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Efficacy of Modafinil Compared to Dextroamphetamine for the Treatment of Attention Deficit Hyperactivity Disorder in Adults

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ABSTRACT

Our objective was to compare the efficacy of the new wake-promoting drug modafinil to that of dextroamphetamine for the treatment of attention deficit hyperactivity disorder (ADHD) in adults. Twenty-two adults who met DSM-IV criteria for ADHD participated in a randomized, double-blind, placebo-controlled, three-phase crossover study comparing placebo, modafinil, and dextroamphetamine for the treatment of ADHD. The twice-daily study medications were titrated to doses of optimum efficacy over 4-7 days and then held constant during the rest of each 2-week treatment phase. Measures of improvement included the DSM-IV ADHD Behavior Checklist for Adults, the Controlled Oral Word Association Test (COWAT, using the letters C, F, and L version), Stroop, and Digit Span (Wechsler Adult Intelligence Scale version). For the 21 (96%) completers, the mean (±SD) optimum doses of modafinil and dextroamphetamine were 206.8 mg/day ± 84.9 and 21.8 mg/day ± 8.9, respectively. Scores on the DSM-IV ADHD Checklist ($p < 0.001$) were significantly improved over the placebo condition following treatment with both active medications. Performance on the COWAT ($p < 0.05$) reached trend levels of significance. Both medications were generally well tolerated. This preliminary study suggests that modafinil may be a viable alternative to conventional stimulants for the treatment of adults with ADHD.

INTRODUCTION

Of the approximately 5% of children with attention deficit hyperactivity disorder (ADHD), 18-30% of them may carry the diagnosis into adulthood (Mannuzza et al. 1993). Stimulants have been the treatment of choice for ADHD in both children and adults (Biederman 1998), but they may have undesirable side effects and potential for abuse (Zametkin and Rapoport 1987). Modafinil, a medication with few side effects and a low abuse potential (Ferraro et al. 1997; Wong et al. 1999) would be a useful addition to current ADHD treatments.

Modafinil, 2-[(diphenylmethyl)sulfinyll acetamide, is a new wake-promoting agent approved for the treatment of excessive daytime sleepiness associated with narcolepsy. Modafinil has a rapid onset of action

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(peak plasma concentrations are achieved within 2 to 4 h), an elimination half-life of about 15 h, and has a relatively benign safety profile (US Modafinil in Narcolepsy Study Group 1998; Wong et al. 1999). Modafinil is chemically and pharmacologically distinct from traditional psychostimulants. Unlike amphetamine stimulants, modafinil probably promotes vigilance via non-dopaminergic/adrenergic mechanisms (Ferraro et al. 1997; Lin et al. 1992, 1996; Simon et al. 1995). Instead, modafinil appears indirectly to activate the frontal cortex via the hypothalamus and/or the tuberomammilary nucleus (Chemelli et al. 1999; Eastbrooke et al. 1999; Lin et al. 1996). Whether agents that activate the hypothalamic arousal system could be of benefit for ADHD is unknown. It is noteworthy that the same stimulants effective for the treatment of ADHD are also effective for narcolepsy. Together, these neurochemical and pharmachological properties suggest that modafinil may have some value in the treatment of ADHD, but to date there have been no clinical trials of this drug in those with ADHD.

The primary intent of this study was, therefore, to determine if modafinil is a viable alternative to stimulants for the treatment of ADHD, and if so, at what doses. We compared the efficacy of modafinil, dextroamphetamine (^-amphetamine), and placebo in adults with ADHD using a randomized, double-blind, placebo-controlled, three-phase crossover study design. Our hypothesis was that the wake-promoting drug modafinil would be effective in the treatment of ADHD.

METHODS

Subjects

The subjects were people more than 21 years old from a single local community. They were told of the study by their health care providers, and if they expressed an interest were told how to contact the outpatient clinic of the first author. Those subjects meeting entry criteria were consecutively identified. The nature of the study was fully explained before obtaining written informed consent from the 22 participants. All patients underwent an assessment for ADHD, including a neurological exam; clinical, developmental, and childhood histories; and a semi-structured interview. To be given a diagnosis of adult ADHD, subjects had to (a) meet the full Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV; American Psychiatric Association 1994) criteria for the disorder by the age of 7 years as well as currently, (b) describe a chronic course of ADHD symptoms, (c) endorse at least a moderate level of impairment from the symptoms, and (d) provide corroborating history of the disorder from at least one parent or older sibling. The history included inquiry as to the nature and extent of the subject's behaviors that could be indicative of childhood ADHD. We also looked for other evidence of ADHD, such as from report cards, schoolwork, or results of prior psychological testing.

The DSM-IV ADHD Behavior Checklist for Adults was also used to select study subjects. This DSM-IV-based scale has age-matched cutoff values and scoring above the 93rd percentile of symptom severity, which has been found to be a good predictor of a correct diagnosis of ADHD (Murphy and Barkley 1996). This 18-item checklist has two 9-item subscales for evaluating inattentive and hyperactive-impulsive symptoms. Each item is rated for severity in terms of how often the symptoms are present (maximum score of 54 points). Therefore, to be eligible for the study, patients were required to score above the 93rd percentile of severity for at least one subtype of ADHD on both the childhood and adult versions of this scale. For example, to be eligible, adults aged between 17 and 29 years had a combined score of 14.7 or higher, and those between 30 and 49 years a score of 12.0 or higher on the adult scale. Subjects were then diagnosed as having ADHD of the primarily inattentive subtype, the primarily hyperactive-impulsive subtype, or the combined subtype.

Exclusion criteria included narcolepsy and conditions associated with altered cognitive abilities including schizophrenia, Tourette's disorder, and diagnosable neurologic conditions. Motor tasks including the finger to nose to examiner's finger, thumb to forefinger tap, and Romberg test were used to exclude subjects with neurological soft signs that may be associated with frontal lobe cognitive deficits (Thienemann and Koran 1995). Medical conditions likely to effect mood and cognition, such as metabolic disorders, mental retardation, untreated endocrine disorders, and pregnancy, precluded entry into the study. Subjects using any cannabis, cocaine, heroin, or nonprescription amphetamines within 6 months of beginning drug trials were excluded. Subjects taking tricyclic antidepressants, venlafaxine, or bupropion within 3 months of

starting the study or prescription stimulants within 2 weeks prior to the beginning of the study were not included because the efficacy of these drugs for ADHD symptoms (Wilens et al. 1995) would make the interpretation of our results more difficult. Twenty-nine people were considered for this study, and of these, 22 met the criteria and were enrolled. Four people were excluded because they did not meet DSM-IV criteria for ADHD, two because of illicit substance use, and one because of remote head injury and neurologic soft signs on exam. The subjects were screened for other DSM-IV psychiatric diagnoses by history taking, consultation of medical records, and the use of the Beck Depression Inventory (Beck 1970) and the Hamilton Anxiety Rating Scale (Clark 1994). Family histories were obtained including an inquiry of psychiatric diagnoses, medications prescribed, and prior hospitalizations.

Procedure

The study design included three randomized, 2-week drug treatment phases of placebo, modafinil, and d-amphetamine, separated by 4-day washout periods between phases to minimize carryover effects of the previous medication (Fig. 1). The rationale for the relatively brief treatment phases was because of the rapid onset and short duration of action of d-amphetamine and probably modafinil (about 10 h, based on an open-label modafinil feasibility study on two ADHD patients prior to this study—unpublished data). Subjects received drugs or placebo in unmarked capsules, which contained lactose, 50 mg of modafinil, or 5 mg of d-amphetamine. Throughout, a pharmacy prepared, distributed, and tracked all the drugs separately from raters and subjects in order to maintain double-blind conditions. Daily dosing was on awakening and again 5 h later. Each drug phase began with one capsule twice daily and was increased by an additional capsule twice daily every 1 to 2 days as tolerated up to four capsules per dose (a maximum of eight capsules a day of placebo, 400 mg of modafinil, or 40 mg of d-amphetamine). At each dosage interval, the clinician (F.T.) consulted with the subjects by phone to check on progress and for side effects. The phone checks occurred at least five times during each of the three drug phases. The subjects met with the clinician at least three times during each drug phase: (a) before beginning the drug, (b) when an optimum dose was reached, and (c) on the last day of each trial when ratings and tests were done. An optimum daily dosage was one in which the benefits outweighed the side effects and was decided by consensus of the subject and the clinician. This dose was selected within 4 to 7 days, and treatment at that fixed dose was maintained for another 7 to 10 days.

Measures

Rating scales and cognitive testing were done at the clinic on four occasions: before beginning drug treatment (baseline) and on the last day of each drug treatment phase within 3 h of the last dose. Baseline assessments ensured that all subjects had experienced the rating scales and tests prior to drug trial assess-

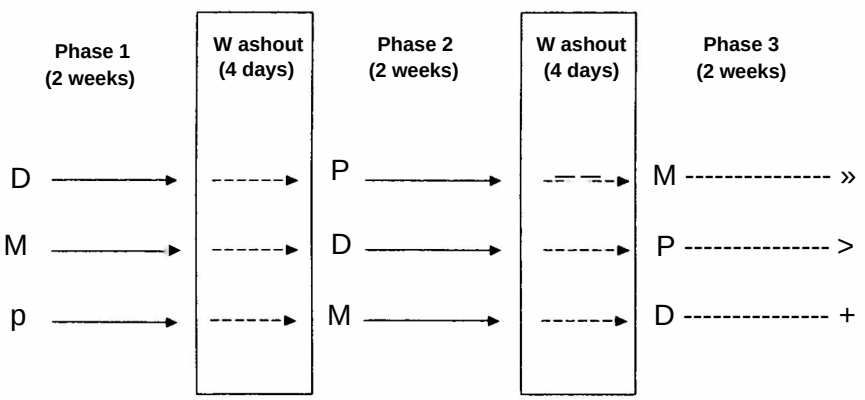

FIG. 1. This was a randomized double-blind, placebo-controlled, three-phase crossover study. Subjects received modafinil (M), dextroamphetamine (D), or placebo (P) in each study phase.

ments. At baseline, family history and demographic data were collected. For a subject to be considered to have a family history of ADHD, the relatives in question had to have been diagnosed with the disorder. The subjects were screened for current and past psychiatric diagnoses meeting DSM-IV criteria. This included inquiry as to present symptoms, past diagnoses, hospitalizations, and medications. For assessing change during treatment, we used three rating scales: one scale for ADHD and one each for depression and anxiety. The self-rated ADHD Behavior Checklist for Adults is a severity rating scale specifically designed for adults over 18 (described above). The other two scales were the self-rated 21-item Beck Depression Inventory, with a maximum score of 63 (Beck 1970), and the clinician-administered 14-item Hamilton Anxiety Rating Scale, with a maximum score of 56 (Clark 1994). The latter two scales were used to look for drug effects on mood that could influence the results of the ADHD scales. On the last visit of each drug trial, as part of the clinician review of the subject's status, a 17-item checklist was completed to screen for the typical stimulant side effects, such as irritatibility, appetite suppression, insomnia, and rebound effects between doses or between drug trials (Barkley and Murphy 1998).

Three tests of cognitive functioning were administered by the clinician (F.T.). The version using the letters C, F, and L of the Controlled Oral Word Association Test (COWAT) was used to measure verbal fluency, task persistence, and divided attention (Benton and Hamshire 1989). There is one trial for each letter (C. F, and L), and the task is to say as many words as possible in 1 minute that begin with the letter. Rules about not using proper nouns and the same root word are explained to the subject. The Wechsler Adult Intelligence Scale-Revised digit span subtests (forwards and backwards) were used to assess working memory and concentration abilities (Kovner et al. 1998). The task is to repeat, after the examiner, successively longer strings of numbers without mistakes. The Stroop Color-Word Interference Test was used as a measure of focused (undivided) attention (Golden 1976). The Stroop tests the rapidity of correctly reading aloud the colors on each of three lists. The first is a list of words (colors) written in black ink, next a list of colored bars, and last a list of words (colors) written in the wrong color ink. The test is scored according to the number of correct responses given in 45 sec.

Statistical analysis

To compare the effects of modafinil to d-amphetamine and placebo for ADHD treatment, repeated measures analyses of variance (ANOVAs) were performed. There were no violations of assumptions of the repeated measures ANOVAs in any analysis. An intent-to-treat design was used where the baseline score was carried forward for the single patient without complete data. In the case of a significant drug effect, planned comparisons between the drug and placebo groups were conducted using a pooled error term. To reduce the probability of type I errors, a Bonferroni correction to the p values was used for each study measure. This resulted in a significance level of 0.002. Although only tests with p values of 0.002 or less are considered statistically significant, the other p values and significance are included for descriptive purposes only.

Prior to these analyses, we used paired t tests to determine if the placebo means differed from baseline means, and there were no statistical differences on any measure. Prior to analyses, we also tested for sequence (carryover effects) and period (repeated administration or practice) effects. Sequence was tested using the sequence of drug treatments as the between-groups factors in repeated measures ANOVAs. To test for period effect, repeated measures ANOVAs were performed where the repeated measures were the first, second, and third administration of the measures regardless of treatment. There were no sequence or period effects ($p < 0.01$). Treatment response scores were the change scores between placebo and the drug condition on the DSM-IV ADHD Behavior Checklist for Adults. Drug treatment responses were correlated with the final drug dose as a check on how effectively true optimum drug levels were achieved. There should be little correlation if optimum dosing was indeed accomplished. Treatment responses to both drugs were correlated with each other, with the total number of side effects, and with baseline scores. In other drug trials of ADHD adults, a favorable response to drug treatment has been defined as a 30% or more reduction of ADHD symptoms (Spencer et al. 1998). Using this standard, a McNemar's test was used to determine if the number of subjects with a "favorable response" differed between the two drug treatments. Lastly, McNemar's tests for correlated proportions were used to determine if the percentages of patients reporting specific side effects differed depending on active drug or placebo.

RESULTS

The 22 patients averaged 40.8 years of age (SD = 12.5) with a median age of 43 and a range from 18 to 59. Nine of the patients were women (41%), and 13 (59%) were men. All patients had a high school education, and 12 (55%) had completed college. Fifteen (75%) required tutoring by the 12th grade. All but 2 (9%) subjects (adopted) had a family history of ADHD, and 16 (73%) of these had at least one child or sibling with the disorder. Eleven (50%) subjects were of the inattentive ADHD subtype, 9 (41%) were of the mixed ADHD type, and 2 (9%) were of the hyperactive-impulsive ADHD subtype. The mean baseline Hamilton anxiety score was 11.4 (SD = 7.0) and ranged from 3 to 27. The mean baseline Beck Depression Inventory Score was 11.9 (SD = 9.3), with a range of 0 to 33. Prior to this study, 1 (5%) subject had prior treatment with one stimulant and 4 (18%) had two prior stimulant trials. Eleven (41%) had at least one lifetime comorbid axis I disorder, but only one (5%) had current ratings of both depression and anxiety that were severe. The most common comorbidities were as follows: 10 (46%) subjects had at least one prior episode of depression, and 3 (14%) subjects had both generalized anxiety disorder and a past history of alcohol dependence. One subject (5%) was dropped from the study after enrollment but before drug trials began due to an emergent hyperthyroid condition.

The mean ± SD daily doses of modafinil and d-amphetamine were 206.8 ± 84.9 mg and 21.8 ± 8.9 mg, respectively. With respect to baseline measures, there were no significant differences between baseline and placebo scores for any scales or cognitive tests. Tables 1 and 2 depict the averaged data collected at baseline and at the end of each treatment phase. Sequence effects and Sequence X Treatment effects were examined for all measures, and none was significant. There were also no significant period effects. Therefore, sequence or period effects did not bias the following analyses. Table 1 shows that, using planned ANOVA comparisons, modafinil and d-amphetamine treatments resulted in a significant reduction of ADHD symptoms by the DSM-IV ADHD scale in comparison to the placebo condition ($p < 0.001$). On average, patients had less severe ADHD symptoms during the modafinil trial compared to the d-amphetamine trial, but these differences were not statistically significant.

Table 2 depicts the results of cognitive testing, which were in the direction of improvement but did not reach statistical significance. However, performance on the COW AT trended toward significance during both active drug conditions ($p = 0.02$). With respect to the mood scores, there were no significant differences between placebo and either active drug treatment. With respect to the mood scales, analyses showed that there were no differences between active drug and placebo conditions for either the Beck Depression Inventory or the Hamilton Anxiety Scale.

In other medication response studies, a 30% or more reduction in ADHD symptom measures is considered a favorable response to medication. Ten (48%) subjects had a favorable response to d-amphetamine and 10 (48%) to modafinil. Six (29%) subjects had a favorable response to both drugs, 4 (19%) to modafinil alone, 4 (19%) to d-amphetamine alone, and 7 (33%) to neither drug. There was no association between favorable treatment response to the two drugs (McNemar $\%^2 = 0$). Also, on the DSM-IV ADHD measure, there were no significant correlations between responses to either drug condition and the final drug dosages, number of side effects on that drug, baseline ADHD scores, or retrospective childhood ADHD scores.

At the end of the study, before unblinding, subjects were asked their opinion about which medication resulted in the best improvement of their symptoms. Nine (43%) subjects chose modafinil, and five (24%) of these subjects were of the inattentive ADHD subtype. Ten (48%) subjects chose d-amphetamine, and six (29%) of these subjects were of the inattentive ADHD subtype. Two (10%) subjects chose placebo. After unblinding, 11 (52%) subjects elected to continue long-term treatment with modafinil, and 10 (48%) subjects chose d-amphetamine.

Table 3 presents the adverse effects reported by subjects. Insomnia, irritability, muscle tension, and appetite suppression were the most common adverse effects. The rebound effects occurred in the evenings and were between 30 min and 1 h in duration. No rebound effects were reported during the drug washout periods. All three subjects who developed transient lingual dyskinesia reported that the condition resolved when the drug dose was lowered. McNemar's tests showed no significant differences in the prevalence of side effects between the active drugs and placebo conditions.

Table 1. Results of ADHD Behavior Checklist for Adults: Mean (Standard Deviation)

Measure	Baseline	Placebo	d-Amphetamine	Modafinil	Overall drug effect: ANOVA F score (df = 2,28)	Placebo vs. d-amphetamine: ANOVA F score (df = 1,17)	Placebo vs. modafinil: ANOVA F score (df = 1,17)	Modafinil vs. d-amphetamine: ANOVA F score (df = 1,17)
DSM-IV ADHD Checklist (total)[11]	30.3 (8.9)	28.8 (10.0)	20.0 (11.3)	18.3(11.2)	10.66***	16.79***	18.43***	0.36
DSM-IV ADHD Checklist Hyperactivity subscore)[b]	13.1 (6.1)	12.2 (6.8)	9.0 (5.4)	7.3 (6.4)	7,97**	7.92* *	12.73**	1.84
DSM-IV ADHD Checklist (Inattention subscore)[b]	17.2 (3.3)	16.6 (4.3)	11.0 (6.7)	10.5 (5.3)	13.91**	13.91**	19.82***	0.094

ADHD, attention deficit hyperactivity disorder; **DSM-TV, Diagnostic and Statistical Manual of Mental Disorders** (4th ed.).

"ADHD Checklist score range is 0-54.

[b]ADHD Checklist subscore range is 0-27.

***p <** 0.05; ****p <** 0.01; ***p < 0.001.

Table 2. Cognitive Test Results: Mean (Standard Deviation)

Measure	Baseline	Placebo	d-Amphetamine	Modafinil	Overall drug effect: ANOVA F score (df = 2,28)	Placebo vs. d-amphetamine: ANOVA F score (df .= 1,17)	Placebo vs. modafinil: ANOVA F score (df = 1,17)	Modafinil vs. d-amphetamine: ANOVA F score (df = 1,17)
COW AT Test[3]	63.7 (22.5)	**ISA** (25.0)	86.5 (10.6)	**81.1** (9.3)	4.84*	6.28*	5.00*	0.19
Digit Span (forward)[b]	9.7 (2.8)	10.0 (2.7)	10.3 (2.3)	10.3 (2.3)	0.31 (**p** = 0.74)			
Digit Span (backward)[c]	7.1 (2.6)	7.0 (2.0)	7.6 (2.3)	7.5 (2.5)	1.97 (**p** = 0.15)			
Stroop-Color[3]	43.9 (7.2)	46.9 (6.7)	50.2 (8.0)	48.0 (7.3)	2.25 (**p** = 0.13)			
Stroop-Word[3]	47.0 (7.3)	46.9 (8.8)	48.8 (9.1)	48.8 (7.6)	2.06 (**p** = 0.016)			
Stroop-Color-Word[3]	46.2 (10.4)	48.1 (8.6)	52.0 (8.0)	51.6 (9.9)	2.58 (**p** = 0.10)			

ANOVA, analysis of variance; COW AT, Controlled Oral Word Association Test.

[3] Age-corrected **T** scores, percentile of norm.

[b]Digit Span score range (forward) is 0-16.

[c]Digit Span score range (backward) is 0-14.

***p <** 0.05.

Table 3. Number (and Percent) of Subjects with Adverse Events During Treatment[11]

Adverse event	Placebo vs.	d-amphetamine	Modafinil
Insomnia	4(19)	8 (38)	4(19)
Irritability	2(10)	3(14)	4(19)
Muscle tension	1 (5)	5(24)	4(19)
Appetite suppression	0	4(19)	4(19)
Anxiety	0	4(19)	2(10)
Headaches	1 (5)	2(10)	2(10)
Rebound	0	3(14)	2(10)
Dizziness	1 (5)	2(10)	0
Lingual dyskinesia	0	1 (5)	2(10)

"No significant differences between placebo and either drug condition.

DISCUSSION

Treatment with modafinil was effective and well tolerated in this randomized, double-blind, placebo-controlled, crossover study of 21 adults with ADHD. The effective dose of modafinil in this study (206.8 mg/day) was within the range of effective dosing for the treatment of narcolepsy (US Modafinil in Narcolepsy Study Group 1998). Although this was a crossover study of short duration, the magnitude of improvement in ADHD symptoms after modafinil treatment was comparable to the magnitude of improvement following treatment with d-amphetamine. The 48% favorable response rate to treatment with modafinil was similar to that reported in studies of the typical stimulants for the treatment of ADHD in adults (54%) (Wilens et al. 1995). No subjects discontinued treatment with either modafinil or d-amphetamine. These results support the hypothesis that modafinil may be a viable treatment for ADHD in adults. The viability of modafinil is also supported by a trend level improvement of the COW AT, which tests for verbal fluency, task persistence, and divided attention. The optimum dosages of modafinil appeared to vary widely between individuals (mean = 206.8mg/day, SC = 84.9 mg/day).

There was no correlation between the severity of childhood or baseline ADHD symptoms and the reduction of ADHD symptoms. It is possible that there were other predictors of drug response that masked the usual correlation of illness severity to the degree of drug response phenomenon. There was no significant correlation between the reduction of ADHD symptoms from one drug to the other, which suggests that the mechanism of action of the two drugs may be different.

The pharmacologic mechanisms underlying the apparent beneficial actions of modafinil in ADHD are of interest. Recent animal studies suggest that modafinil's action is quite selective for the hypothalamus and tuberomamillary nucleus (TMN) (Chemelli et al. 1999; Eastbrooke et al. 1999). Preclinical data also suggest that, unlike amphetamine stimulants, modafinil produces arousal through a mechanism that does not appear to involve enhanced dopaminergic activity (Ferraro et al. 1997). Instead modafinil may activate hypothalamic and TMN arousal pathways involving hypocretin neurons from the lateral hypothalamus and/or histaminergic neurons from the TMN that have exitatory projections including heavy innervation to the frontal cortex (Chemelli et al. 1999). These findings are especially interesting in light of the important role that hypofunctionality of the prefrontal cortex and diminished executive functioning may play in the etiology of ADHD (Castellanos 1997). Whether modafinil is indeed efficacious for ADHD by these mechanisms is undetermined.

These findings should be considered in light of some methodological limitations. The short (2 weeks) exposure to medications and 4-day washout periods between trials may have been too brief to examine the therapeutic effect of modafinil fully. Despite the short duration of the drug trials, our statistical analyses suggest that our results are not biased by sequence or by the period of drug administration. This is probably because prior studies indicate that both d-amphetamine and modafinil have a rapid onset of action and a short duration of action of 12 h or less (US Modafinil in Narcolepsy Study Group 1998; Wilens et al. 1995).

These results suggest that modafinil, with low abuse potential, may be a well-tolerated treatment option

for adults with ADHD in doses comparable to those used in the treatment of narcolepsy (US Modafinil in Narcolepsy Study Group 1998). Confirmation by larger studies of longer duration with a parallel group design is needed.

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