was ensured because randomization codes could not be obtained prior to logging in the unique participant code. Patients were seen for outcome assessments at weeks 0, 1, 2, 4, 6, and 8 or at unexpected termination.

Interventions

Device Treatments

The active treatment device consisted of daily exposure to a fluorescent light box for 30 minutes as soon as possible after awakening, preferably between 7 and 8 AM (Carex Day-Light Classic, emitting 4000-K white light rated at 10 000 lux at 35.56 cm from screen to cornea, with a UV filter [for spectral emission, see the eFigure in Supplement 1]). Patients used the light box at home and were given standardized verbal and written instructions.

The sham treatment device was a negative ion generator (SphereOne Inc) modified to emit an audible quiet hum but deactivated so that no ions were emitted. Patients were given the same instructions for using the ion generator as used for the light box.

Deception was used, as approved by the instititional review boards, to enhance the plausibility of the sham condition by obscuring the study objectives. Patients were told, using a standard script, that investigators were comparing light and ion treatment and that half the treatment devices were inactive, but without further details. Thus, patients were not aware that all the light devices were active while all the ion generators were inactive. Pretreatment expectations were assessed

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with a modified expectation of response questionnaire (eTable 2 in Supplement 1).[19] Adherence was monitored using daily logs of device treatment times completed by patients and reviewed at each visit. Patients were also instructed to avoid spending an excessive or unusual amount of time outdoors during the study period.

Medication Treatments

The active medication treatment was a daily, fixed dose of fluoxetine hydrochloride, 20 mg, taken in the morning. The placebo was an identical capsule containing inert filler. Adherence was measured by capsule counts at each visit.

Assessments

To preserve treatment blinding, patients were evaluated by telephone at each visit by independent evaluators blinded to treatment condition. Although the HAM-D was originally planned as the primary outcome, pilot testing found the HAM-D had poor interrater reliability on telephone ratings, so it was not used. Instead, the Montgomery-Åsberg Depression Rating Scale (MADRS),[20] evaluated using the structured interview guide,[21] was used. Interrater reliability was assessed using 3 recorded interviews; the intraclass correlation for the MADRS among 5 evaluators was 0.933. Telephone evaluators were replaced if they became unblinded during the study. Response was defined as a reduction of 50% or more from baseline in MADRS scores, and remission was defined as a MADRS score of 10 or lower at the final visit.

Study psychiatrists blinded to treatment condition evaluated patients at each visit using the Clinical Global Impression (CGI) subscales for severity and improvement.[22] Patients also completed self-rated questionnaires during each visit, including the Quick Inventory of Depressive Symptomatology-Self-report (QIDS-SR).[23] Adverse effects were assessed using the Adverse Events Scale,[24] a self-rated scale that assesses severity of 41 adverse events.[25] A treatment-emergent adverse event (TEAE) was defined as any increase in rating during treatment to a score of moderate or severe. For descriptions of the assessments, see eTable 2 in Supplement 1.

Statistical Analysis

All randomized patients were included in the analysis based on modified intent to treat, defined as randomized patients with at least 1 follow-up rating. Missing data were imputed using last observation carried forward. The original sample size was estimated based on a power analysis using end point change scores on the MADRS: 54 patients per condition would allow 80% power to detect a mean difference vs placebo of at least 3.5 points or an effect size of 0.4, regarded as a small to medium-sized treatment effect.[26] Because of slow recruitment and expiration of funding, however, the study was halted before the target sample size was attained.

All treatment variables remained coded and the investigators were blinded to variable identity during the primary analysis. The change in MADRS score from week 0 to week 8 (or termination) was the primary outcome. Analysis of variance (ANOVA) was used, with covariates for baseline MADRS score, site, and sex. A preplanned simple contrast compared each of the active conditions against placebo. Post hoc tests were then conducted to explore differences between pairs of conditions. The changes in QIDS-SR and CGI improvement scores were analyzed similarly. Response and remission rates were analyzed using binary logistic regression with preplanned contrasts (for each active condition against placebo) and covariates for baseline MADRS score, site, and sex. Effect sizes were calculated using Cohen d[26] and numbers needed to treat (NNTs) were estimated. We used χ^2 tests to analyze rates of TEAEs; if the overall 4×2 χ^2 test was significant, post hoc 2×2 χ^2 tests were conducted on paired comparisons. All tests were 2-sided with the significance level set at $\alpha = .05$. All analyses were done using IBM SPSS Statistics for Windows version 22.0 statistical software (IBM Corp).

Results

Sample

Figure 1 shows the participant flow through the phases of the study. A total of 131 eligible participants entered the study and 122 patients were randomized to treatment (32 to light monotherapy, 31 to fluoxetine monotherapy, 29 to combination therapy, and 30 to placebo). **Table 1** shows clinical information on the patients in the 4 conditions. Using 1-way ANOVA, there were no significant differences in any of the clinical variables. The ANOVA for expectation rating score showed no differences between patients randomized to each individual condition ($F_{3,116} = 0.62$; $P = .60$).

Primary Outcome

The mean (SD) change in MADRS score from baseline to the 8-week end point was 16.9 (9.2) in those who received combination therapy, 13.4 (7.5) in those who received light monotherapy, 6.5 (9.6) in those who received placebo, and 8.8 (9.9) in those who received fluoxetine monotherapy (**Table 2**). The ANOVA for change scores on the MADRS showed a significant overall effect ($F_{6,115} = 4.12$; $P = .001$) and a significant effect of condition ($F_{3,115} = 7.01$; $P < .001$). The preplanned simple contrasts found significant effects of light treatment vs placebo ($P = .006$) and combination vs placebo ($P < .001$), but not for fluoxetine vs placebo ($P = .32$). The effect sizes vs placebo for the fluoxetine, light treatment, and combination groups were $d = 0.24$ (95% CI, −0.27 to 0.74), 0.80 (95% CI, 0.28 to 1.31), and 1.11 (95% CI, 0.54 to 1.64), respectively. Post hoc Tukey tests found that the combination was also superior to fluoxetine ($P = .02$). The per protocol results with completed participants were similar to the results of last-observation-carried-forward analyses (eTable 3 in Supplement 1).

Secondary Outcomes

Table 2 shows results for other outcomes. At the 8-week end point for the placebo, fluoxetine monotherapy, light monotherapy, and combination therapy groups, response was achieved by 10 (33.3%), 9 (29.0%), 16 (50.0%), and 22 (75.9%), respectively. The binary logistic regression model for MADRS response had a significant overall effect for treatment condi-

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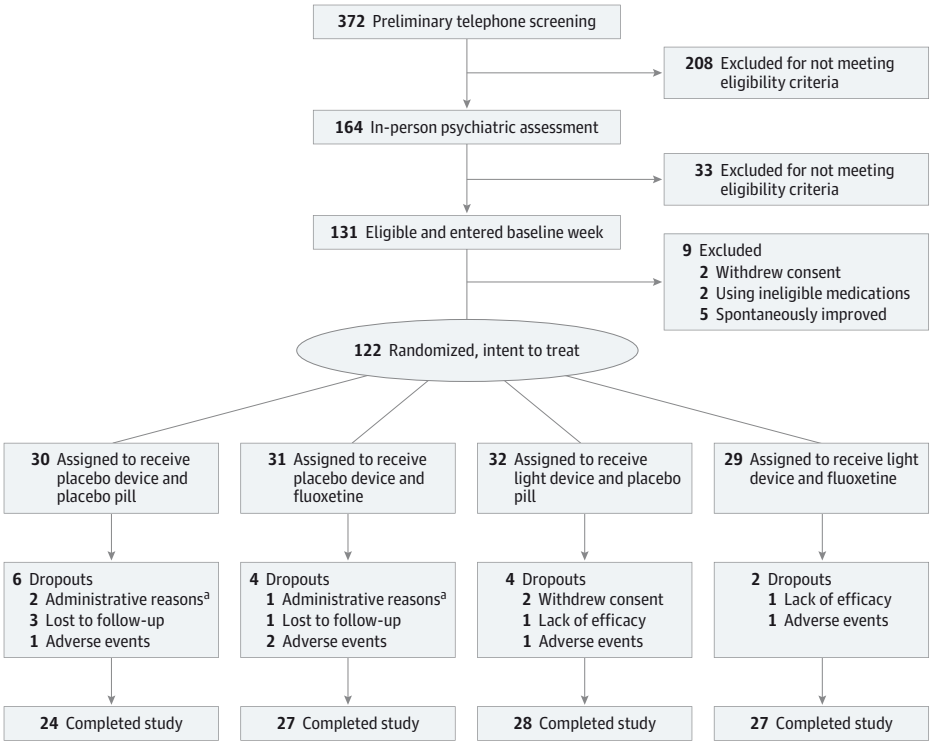
Figure 1. CONSORT Flow Diagram



[a] Patient moved out of town.

Table 1. Clinical Information for Participants[a]

Characteristic	Total (N = 122)	Treatment Group			
		Placebo (n = 30)	Fluoxetine Monotherapy (n = 31)	Light Monotherapy (n = 32)	Combination Therapy (n = 29)
Female, No. (%)	76 (62.3)	22 (73.3)	22 (71.0)	17 (53.1)	15 (51.7)
Married or cohabiting, No. (%)	35 (28.7)	6 (20.0)	5 (16.1)	12 (37.5)	12 (41.4)
Age, mean (SD), y	36.8 (11.2)	36.2 (11.5)	37.3 (11.2)	35.1 (9.6)	38.9 (12.6)
Duration of current MDD episode, wk					
Mean (SD)	75.6 (115.0)	45.0 (50.9)	88.9 (162.5)	79.5 (90.2)	90.0 (130.3)
Median (range)	31 (2-728)	24 (2-207)	24 (2-728)	36 (5-270)	38 (2-520)
Past MDD episodes, mean (SD), No.[b]	1.8 (1.9)	2.5 (2.3)	1.3 (1.3)	2.0 (2.0)	1.3 (1.7)
Score at wk 0, mean (SD)					
HAM-D	22.4 (2.8)	22.2 (2.3)	23.2 (3.2)	22.2 (3.0)	22.0 (2.8)
MADRS	26.6 (4.8)	25.8 (4.5)	26.6 (4.7)	27.0 (5.8)	26.9 (4.1)
CGI severity subscale	4.5 (0.7)	4.3 (1.0)	4.5 (0.6)	4.5 (0.6)	4.4 (0.7)
QIDS-SR	15.1 (3.5)	15.7 (3.9)	15.2 (2.9)	14.8 (3.7)	14.5 (3.5)
Expectation rating	10.7 (2.7)	11.0 (3.0)	10.0 (2.8)	10.9 (2.8)	10.7 (2.3)

Abbreviations: CGI, Clinical Global Impression; HAM-D, Hamilton Depression Rating Scale; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-report.

[a] No differences were found between treatments for any of the variables (all $P > .09$).

[b] Excluding current episode.

tion ($df = 3$; $P = .007$) and the preplanned contrasts showed a significant effect for combination vs placebo (β = 1.70; $df = 1$; $P = .005$) but not for fluoxetine vs placebo (β = 0.29; $df = 1$; $P = .69$) or light treatment vs placebo (β = 0.77; $df = 1$; $P = .17$). The NNT for response for combination vs placebo was 2.4 (95% CI, 1.6-5.8). Remission was achieved by 9 (30.0%) in the placebo group, 6 (19.4%) in the fluoxetine monotherapy group, 14 (43.8%) in the light monotherapy group, and 17 (58.6%) in the combination therapy group. The binary logistic regression model for MADRS remission had a significant overall effect for treatment condition ($df = 3$; $P = .01$) and a significant preplanned contrast effect for combination vs placebo (β = 1.33; $df = 1$; $P = .02$) but not for fluoxetine vs placebo (β = −0.63; $df = 1$; $P = .31$) or light treatment vs placebo (β = 0.64; $df = 1$; $P = .27$). The NNT for remission for combination vs placebo was 3.5 (95% CI, 2.0-29.9).

For other outcomes, the ANOVA for the change in CGI improvement scores (Table 2) showed a significant overall ef-

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Table 2. Outcome Measures[a]

Measure	Treatment Group				Significant Comparisons
	Placebo (n = 30)	Fluoxetine Monotherapy (n = 31)	Light Monotherapy (n = 32)	Combination Therapy (n = 29)	
Change in MADRS score from wk 0 to end point, mean (SD)	6.5 (9.6)	8.8 (9.9)	13.4 (7.5)	16.9 (9.2)	Light > placebo (P = .006)[b]; combination > placebo (P < .001)[b]; combination > fluoxetine (P = .02)[c]
MADRS response at end point, No. (%)	10 (33.3)	9 (29.0)	16 (50.0)	22 (75.9)	Combination > placebo (P = .005)[d]
MADRS remission at end point, No. (%)	9 (30.0)	6 (19.4)	14 (43.8)	17 (58.6)	Combination > placebo (P = .02)[d]
CGI improvement at end point, mean (SD)[e]	3.30 (1.69)	2.94 (1.12)	2.47 (1.14)	1.97 (1.24)	Light > placebo (P = .01)[b]; combination > placebo (P < .001)[b]
Change in QIDS-SR score from wk 0 to end point, mean (SD)	3.7 (5.1)	4.0 (4.6)	5.1 (3.9)	7.1 (5.6)	Combination > placebo (P = .004)[b]

Abbreviations: CGI, Clinical Global Impression; MADRS, Montgomery-Åsberg Depression Rating Scale; QIDS-SR, Quick Inventory of Depressive Symptomatology–Self-report; >, superior to.

[a] All outcomes are based on intent-to-treat, last-observation-carried-forward analysis.

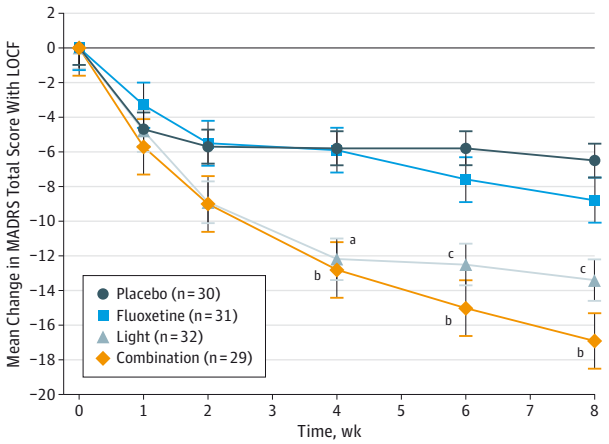
[b] Analysis of variance with preplanned simple contrasts.

[c] Post hoc Tukey highly significant difference tests.

[d] Binary logistic regression with preplanned contrasts.

[e] Lower scores indicate greater improvement.

Figure 2. Change Scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) From Baseline to End Point With Last Observation Carried Forward (LOCF) at Each Treatment Week



Error bars indicate standard error.

[a] P < .01 vs placebo and P < .01 vs fluoxetine.

[b] P < .005 vs placebo and P < .005 vs fluoxetine.

[c] P < .05 vs placebo.

fect ($F_{5,116}$ = 3.62; P = .004) and a significant effect of condition ($F_{3,116}$ = 5.70; P = .001). Preplanned simple contrasts found significant effects for light treatment vs placebo (P = .01) and combination vs placebo (P < .001) but not for fluoxetine. Similarly, the ANOVA for change in QIDS-SR score was significant in overall effect ($F_{6,115}$ = 2.72; P = .02) with a significant overall effect of condition ($F_{3,115}$ = 3.27; P = .02). Preplanned simple contrasts found significant effects for combination vs placebo (P = .004) but not for light treatment or fluoxetine.

Figure 2 shows the mean MADRS change scores from baseline at each treatment visit. Post hoc Bonferroni tests found significant superiority of combination treatment vs both placebo and fluoxetine at weeks 4, 6, and 8. Light treatment was significantly superior to placebo at weeks 4, 6, and 8 and superior to fluoxetine at week 4.

An exploratory ANOVA was conducted to examine whether time of year affected outcomes (eTable 4 in Supplement 1). There were no significant differences in MADRS outcomes comparing season of treatment, whether in the total sample or in the subsample who received a light device.

Treatment-Emergent Adverse Events

There was a single serious adverse event during the trial: a participant in the combination treatment condition was hospitalized for worsening suicidal ideation after treatment week 4. This was judged, by both the treatment team and the patient, to be more likely related to an unexpected severe stressor (a sexual assault that occurred the week prior to hospitalization) than to the treatment itself.

The percentage of patients reporting at least 1 TEAE was not significantly different between conditions (placebo, 16 patients [53.3%]; fluoxetine, 25 patients [80.6%]; light treatment, 20 patients [62.5%]; combination, 15 patients [51.7%]; χ^2_3 = 6.85; P = .08). **Table 3** shows the TEAEs reported in more than 5% of patients. Most TEAEs were transient. There were no switches to hypomania. The percentage of patients reporting at least 1 TEAE self-rated as severe during treatment was not significantly different between conditions (placebo, 24 patients [43.3%]; fluoxetine, 25 patients [67.7%]; light treatment, 16 patients [50.0%]; combination, 11 patients [37.9%]; χ^2_3 = 0.63; P = .89). Similarly, there were no significant differences between conditions in overall dropout rates in the study or in dropouts due to TEAEs.

Discussion

The main result of this study was that both light monotherapy and the combination treatment had significant benefits compared with a sham-placebo condition in adults with nonseasonal MDD. The combination treatment showed significant results for both the primary outcome (change in MADRS total score) and key secondary outcomes (including MADRS response and remission rates). The benefits of the combination treatment were apparent in both interviewer-rated (MADRS, CGI improvement) and patient-rated (QIDS-SR) out-

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Table 3. Treatment-Emergent Adverse Events[a]

Treatment-Emergent Adverse Event	Patients by Treatment Group, %			
	Placebo (n = 30)	Fluoxetine Monotherapy (n = 31)	Light Monotherapy (n = 32)	Combination Therapy (n = 29)
Gastrointestinal				
Nausea	8.0	20.8	3.2	3.6
Diarrhea[b]	0.0	0.0	23.1[c]	7.4
Heartburn	0.0	7.7	6.7	3.6
Decreased appetite	12.5	8.0	10.7	7.4
Increased appetite[b]	4.0	16.7[d]	23.1[d]	0.0
Weight gain	0.0	3.7	6.9	0.0
Central nervous system				
Anxiety	8.0	8.7	6.7	11.5
Agitation	8.0	11.5	6.7	0.0
Headache	0.0	3.6	7.1	3.6
Irritability	3.8	12.0	7.1	3.6
Sleepiness[b]	8.0	42.1[e]	6.7	17.4
Increased sleep	3.8	26.1	18.5	11.5
Decreased sleep	8.0	31.8	10.3	3.7
Sleep disturbance	8.0	20.8	10.7	21.7
Sexual dysfunction				
Decreased sex drive	3.8	12.5	6.7	16.7
Delayed orgasm[b]	0.0	17.4[e]	0.0	3.7
Male erection problem	0.0	4.2	7.4	0.0
Delayed ejaculation	4.0	9.1	3.6	3.8
Other				
Dizziness	4.2	7.4	14.3	3.6
Palpitations	4.0	7.7	3.3	0.0
Tremor	3.8	7.4	0.0	3.6
Twitching	0.0	3.6	0.0	11.5
Muscle pain	0.0	3.6	11.5	3.6
Weakness or fatigue	8.0	36.8	7.1	11.5
Dry mouth	8.0	11.5	6.7	3.6
Rash	0.0	7.4	0.0	3.6

[a] Events for which more than 5% of patients in any group reported an increase from baseline to at least moderate severity, as measured by self-report on the Adverse Events Scale.

[b] $P < .05$ by overall χ^2 analysis with Fisher exact test as appropriate, $df = 3$.

[c] $P < .05$ vs placebo and fluoxetine monotherapy by post hoc paired χ^2 analysis with Fisher exact test as appropriate, $df = 1$.

[d] $P < .05$ vs combination therapy by post hoc paired χ^2 analysis with Fisher exact test as appropriate, $df = 1$.

[e] $P < .05$ vs placebo and light monotherapy by post hoc paired χ^2 analysis with Fisher exact test as appropriate, $df = 1$.

come scales. Light monotherapy was significantly superior to the sham-placebo condition in the primary outcome and in CGI improvement scores, but not in other secondary outcomes.

This trial represents, to our knowledge, the first adequate-duration, placebo-controlled comparison of light monotherapy and combination light and antidepressant treatment. Previous studies of light monotherapy have been very short in duration or not sham controlled. For combination treatment, Martiny et al[27,28] previously found that sertraline hydrochloride, 50 mg/d, combined with bright white light (10 000-lux fluorescent light for 60 min/d) was superior to sertraline combined with "placebo" dim red light (50 lux for 30 min/d), similar to the results in our study. Limitations of the study by Martiny[27] included the 5-week study duration, which may be too short to evaluate medication response, and lack of a placebo-only condition. Our randomized double-dummy design, in which patients used a device and took a pill, controls for the nonspecific effects of light therapy or medication. The ion generator appeared to be a credible sham treatment in that expectation ratings were not significantly different between conditions.

In post hoc exploratory analyses, the combination treatment was also significantly superior to fluoxetine monotherapy, although there were no significant differences between fluoxetine and placebo. Fluoxetine is an efficacious antidepressant[29] but the smaller-than-planned sample size may have limited the statistical power to detect differences. In SAD studies, light therapy often has a rapid effect within 1 to 2 weeks. In this study, there was steady improvement with both light conditions throughout the 8 weeks. Post hoc statistical separation from placebo occurred only after 4 weeks, a pattern of response more similar to that of antidepressants.

All treatments were generally well tolerated with low rates of withdrawals owing to adverse events and no differences between conditions. The higher rate of TEAEs in this study is likely related to using a patient-rated scale instead of relying on spontaneous reports as per usual in clinical trials. The fluoxetine monotherapy was associated with a greater frequency of some TEAEs than placebo (sleepiness, delayed orgasm in women) and combination treatment (increased appetite), while the light monotherapy had higher rates of some TEAEs than

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placebo (diarrhea) and combination treatment (diarrhea, increased appetite). Interestingly, the combination treatment did not show higher rates in any TEAE, which suggests that the combination may mitigate some of the adverse effects of fluoxetine and light alone.

The mechanism of action of light therapy is still unknown, but major hypotheses in SAD involve resynchronizing circadian rhythms and/or restoring neurotransmitter dysfunction.[30-32] Nonseasonal MDD may also be associated with disturbances in circadian rhythms.[11,33] Bright light has predictable circadian phase-shifting effects in humans,[34] but studies of light therapy in SAD have not consistently demonstrated correlations of phase shift with response.[31,35] Rapidly depleting serotonin[36,37] and catecholamines[38] can reverse the antidepressant effects of light therapy in SAD, thereby suggesting that bright light may have direct monoaminergic effects similar to those seen with antidepressants.[39] Further studies will be required to determine whether any of these effects mediate the antidepressant effect of light therapy in MDD.

Limitations

The study used a double-dummy design in which patients used a treatment device and took a pill each day. Designing a sham control condition for bright light, which cannot be completely disguised, is challenging.[40] Sham conditions have used low-intensity light or nonlight conditions to control for the nonspecific behavioral effects of light treatment (eg, waking at a particular time, sitting quietly for 30 minutes, using a novel device, etc). Low-intensity light is problematic because many participants are aware that bright light is active and there is no consensus for the threshold intensity of an "inactive dose" of light. Hence, nonlight sham interventions, such as a deactivated ion generator, have been used.[41,42] Ion generators are viewed by participants as a credible treatment for depression, likely because beneficial effects of negative ions on mood have been reported.[43,44]

Because the preplanned sample size was not attained, the study had limited power to detect clinically significant differences between active conditions. This study also compared fixed-dose strategies. It is possible that higher dosing, for both medication and light treatment, might lead to greater response. However, fluoxetine hydrochloride dosages higher than 20 mg/d do not show greater efficacy.[45,46] Our study used a standard light therapy protocol that has been effective in SAD studies, but there has been little study of the optimal parameters batment in nonseasonal MDD. The study did not control or measure the patients' naturalistic light exposure.

Generalizability

The study was conducted in outpatient psychiatry clinics and excluded significant psychiatric and medical comorbidity, similar to registration trials for new antidepressants. However, results may not be generalizable to primary care or to complex patients. All sites were situated between 39° and 49° north latitudes, and effects of light may not generalize to other latitudes.

Conclusions

Light treatment, whether in monotherapy or particularly in combination with fluoxetine, is efficacious and well tolerated in the treatment of nonseasonal MDD. The treatment effects were large and NNTs were clinically relevant. Further studies exploring mediators and moderators of response will be important.

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