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Using the Test of Variables of Attention to Determine the Effectiveness of Modafinil in Children With Attention-Deficit Hyperactivity Disorder (ADHD): A Prospective Methylphenidate-Controlled Trial

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Abstract

The efficacy of modafinil in comparison with methylphenidate in treatment of pediatric attention-deficit hyperactivity disorder (ADHD) has not been thoroughly investigated. This study compared the effect of modafinil versus methylphenidate on continuous attention task in children with ADHD, using the Test of Variables of Attention. Twenty-eight participants completed a baseline test followed by administration of a single dose of either methylphenidate or modafinil, after which the test was repeated. The test was performed a third time, after each subject received a dose of the medication not previously administered. Comparison of scores showed mean baseline, postmethylphenidate, and postmodafinil scores of –2.04, 0.017, and 0.09, respectively. No difference was found between improvements observed with either medication ($P < .05$). Adverse events for both agents were mild and self-limited, including abdominal pain, diarrhea, and hyposomnia. The authors conclude that modafinil is as effective as methylphenidate; however, a larger scale long-term study is required to confirm these results.

Keywords

attention-deficit hyperactivity disorder, modafinil, methylphenidate, Test of Variables of Attention, ADHD

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Attention-deficit hyperactivity disorder (ADHD) is the most common neuropsychiatric disorder of childhood and adolescence, with a worldwide prevalence of 8% to 12% among school-aged children.[1] The pathophysiological process underlying this disorder is not entirely understood; however, imbalances in the noradrenergic and dopaminergic systems are believed to account for some of its core symptoms.[2]

Treatment of ADHD is based on integration of pharmacotherapy and nonpharmacological interventions, with the drugs of choice being sympathomimetic stimulants, such as methylphenidate, and amphetamine derivatives.[3] These agents inhibit the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase their release at presynaptic terminals.[4] Despite the proven efficacy of stimulants in most individuals, approximately 10% to 30% of patients do not respond adequately to the treatment or demonstrate intolerable adverse effects.[5]

In the past decade, modafinil, a nonsympathomimetic wakefulness-promoting agent, structurally and pharmacologically different from the classical stimulants, has been suggested as an alternative therapy for the treatment of ADHD.[6,7] Although its precise mechanism of action remains to be determined, modafinil is thought to modulate the release of glutamate, γ-aminobutyric acid (GABA), histamine, and hypocretin. This results in hypothalamus-based wakefulness,

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as opposed to the diffuse neuronal activation caused by conventional wake-promoting stimulants.[8]

Most studies hitherto have tested the efficacy of modafinil in comparison with placebo.[9-11] One randomized controlled trial, conducted by Amiri et al,[12] compared the effects of modafinil versus methylphenidate in children and adolescents with ADHD; however, the study did not use a crossover design, and each participant only received 1 medication, which might make the results prone to the influence of confounding factors.[12]

The aim of the present study was to compare the effects of a single administration of modafinil on ADHD symptoms in children and adolescents with those of a single methylphenidate challenge, using the Test of Variables of Attention. This computerized continuous performance test was developed in California in the 1990s and is one of the most commonly used continuous performance tests.[13,14] In this test the examinee has to press a button in response to a target stimulus (a circle at the *top* of a square that appears on the screen) and to refrain from responding to a nontarget stimulus (a circle in the *bottom* of a square that appears on the screen). In its current version it lasts 21.6 minutes, and the main variables measured include omission errors (number of targets that were missed), commission errors (number of false responses to nontargets), response time (mean response latency in milliseconds), and variability (the standard deviation of response times). Additional variables, of less importance in the total score weighting, are postcommission response time (a measure of how long after a commission error the next response is executed), multiple responses (a measure of how many times the button is pressed repeatedly, which may indicate additional problems), and anticipatory responses (time during the test in which the examinee presses the button before the stimulus has been replaced by a consecutive stimulus). A total score is calculated by weighting the score of all the variables throughout the 4 quarters of the test, and the score expresses the standard deviation of the mean. In our study this score is the *qualitative* result of the test. As a rule, a score between –1.8 and +1.8 is considered a normal range. Most subjects with ADHD achieve a score below –1.8, and when they repeat the test with an effective stimulant (or another medication found effective for ADHD) the score is expected to improve. In cases where the examinee presses the button before the stimulus has been changed too many times, the anticipatory response is too high, and the total score is missing (ie, the test does not have a qualitative result). This phenomenon usually appears at the beginning of the test. In such cases, even when the total calculated mean score is missing, the output of the crude data of the 4 major variables (percentiles of the omission errors, percentiles of the commission errors, response time, and response time standard deviations) is displayed as column graphs. Looking at these graphs allows the examiners to make a *qualitative* decision whether the performance was better or worse when using a stimulant drug in comparison to the baseline test.

Table 1. Results of the Qualitative Assessment of the Test of Variable of Attention Following a Single Administration of Either Methylphenidate or Modafinil

Participant	Sex	Age, y	Postmethylphenidate Subjective Assessment	Postmodafinil Subjective Assessment
1	M	12	Improvement	No change
2	M	12.5	Improvement	Improvement
3	M	7	Improvement	Improvement
4	M	11	Improvement	Improvement
5	M	7	No change	No change
6	M	9.5	Improvement	Improvement
7	M	11.5	Improvement	Improvement
8	M	10	No change	No change
9	M	11.5	No change	Deterioration
10	M	15	No change	No change
11	M	13	Deterioration	No change
12	M	7	No change	Improvement
13	M	8	Improvement	Improvement
14	F	13	Improvement	Deterioration
15	M	10.5	Improvement	No change
16	M	7	Improvement	Improvement
17	M	14	No change	Improvement
18	M	8	Improvement	Improvement
19	M	6.5	Improvement	Improvement
20	M	15	Improvement	Deterioration
21	M	6.5	Deterioration	Improvement
22	M	6	Improvement	Deterioration
23	M	10	Deterioration	Improvement
24	M	6.5	Deterioration	Improvement
25	M	10	No change	Improvement
26	M	12	Deterioration	No change
27	F	15.5	Improvement	Improvement
28	M	8	Improvement	Improvement

Methods

Patients

Participants were randomly selected from our pediatric ADHD outpatient clinic. Twenty-eight patients (26 boys and 2 girls) ranging from 6 to 15 years of age (mean age, 10.1 $\pm$ 2.9 years) were included. To reduce the possibility of a diagnostic error, we selected only patients with the classic combined subtype of ADHD (with features of both inattention and hyperactivity–impulsivity). Other inclusion criteria were fulfillment of the clinical criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)* for ADHD[15] and hyperactivity index *t* score of at least 65 at the Teacher Conners Rating Scales and Parent Conners Rating Scales. Patients with major psychiatric conditions (based on the *DSM-IV* criteria), mental retardation, autistic spectrum disorder, or epilepsy were excluded. Other exclusion criteria included heart disease, hypertension, sleep disorders, migraine, and previous history of either Steven-Johnson syndrome or hypersensitivity reaction to modafinil, methylphenidate, or other psychostimulants.

Study Design

The effect of a single dose of either modafinil or methylphenidate on attention was evaluated using the Test of Variables of Attention, one

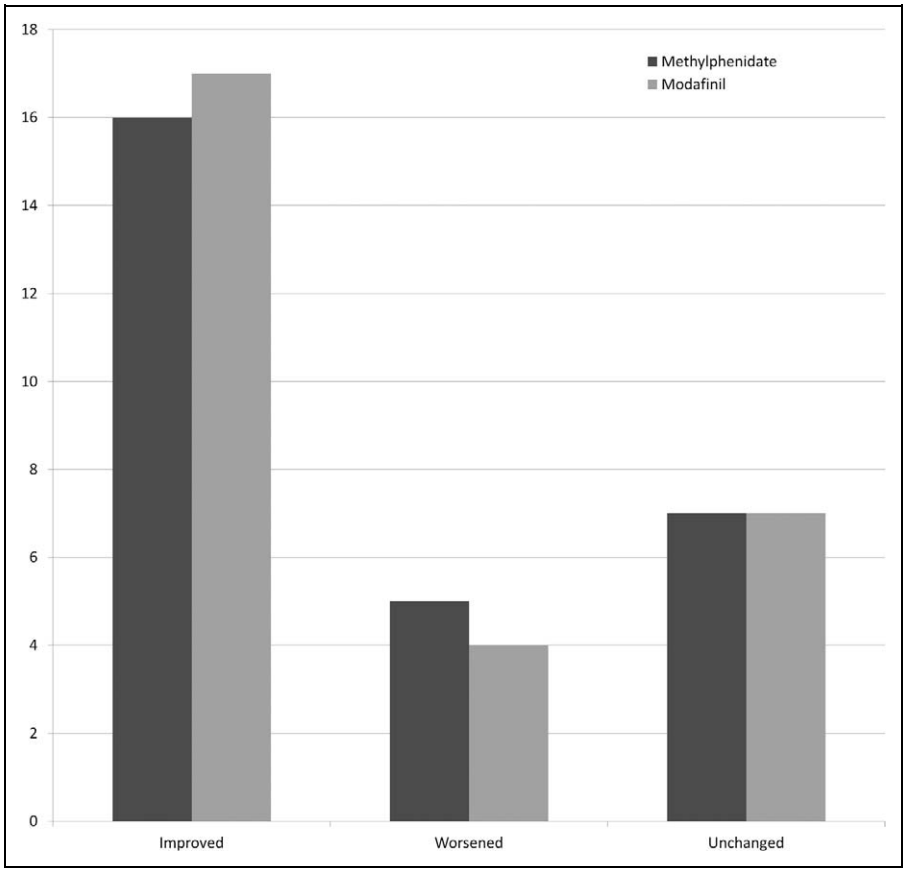

Figure 1. Results of the quantitative assessment of attention following a single administration of either methylphenidate or modafinil.

of the most widely used continuous performance tests.[16-19] The Test of Variables of Attention is characterized by a robust internal consistency when used to assess children diagnosed with ADHD and is highly sensitive to medication titration effects on ADHD symptoms.[18,19]

A randomized, double-blind, crossover study design was used. Initially, all participants were requested to perform a baseline Test of Variables of Attention procedure, following which they were randomly assigned to receive a single dose of either modafinil (100 mg) or methylphenidate (10 mg). After an average of 90 minutes, a second Test of Variables of Attention was performed. Within the following 2 weeks, the participants received a single dose of the medication that they had not previously received (either 10 mg methylphenidate or 100 mg modafinil). An average of 90 minutes later, they were requested to perform the third, and last, Test of Variables of Attention procedure. Neither the patients nor the interpreter was informed what medication was given at each trial. The test results were summarized as numerical quantitative values (ADHD score). In addition to the numerical ADHD scores, we added qualitative evaluations that were made by the examiner and were based on side observations of the patients during the test performance and on the column graphs of the 4 major test variables (percentiles of the omission errors, percentiles of the commission errors, response time, and response time standard deviations). These evaluations were particularly helpful in cases where the ADHD scores were missing. All the procedures were performed during the morning. Patients and their families were subsequently contacted and requested to report any adverse effects that might have occurred.

Statistical Analysis

Statistical analysis was performed using the SPSS statistical package version 15 (SPSS, Chicago, Illinois). The sensitivity, specificity, and positive value were computed. All P values were 2-sided, and statistical significance was defined as $P < .05$.

Results

Qualitative Assessment

The results of the qualitative evaluation for each participant are shown in Table 1. In summary, the performance of 17 subjects (60.7%) was improved with modafinil, in comparison to 16 (57.1%) who improved with methylphenidate. In 4 participants (14.3%) the performance deteriorated following the modafinil challenge, in comparison with 5 (17.9%) after the administration of methylphenidate. In 7 participants (25.0%) neither modafinil nor methylphenidate affected the performance in the Test of Variables of Attention procedure. It is noteworthy that 17 participants (60.7%) reacted similarly to both medications: 11 had a positive response to both modafinil and methylphenidate, whereas 6 had a negative response to both challenges. No statistically significant difference was found between the proportions of subjects who showed improvement, deterioration, or no change in their Test of Variables of Attention performance, when

Table 2. Results of Attention-Deficit Hyperactivity Disorder (ADHD) Scores Based on the Test of Variables of Attention

Participant	Sex	Age, y	Baseline ADHD Score	Postmethylphenidate Score	Postmodafinil Score
1	M	12	–5.49	NA	–5.87
2	M	12.5	–3.18	0.46	0.29
3	M	7	–5.71	–1.27	0.47
4	M	11	NA	NA	NA
5	M	7	NA	NA	NA
6	M	9.5	–4.2	–4.2	–0.2
7	M	11.5	–4.46	1.55	–1.09
8	M	10	2.36	2.71	0.84
9	M	11.5	NA	NA	NA
10	M	15	NA	NA	NA
11	M	13	–1.09	–2.88	–0.88
12	M	7	–2.54	–2.14	–1.34
13	M	8	–0.38	3.61	1.2
14	F	13	NA	NA	NA
15	M	10.5	–3.79	1.25	–2.41
16	M	7	0.84	1.02	3.31
17	M	14	NA	NA	2.11
18	M	8	NA	3.78	2.27
19	M	6.5	1.55	3.3	3.44
20	M	15	NA	NA	NA
21	M	6.5	–2.34	–3.75	–0.072
22	M	6	–2.51	–0.38	–3.23
23	M	10	–2.63	NA	0.09
24	M	6.5	NA	NA	3.03
25	M	10	–7.55	NA	–2.4
26	M	12	–3.11	NA	–3.14
27	F	15.5	–3.59	NA	–0.2
28	M	8	–3.12	0.96	1.05

Abbreviation: NA, not applicable (score could not be accurately calculated).

given the 2 medications ($P = .22$). A graphic representation of these results is provided in Figure 1.

Test of Variables of Attention Scores

Numerical ADHD scores of the Test of Variables of Attention procedure for the baseline, postmodafinil, and postmethylphenidate performances were available for 14 subjects. In the remaining 14 participants, no scores or partial scores were obtained (Table 2).

The mean baseline score for the participants whose scores were available in all 3 stages of the Test of Variables of Attention procedure was –2.04, the mean postmodafinil score was 0.09, and the mean postmethylphenidate score was 0.017. Both methylphenidate and modafinil significantly improved performance on the Test of Variables of Attention ($P < .05$), but there was no statistically significant difference between the improvement seen with the 2 medications ($P = .9$) (Figure 2).

Adverse Events

Four participants (14.3%) experienced adverse events following modafinil challenge, including abdominal pain, diarrhea, and hyposomnia. Seven participants (25%) reported adverse events after administration of methylphenidate, including abdominal pain, diarrhea, hyposomnia, and headaches. No statistically significant difference was found between the global incidences of adverse events caused by the 2 medications; however, headache was reported only after administration of methylphenidate (4 participants).

Discussion

The current study sought to investigate the efficacy and tolerability of a single dose of modafinil in comparison with methylphenidate in pediatric patients with ADHD. In this regard, our study is the first crossover double-blind, randomized, modafinil–methylphenidate trial comparing the effects of these 2 medications using the Test of Variables of Attention procedure quantitative assessment as well as qualitative assessments. Our study shows that modafinil administration significantly improves the ADHD scores of subjects upon performance of the Test of Variables of Attention procedure and that this improvement is not significantly different than that achieved with methylphenidate. With regard to adverse events, their incidence after modafinil or methylphenidate administration was not significantly different, with the exception of headaches, which were exclusive to methylphenidate. All adverse events caused by both modafinil and methylphenidate were minimal and resolved spontaneously.

To date, several studies have examined the effects of modafinil on children and adolescents with ADHD, most of which were either open-label or conducted in comparison to placebo. Three large randomized, double-blind, placebo-controlled trials, which included 190 to 248 subjects each and lasted 7 to 9 weeks, evaluated the use of modafinil in pediatric patients with ADHD, with the primary efficacy measure being the ADHD Rating Scale–IV. The results in all 3 studies were consistent, showing a significant improvement (decrease) in the ADHD Rating Scale–IV scores of subjects compared with placebo.[9-11]

Two studies by Rugino et al[20,21] evaluated the efficacy and safety of modafinil in children with ADHD using the standardized Test of Variables of Attention as well as the Conners Teacher Rating Scale–Revised. The first was an open-label trial in 11 subjects that lasted 4 to 5 weeks, whereas the second was a randomized, placebo-controlled trial in 22 subjects that lasted 5 to 6 weeks. Both studies demonstrated significant improvement in ADHD symptoms, as reflected by both outcome measures used; moreover, modafinil was well tolerated in both studies, with most adverse events being mild and transient. No cases of anorexia or weight loss were reported.[20,21]

Thus far, only 1 study has compared the effects of modafinil with those of methylphenidate. A double-blind randomized clinical trial by Amiri et al[12] was done in 60 children with ADHD who received either modafinil or methylphenidate for a period of 6 weeks. Efficacy outcomes were assessed using the Parent and Teacher ADHD Rating Scale–IV. This study found no significant difference between the outcomes of the 2 groups, with both groups demonstrating significant improvement in comparison to baseline. Unlike our study, in this study each

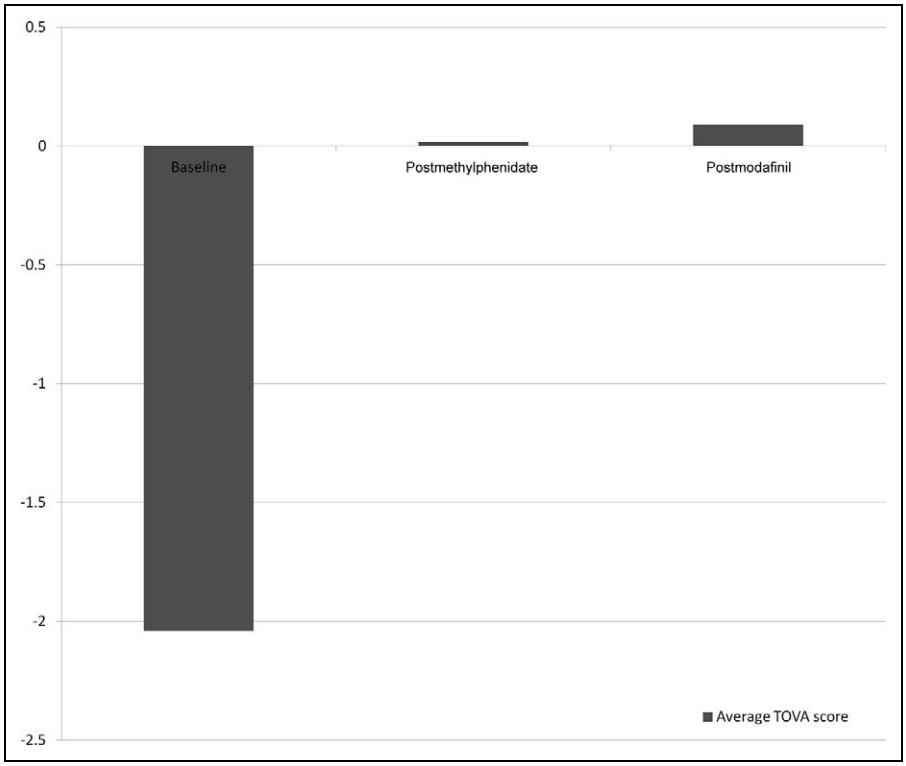

Figure 2. Results of attention-deficit hyperactivity disorder (ADHD) scores based on the Test of Variables of Attention (TOVA).

group of subjects received only 1 medication, which may make the results prone to the influence of confounding covariates. In terms of adverse events, their study reported somewhat decreased incidence of appetite and insomnia in the modafinil group in comparison with the methylphenidate group.[12]

Since our study design uses only a single administration of each drug, the lack of serious adverse effects is meaningless in terms of long-term treatment; however, previous studies showed that modafinil is well tolerated and relatively safe. However, despite the fact that modafinil is as safe as methylphenidate in many respects (and perhaps even has a lower rate of side effects), it was not approved by the US Food and Drug Administration (FDA). One of the arguments against its approval was a minor risk of serious skin reaction such as the Steven-Johnson syndrome, reported by Biederman et al.[10] Interestingly, while a few cases of serious skin reactions or suspected skin reactions were reported as probably related to modafinil among nearly 1000 children and adolescents treated with modafinil for ADHD, only 5 cases of serious skin reactions were reported out of nearly 680 000 patients worldwide who received modafinil for other causes, mainly sleep disorders.[22] In general, most of these patients were adults with daytime sleepiness, and they differed from the children who received the modafinil for ADHD symptoms by their older age and relatively smaller daily doses of modafinil.

In addition to the fact that our study provides no information on long-term drug effects and long-term adverse effects, the main limitations of our study were the small number of participants and even smaller number of participants for whom numerical scores could be obtained.

Conclusions

As shown in previous studies, modafinil may serve as an effective alternative treatment for ADHD in pediatric patients who do not respond well to methylphenidate or other stimulants. Further larger scale research in this field is warranted to assess its long-term safety in children and adolescents.

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Author Contributions

HRG and NZ designed the study; NN and OBB performed the study; HRG, OS, NN, and NZ analyzed data; HRG, OS, NN, and NZ performed literature search; HRG, OS, and NZ wrote the paper. All authors read and approved the final version.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethics Approval

The study was approved by the Carmel Medical Center Institutional Review Board (Helsinki Committee).

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