A review of the use of modafinil for attention-deficit hyperactivity disorder

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Modafinil (Provigil™) is a novel wakefulness-promoting agent that has been shown to have greater efficacy than placebo in the treatment of attention-deficit hyperactivity disorder (ADHD) in children and adults. In particular, three large, drug-company sponsored trials of a film-coated formulation of modafinil (modafinil-ADHD; Sparlon™) in children and adolescents with ADHD demonstrated consistent improvements in ADHD symptoms compared with placebo. Mean reductions in symptom ratings (measured using the ADHD-Rating Scale-IV school version questionnaire) ranged from 15.0 to 19.7 (7.3 to 10.1 for placebo). The most common adverse events were insomnia, headache and decreased appetite. Modafinil was generally well tolerated with most side effects considered mild to moderate in severity. Modafinil may have advantages over current therapies for ADHD in that it can be administered once daily and has fewer reinforcing properties than traditional stimulants. Modafinil could potentially be a valuable new treatment option for patients with ADHD. However, rigorous comparative studies with current first-line treatments for ADHD and longer-term independent studies are necessary before modafinil's role in the treatment of ADHD can be fully established.

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Attention-deficit hyperactivity disorder (ADHD) is a disorder characterized by a heterogeneous profile of symptoms including difficulties with attention, hyperactivity and/or impulsivity. It is associated with significant functional impairment [1], is known to impact heavily on the sufferer's academic and social development [2], and places a considerable burden on society in terms of financial cost and stress to families [3]. Both children and adolescents with ADHD are known to be impaired on a number of neuropsychological functions including executive function, vigilance, verbal learning and memory. Sex ratios among children consistently show that ADHD is predominant in boys, although, in general, qualitative differences between boys and girls meeting diagnostic criteria have not been observed [4]. In the USA, estimates of the prevalence of ADHD (assessed using the Diagnostic and Statistical Manual of Mental Disorders – 4th edition [DSM-IV] diagnostic criteria) range at 7–16% [5], with worldwide prevalence rates ranging from 2 to 8% (in lower prevalence studies) to 16–20% (in higher prevalence studies) [6].

It is now well recognized that features of ADHD often persist into adulthood, although the reported incidence varies considerably depending on diagnostic criteria, socio-economic status, geographic source of the sample and gender balance [7]. Some have estimated that between 18 to 36% of children with ADHD may carry the diagnosis into adulthood [8], while other studies have suggested that ADHD symptoms can continue into adulthood in up to 75% of diagnosed children [1,9]. In a recent general-population study of 966 randomly selected adults, 2.9% met diagnostic criteria for ADHD, with 16.4% meeting criteria for 'broad' ADHD [10]. Numerous researchers have shown that adults who are classified as having ADHD have a lower socio-economic status, more work difficulties and a higher incidence of substance abuse compared with non-ADHD adults [11]. Impaired neurocognitive performance related to

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frontal lobe functions has also been described in the adult ADHD population [12–15], as has evidence of frontal dopaminergic hypoactivity [1,16]. These neurocognitive deficits are reminiscent of those seen in childhood ADHD, particularly the attentional, inhibitory and executive impairments.

For several decades, ADHD has predominantly been treated with stimulant drugs such as methylphenidate and amphetamine [17,18], with second line agents including the tricyclic antidepressants and α-2 agonists [19]. Nevertheless, despite several pharmacotherapies being available, a considerable number of patients (20–30%) remain unsatisfactorily treated. Concerns about side effects (such as tics, loss of appetite, height reduction and insomnia) and the abuse of conventional stimulants have also fuelled the search for alternative treatments for ADHD. In particular, recent evidence has indicated that the novel wakefulness-promoting agent modafinil (currently marketed for narcolepsy under the tradename Provigil™) may be effective in the treatment of ADHD [20–23]. Modafinil is structurally and pharmacologically distinct from conventional ADHD treatments, with little overt dopaminergic action or evidence of abuse liability [24]. The present review examines the potential of modafinil for use in both pediatric and adult populations with ADHD, in terms of symptom relief and cognitive enhancing benefits. A license for the use of a new formulation of modafinil in children and adolescents (but not adults) with ADHD is currently being sought by the manufacturer of modafinil.

Overview of the ADHD market

Currently, stimulant medication and in particular methylphenidate is the first-line choice for ADHD and has proved to be an efficacious treatment for this disorder, with approximately 70–80% of patients demonstrating a favorable response. For those patients who fail to respond to stimulant therapy or have marked side effects, second-line nonstimulant agents are also available. These include the tricyclic antidepressants, the α-agonists clonidine and guanfacine and drugs, such as buproprion and atomoxetine [25]. In addition, the ongoing development of ADHD medications has led to alternative and extended-release delivery systems of stimulant drugs [26]. The long-acting stimulants are similar to the immediate-release drugs both in terms of efficacy and side effects [19]. In the USA, two drugs currently dominate the ADHD market: the slow-release formulation of methylphenidate (Concerta™) and the mixed-salts amphetamine product (Adderall XR™). Despite initial enthusiasm, a recently launched nonstimulant ADHD treatment, atomoxetine (Strattera™), is proving to be disappointing due to an unfavorable side-effect profile when compared with older treatments [27]. Atomoxetine has been associated with a rare but severe risk of hepatotoxicity in children [101] and a small but statistically significant increase in suicidal ideation in patients treated with the drug [102]. Thus, modafinil may have an advantage over current ADHD drugs because of its low side-effect profile, long half-life and reduced regulatory control requirements (modafinil is classified as a schedule IV drug in the USA).

Introduction to modafinil

Modafinil was licensed in the USA for the treatment of narcolepsy in 1997 [28]. Since then, it has largely superseded the use of traditional stimulants, such as methylphenidate, in this disorder. Modafinil is known for its ability to potently increase waking in animals and humans, with less peripheral or central side effects and less abuse potential than amphetamine [29]. Modafinil has been used, off-license, with varying degrees of success in a wide range of disorders including depression [30–33], alcoholic organic brain syndrome [34], myotonic dystrophy [35], Parkinson's Disease [36–38], cerebral palsy [39], multiple sclerosis [40], brain injury [41], attention-deficit hyperactivity disorder [20–23], schizophrenia [42–46] and drug addiction [47]. Modafinil has also been shown to have cognitive enhancing effects in healthy individuals [48–50].

Modafinil is currently indicated for the treatment of excessive daytime sleepiness associated with chronic pathological conditions, such as narcolepsy, sleep apnea and chronic shift work sleep disorder [51]. In 2004, modafinil accounted for approximately 10% (1,933,000 prescriptions) of analeptic agents dispensed in the USA; a 4% increase in market share from 2002 [103]. It has been estimated that over 20,000 patients are already being prescribed modafinil 'off label' for ADHD [104].

Chemistry of modafinil

Modafinil is a novel wakefulness-promoting compound. The chemical designation for modafinil is 2-[(diphenylmethyl)sulfinyl]acetamide. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.36. Modafinil is a racemic compound, with the enantiomers known to have similar pharmacological actions in animals [52]. Modafinil is a white to off-white, crystalline powder that is practically insoluble in water.

Pharmacodynamics of modafinil

The precise mode of action of modafinil remains unknown. The most striking difference between traditional stimulants and modafinil is that modafinil appears to produce arousal through a mechanism that does not directly stimulate the dopaminergic system at therapeutic doses [53–56], although there is evidence that it may indirectly modulate this system [57–59]. Modafinil, unlike amphetamine, does not stimulate the release of dopamine from preloaded synaptosomes, it has no reported anxiogenic effects and does not induce stereotypy in rats [60,61]. The low-abuse potential of modafinil also suggests a nondopaminergic pathway activity [29] and likely treatment benefits over stimulants, such as methylphenidate. There are suggestions that the wakefulness-promoting effects of modafinil may require an intact noradrenergic system [54], although other authors have argued against a noradrenergic mechanism of action [62,63]. It has also been postulated that a catecholaminergic tone, particularly in the cortical noradrenergic neurones, is required for modafinil to exert a serotonin-mediated inhibition, or reduction, of γ-amino-n-butyric acid (GABA) release in the cerebral cortex [64]. Recent evidence has suggested that modafinil might possibly be acting to promote

histamine release [65] via a mechanism that is similar to the newly discovered neuropeptides orexin-A and -B, which are central to canine models of narcolepsy [66]. Low doses of modafinil have also been shown to enhance serotonin transmission when taken concomitantly with antidepressant drugs [67].

Pharmacokinetics & metabolism of modafinil

A new formulation of modafinil (called modafinil-ADHD, when necessary to distinguish it from the Provigil™ formulation) has recently been investigated and has been shown to have release and absorption characteristics that are significantly different from the formulation already approved for sleep disorders and sleep apnea (although studies in directly comparable populations are not available) [68]. A recent conference abstract described an evaluation of the pharmacokinetics of film-coated tablets of modafinil-ADHD in children and adolescents with ADHD [69]. Modafinil-ADHD doses were titrated to a maximum of 425 mg/day in 528 patients from four pooled Phase III studies. The elimination half-life of modafinil for the youngest (lighter) patients was 6–7 h and 9–10 h for the oldest (heavier) patients. The dependence of the oral clearance rate on weight was nonlinear and was found to be greater after a 12-day half-life induction than on the first day of the trials. Weight-based dosing consistently provided median exposures of approximately 150 µg × h/ml and the time to peak plasma concentrations was 2–3 h after once daily weight-based dosing. The volume of distribution was linearly related to weight. The pharmacokinetic profile of modafinil-ADHD was reported to remain unchanged with up to 1 year of dosing.

In adults, the peak plasma concentrations of a single oral dose of modafinil (not modafinil-ADHD) are obtained 2–4 h after oral administration with an elimination half-life of 12–15 h [70]. The effective elimination half-life of modafinil after multiple doses is approximately 15 h [71]. The enantiomers of modafinil exhibit linear kinetics with multiple dosing of 200–600 mg/day in healthy volunteers. Steady states of total modafinil and L-modafinil are reached after 2–4 days of dosing. Modafinil's enantiomers have different pharmacokinetic profiles: the half-life of the L-isomer is approximately three-times that of the D-isomer in humans and, at steady state, total exposure to the L-isomer is approximately three-times that for the D-isomer. The presence of food in the stomach delays the achievement of maximum plasma concentrations of modafinil by approximately 1 h, but does not reduce the extent of absorption [52].

Modafinil is metabolized primarily into two products, modafinil acid and modafinil sulfone, which are excreted in the urine. Less than 10% of orally administered modafinil is excreted unchanged in the urine [72], with the major route of elimination of modafinil (approximately 90%) being hepatic metabolism. In humans, modafinil demonstrates a possible low-level enzyme induction effect after chronic administration of doses greater than 400 mg/day [52]. Induction of hepatic metabolizing enzymes has also been observed *in vitro*, after incubation of primary cultures of human hepatocytes with modafinil [70].

Clinical efficacy of modafinil in ADHD

Modafinil is not approved for use in ADHD and its clinical efficacy as a treatment for this disorder has not been established with the use of large, long-term clinical studies. No comparative studies with current first-line treatments for ADHD in children have been reported. Nevertheless, there have been three recent reports of short 7–9 week double-blind, placebo-controlled studies of modafinil-ADHD in children with ADHD [23,73,74] that support the use of modafinil in this condition. In total, there are currently six double-blind, placebo-controlled trials [21,23,73–80] assessing the efficacy of modafinil in children with ADHD (three of which are published in full) [21,23,74]. Details of these studies (some of which have been reported in the literature more than once) are presented in TABLE 1. Three of these studies [23,73,74] evaluated the efficacy of modafinil-ADHD (two used a flexible dose design, one a fixed dose approach), while the other three [21,77,80] used the original Provigil™ formulation of modafinil. In addition to this, there are two open-label studies of modafinil in children with ADHD (one of which is published) [20,81], as shown in TABLE 2. Results from studies of modafinil in adult patients with ADHD [22,53,82,83,105] are described in TABLE 3. None of the adult studies used the new modafinil-ADHD formulation.

The primary outcome measure for the majority of studies in children was the school version of the Attention-Deficit Hyperactivity Disorder Rating Scale IV (ADHD-RS-IV). This is an 18-point questionnaire in which each item corresponds to one of the 18 DSM-IV symptom criteria for ADHD [84]. Results are based on an interview with a parent (the home version) or a teacher (the school version). On this scale, higher scores indicate greater severity of the condition. In general, children with ADHD showed reductions in hyperactivity, inattention and impulsivity with modafinil [21,23,73,74,77,80]. Two very similar, 9-week, flexible dose studies, designed to evaluate the safety and efficacy of modafinil-ADHD in children and adolescents with ADHD (n = 248 [23] and n = 198 [73]) demonstrated significant improvements in ADHD symptomatology on the ADHD-RS-IV (school version). Mean changes from baseline to final visit for the modafinil-ADHD groups versus the placebo groups were -15.0 ± 11.8 versus -7.3 ± 9.7 ($p < 0.0001$) [23] and -17.5 ± 13.1 versus -9.7 ± 10.3 ($p < 0.0001$) (FIGURE 1) [73]. Similarly, significant improvements in clinician-rated impressions of improvement – measured using the Clinical Global Impressions of Improvement Scale (CGI-I) – were also seen at the final visit: 48% [23] and 52% [73] of patients treated with modafinil-ADHD were classified as 'responders' versus 17% [23] and 18% [73] of patients on placebo (FIGURE 2). Treatment responders were defined as patients rated as 'much improved' or 'very much improved' on the CGI-I. In a 9-week, fixed dose study in 189 children with ADHD [74], in which patients received 7 weeks of double-blind treatment of modafinil-ADHD followed by an abrupt, double-blind, discontinuation and 2-week observation period, similar efficacy to the flexible dose studies was noted (ADHD-RS-IV school version mean change from baseline to

Table 1. Double-blind, placebo-controlled trials of modafinil in children with ADHD.

Study	Participant details	Study details	Study results	Main adverse events	Withdrawals from drug groups (%)	Funding source	Ref.
Biederman *et al.*	n = 248 (164 D; 82 P); 174 M, 72 F; mean age 10.3 years, mean weight 42.9 kg	Between subjects, multicenter, randomized, flexible dose study (dose range 170–425 mg, once daily modafinil-ADHD, mean dose 361 mg); 9 weeks duration (after 4 weeks patients had the option to move to an open-label design)	Significant improvements in ADHD-RS-IV, CGI-I (48% 'responders' on modafinil, 17% on placebo), CPRS, SSRS and CHQ	Insomnia (29%), headache (20%), reduced appetite (16%), weight loss	3% for an ADR, 21% for lack of efficacy, 41% overall	Cephalon	[23,76]
*Greenhill *et al.*	n = 198 (131 D, 67 P); age range 6–17 years	Between subjects, flexible dose study (dose range 170–425 mg, once daily modafinil-ADHD, mean dose 361 mg); 9 weeks duration	Significant improvements in ADHD-RS-IV, CGI-I, TOVA	Insomnia (28%), headache (22%), reduced appetite (18%)	5% for an ADR (no further details)	Cephalon	[73]
Swanson *et al.*	n = 189 (125 D, 64 P); age range 6–17 years	Between subjects, multicenter, fixed dose titration study (44 patients received 340 mg, once daily modafinil-ADHD; 81 patients received 425 mg); 7 weeks duration + 2 weeks of blinded non-tapered withdrawal of drug in half the patients to assess the effect of abrupt discontinuation	Significant improvements in ADHD-RS-IV, CGI-I (49% 'responders' on modafinil, 25% placebo), CPRS, SSRS and CHQ. No evidence of withdrawal or discontinuation syndrome	Insomnia (24%), headache (17%), reduced appetite (14%)	9% for an ADR, 14% because of lack of efficacy, 37% overall	Cephalon	[74,75]
*Biederman *et al.*	n = 248; age range 6–14 years (average age 9 years); average weight of children receiving a maximum dose of 300 mg was 35.5 kg	Between subjects study to evaluate the effect of different dose regimens of 300 mg and 400 mg modafinil. Four groups, doses split morning/ midday: 300/0 mg, 100/200 mg, 200/100 mg 200/200 mg. 7–10 day placebo run-in and 4 weeks treatment	Significant improvements in ADHD-RS-IV home version (300/0 group), ADHD-RS-IV school version (300/0 group; 200/100 group), CADS-P (300/0 group; 100/200 group)	Insomnia, abdominal pain, anorexia, cough, fever, rhinitis	10% from whole study group (no further details)	Cephalon	[77–79]
Rugino and Samsock	n = 24 (11 D, 11 P); 15 M, 9 F; age range 5–15 years	Randomized, flexible dose study (dose range 200–300 mg, mean dose 264 mg). Average duration 6 weeks ± 3.3 weeks (study concluded for each patient once dose had been stable for 5 days)	Significant improvements in TOVA, CTRS, CPRS and parental questionnaires of response. No effect on ADHD-RS-IV	Insomnia (36%), stomach ache (18%), headache (9%), transient mood disorder (9%)	8% for an ADR (repeated emesis), 15% overall	Not disclosed	[21]
*Swanson *et al.*	n = 48; age range 6–13 years	Within-subjects study to evaluate different once-daily doses. Dose range 100–400 mg. 4 weeks duration. Assessed in an analog classroom setting	Significant improvements on ADHD-RS-IV (300 mg and 400 mg doses only). No effect on SKAMP	Abdominal pain, headache (in > 10% patients)	12.5% (no further details)	Cephalon	[80]

*Indicates those studies that are not yet published in full and have only been reported in conference abstracts to date.

ADHD-RS-IV: Attention-deficit hyperactivity disorder-Rating Scale-IV; ADR: Adverse drug reaction; CADS-P: Conners' ADHD/Diagnostic and Statistical Manual-IV Parents Scale; CGI-I: Clinical Global Impression of Improvement Scale; CHQ: Child Health Questionnaire; CPRS: Conners' Parent Rating Scale-Revised Short Form; CTRS: Conners' Teacher Rating Scale-Revised Short Form; D: Drug; F: Female; M: Male; P: Placebo; SKAMP: Swanson Kotkin Agler M-Flynn and Pelham Rating Scale; SSRS: Social Skills Rating System; TOVA: Test of Variables of Attention.

Table 2. Open-label trials of modafinil in children with ADHD.

Study	Participant details	Study details	Study results	Adverse events	Study withdrawals (%)	Funding source	Ref.
*Swanson *et al.*	n = 220; age range 6–14 years	8-week open-label trial to assess continued efficacy and tolerability of modafinil in patients who completed a previous double-blind study. Titrated dose range 100–500 mg/day in divided doses	Significant improvements on ADHD-RS-IV (home version), CADS-P, CGI-C (76% of children showed improvement)	Insomnia (13%), headache (10%)	25%	Cephalon	[81]
Rugino and Copley	n = 11; 9 M, 6 F; age range 5–15 years (mean 9.6 years)	Dose-titrated study (final dose range 50–400 mg, once-daily modafinil), average study duration 4.6 weeks (range 2–7 weeks), with patients evaluated once dose stable for 2 weeks	Significant improvements from baseline on ADHD-RS-IV, CTRS, CPRS, TOVA. Effects were generally maintained beyond the school day	Insomnia (20%), stomach ache, light-headedness, disorientation, tremors and biting of fingers and hands	9% because of an ADR (disorientation and tremors during sleep), 27% overall	Not disclosed	[20]

*Indicates those studies that are not yet published in full and have only been reported in conference abstracts to date.
ADHD-RS-IV: Attention-deficit hyperactivity disorder-Rating Scale-IV; ADR: Adverse drug reaction; CADS-P: Conners' ADHD/DSM-IV Parents Scale; CGI-C: Clinical Global Impression of Change Scale; CPRS: Conners' Parent Rating Scale-Revised Short Form; CTRS: Conners' Teacher Rating Scale-Revised Short Form; F: Female; M: Male; TOVA: Test of Variables of Attention.

week 7 was -19.7 ± 11.42 for drug vs -10.1 ± 9.64 for placebo; CGI-I responder rate was 49% for modafinil-ADHD vs 25% for placebo). Abrupt discontinuation of modafinil did not appear to affect physical or emotional health, as observed during the 2-week observation period following discontinuation of modafinil-ADHD using the Subject's Treatment Emergent Symptoms Scale (STESS) [74]. An unpublished study of the effects of four different dosing regimens of modafinil 300–400 mg (not modafinil-ADHD) in 248 children [77] indicated that modafinil 300 mg/day significantly improves ADHD symptoms, with no additional benefit gained from twice-daily dosing of modafinil. In addition, modafinil 400 mg (split 200-mg morning, 200-mg midday) in children weighing more than 30 kg had significant benefits over placebo, but did not confer any greater advantages than 300 mg/day [78]. Beneficial effects of modafinil have also been noted in two smaller, double-blind, placebo-controlled studies (n = 24, n = 48) [21,81].

The efficacy of modafinil in adult patients with ADHD is far less established. There are currently no published long-term studies of the effects of modafinil in adult patients with ADHD. An unpublished trial conducted by the manufacturer of modafinil in 113 patients indicated that modafinil was not effective in reducing the symptoms of ADHD [105]. By contrast, however, a separate study of the efficacy of modafinil versus dextroamphetamine (n = 22) in the treatment of adults with ADHD demonstrated that both modafinil and dextroamphetamine, resulted in a significant reduction in ADHD symptoms (mean change from baseline of -12.0 for modafinil vs -1.5 for placebo, as measured using the total score on the DSM-IV ADHD Behavior Checklist; $p < 0.001$), together with trends toward improvement on various cognitive measures (the Stroop Test, digit span and verbal fluency) [53]. A small pilot study in adults with ADHD (n = 8) suggested that modafinil helps to improve driving and lane positioning compared with the control level [82], while a recent cognitive study of modafinil in adult patients with ADHD showed that a single dose of modafinil improves verbal memory, visual memory, planning abilities and response inhibition [22].

In terms of comparative effects of methylphenidate and modafinil, no direct studies of their effects on the symptoms of ADHD have been conducted. Nevertheless, modafinil and methylphenidate have distinct cognitive effects in patients with ADHD, and it is likely that this might result in subtly different behavioral effects. Methylphenidate appears to primarily affect spatial working memory and planning, as well as enhancing sustained attention [85,86]. By contrast, modafinil has robust effects on verbal memory, visual memory and planning, but does not consistently affect spatial working memory or sustained attention [22]. Both drugs improve response inhibition in ADHD [22,87], suggesting a possible neuropsychological substrate for the positive behavioral effects of ADHD treatments. It has been hypothesized that one of the key differences between conventional stimulants and modafinil might be distinct effects on arousal, with stimulants, such as amphetamine and methylphenidate, potentially exerting their effects through both stimulated (catecholaminergic) arousal and normal (histaminergic) wakefulness, with drugs, such as modafinil, possibly acting through selective activation of the latter, more reflective type of calm wakefulness [88–90].

Table 3. Trials of modafinil in adults with ADHD.

Study	Participant details	Study details	Study results	Adverse events	Study withdrawals (%)	Funding source	Ref.
*Cephalon unpublished	n = 113, no further details	Double-blind, placebo controlled 100 mg or 400 mg/day. No details of study duration	No significant effects on the ADHD-RS-IV (no other measures reported)	Not reported	Not reported	Cephalon	[105]
Turner *et al.*	n = 20; mean age 28±9 years, mean NART verbal IQ of 108±6	Randomized, double-blind, placebo controlled within subjects, crossover design to assess the effects of 200 mg modafinil on cognition in adult patients with ADHD. Two sessions separated by at least a week	Significant improvements in verbal memory, visual memory, planning, decision-making, attention	Patients reported feeling more excited on drug, modafinil increased blood pressure and pulse readings over 4 h	None	Wellcome Trust, MRC UK	[22]
*Freeman *et al.*	n = 8 ADHD; n = 8 controls; age range 18–35 years	Double-blind, counter-balanced, placebo-controlled, single-dose study to assess the effect of 200 mg modafinil on driving performance in ADHD. Two sessions separated by a week	Modafinil improved lane positioning in all patients compared with control level	Not reported	Not reported	Not disclosed	[82]
Norton	n = 2; 2 M; ages 17 and 21 years	Case study of two patients maintained for >3 months on modafinil. Both initiated on 200 mg, with elder patient increased to 400 mg daily	Improved concentration and symptoms 4–6 weeks into trial	None	None	None	[83]
Taylor and Russo	n = 22; 9 F, 13 M; average age 40.8 years (range 18–59 years)	Randomized, double-blind, placebo-controlled, three-phase crossover study: placebo, dexamphetamine (21.8±8.9 mg/day), modafinil (206.8±84.9 mg/da). Of 4 days washout periods. Doses titrated for 5–7 days, then kept constant for each two week treatment phase	Significant improvements on the DSM-IV ADHD checklist for adults. Trends towards significant effects on the COWAT, Stroop, digit span tests. Modafinil not significantly different from dexamphetamine	Insomnia, irritability, muscle tension, reduced appetite. No effect of modafinil on mood scales, BDI or HAM-A	4% (unrelated to drug) (Note: after unblinding 52% of patients elected to continue with modafinil)	Not disclosed	[53]

*Indicates those studies that are not yet published in full and have only been reported in conference abstracts or press releases to date.
ADHD-RS-IV: Attention-deficit hyperactivity disorder-Rating Scale-IV; BDI: Beck Depression Inventory; COWAT: Controlled Oral Word Association Test; DSM-IV: Diagnostic and Statistical Manual of Mental Disorders – 4th edition; F: Female; HAM-A: Hamilton Anxiety Rating Scale; M: Male; NART: National Adult Reading Test.

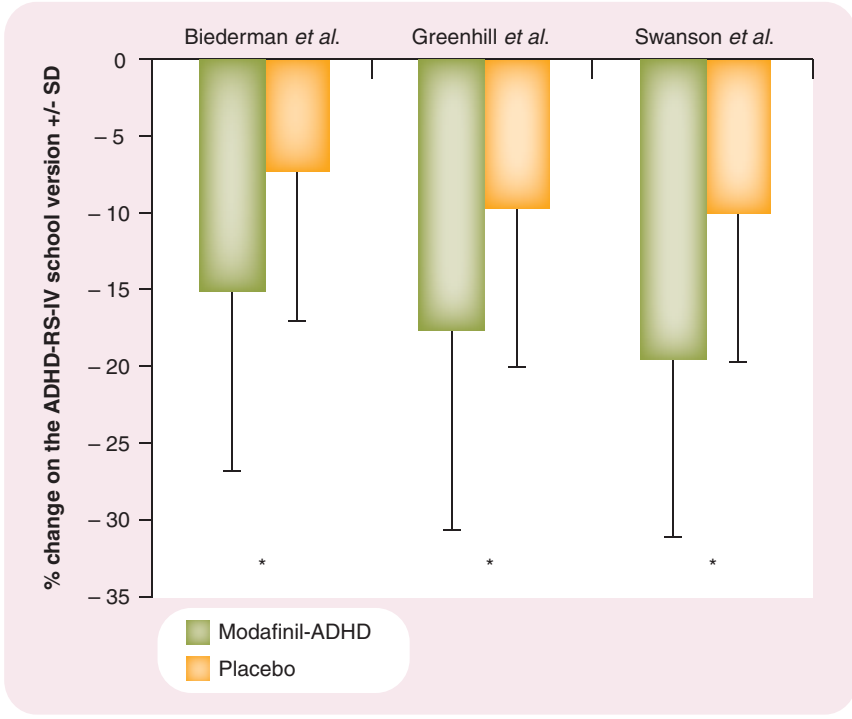

Figure 1. Percentage change in ADHD symptom ratings as measured using the full ADHD-Rating Scale-IV questionnaire (school version). Patients receiving drug showed a significantly greater (*$p < 0.05$) improvement in ADHD symptoms compared with the placebo group in three randomized controlled trials of modafinil-ADHD in children with ADHD. Two were flexible dose studies [23,73], one was a fixed dose trial [75].
ADHD-RS-IV: Attention-deficit hyperactivity disorder-Rating Scale-IV.

Postmarketing surveillance of modafinil in ADHD

Modafinil is not currently licensed for use in ADHD. It is likely that, if approved for use in children and adolescents with ADHD, modafinil will receive a license initially in the USA. If licensing is granted by the FDA, it is essential that rigorous surveillance of the effects of long-term administration of modafinil-ADHD in children and adolescents be undertaken.

Safety & tolerability of modafinil in ADHD

Modafinil is generally well tolerated, with the majority of adverse events in clinical trials being rated as mild to moderate. In seven of the eight studies of modafinil in children with ADHD [20,21,23,73,74,77,80,81], the most frequently reported side effect was insomnia, with the incidence rate ranging from 13 to 36% (TABLE 1). Other frequently reported side effects include headaches, decreased appetite, abdominal pain, weight loss, fever, rhinitis and cough. FIGURE 3 illustrates the side-effect profile of modafinil in a recently published study of modafinil-ADHD in children with ADHD [23]. Reports from other studies are of a similar nature and incidence [20,21,73,74,77,80,81]. Most side effects have been reported to resolve either with continued therapy or with a reduction in dose. Statistically significant, but not clinically relevant, weight loss has been observed following 9 weeks of modafinil administration in children [23]. Modafinil does not appear to adversely affect blood pressure, heart rate, vital signs or EEG measures in children [23,74,80].

Severe adverse events that have occurred during modafinil treatment have included erythema multiforma, insomnia, Stevens–Johnson syndrome, duodenitis, peptic ulcer, hypertonia, severe asthma attack, moderate influenza and repeated emesis [21,23,74]. All, with the exception of Stevens–Johnson syndrome, which occurred in a 7-year-old boy 5 days after the discontinuation of modafinil, were considered to be unrelated to the study drug. Discontinuation rates from studies as a direct result of an adverse event vary between studies, but are generally less than 10% (TABLE 1). In the most recently published double-blind study of modafinil in children with ADHD, the discontinuation rate because of an adverse event was 3% (4% in the placebo group) [23]. Reasons for discontinuation in the modafinil group were somnolence, dystonia and tachycardia. In this study a further 21% of the modafinil-ADHD group discontinued because of a lack of efficacy, with an overall discontinuation rate of 41% from the drug group [23]. In other studies, discontinuation rates in the active groups because of an adverse drug reaction are between 5 and 9%, with overall withdrawal rates between 10 and 37% (TABLE 1) [20,21,23,73,74,77,80,81].

In adults with ADHD there are no rigorous long-term studies of efficacy and safety available. In a 2-week study of the effects of modafinil in adults with ADHD the most common adverse effects were insomnia, irritability, muscle tension and appetite suppression [53]. Rebound effects were also observed to occur in the evenings and were between 30 min and 1 h in duration [53]. Three patients (14%) developed transient lingual dyskinesia, which resolved when the drug dose was lowered. After unblinding of this study, 52% of patients elected to continue with long-term treatment with modafinil [53]. No effects on ratings of depression or anxiety were observed [53]. In a single-dose cognitive study of modafinil in adult patients with ADHD, the only reported subjective effect of drug that was significantly different from placebo was a heightened sense of excitement [22]. Modafinil also resulted in statistically significant physiological effects on blood pressure and pulse in this study, although they were not considered clinically relevant [22].

Despite reports from the literature indicating that modafinil has a relatively low potential for abuse [91], modafinil does demonstrate some reinforcing properties in healthy adult volunteers [92]. The manufacturer of modafinil advises that patients with a history of drug or stimulant abuse should be closely monitored [51]. In

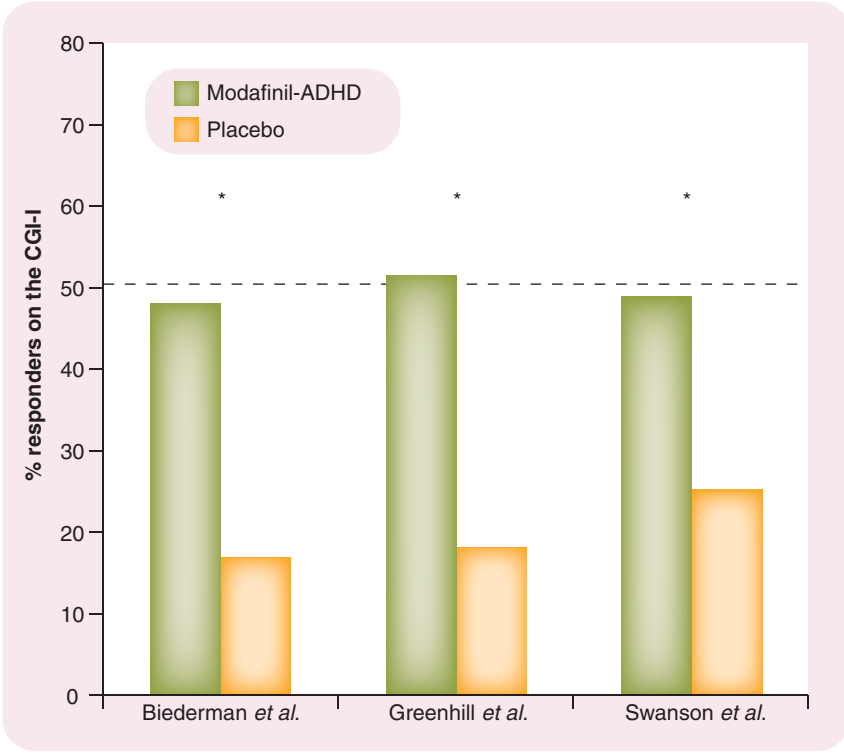

Figure 2. Percentage change in clinician-rated CGI-I. Patients receiving drug showed a significantly greater (*p<0.05) improvement compared with the placebo group in three randomized controlled trials of modafinil-ADHD in children with ADHD. Two were flexible dose studies [23,73], one was a fixed dose trial [74].
ADHD: Attention-deficit hyperactivity disorder; CGI-I: Clinical global impression of improvement.

addition, the manufacturer's datasheet cautions that modafinil can produce psychoactive and euphoric effects, alterations in mood, perception, thinking and feeling [51]. Certain patients might also be susceptible to psychosis following modafinil, with several reported cases of modafinil-induced psychosis, both in patients with schizophrenia and in healthy adult volunteers [44,45,93,94]. Readers are directed to the product monograph and summary of product characteristics for details of drug interactions with modafinil [51,52].

Regulatory affairs

The manufacturer of modafinil, Cephalon Inc., has indicated its intention to market modafinil for the treatment of ADHD under the brand name Sparlon™ (initially the trade name was intended to be Attenace™ [106]), otherwise known as modafinil-ADHD [68]. Cephalon submitted a supplemental new drug application to the US FDA in December 2004 to 'market modafinil for the treatment of ADHD in children and adolescents aged 6–17 years old [107]. In October 2005 it was announced that it had received initial approval from the FDA [108] and, subject to final FDA approval, the company hopes to launch modafinil-ADHD in 2006 [109]. Modafinil-ADHD will be small, film-coated tablets that are expected to be available in 85, 170, 255, 340 and 425 mg strengths to allow for tailored dosing in children and adolescents with ADHD using single tablets. Cephalon currently has no intention to market modafinil-ADHD for use in adults with ADHD (CEPHALON INC., PERS. COMM.).

Conclusion

Modafinil-ADHD (and modafinil) has been shown to be effective in reducing ADHD symptoms of both inattention and hyperactivity-impulsivity in children and adolescents when compared with placebo. In addition, modafinil-ADHD significantly improves patients' overall clinical condition, as assessed by the clinician-rated CGI-I. Despite these promising results, however, only approximately 50% of participants (range 48–52%) who received the drug in three large, randomized, placebo-controlled trials were considered 'responders' after 7–9 weeks of double-blind therapy with modafinil-ADHD (FIGURE 2) [23,73,74]. Furthermore, overall withdrawal rates from the drug groups in these studies (prior to study conclusion) were approximately 40% [23,73,74]. Thus, it remains to be determined whether modafinil will become a useful therapy for the treatment of ADHD, or if it is likely to be reserved as a second-line treatment. It is also possible that modafinil might have a role in regimes of combined drug treatment, although this has not been researched to date.

Modafinil is suitable for once-daily dosing in the pediatric population, with no apparent additional benefit derived from twice-daily administration [77]. There are indications (from a small pilot study [80]) that a daily dose of at least 300-mg modafinil (not modafinil-ADHD) is required to obtain significant improvements in behavioral ratings in 6–13 year old children. A larger trial has suggested that there is no significant additional benefit of 400 mg/day modafinil over 300 mg/day in a similarly aged group [77]. Thus, further research is needed to determine weight-based dosing guidelines of modafinil in children. In terms of the formulation of modafinil, the current preliminary trials in pediatrics show similar levels of symptom improvement irrespective of whether the patients were administered modafinil or modafinil-ADHD [20,21,23,73,74,77,80,81]. Additional research is needed to establish both the pharmacokinetic properties of modafinil compared with modafinil-ADHD in children and to determine if there is any additional benefit to be gained from using the film-coated modafinil-ADHD formulation.

Fewer studies of modafinil in adults with ADHD have been conducted. Nevertheless, there are suggestions that modafinil may also have beneficial effects in older patients with ADHD,

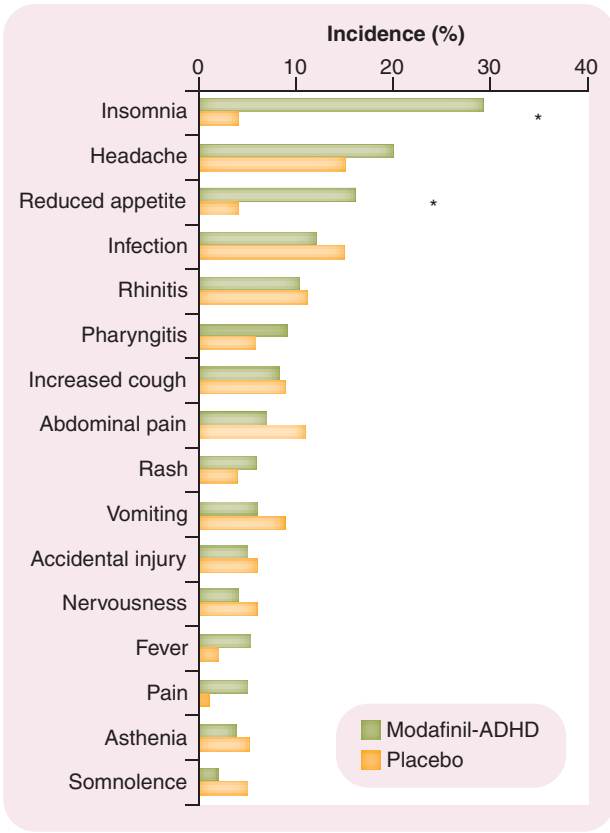

Figure 3. Incidence of side effects in a randomized, placebo-controlled trial of the effects of modafinil in 248 children with ADHD (164 patients received modafinil-ADHD, 82 received placebo) [23].
*Indicates those side effects where a significant difference ($p < 0.05$) between placebo and modafinil-ADHD was observed.
ADHD: Attention-deficit hyperactivity disorder.

both in terms of improving the symptoms [53,83] and ameliorating the cognitive deficits associated with the disorder [22,82]. An important area for future research will be to establish the therapeutic dose range of modafinil in child and adult populations of ADHD. Currently, the majority of trials of modafinil in adults have used doses far lower than those used in children (an average of 200 mg in adults compared with an average of 360 mg in children [22,23,53,82,83,73]).

Expert commentary

Despite promising results indicating modafinil's effectiveness in targeting the symptoms of ADHD in children and adolescents, it is not yet established whether modafinil offers any clinical advantages over current first-line therapies. Long-term safety and effectiveness in children has not been rigorously established, with only limited data available on modafinil's long-term effects in children. Nevertheless, it is encouraging that research projects have been initiated to examine the long-term effects of modafinil in ADHD. A 1-year, open-label, flexible-dose study to evaluate the safety and continued efficacy of modafinil-ADHD in children and adolescents with ADHD has recently been completed [110] and the results are awaited with interest. Results from the longer-term use of modafinil-ADHD in children and adolescents are also expected to be presented at the annual American Psychiatric Association conference in May 2006 [111].

In addition, the majority of studies to date have been initiated from the same group of investigators and funded by the manufacturer of modafinil. Independent studies are required to establish modafinil's effect on more heterogeneous samples from within both community and hospital settings, particularly as several of the studies excluded patients that were either treatment resistant to more than one of the currently available treatments for ADHD, who were currently well controlled patients or who were happy with their current therapy [23,74]. Systematic studies to establish dosing guidelines for the treatment of children are also required, especially in the light of the fact that modafinil's pharmacokinetic profile alters with age and weight. Based on limitations in the current literature [74], doses exceeding 340-mg modafinil-ADHD should be reserved for patients weighing more than 30 kg.

Although comparative studies of modafinil and current therapies have not been performed, it is possible to compare treatment effect sizes from different studies. Recent evidence has indicated that the average treatment effect size for immediate release stimulants in ADHD is approximately 0.91 (0.95 for slow-release formulations) and 0.62 for nonstimulants, although there is considerable variability within the groups [19]. Modest effect sizes of 0.69 and 0.63 (on the ADHD-RS-IV school version) have been observed with modafinil-ADHD [73,76]. This suggests that modafinil's efficacy is more likely to be similar to that of other nonstimulant therapies than to current stimulant drugs.

If licensed for ADHD, the cost–effectiveness of modafinil-ADHD, compared to generic stimulants, will need to be assessed. While clinicians will no doubt be encouraged by the possibility of prescribing a drug with a long half-life and low potential of abuse to children with ADHD, it is likely that they will be cautious about its use until its efficacy compared with cheaper first-line therapies is established.

Five-year view

Modafinil is not yet licensed for the treatment of ADHD in children or adults. However, it is anticipated that modafinil-ADHD will be approved for use in children and adolescents with ADHD in the USA in the near future. As discussed, modafinil has several advantages over conventional stimulants. If modafinil-ADHD is shown to be equivalent or superior to current treatments for ADHD, through the use of rigorous comparator studies, then it has the potential to become an important agent in the treatment of ADHD. In countries where modafinil is not currently intended to be licensed for use in ADHD, an increase in off-label prescribing can be expected. Provigil™ has recently come under a number of patent challenges, with indications that a generic form of modafinil may be available as early as October 2011 [112,113,114]. This is likely

to have a bearing on the prescribing rates of modafinil, with prescribers potentially more likely to consider using modafinil if a cheaper, generic version is available.

Within the next 5 years a clearer understanding of modafinil's place within the ADHD formulary is likely to be established, as will knowledge of modafinil's effects on specific diagnostic subtypes of ADHD. It is also likely that, as brain imaging, genetic and pharmacogenetic techniques develop, current conceptions of ADHD will change. Future research in this area, together with a greater understanding of modafinil's pharmacological profile, will help determine modafinil's role in the treatment of ADHD and contribute to our understanding of the neural mechanisms of ADHD. These developments will no doubt foster research into increasingly targeted agents for the treatment of specific subtypes of disorders, such as ADHD.

Information resources

- Biederman J. Attention-deficit/hyperactivity disorder: a selective overview. *Biol. Psychiatry* 57(11), 1215–1476 (1 June 2005). Special issue discussing some of the latest trends in ADHD research.
- US National Institutes of Health Clinical Trials Database. www.clinicaltrials.gov
- 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* 116(6), E777–E784 (2005).
- Cephalon, Inc. www.cephalon.com/

Key issues

- Attention-deficit hyperactivity disorder (ADHD) is estimated to affect approximately 7–16% of the USA population, with a predominance of males being diagnosed. Currently, up to 30% of patients remain unsatisfactorily treated for ADHD despite the widespread usage of stimulant drugs, such as methylphenidate and amphetamine.
- Modafinil is a novel wakefulness-promoting agent licensed for the treatment of excessive daytime sleepiness associated with narcolepsy as well as the treatment of excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. The precise mechanism of action of modafinil is unknown, although it appears to have a much reduced dopaminergic action compared with conventional stimulants used for the treatment of ADHD, with less potential for addiction.
- Modafinil is not currently licensed for the treatment of ADHD. However, the manufacturer has indicated its intention to market modafinil-ADHD (a film-coated formulation of modafinil) for the treatment of ADHD in children and adolescents in the USA in 2006, subject to final FDA approval.
- Three large 7–9 week studies have indicated that modafinil-ADHD is effective in reducing the symptoms of ADHD in children, as measured with the ADHD-RS-IV and that it may also have beneficial behavioral and cognitive effects in adults.
- Modafinil has several advantages as a potential ADHD therapy over methylphenidate and amphetamine. It has a favorable side-effect profile, a long half-life suitable for once-daily dosing and it is subject to fewer regulatory restrictions than methylphenidate.
- Modafinil has not, however, been subjected to rigorous, comparative assessment against current first-line treatments for ADHD. Longer-term studies are required to fully establish modafinil's effects in a pediatric population.
- It remains to be established whether modafinil will be an effective long-term treatment for ADHD and how it will compare to current ADHD therapies.

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•• of considerable interest

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