

Modafinil의 주의력결핍 과잉행동장애 치료효과에 대한 체계적 문헌 고찰

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Modafinil for the Treatment of Attention Deficit Hyperactivity Disorder: A Systematic Review

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주의력결핍 과잉행동장애는 미국에서 약 200만 명의 어린이에게 나타나는 심각한 만성 신경행동학적 장애이다. 주의력결핍 과잉행동장애 치료의 중심은 약물요법이다. 그러나 현재 환자의 약 30%는 주의력결핍 과잉행동장애를 적응증으로 갖도록 허가된 의약품들을 사용해도 적절한 치료효과를 얻지 못하고 있는 상황이다. Modafinil은 methylphenidate나 amphetamines와 같은 각성제와는 다른 약리학적 기전으로 중추신경계를 향진시킨다. 본 연구는 modafinil의 주의력결핍 과잉행동장애 치료효과에 대한 최신 지견을 얻고자, 1990년부터 2010년 3월까지 MEDLINE에 등재된 논문을 ADHD와 Modafinil이라는 MeSH terms로 검색하여 추출한 자료 중에서 대조군이 사용된 무작위 배정 및 이중맹검 임상연구 사례만을 선별하여 임상적 유용성을 평가하였다. 현재 modafinil은 주의력결핍 과잉행동장애 치료제로 허가된 의약품은 아니지만 최근 여러 국가에서 시행된 연구들은 modafinil이 안전하고 효과적인 주의력결핍 과잉행동장애 치료제일 수 있다는 결과를 보여주고 있다.

□ Key words - Attention deficit hyperactivity disorder; Modafinil

Attention deficit hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood.¹⁾ ADHD is characterized by symptoms including difficulties with attention, impulsivity, and hyperactivity. It is estimated that between 3 and 5 percent of children have ADHD, or approximately 2 million children in the United States. ADHD places a considerable burden on society regarding financial cost. The direct cost of medical care for patients with ADHD is double that of the cost of medical care for the rest of the population.²⁾

Pharmacotherapies used for ADHD include stimulants (methylphenidate and amphetamines) and atomoxetine.³⁻⁵⁾ While these medications are effective in patients with ADHD, approximately 30% of all patients do not respond adequately to stimulants or experience poor tolerability.⁶⁾

Thus there is a need for effective and well tolerated agents in patients with ADHD. Modafinil, currently marketed as Provigil, is approved in the United States to improve wakefulness in adults with excessive sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift-work sleep disorder. Modafinil has not yet been approved for the treatment of ADHD. However, recent studies have suggested that modafinil may be effective in the treatment of ADHD with fewer adverse effects than agents currently approved for ADHD.⁷⁻¹¹⁾ The purpose of this article is to evaluate published literature concerning the use of modafinil for the treatment of ADHD. A MEDLINE search (from January 1990 to March 2010) was conducted using a combination search term ADHD and modafinil with limits of randomized controlled trials and humans.

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MODAFINIL

Modafinil is a wakefulness-promoting agent. The chemical name for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide.

The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36.¹²⁾ Modafinil's precise mechanism of action is not known.¹³⁾ Unlike the wakefulness induced by traditional stimulants, modafinil induced wakefulness appears not to be mediated by dopamine. Modafinil induced wakefulness is not blocked by dopamine antagonists and does not affect the firing rates of dopaminergic or noradrenergic neurons.¹⁴⁻¹⁵⁾ Increase the brain's expression of the gene *c-fos* is a marker of neuronal activation. Diffuse areas of the brain are activated after amphetamine administration, while modafinil produces a more localized *c-fos* activation, especially the anterior hypothalamus.¹⁶⁻¹⁷⁾ Clinical studies and postmarketing surveillance have shown that modafinil has a low potential for abuse.¹⁸⁾ Modafinil is readily absorbed, reaching maximum plasma concentrations at 2-4 hours after oral administration. The elimination half-life of modafinil is approximately 12-15 hours, with the primary route of elimination being metabolic, mainly in the liver.¹³⁾

LITERATURE REVIEW

Taylor FB and Russo J conducted a randomized, double-blind, placebo-controlled, three phase, crossover study to compare the efficacy of modafinil, dextroamphetamine, and placebo in adults with ADHD.⁷⁾ This study included 22 people more than 21 years old from a single local community. They were assessed for ADHD by the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition (DSM-IV) criteria. The DSM-IV ADHD Behavior Checklist for Adults was also used to select study subjects. To be eligible for this study, patients were required to score above 93rd percentile of severity for at least one subtype of ADHD on both the childhood and adult versions of this scale. Two week drug treatment phases were separated by 4 day washout periods between phases. Study medications were given twice daily to patients, and titrated to doses of optimum efficacy selected within 4 to 7 days. Treatments at the fixed doses were maintained for another 7 to 10 days. One patient was dropped from the study after enrollment but before drug trials began due to an emergent hyperthyroid condition. The mean daily doses of modafinil and dextroamphetamine were 206.8 mg and 21.8 mg. Scores on the DSM-IV ADHD Behavior Checklist were significantly improved over the placebo condition following modafinil and dextroamphetamine treatments ($P < 0.001$).

Insomnia, irritability, muscle tension, and appetite suppression were the most common adverse effects, but no patients discontinued treatment with either modafinil or dextroamphetamine. There are limitations in this study. The treatment period of this study was short and the number of subjects was small. Therefore, large and long-term studies should be conducted to use modafinil for the treatment of ADHD in clinical practice.

In 2003, a randomized, double-blind, placebo-controlled study was conducted to test the hypothesis that modafinil significantly improves clinical features affecting children with ADHD.⁸⁾ Twenty-four children who met the DSM-IV criteria for ADHD were included in this study. They were randomized to receive modafinil or placebo. Two children were excluded from data analysis because of repeated emesis and untoward social circumstances (house fire), respectively before the first postmedication evaluation. Among 22 patients who completed this study, 11 patients had received modafinil and 11 had received placebo. Researchers used flexible doses titrated to effect. Once the dose was stable for at least 5 days, the study was concluded that no further upward titration was indicated or no further upward titration was desired. Statistical review of the demographic information and pretreatment values comparing the modafinil group with the placebo group showed no statistically significant differences. The primary outcome measurements were the Test of Variables of Attention (TOVA) ADHD *z* score and the Conners DSM-IV ADHD total scale. The placebo group manifested a slight decline of the ADHD score with an average difference of -1.02, whereas the modafinil group exhibited improvement with an average difference of +2.53 ($P \leq 0.02$). On the Conners DSM-IV ADHD total scale, the children receiving modafinil exhibited greater post treatment improvement from 76.6 to 68.2 than the children receiving placebo from 77.7 to 76.0 ($P < 0.05$). All adverse effects were minor and transient with only one patient requiring discontinuation of modafinil because of repeated emesis. The most common adverse event was delayed onset of sleep, but the incidence was equal for modafinil and placebo groups. This study did not use an intent-to-treat analysis. Treatment period was also short and the number of subjects was small.

In the United Kingdom, a double-blind, randomized, placebo-controlled crossover study was conducted to assess the positive effects of modafinil in adult patients with ADHD.⁹⁾ Twenty patients (7 female) with a DSM-IV

diagnosis of ADHD were included in this study. Their mean age was 28 ± 9 years. The researchers randomized 10 patients to receive a single dose of placebo first, followed by 200 mg modafinil, and 10 patients to receive the drug first, followed by placebo. Blood pressure and pulse were measured for the physiologic effects of modafinil. Modafinil increased both diastolic blood pressure ($p=0.034$) and systolic blood pressure ($p=0.058$) compared to placebo. Patients who received modafinil had feeling more excited compared to patients who received placebo in visual analog scales ($p=0.012$). Using the one-touch Tower of London spatial planning task (NTOL), patients with modafinil were significantly better in obtaining a correct solution than with placebo ($p=0.009$). Patients given modafinil had greater capacity to inhibit responding compared to patients given placebo ($p=0.028$) when measured with the stop-signal reaction time task (STOP). The researchers did not report the adverse effects of modafinil. This study evaluated the effects of a single dose of modafinil. Therefore, studies with multiple doses should be needed to examine a full clinical effect of modafinil on ADHD.

Another study evaluated a new formulation of modafinil (modafinil film-coated tablets) in children and adolescents with ADHD.¹⁰ The researchers conducted a 9-week, multicenter, randomized, double-blind, placebo-controlled, flexible-dose study. Patients with a DSM-IV diagnosis of ADHD who were 6 to 17 years of age were included in this study. Patients were randomly assigned at a ratio of 2:1 to receive 9 weeks of modafinil (164 patients) or placebo (82 patients). Efficacy was measured using the School and Home Versions of the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV). Patients with modafinil significantly improved the core symptoms of ADHD with greater reductions in the ADHD-RS-IV School Version mean total scores (-15.0 in modafinil group versus -7.3 in placebo group, $p < 0.0001$). The ADHD-RS-IV Home Version also showed similar differences in the improvement of ADHD symptoms between two groups (-14.3 in modafinil group versus -7.0 in placebo group, $p < 0.0001$). In modafinil-treated patients, the most common adverse effects were insomnia, headache, and decreased appetite. However, no patients was dropped from this study due to these adverse effects. The rates of discontinuation as a result of adverse effects were similar in both modafinil group and placebo group (3% in modafinil group versus 4% in placebo group). Limitations of this study were as follows. This study excluded patients well

treated with stimulants who might be responsive to modafinil treatment. Study duration was also short.

In Iran, a 6 week double-blind, randomized clinical trial was conducted to study the efficacy of modafinil for ADHD in children and adolescents as compared to methylphenidate.¹⁹ This study enrolled 60 outpatients between the ages of 6 to 15 with a DSM-IV diagnosis of ADHD. They were randomized in a 1:1 ratio to take modafinil or methylphenidate. Modafinil and methylphenidate were titrated up during the study. The Parent and Teacher ADHD Rating Scale-IV was used to measure outcome. Both modafinil-treated patients and methylphenidate-treated patients showed a significant improvement in ADHD symptoms during this study. There is no significant difference on the reduction of the Parent and Teacher ADHD Rating Scale between baseline and end-point ($p=0.62$ and $p=0.75$, respectively). Adverse effects observed over the study were mild to moderate, and tolerable. In methylphenidate-treated patients, decreased appetite and difficulty falling asleep were observed more frequently ($p=0.03$ and $p=0.05$, respectively). This study had a small number of subjects and short study duration. So further studies are needed.

Kahbazi M, Ghoreishi A, Rahiminejad F, et al conducted a study to evaluate the efficacy of modafinil for ADHD in children and adolescents.²⁰ This 6 week randomized, double-blind, placebo-controlled study included 46 outpatients. They were between the ages of 6 to 15 with a DSM-IV diagnosis of ADHD. The researchers randomly assigned the patients to receive modafinil or placebo. Using the Parent and Teacher ADHD Rating Scale, there were significant difference on the reduction of scores ($p < 0.001$). In terms of adverse effects, decreased appetite was observed more often in modafinil-treatment patients ($p=0.05$). Similar to other studies above, the number of subjects was small and study duration was short in this study (Table 1).

SUMMARY

The results from six randomized controlled studies demonstrate that modafinil is effective in the treatment of ADHD symptoms with tolerable adverse effects.^{7-10,19-20} However, there are limitations in the above studies. In most studies, the number of subjects was relatively small. Three of the six randomized controlled studies had only less than 25 subjects included. With such small subjects, it's hard to

Table 1. Summary of clinical studies of modafinil for the treatment of attention deficit hyperactivity disorder

| Author | Study Design | Number of Subjects | Study Duration | Inclusion Criteria | Exclusion Criteria | Modafinil Dose | Outcomes |
|--|---|--------------------|---|---|---|----------------|---|
| Taylor FB, Russo J. ⁷⁾ | randomized, double-blind, placebo-controlled, three phase, cross-over | 22 | 3 phases of a 2 week treatment with a 4 day wash-out period | more than 21 years old; DSM-IV ADHD Behavior Checklist for Adults, above 93 rd percentile of severity for at least one subtype of ADHD on both the childhood and adult versions; met DSM-IV criteria for diagnosis of ADHD | narcolepsy; conditions of cognitive impairment; neurologic soft signs associated with frontal lobe cognitive deficits; conditions likely to affect mood and cognition | NA | Improved DSM-IV ADHD Behavior Checklist scores |
| Rugino TA, Samsock TC. ⁸⁾ | randomized, double-blind, placebo-controlled | 24 | 5-6 weeks | met DSM-IV criteria for diagnosis of ADHD; reliable transportation; regular school attendance | acute medical or uncontrolled psychiatric illness; allergy to modafinil or any of its components; cardiac abnormalities; use of central nervous system drugs within 30 days; >3 migraines within 3 mo of study; females with potential of pregnancy during study; uncontrolled seizure disorder; sleep disorder with insomnia; history of manic episodes or psychosis | 200-300 mg/day | Improved the Test of Variables of Attention (TOVA) ADHD z score and the Conners DSM-IV ADHD total scale |
| Turner DC, Clark L, Dowson J, <i>et al.</i> , ⁹⁾ | double-blind, randomized, placebo-controlled cross-over | 20 | a few hours | met DSM-IV criteria for diagnosis of ADHD; symptoms often interfere with ability to function, not explained by presence of another disorder | significant visual or motor impairment; use of medication contraindicated with modafinil; history of pervasive developmental disorders, neurologic disorders, schizophrenic or psychotic disorders, bipolar disorder, hypertension or cardiac disorder, epilepsy, and current history of major depressive disorder; substance abuse in past 2 months | 200 mg/day | Improved the one-touch Tower of London spatial planning task (NTOL); faster the stop-signal reaction time task (STOP) |
| Bederman J, Swanson JM, Wigal SB, <i>et al.</i> , ¹⁰⁾ | randomized, double-blind, placebo-controlled | 248 | 9 weeks | 6 to 17 years of age; met DSM-IV criteria for diagnosis of ADHD; 5 th –95 th percentile for height and weight | history or current diagnosis of pervasive developmental disorder; schizophrenia or other psychotic disorders; evidence of suicide risk; current psychiatric comorbidity that required pharmacotherapy; clinically significant drug sensitivity to stimulants; a history of alcohol or substance abuse as defined by DSM-IV criteria; consumption of >250 mg/day caffeine; absolute neutrophil count <1×10 ⁹ /L; hypertension; ingestion of psychotropic medications within 2 weeks | 170-425 mg | Reduced the School and Home Versions of the Attention-Deficit/Hyperactivity Disorder Rating Scale-IV (ADHD-RS-IV) |
| Amiri S, Mohammadi MR, Mohammadi M, <i>et al.</i> , ¹⁹⁾ | double-blind, randomized | 60 | 6 weeks | 6 to 15 years of age; met DSM-IV criteria for diagnosis of ADHD | disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation; clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs within 6 months | 200-300 mg/day | Improved ADHD symptoms |

Table 1. Summary of clinical studies of modafinil for the treatment of attention deficit hyperactivity disorder(continued)

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|---|--|----|---------|---|--|----------------|--|
| Kahbazi M, Ghoreishi A, Rahiminejad F, <i>et al.</i> , ²⁰⁾ | randomized, double-blind, placebo-controlled | 46 | 6 weeks | 6 to 15 years of age; met DSM-IV criteria for diagnosis of ADHD | history or current diagnosis of pervasive developmental disorders, schizophrenia or other psychiatric disorders; any current psychiatric comorbidity that required pharmacotherapy; any evidence of suicide risk and mental retardation; clinically significant chronic medical condition, including organic brain disorder, seizures and, current abuse or dependence on drugs within 6 months; hypertension; consumption of >250 mg/day caffeine | 200-300 mg/day | Improved the Teacher and Parent ADHD Rating Scale-IV |
|---|--|----|---------|---|--|----------------|--|

apply the results of above studies to clinical practice. Also, no studies conducted for the chronic modafinil treatment of ADHD. A 9 week study was the longest one among above studies. Therefore, large and long-term clinical studies should be conducted to use modafinil for the treatment of ADHD in clinical practice.

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