Adjunctive Armodafinil in Schizophrenia

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1The Zucker Hillside Hospital, Glen Oaks, New York; 2Duke University, Durham, North Carolina; 3Yale University School of Medicine, New Haven, Connecticut; 4Cephalon, Inc, Frazer, Pennsylvania
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The Zucker Hillside Hospital, Glen Oaks, New York; Duke University, Durham, North Carolina; Yale University School of Medicine, New Haven, Connecticut; Cephalon, Inc., Frazer, Pennsylvania

Abstract

Background: Schizophrenia is a chronic and disabling mental illness. Various psychosomatic interventions that aim to change sleep and circadian patterns hold promise for improving the efficacy of existing antipsychotic treatment. Here we report the results of a randomized, double-blind, placebo-controlled study investigating the adjunctive use of armodafinil, a wake-promoting medication, in adult schizophrenia patients who failed to respond to treatment with conventional antipsychotics.

Methods: A total of 60 patients meeting the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) criteria for schizophrenia with treatment-resistant symptoms and a total score of 80 or more on the Positive and Negative Syndrome Scale (PANSS) were randomized to one of 4 groups: placebo, armodafinil 50 mg, 100 mg, or 200 mg once daily. Patients were excluded if they had a history of schizophrenia or a related psychoses longer than 6 weeks or more than 4 weeks of antipsychotic treatment. Patients were withdrawn from antipsychotic medication for at least 6 weeks, and Stabiblized antipsychotic medication was maintained during the study. All patients were administered the 18-item Clinical Global Impressions-Severity Scale (CGI-S), the Epworth Sleepiness Scale (ESS), and the Barnes Akathisia Scale at baseline and following 2 weeks of medication.

Results: Armodafinil was generally well tolerated; most adverse events were minor and did not lead to withdrawal. Mean changes from baseline in ESS scores were greater with armodafinil 100 mg and 200 mg than with placebo (-4.43 vs -0.49 and -0.50, respectively). One patient in the placebo group had a serious adverse event involving worsening psychosis. Armodafinil significantly improved cognitive function and symptoms of extrapyramidal symptoms and akathisia. Armodafinil 100 mg and 200 mg did not worsen positive symptoms compared with placebo.

Conclusions: Armodafinil showed an apparent benefit on cognitive deficits as assessed by the MATRICS Consensus Cognitive Battery. Overall results from the CGI-S, PANSS, and ESS showed no apparent benefit from armodafinil administration compared with placebo. Armodafinil 200 mg was superior to the negative symptoms of schizophrenia, as measured by the PANSS negative symptom subscale, without worsening positive symptoms. Armodafinil was generally well tolerated and did not cause or worsen extrapyramidal symptoms, akathisia, or akathisia. The effect of armodafinil 200 mg on negative symptoms of schizophrenia warrants future evaluation in larger, appropriately powered clinical trials.

References


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Abstract

Background: Armodafinil, a wake-promoting agent, has been evaluated in clinical trials in patients with symptoms of schizophrenia. However, the effects of armodafinil on cognitive and functional outcomes in everyday life have not been determined. The purpose of this study was to determine whether armodafinil improves patient functioning, cognitive performance, and symptomatology compared with placebo in a randomized, double-blind, placebo-controlled trial.

Methods: A multinational, 2-week, double-blind, placebo-controlled, parallel-group, fixed-dose, phase III trial, concept of study was conducted between July and December 2007 at 31 centers in the United States. The study was approved by local institutional review boards and national health authorities. The study was conducted in full accordance with the Good Clinical Practice guidelines of the International Conference on Harmonization and the guidelines of the Declaration of Helsinki. The study is registered at clinicaltrials.gov (NCT00119517). A total of 105 patients were randomized to placebo (n = 15), 50 mg armodafinil (n = 15), 100 mg armodafinil (n = 15), or 200 mg armodafinil (n = 15), or armodafinil dose modifications; 49 patients completed the final visit. The study tests whether armodafinil improves patient functioning, cognitive performance, and symptomatology compared with placebo in a randomized, double-blind, placebo-controlled trial.

Results: The efficacy analysis set included all patients who received ≥1 dose of study drug. The safety analysis set included all patients who received ≥1 dose of study drug. Of 105 patientsscreened, 60 were randomly assigned (1:1:1:1) to armodafinil 50 mg, 100 mg, 200 mg, or placebo; 49 patients completed the final visit. No apparent improvement in cognition, as measured by the MATRICS compositescore, was observed with armodafinil compared with placebo. Armodafinil was generally well tolerated; diarrhea and headache were the most commonly reported adverse events. There were no apparent differences in safety or tolerability between armodafinil and placebo.

Conclusions: Armodafinil showed no apparent benefit on cognitive deficits as assessed by the MATRICS Battery. Overall results from the CDA, SANS, and CGI-S showed no apparent benefit from armodafinil administration compared with placebo. Armodafinil 200 mg showed no apparent benefit on cognitive deficits, as measured by the MATRICS composite score, compared with placebo.

This study was sponsored by Cephalon, Inc., Frazer, Pennsylvania. Funding for editorial, design, and production support provided by Cephalon, Inc., to the Curry Rockefeller Group LLC, Tarrytown, NY.

Keywords: Armodafinil, Schizophrenia, Working memory, Cognition, Functioning

Figure 1. Disposition of Patients

Table 1. Baseline Patient Demographics and Clinical Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Armodafinil 50 mg</th>
<th>Armodafinil 100 mg</th>
<th>Armodafinil 200 mg</th>
<th>Placebo</th>
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<tr>
<td>Age (years)</td>
<td>35.1 (10.1)</td>
<td>34.4 (9.7)</td>
<td>34.3 (9.7)</td>
<td>36.0 (7.7)</td>
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<tr>
<td>Gender</td>
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<td>22</td>
<td>22</td>
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<td>Female</td>
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<td>Other</td>
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Table 2. Conclusions: Primary Efficacy Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Armodafinil 50 mg</th>
<th>Armodafinil 100 mg</th>
<th>Armodafinil 200 mg</th>
<th>Placebo</th>
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<tr>
<td>SANS total score</td>
<td>21.5 (8.7)</td>
<td>21.3 (8.7)</td>
<td>21.4 (8.7)</td>
<td>21.2 (8.7)</td>
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<tr>
<td>PANSS positive symptoms</td>
<td>26.8 (9.7)</td>
<td>26.4 (9.7)</td>
<td>26.6 (9.7)</td>
<td>26.5 (9.7)</td>
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<tr>
<td>PANSS negative symptoms</td>
<td>11.6 (5.7)</td>
<td>11.6 (5.7)</td>
<td>11.6 (5.7)</td>
<td>11.6 (5.7)</td>
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Table 3. Conclusions: Secondary Efficacy Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Armodafinil 50 mg</th>
<th>Armodafinil 100 mg</th>
<th>Armodafinil 200 mg</th>
<th>Placebo</th>
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<tr>
<td>CGI-S</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
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<tr>
<td>CGI-I</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
<td>4.5 (0.6)</td>
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<tr>
<td>GAF</td>
<td>60 (15)</td>
<td>60 (15)</td>
<td>60 (15)</td>
<td>60 (15)</td>
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Table 4. Change in Vitals Signs from Baseline to Final Visit

<table>
<thead>
<tr>
<th>Variable</th>
<th>Armodafinil 50 mg</th>
<th>Armodafinil 100 mg</th>
<th>Armodafinil 200 mg</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Blood pressure</td>
<td>120/70</td>
<td>120/70</td>
<td>120/70</td>
<td>120/70</td>
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<td>Heart rate</td>
<td>72</td>
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Table 5. Change in Antihypertensive Medication from Baseline to Final Visit

<table>
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<tr>
<th>Variable</th>
<th>Armodafinil 50 mg</th>
<th>Armodafinil 100 mg</th>
<th>Armodafinil 200 mg</th>
<th>Placebo</th>
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<tr>
<td>Antihypertensive medication</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

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Presented at the 49th Annual
New Research Approaches for Mental Health Interventions
June 29–July 2, 2009 • Hollywood, Florida

Abstract

Background: Armodafinil, a longer-lasting isomer of modafinil, is a non-amphetamine, wake-promoting medication. Modafinil improves cognition in patients with schizophrenia, but its longer-lasting isomer, armodafinil, has not been rigorously studied in this patient population. This study examined the effect of armodafinil on changes in cognitive status and symptomatology in patients with schizophrenia.

Methods: A multicenter, 4-week, double-blind, placebo-controlled, parallel-group, fixed-dose study. A total of 56 patients were randomly assigned to once-daily placebo or armodafinil 50, 100, or 200 mg. Safety analysis set included all patients enrolled in the study. Efficacy analysis set included patients who had all safety assessments at baseline and weeks 1, 2, and 4.

Results: The demographic characteristics of the randomized groups were generally comparable. Armodafinil was generally well tolerated; diarrhea and headache were the most commonly reported adverse events. Armodafinil showed no apparent beneficial effect on mean composite change in MATRICS, the primary outcome measure; the mean change was 2.2 (95% CI = –0.6 to 5.0) for armodafinil 50 mg, 2.6 (95% CI = –0.7 to 5.9) for armodafinil 100 mg, and 2.2 (95% CI = –1.1 to 5.5) for armodafinil 200 mg, as compared with placebo (2.0 [95% CI = –1.2 to 5.3]).

Conclusions: Armodafinil did not appear to benefit patients with schizophrenia.

Key Words: Armodafinil; Cognition; Schizophrenia

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Abstract

Background: Armadafinil is a wake-promoting agent with potential therapeutic efficacy in schizophrenia. This study assessed the efficacy and safety of armadafinil when added to standard antipsychotic medications in adults with schizophrenia.

Methods: A randomized, double-blind, placebo-controlled, parallel, group, fixed-dose, trial was conducted. Three hundred ninety-six patients were randomized to armadafinil 50 mg (n = 15), 100 mg (n = 15), 200 mg (n = 15), or placebo (n = 15); 49 patients completed baseline assessments. Efficacy and safety were assessed in the Safety Evaluable subgroup (n = 14 for each arm).

Results: This was a proof-of-concept study that found that armadafinil was generally well tolerated and added a small but statistically significant effect size of 0.15 (95% confidence interval, 0.05 to 0.24) to antipsychotic medication when added to long-term antipsychotic medication in adults with schizophrenia. In safety analyses, there were no statistically significant differences between arms.

Conclusions: Armadafinil showed no apparent benefit in cognitive deficits as assessed by the MATRICS Battery. Overall results from the CIS, SANS, and CGI showed no apparent benefit from armadafinil administration compared with placebo. Armadafinil 200 mg was well tolerated, and no new or worsening psychiatric symptoms were observed.

Background

Recent advances in our understanding of the neurobiological basis of schizophrenia and the introduction of atypical antipsychotics have improved outcomes; however, negative symptoms, cognitive impairments, and residual symptoms often remain despite treatment with antipsychotics. Armadafinil, a wake-promoting agent with potential therapeutic efficacy in schizophrenia, is a newer treatment option to aid in the management of residual symptoms, negative symptoms, and cognitive impairments. In this study, we assessed the efficacy and safety of armadafinil added to standard antipsychotic medications in adults with schizophrenia.

Methods

Eligibility Criteria

Inclusion criteria included age ≥18 years, stable antipsychotic dose for ≥6 weeks prior to screening, and positive and negative symptom scores ≥20 on the Scale for the Assessment of Positive and Negative Symptoms (SANS). Exclusion criteria included a history of suicide attempt within 6 months, recent (<4 weeks) hospitalization, a major medical or psychiatric disorder (other than schizophrenia), a history of alcohol or substance abuse or dependence in the previous 12 months, or a history of sleep disorder.

Randomization

Patients were randomized to either armadafinil 50 mg (n = 15), 100 mg (n = 15), 200 mg (n = 15), or placebo (n = 15) using a computer-generated randomization scheme.

Efficacy and Safety Measures

Efficacy was assessed using the Impression of Severity of Illness (CGI-S) ratings, Scale for the Assessment of Negative Symptoms (SANS), Modified Simpson-Angus Extrapyramidal Symptoms Rating Scale, Total 6-Item 18-Item Positive and Negative Syndrome Scale (PANSS), and Cognitive Assessment Battery. Safety was assessed using adverse events, laboratory tests, vital signs, and physical examination.

Results

Safety Evaluable subgroup (n = 14 for each arm) showed no apparent benefit of armadafinil added to placebo. For the primary efficacy variable, mean change from baseline in the PANSS negative symptoms subscale was 0.15 (95% confidence interval, 0.05 to 0.24) with armadafinil 200 mg. Adverse events were generally well tolerated; no new or worsening psychiatric symptoms were observed. Armadafinil 200 mg was well tolerated, and no new or worsening psychiatric symptoms were observed.

Conclusions

Armadafinil showed no apparent benefit in cognitive deficits as assessed by the MATRICS Battery. Overall results from the CIS, SANS, and CGI showed no apparent benefit from armadafinil administration compared with placebo. Armadafinil 200 mg was well tolerated, and no new or worsening psychiatric symptoms were observed. Armadafinil was generally well tolerated and did not cause new or worse psychiatric symptoms, extrapyramidal symptoms, or akathisia.

The effect of armadafinil 200 mg on negative symptoms of schizophrenia warrants future evaluation in larger, appropriately powered clinical studies.

References


Shaw BS. Sleep. 2006;29(suppl):A64.


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Key exclusion criteria: history of suicide attempt within 6 months, recent (<4 weeks) hospitalization, a major medical or psychiatric disorder (other than schizophrenia), a history of alcohol or substance abuse or dependence in the previous 12 months, or a history of sleep disorder.

The demographic characteristics of the randomized groups were generally comparable (Table 1).

Primary Efficacy Variable

No apparent improvement in cognitive deficits was observed with armadafinil compared with placebo on the MATRICS composite score (Table 2).
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Abstract

Background: Armodafinil, a prodrug of modafinil, is associated with psychosis and other negative symptoms of schizophrenia. This 4-week, double-blind, proof-of-concept study evaluated the efficacy and tolerability of armodafinil as adjunctive therapy in adults with schizophrenia.

Methods: A multicenter, 4-week, double-blind, placebo-controlled, parallel-group, fixed-dose study was conducted between July and December 2007 at 11 centers in the United States. Patients with schizophrenia for ≥8 weeks, receiving 1 of 3 antipsychotic medications, were randomized to once-daily placebo or armodafinil 50, 100, or 200 mg. The primary outcome was change from baseline to final visit in the MATRICS composite score. Secondary outcomes included changes in PANSS total and subscale scores, and CGI-Severity of Illness (CGI-S) score. Safety endpoints included adverse events and laboratory tests. This study was sponsored by Cephalon, Inc., Frazer, Pennsylvania. Funding for editorial, design, and production support provided by Cephalon, Inc., to the Curry Rockefeller Group, LLC, Tarrytown, NY.

Results: Of 105 patients screened, 60 were randomly assigned (1:1:1:1) to armodafinil 50 mg, 100 mg, 200 mg, or placebo. Baseline characteristics were generally comparable among the groups. Armodafinil was generally well tolerated. The most common adverse events were gastrointestinal, headache, and somnolence. There were no deaths or serious adverse events. Significant improvements were observed in PANSS negative symptoms (0.78, 2.60, and 0.75), CGI-S (1.38, 2.70, and 2.60), and MATRICS (0.36, 0.65, and 0.87) compared with the placebo group for armodafinil 50 mg, 100 mg, and 200 mg, respectively. There were no differences on the Simpson-Angus Scale, Barnes Akathisia Scale, or Clinical Global Impression Scale; all were considered to be clinically meaningful by the investigators. A placebo response was observed in the CGI-S, but no differences were found on the SANS or ESS.

Conclusions: Armodafinil showed an apparent beneficial effect on cognitive deficits as assessed by the MATRICS Battery. Overall results from the CGI-S, SANS, and ESS did not show an apparent benefit from armodafinil administration compared with placebo. Armodafinil 200 mg improved the negative symptoms of schizophrenia, as measured by the SANS negative symptoms subscale, without worsening positive symptoms. Armodafinil was generally well tolerated and did not cause or worsen psychiatric exacerbation or extrapyramidal symptoms. The effect of armodafinil 200 mg on negative symptoms of schizophrenia warrants further evaluation in larger, appropriately powered clinical studies.

Key Terms: Armodafinil, Schizophrenia, Cognitive impairment, Adjunctive therapy

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Conclusions: Armodafinil showed an apparent beneficial effect on cognitive deficits as assessed by the MATRICS Battery. Overall results from the CGI-S, SANS, and ESS did not show an apparent benefit from armodafinil administration compared with placebo. Armodafinil 200 mg improved the negative symptoms of schizophrenia, as measured by the SANS negative symptoms subscale, without worsening positive symptoms. Armodafinil was generally well tolerated and did not cause or worsen psychiatric exacerbation or extrapyramidal symptoms. The effect of armodafinil 200 mg on negative symptoms of schizophrenia warrants further evaluation in larger, appropriately powered clinical studies.

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