Modafinil improves symptoms of ADHD compared with placebo in young people

Biederman J, Swanson JM, Wigal SB, *et al*. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. *Pediatrics* 2005;**116**:E777–84.

Q Is modafinil an effective treatment for attention deficit hyperactivity disorder (ADHD) in young people?

METHODS

Design: Multicentre randomised controlled trial.

Allocation: Unclear.

Blinding: Double blind.

Follow up period: 9 weeks.

Setting: 24 sites in the USA. Recruitment: November 2003 to June 2004.

Patients: 246 young people (aged 6–17 years) with moderate or worse ADHD (Clinical Global Impression of Severity of Illness (CGI-S) rating ⩾4); above normal score on ADHD Rating Scale-IV (ADHD-RS-IV) School Version (⩾1.5 SD above age and gender norms; IQ ⩾80 (Wechsler Intelligence Scale). Exclusions: previous or current significant psychiatric disorder or active clinical comorbidities; current successfully managed ADHD; ADHD non-responsive to at least two previous treatments with stimulant therapies; previous sensitivity to stimulants.

Intervention: Following a 1–4 week washout period, flexible dose modafinil (titrated according to efficacy and tolerability; maximum dose 425 mg/day; minimum dose 170 mg/day) or placebo.

Outcomes: Symptom severity (ADHD-RS-IV School and Home Versions); adverse events.

Patient follow up: 59% in treatment group; 39% in placebo group at 9 weeks.

MAIN RESULTS

Modafinil significantly improved symptoms of ADHD after nine weeks (mean score change (ADHD-RS-IV School Version): −15.0 with modafinil *v* −7.3 with placebo, p<0.0001; total effect size: 0.69, 95% CI 0.57 to 0.82). This trend was seen at all follow-up points (weeks 1, 2, 3, 5, 7, and 9; results presented graphically). Common adverse events were more frequent in the modafinil group compared with placebo, including insomnia (48/164 (29%) with modafinil *v* 3/82 (4%) with placebo, p<0.05) and loss of appetite (26/164 (16%) with modafinil *v* 3/82 (4%) with placebo, p<0.05), although these were considered mild and did not lead to treatment withdrawal.

For correspondence: Dr Joseph Biederman, Pediatric Psychopharmacology Research Unit, Massachusetts General Hospital, Yawkey Center for Outpatient Care, Boston, MA 02114, USA; jbiederman@partners.org

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CONCLUSIONS

Modafinil improves symptoms of ADHD as assessed by teachers and by parents compared with placebo. Common adverse events were mild and usually resolved quickly.

NOTES

High dropout may have affected the analysis between groups. The higher dropout rate in the placebo group may be explained by the option given to all participants to switch to open label treatment after four weeks.

Commentary

Attention deficit hyperactivity disorder (ADHD) is now the most commonly reported paediatric psychiatric disorder. Electrophysiological investigations have demonstrated a neurophysiological basis for ADHD,[1] and central nervous system stimulant medications (particularly methylphenidate and dexamfetamine (dexamphetamine)) are accepted as the most effective treatment.[2] The current contentious issue with such medication recommendations is the potential for stimulant misuse and future substance abuse. Yet non-treatment may result in educational failure, poor job prospects, and impaired personal/marital relationships.

In this context, modafinil may offer an exciting alternative. Its pharmacological activity appears narrower than traditional stimulants and limited to activation of the cortex—it was initially approved to increase wakefulness in patients with narcolepsy. Unlike the usual stimulants, it does not appear to activate brain centres involved in euphoria and substance abuse. Biederman *et al* provide the first multicentre randomised, double blind, placebo controlled study of modafinil in children and adolescents with ADHD. The positive treatment outcomes of reduced symptom severity ratings, with few side effects, strongly support its clinical usefulness.

However, potential patients were excluded if they were doing well on their current stimulant medication, or if they had previously responded poorly to stimulants, so currently we do not know how either good or poor responders to the usual stimulants will function on modafinil. Also, 41% of patients discontinued modafinil before the end of the trial, and while half of these were attributed to lack of efficacy, that figure may well be higher. Finally, as the authors mention, we need studies of the long-term effects of modafinil in children. Despite these limits, modafinil holds promise as an alternative ADHD treatment.

Although this study demonstrates effects on the core symptoms of ADHD, the mechanism of action of modafinil is poorly understood. Electrophysiological studies of the specificity of modafinil in normalising typical ADHD EEG profiles could help clarify its mechanism in these patients.

Robert J Barry, PhD, DSc, and Adam R Clarke, PhD
Brain & Behaviour Research Institute, and School of Psychology, University of Wollongong, Wollongong 2522, Australia

1 Barry RJ, Clarke AR, Johnstone SJ. A review of electrophysiology in attention-deficit/hyperactivity disorder: I. Qualitative and quantitative electroencephalography. *Clin Neurophysiol* 2003;**114**:171–83.
2 Clarke AR, Barry RJ, Bond D, *et al*. Effects of stimulant medication on the EEG of children with attention-deficit/hyperactivity disorder. *Psychopharmacol* 2002;**164**:277–84.

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Notes