Modafinil for Atypical Depression: Effects of Open-label and Double-blind Discontinuation Treatment

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Abstract: Atypical depression, with features of hypersomnia, hyperphagia, anergia, and rejection sensitivity, is a common presentation of major depressive disorder. There are few available effective therapies for this disorder. We test modafinil, a novel wake-promoting agent, as monotherapy for atypical depression in a double-blind, placebo-controlled, relapse prevention trial after open-label treatment. We found that modafinil significantly improved atypical depression symptoms during 12 weeks of open-label treatment (mean ± SD Hamilton Depression Scale (29-item version) score changed from 34 ± 8.2 at baseline to 9.7 ± 9.3, $P < 0.0001$), and that benefits were maintained alike in both the continuation and placebo arms during the double-blind treatment phase ($P = 0.92$). Modafinil was well tolerated and the drug was associated with significant weight loss compared with placebo ($P = 0.01$).

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Major depression with atypical features (or atypical depression) describes a subgroup of depressed patients who have reactive mood with features of hypersomnia, hyperphagia, anergia, and rejection sensitivity (Diagnostic and Statistical Manual of Mental Disorders-IV). Despite this form of depression being relatively common,[1] there are limited therapeutic options available for this depressive subtype. Although monoamine oxidase inhibitors produce a good response,[2] associated dietary restrictions and potential adverse effects do not allow them to be considered first-line treatment. Tricyclic antidepressants (TCAs) have a much lower response rate.[2,3] Selective serotonin reuptake inhibitors (SSRIs) are also of limited efficacy.[3] Indeed, TCAs and SSRIs seem to have less efficacy in atypical depression than in non-atypical depression.[4]

An alternative strategy may be beneficial for treatment of atypical depression, as the disease may be different from 'typical' or melancholic depression. There is evidence to suggest that atypical depression differs in terms of sex prevalence, suicidality, and biological characteristics. Compared with nonatypical depression, atypical depression patients are more likely to be women, have an earlier age of onset of depression, have a higher rate of suicide attempts, have greater numbers of disability days and restricted activity days, and are more likely to use antidepressants and visit hospital emergency departments for neuropsychiatric reasons.[5] Atypical depression also seems to have a reversed neuroendocrine disturbance compared with melancholic depression. Atypical depression patients have reduced hypothalamic-pituitary axis (HPA) activity and a relative cortisol-releasing hormone deficiency, whereas melancholic depression patients have excess HPA activity and cortisol-releasing hormone secretion.[6] There is a significantly higher cortisol response to noradrenergic agents in patients with atypical depression than with melancholic depression patients, suggesting there is less of a dysfunction within the noradrenergic system.[7] Additionally, melancholic depression patients may have dysfunctional 5-HT_{1A} autoreceptors, whereas atypical depression patients may have normal autoreceptor function secondary to low HPA activity.[8] There is also evidence to suggest that atypical features of depression are more prevalent in patients with bipolar disorder, particularly bipolar II disorder.[9] Finally, there is evidence to suggest that atypical depression patients have heightened right hemispheric activation (as assessed by perception of chimeric faces), in contrast to melancholic depression patients.[10]

Modafinil, a novel wake-promoting agent, may help improve outcomes for atypical depression patients. Modafinil is currently approved for treatment of excessive sleepiness associated with narcolepsy,[11] shift work sleep disorder,[12] and residual sleepiness in obstructive sleep apnea as an adjunct to nasal continuous positive airway pressure therapy.[13] In addition, modafinil has been shown to reduce fatigue in multiple sclerosis,[14] suggesting a potential role for treating hypersomnia and anergia in atypical depression. More direct evidence for its potential use in depression has come from a study that has shown benefit in anergic depression.[15]

In addition, modafinil as an augmentation agent to SSRI therapy has been shown to significantly reduce fatigue in patients with major depressive disorder experiencing fatigue and excessive sleepiness in randomized, placebo-controlled trials.[16,17] Prospective open-label,[18] retrospective chart review,[19] and retrospective case series[20] studies indicate modafinil's effectiveness as an adjunctive agent for depressive symptoms. Indeed, adjunctive modafinil at initiation of treatment with an SSRI may enhance the degree and onset of therapeutic effects in depressive patients.[21]

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There have been limited studies with modafinil as monotherapy for depression, however. We are aware of only a retrospective chart review that indicated modafinil may be effective as monotherapy for depression.[22] Despite the paucity of clinical data, there are some theoretical reasons to suggest that modafinil may be effective as monotherapy for atypical depression. Epidemiological data suggest that atypical depression can be defined by 2 of the 3 symptoms of excessive physical fatigue, overeating, and oversleeping[1]; modafinil has the potential for improving these 3 very symptoms as a wake-promoting agent. Modafinil's exact mechanism of action is unclear, but its histaminergic,[22] serotoninergic,[23] noradrenergic,[24] or dopaminergic[24] properties may be relevant. In addition, it may act on the neuropeptide orexin/hypocretin in the hypothalamus.[25]

Modafinil's potential efficacy in depression may be independent of its wake-promoting effect.[22] Modafinil has been shown in animal studies to increase the efficacy of serotonin release, possibly without involving the reuptake process.[23] It has been shown by using in vivo microdialysis that this drug differentially modulates extracellular serotonin in the frontal cortex of the rat (among other areas), with the possibility that this may have antidepressant effects.[23]

Despite the evidence as indicated above, as far as we know, there are currently no prospective open-label or double-blind, placebo-controlled trials of modafinil monotherapy for depression with atypical features (and indeed, as monotherapy for any form of depression). Our aim in this 6-month study was to evaluate the effectiveness and safety of open label modafinil (200–400 mg/d) as monotherapy in adults with major depression with atypical features, followed by a double-blind, placebo-controlled, relapse prevention phase. Our hypothesis was that open-label modafinil would significantly improve symptoms in patients with major depression with atypical features, and that in a double-blind, placebo-controlled phase, maintenance on modafinil would be associated with a lower rate of relapse than replacement with placebo. We test this hypothesis by using the 29-item version of the Hamilton Depression Scale (HAM-D-29) as the primary outcome measure, a scale that incorporates key atypical depression features, such as hyperphagia and hypersomnia.

METHODS

This is a 12-week, open-label study with modafinil followed by a 12-week, double-blind, randomized parallel treatment period with either modafinil or matching placebo. Inclusion criteria were as follows: (1) adults 18 to 65 years old; (2) DSM-IV criteria for major depressive episode with atypical features, as assessed by the Atypical Depression Diagnostic Scale (ADDS);[26] (3) minimum score of 18 on the HAM-D-29 (with atypical items) at baseline;[27] (4) baseline Clinical Global Impressions Severity (CGI-S) score[28] of 4 or more; (5) written informed consent; and (6) a negative serum pregnancy test for women of childbearing potential. The exclusion criteria were as follows: (1) any current primary DSM-IV Axis I disorder other than depression; (2) history of DSM-IV diagnosis of bipolar I disorder, schizophrenia or other psychotic disorder, mental retardation or other pervasive developmental disorder, or cognitive disorder due to a general medical condition; (3) history of substance abuse or dependence within the last 3 months; (4) suicide risk or serious suicide attempt within the last year, (5) clinically significant medical condition or laboratory of electrocardiogram abnormality, (6) history of nonresponse to 3 prior adequate trials of antidepressants, (7) women of childbearing potential who are unwilling to practice an acceptable method of contraception, (8) history of sensitivity to modafinil, (9) use of an investigational medication within the last 28 days, (9) use of antidepressant medication within 28 days of screening, and (10) patients needing concurrent psychotropic medications.

The primary outcome measure was the HAM-D-29 score. Secondary measures were the Epworth Sleepiness Scale (ESS),[29] Fatigue Severity Scale (FSS),[30] Brief Fatigue Inventory (BFI) item 3 (assessing worst level of fatigue in the last 24 hours),[31] Hopkins Symptom Checklist-90 (SCL-90),[32] ADDS,[26] the Clinical Global Impressions Score (CGI-S),[28] and the SOSS (Severity of Symptoms Scale),[33] which were all administered at baseline. Modafinil was given as a single daily dose with breakfast and titrated according to the following schedule: days 1 to 3, 100 mg/d; days 4 to 14, 200 mg/d; days 15 to 84, up to 400 mg/d, depending on patient tolerability and clinical response, with dose increased by increments of 100 mg. The dose was kept within the 200–400 mg/d range. Follow-up visits during this open-label period included administration of the HAM-D-29, CGI-Improvement, ESS, BFI, FSS, SOSS, and vital signs at weeks 2, 4, 6, 8, 10, and 12. Safety evaluation included changes in vital signs and weight, and emergence of adverse events rated as moderate or severe (increase of 2 or more points at any time for any symptom compared with baseline level of severity). At week 12, the ADDS and CGI-S were administered; in women of childbearing potential, a serum pregnancy test was repeated.

Patients who demonstrated at least minimal improvement after 12 weeks (ie, CGI-Improvement score ≤ 3) were randomly assigned to either (1) continue treatment with modafinil at their current dose or (2) switch to treatment with matching placebo for 12 weeks for the double-blind portion of the trial. Assessments identical to those conducted at follow-up visits during the open-label period were done at weeks 14, 16, 18, 20, 22, and 24 (Fig. 1). Baseline patient characteristics are delineated in Table 1. Randomization was achieved in the following way: random numbers were chosen from a statistical distribution with a computer program and each patient was assigned a number. Those patients who randomly received a certain number or higher from the computer program were placed in one group, whereas the remaining patients were placed in the other group.

All analyses were done with intention to treat and last observation carried forward. Statistical testing in the open-label phase was by means of the Wilcoxon Signed Rank Test for the change score. In the double-blind phase, the Kruskal-Walli statistic was used for final visit scores, and χ^2 tests were used for categorical comparisons.

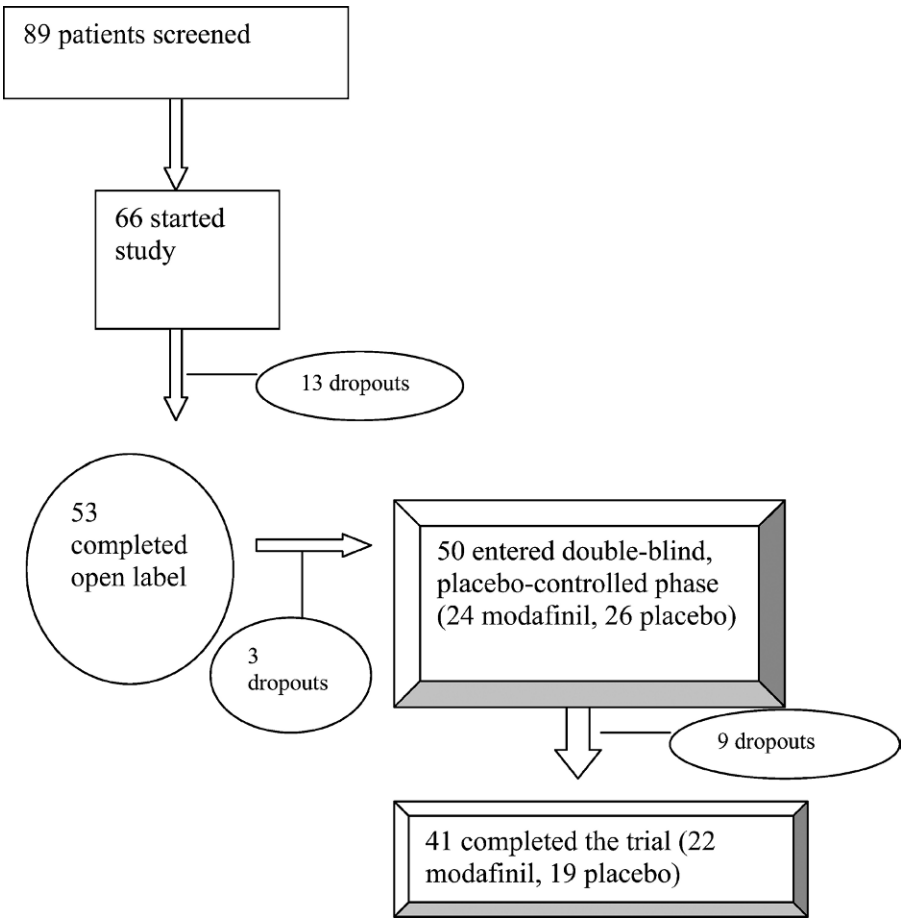

FIGURE 1. Flowchart of study enrollment.

RESULTS

At Baseline

Eighty-nine patients were screened for this study. Sixty-six patients who met criteria for the study were enrolled in the open-label phase. Fifty-three of these patients completed the open-label phase. Thirteen dropped out because of loss to follow-up (n = 3), adverse effects (n = 3), rash from yard work (n = 1), time commitments (n = 2), un-related chest pain (n = 1), worsening depression (n = 1), and unknown reasons (n = 2). Of the 53 patients who completed the open label part of the trial, 50 demonstrated at least minimal improvement and agreed to continue with the randomized, double-blind phase. These 50 patients were randomized to 24 on modafinil and 26 on placebo. There were no statistical differences between the patients randomized to drug and those randomized to placebo in terms of sex, race, or marital status (Table 1). Forty-one patients completed the full

TABLE 1. Patient Characteristics at Baseline

	Open-label Phase (n = 66)	Double-blind Phase (Modafinil n = 26, Placebo n = 24)	Double-blind Modafinil Patients Only	Double-blind Placebo Patients Only	*P* Values Comparing Double-blind Modafinil vs. Placebo Patients
Mean age	39.53 ± 10.54 years	39.48 ± 9.44 years	40.33 ± 9.39	38.692 ± 9.59	$P = 0.54$
Gender	58 females, 8 males	43 females, 7 males	22 females, 2 males	21 females, 5 males	$P = 0.27$
Race	46 whites, 20 non-whites	33 whites, 17 non-whites	15 whites, 9 non-whites	18 whites, 8 non-whites	$P = 0.62$
Marital status	47 not married, 19 married	35 not married, 15 married	15 not married, 9 married	20 not married, 6 married	$P = 0.27$

phase of double-blind treatment with 22 on modafinil and 19 on placebo. There were thus 9 early terminations (7 on placebo and 2 on modafinil).

Primary Outcome Measure

At the end of open-label treatment, modafinil was associated with significant improvement on the HAM-D-29 compared to baseline ($P < 0.0001$), with the score changing from a mean of 34.0 (±8.2) at baseline to 9.7 (±9.3) at week 12 (Fig. 2). In the randomized subsample (n = 50), the mean HAM-D-29 score at baseline was 33.6 (±6.9) and 8.7 (±9.3) at week 12. At randomization, there was no statistically significant difference in HAM-D-29 scores between the modafinil and placebo groups ($P = 0.93$). At the end of the double-blind phase, the HAM-D-29 scores for modafinil did not separate from placebo ($P = 0.92$). Additionally, there was no significant difference between modafinil and placebo in terms of response (HAM-D-29 scores with greater than or equal to 50% drop: $P = 0.74$) and remission (end HAM-D-29 score less than 7: $P = 1.0$). Figure 3 presents the HAM-D-29 scores for only the subsequently randomized patients through both the open label and double-blind phases of the study.

Secondary Outcome Measures

Significant improvement was noted on the SCL-90 total score at week 12, with the mean score decreasing from 1.25 ± 0.68 to 0.49 ± 0.61 ($P < 0.0001$). During the double-blind phase, statistically significant advantages were found for modafinil over placebo on change score from randomization (week 12) to end point (week 24) with respect to the SCL-90 anxiety subscale ($P = 0.02$), and similar trends were noted on the depression subscale ($P = 0.09$) and overeating subscale ($P = 0.06$). However, the drug did not separate from placebo with respect to the total SCL-90 score at the end of the double-blind phase ($P = 0.18$). A similar pattern, that is, no difference between treatments, was found for all of the other secondary measures, including the CGI-S, BFI, ESS, FSS, and ADDS (Table 2).

Safety Assessment

Treatment-emergent adverse effects in the open-label phase were as follows: nausea (15%), bad taste in the mouth (12%), palpitations (11%), thirst (11%), headaches (9%), dry mouth (8%), trouble with orgasm (8%), erection difficulties (8%), and trembling (6%). However, when the patients on modafinil were compared with patients on placebo in the double-blind phase, there were no significant differences between the 2 groups in terms of the aforementioned complaints or any other adverse effects ($P > 0.10$).

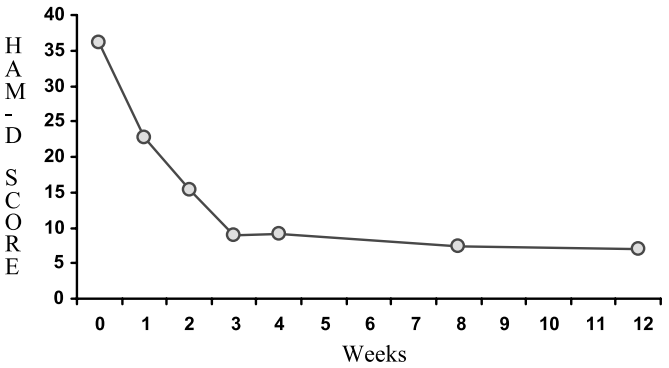

FIGURE 2. HAM-D-29 Scores as a function of time in treatment with modafinil in the open-label phase.

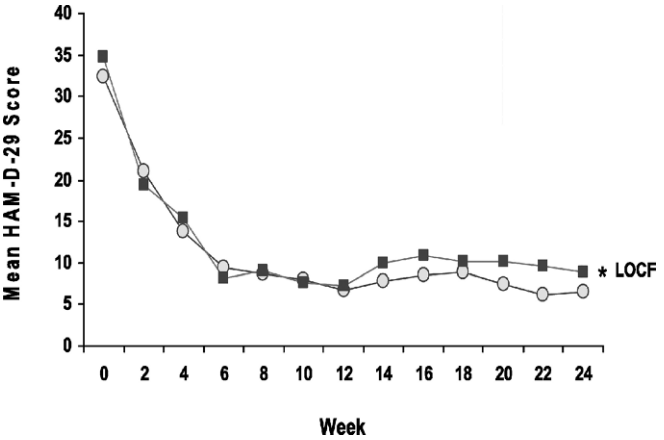

FIGURE 3. HAM-D-29 Scores for the Randomized Patients Throughout the Study. Change from baseline to week 24 with LOCF (Last Observation Carried Forward), $P > 0.10$. Circles represent modafinil; squares, placebo.

Heart rate showed a statistically significant mean ± SD increase of 3.45 ± 9.02 beats per minute in the open-label phase ($P = 0.001$). Weight significantly decreased by 5.03 ± 5.29 lb ($P < 0.0001$). Body mass index also significantly decreased ($P < 0.0001$). However, systolic blood pressure ($P = 0.13$) and diastolic blood pressure ($P = 0.60$) showed no significant changes through the open-label period. At the end of the double-blind period, there was no significant difference in pulse ($P = 0.10$), systolic blood pressure ($P = 0.38$), or diastolic blood pressure ($P = 0.60$). However, weight did significantly decrease further with modafinil compared to placebo (a loss of 3.82 ± 6.0 lb on modafinil vs. a gain of 1.57 ± 17.0 lb on placebo, $P = 0.01$). Body mass index did also decrease further ($P = 0.02$). Although weight did decrease during the double-blind phase among the modafinil patients, only 1 patient in this group had more than a 7% loss in body weight (13.2% loss in 1 patient). The mean percentage loss in weight was 1.73%.

DISCUSSION

Modafinil is a novel activating agent that has the potential to have efficacy in atypical depression; our results in the open label part of the study suggest that modafanil is safe and effective for this patient population. Patients improved on the main outcome measure and the secondary measures. Modafinil had minimal adverse effects and was generally well tolerated. Indeed, modafinil caused weight loss, an effect that may be desirable in this population, given increased appreciation of the relation between weight and medical morbidity.

We also wanted to test modafinil's efficacy for relapse prevention with the double-blind, placebo-controlled portion

TABLE 2. Secondary Outcome Measures in Open-label and Double-blind Phases of the Study

Measure	Open-label Mean Before Treatment	Open-label Mean After Treatment	*P* Values (open-label)	Double-blind Mean Before Drug	Double-blind Mean After Drug	Double-blind Mean Before Placebo	Double-blind Mean After Placebo	*P* Values (double-blind)
SCL-90	1.35 ± 0.68	0.49 ± 0.61	<0.0001	0.36 ± 0.37	0.24 ± 0.25	0.29 ± 0.38	0.27 ± 0.38	0.18
CGI-S	5.13 ± 0.65	2.50 ± 1.45	<0.0001	2.08 ± 1.10	1.83 ± 1.11	2.12 ± 1.0	2.52 ± 1.56	0.12
BFI item 3	7.92 ± 2.04	4.23 ± 3.02	<0.0001	4.04 ± 2.87	3.52 ± 2.74	2.88 ± 2.52	3.28 ± 2.73	0.93
BFI total	52.29 ± 17.67	22.61 ± 20.99	<0.0001	18.92 ± 17.17	15.83 ± 15.43	14.58 ± 17.70	18.84 ± 20.85	0.43
ESS	10.92 ± 5.15	5.85 ± 5.11	<0.0001	5.63 ± 4.77	6.0 ± 4.35	4.31 ± 4.11	6.24 ± 4.79	0.91
FSS	42.23 ± 9.90	29.20 ± 12.56	<0.0001	27.83 ± 11.57	27.17 ± 12.52	24.38 ± 12.05	27.60 ± 12.50	0.70
ADDS appetite/weight	4.21 ± 1.26	1.70 ± 0.97	<0.0001	1.46 ± 0.72	1.45 ± 0.74	1.81 ± 0.98	1.89 ± 1.23	0.56
ADDS eating	4.15 ± 1.08	1.78 ± 1.04	<0.0001	1.45 ± 0.67	1.59 ± 0.91	1.88 ± 1.13	1.61 ± 1.09	1.0
ADDS weight	3.75 ± 1.21	1.27 ± 0.55	<0.0001	1.17 ± 0.49	1.32 ± 0.57	1.23 ± 0.51	1.37 ± 0.76	0.34

of the study. Patients who initially took modafinil in the open-label phase and then took placebo in the double-blind phase continued to do well. Indeed, most of our efficacy measures did not separate modafinil from placebo. This can potentially be explained by several ways. One possibility is that the patients in the trial were innately placebo-responders and that this placebo effect carried on through the entire trial; that is, they may have improved in the open-label phase simply from being exposed to the clinical trial situation.

However, we doubt this is likely because neurovegetative signs such as overeating, oversleeping, and fatigue are not likely easily addressed simply by clinical contact. Additionally, the modafinil-treated patients continued to lose weight more than those treated with placebo, suggesting that all the effects seen are not simply because of placebo response. A second possibility is that, by chance, the placebo group in the double-blind phase consisted of patients who did particularly well after the open-label phase, and thus obscured drug-placebo separation. Although this is possible, it is unlikely given the apparent success of randomization. A third possibility is that effects of modafinil continue for several weeks after early discontinuation and that it takes longer before relapse begins to occur. However, we are unaware of literature supporting this speculation. A fourth possibility is that a large number of the patients had spontaneous improvement over the span of the 6-month trial, leading one to see improvement with either modafinil or placebo. This is quite possible, although atypical depression has been associated with greater disability days, restricted activity days, and number of emergency room visits than melancholic depression,[5] suggesting a disease that may be more severe and less prone to spontaneous improvement. A fifth possibility is that modafinil's effects in the first phase carried over to the second phase such that even patients who were then placed on placebo had a carryover effect from being on modafinil in the first phase of the trial. It is possible that had the trial gone longer, the carryover effect of the drug would fade. There is an indication that this may be the case, as HAM-D-29 scores for modafinil were consistently lower than for placebo, especially toward the end of the study, although this did not reach significance (Fig. 2).

To test between these alternate hypotheses, a longer-term, placebo-controlled discontinuation trial would need to be performed. A testable hypothesis would be that a double-blind, placebo-controlled trial of modafinil would show a greater effect of the drug on remission than placebo over time.

Limitations of this study include the possible carryover effect of drug to placebo, a relatively large number of dropouts (although, of note, there were more dropouts among the placebo group than the drug group), a lack of male patients, and relatively strict exclusion criteria that may limit the generalizability of these findings (especially as atypical depression patients may have multiple Axis I comorbidities). Additionally, as there was no drug control group, it is not possible to know from this study if SSRIs or TCAs would be better for this patient population than modafinil.

In summary, this is the first monotherapy trial of modafinil for atypical depression. We show the drug to be safe and effective for atypical depression in an open-label format, and patients did not deteriorate when the drug was withdrawn in the double-blind phase. Larger scale and longer clinical trials are warranted, including long-term discontinuation trials and prospective double-blind, placebo-controlled, parallel treatment studies.

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