Adverse Event	amlodipine M=% (N=1218)	amlodipine F=% (N=512)	Placebo M=% (N=914)	Placebo F=% (N=336)
Edema	5.6	14.6	1.4	5.1
Flushing	1.5	4.5	0.3	0.9
Palpitations	1.4	3.3	0.9	0.9
Somnolence	1.3	1.6	0.8	0.3

The following events occurred in ≤1% but >0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience where a causal relationship is uncertain; they are listed to alert the physician to a possible relationship: **Cardiovascular:** arrhythmia (including ventricular tachycardia and atrial fibrillation), bradycardia, chest pain, hypotension, peripheral ischemia, syncope, tachycardia, postural dizziness, postural hypotension, vasculitis. **Central and Peripheral Nervous System:** hypoesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia,** dysphagia, diarrhea, flatulence, pancreatitis, vomiting, gingival hyperplasia. **General:** allergic reaction, asthenia,** back pain, hot flushes, malaise, pain, rigors, weight gain, weight decrease. **Musculoskeletal System:** arthralgia, arthrosis, muscle cramps,** myalgia. **Psychiatric:** sexual dysfunction (male** and female), insomnia, nervousness, depression, abnormal dreams, anxiety, depersonalization. **Respiratory System:** dyspnea,** epistaxis. **Skin and Appendages:** angioedema, erythema multiforme, pruritus,** rash,** rash erythematous, rash maculopapular. **Special Senses:** abnormal vision, conjunctivitis, diplopia, eye pain, tinnitus. **Urinary System:** micturition frequency, micturition disorder, nocturia. **Autonomic Nervous System:** dry mouth, sweating increased. **Metabolic and Nutritional:** hyperglycemia, thirst. **Hemopoietic:** leukopenia, purpura, thrombocytopenia. The following events occurred in ≤0.1% of patients treated with amlodipine in controlled clinical trials or under conditions of open trials or marketing experience: cardiac failure, pulse irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertonia, migraine, cold and clammy skin, apathy, agitation, amnesia, gastritis, increased appetite, loose stools, coughing, rhinitis, dysuria, polyuria, parosmia, taste perversion, abnormal visual accommodation, and xerophthalmia. Other reactions occurred sporadically and cannot be distinguished from medications or concurrent disease states such as myocardial infarction and angina. Amlodipine therapy has not been associated with clinically significant changes in routine laboratory tests. No clinically relevant changes were noted in serum potassium, serum glucose, total triglycerides, total cholesterol, HDL cholesterol, uric acid, blood urea nitrogen, or creatinine. The following postmarketing event has been reported infrequently with amlodipine treatment where a causal relationship is uncertain: gynecomastia. In postmarketing experience, jaundice and hepatic enzyme elevations (mostly consistent with cholestasis or hepatitis) in some cases severe enough to require hospitalization have been reported in association with use of amlodipine. Amlodipine has been used safely in patients with chronic obstructive pulmonary disease, well-compensated congestive heart failure, peripheral vascular disease, diabetes mellitus, and abnormal lipid profiles. **The Atorvastatin Component of CADUET:** Atorvastatin is generally well-tolerated. Adverse reactions have usually been mild and transient. In controlled clinical studies of 2502 patients, <2% of patients were discontinued due to adverse experiences attributable to atorvastatin calcium. The most frequent adverse events thought to be related to atorvastatin calcium were constipation, flatulence, dyspepsia, and abdominal pain. Clinical Adverse Experiences: Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 3.

Table 3. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	Placebo N=270	atorvastatin 10 mg N=863	atorvastatin 20 mg N=36	atorvastatin 40 mg N=79	atorvastatin 80 mg N=94
BODY AS A WHOLE					
Infection	10.0	10.3	2.8	10.1	7.4
Headache	7.0	5.4	16.7	2.5	6.4
Accidental Injury	3.7	4.2	0.0	1.3	3.2
Flu Syndrome	1.9	2.2	0.0	2.5	3.2
Abdominal Pain	0.7	2.8	0.0	3.8	2.1
Back Pain	3.0	2.8	0.0	3.8	1.1
Allergic Reaction	2.6	0.9	2.8	1.3	0.0
Asthenia	1.9	2.2	0.0	3.8	0.0
DIGESTIVE SYSTEM					
Constipation	1.8	2.1	0.0	2.5	1.1
Diarrhea	1.5	2.7	0.0	3.8	5.3
Dyspepsia	4.1	2.3	2.8	1.3	2.1
Flatulence	3.3	2.1	2.8	1.3	1.1
RESPIRATORY SYSTEM					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
SKIN AND APPENDAGES					
Rash	0.7	3.9	2.8	3.8	1.1
MUSCULOSKELETAL SYSTEM					
Arthralgia	1.5	2.0	0.0	5.1	0.0
Myalgia	1.1	3.2	5.6	1.3	0.0

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT): In ASCOT involving 10,305 participants treated with atorvastatin 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with atorvastatin was comparable to that of the group treated with placebo during a median of 3.3 years of follow-up. The following adverse events were reported, regardless of causality assessment, in patients treated with atorvastatin in clinical trials. The events in italics occurred in ≥2% of patients and the events in plain type occurred in <2% of patients. **Body as a Whole:** *Chest pain*, face edema, fever, neck rigidity, malaise, photosensitivity reaction, generalized edema. **Digestive System:** *Nausea*, gastroenteritis, liver function tests abnormal, colitis, vomiting, gastritis, dry mouth, rectal hemorrhage, esophagitis, eructation, glossitis, mouth ulceration, anorexia, increased appetite, stomatitis, biliary pain, cheilitis, duodenal ulcer, dysphagia, enteritis, melena, gum hemorrhage, stomach ulcer, tenesmus, ulcerative stomatitis, hepatitis, pancreatitis, cholestatic jaundice. **Respiratory System:** *Bronchitis, rhinitis*, pneumonia, dyspnea, asthma, epistaxis. **Nervous System:** *Insomnia, dizziness*, paresthesia, somnolence, amnesia, abnormal dreams, libido decreased, emotional lability, incoordination, peripheral neuropathy, torticollis, facial paralysis, hyperkinesia, depression, hypesthesia, hypertonia. **Musculoskeletal System:** *Arthritis*, leg cramps, bursitis, tenosynovitis, myasthenia, tendinous contracture, myositis. **Skin and Appendages:** Pruritus, contact dermatitis, alopecia, dry skin, sweating, acne, urticaria, eczema, seborrhea, skin ulcer. **Urogenital System:** *Urinary tract infection*, urinary frequency, cystitis, hematuria, impotence, dysuria, kidney calculus, nocturia, epididymitis, fibrocystic breast, vaginal hemorrhage, albuminuria, breast enlargement, metrorrhagia, nephritis, urinary incontinence, urinary retention, urinary urgency, abnormal ejaculation, uterine hemorrhage. **Special Senses:** Amblyopia, tinnitus, dry eyes, refraction disorder, eye hemorrhage, deafness, glaucoma, parosmia, taste loss, taste perversion. **Cardiovascular System:** Palpitation, vasodilatation, syncope, migraine, postural hypotension, phlebitis, arrhythmia, angina pectoris, hypertension. **Metabolic and Nutritional Disorders:** *Peripheral edema*, hyperglycemia, creatine phosphokinase increased, gout, weight gain, hypoglycemia. **Hemic and Lymphatic System:** Ecchymosis, anemia, lymphadenopathy, thrombocytopenia, petechia. ***Postintroduction Reports with Atorvastatin:*** Adverse events associated with atorvastatin therapy reported since market introduction, that are not listed above, regardless of causality assessment, include the following: anaphylaxis, angioneurotic edema, bullous rashes (including erythema multiforme, Stevens-Johnson syndrome, and toxic epidermal necrolysis), and rhabdomyolysis. ***Pediatric Patients (ages 10-17 years):*** In a 26-week controlled study in boys and postmenarchal girls (n=140), the safety and tolerability profile of atorvastatin 10 to 20 mg daily was generally similar to that of placebo (see **PRECAUTIONS, Pediatric Use**).

OVERDOSAGE: There is no information on overdosage with CADUET in humans. **Information on Amlodipine:** Single oral doses of amlodipine maleate equivalent to 40 mg amlodipine/kg and 100 mg amlodipine/kg in mice and rats, respectively, caused deaths. Single oral amlodipine maleate doses equivalent to 4 or more mg amlodipine/kg in dogs (11 or more times the maximum recommended clinical dose on a mg/m^2 basis) caused a marked peripheral vasodilation and hypotension. Overdosage might be expected to cause excessive peripheral vasodilation with marked hypotension and possibly a reflex tachycardia. In humans, experience with intentional overdosage of amlodipine is limited. Reports of intentional overdosage include a patient who ingested 250 mg and was asymptomatic and was not hospitalized; another (120 mg) was hospitalized, underwent gastric lavage and remained normotensive; the third (105 mg) was hospitalized and had hypotension (90/50 mmHg) which normalized following plasma expansion. A patient who took 70 mg amlodipine and an unknown quantity of benzodiazepine in a suicide attempt developed shock which was refractory to treatment and died the following day with abnormally high benzodiazepine plasma concentration. A case of accidental drug overdose has been documented in a 19-month-old male who ingested 30 mg amlodipine (about 2 mg/kg). During the emergency room presentation, vital signs were stable with no evidence of hypotension, but a heart rate of 180 bpm. Ipecac was administered 3.5 hours after ingestion and on subsequent observation (overnight) no sequelae were noted. If massive overdose should occur, active cardiac and respiratory monitoring should be instituted. Frequent blood pressure measurements are essential. Should hypotension occur, cardiovascular support including elevation of the extremities and the judicious administration of fluids should be initiated. If hypotension remains unresponsive to these conservative measures, administration of vasopressors (such as phenylephrine) should be considered with attention to circulating volume and urine output. Intravenous calcium gluconate may help to reverse the effects of calcium entry blockade. As amlodipine is highly protein bound, hemodialysis is not likely to be of benefit. **Information on Atorvastatin:** There is no specific treatment for atorvastatin overdosage. In the event of an overdose, the patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma proteins, hemodialysis is not expected to significantly enhance atorvastatin clearance.

*Based on patient weight of 50 kg.

**These events occurred in less than 1% in placebo-controlled trials, but the incidence of these side effects was between 1% and 2% in all multiple dose studies.

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Pediatric Modafinil Eased ADHD Symptoms

BY MARY ELLEN SCHNEIDER
Senior Writer

ATLANTA — Results from new research point to a possible alternative to stimulants for the treatment of attention-deficit hyperactivity disorder in children and adolescents.

Two phase III studies presented at the annual meeting of the American Psychiatric Association show that a once-daily pediatric formulation of modafinil is well tolerated and improves attention-deficit hyperactivity disorder (ADHD) symptoms in children and adolescents.

Modafinil is currently marketed by Cephalon under the brand name Provigil in 100-mg and 200-mg strengths. Provigil is indicated for the treatment of excessive sleepiness associated with narcolepsy, obstructive sleep apnea, hypopnea syndrome, and shift work sleep disorder.

Modafinil appears to work like a gentler stimulant. The findings present possible treatment options.

DR. BIEDERMAN

The company, which funded the phase II trials, is seeking approval from the Food and Drug Administration to market modafinil in 85-mg, 170-mg, 255-mg, 340-mg, and 425-mg strengths. If approved, the drug would be indicated for treatment of ADHD in children and adolescents aged 6-17 years. The company is planning to launch the drug under the brand name Attenace by early 2006.

In one study, 189 patients with ADHD aged 6-17 years were randomized to a 7-week double-blind, fixed-dose treatment with either modafinil or placebo. This regimen was followed by a 2-week withdrawal period in which half of the modafinil-treated patients were placed on placebo without tapering, and half were continued on the drug, said Joseph Biederman, M.D., the lead investigator in the study and professor of psychiatry at Harvard University in Boston.

Modafinil was administered once daily, starting at 85 mg/day, and was rapidly titrated over 7-9 days to dosages of either 340 mg/day for patients who weighed less than 30 kg or 425 mg/day for patients who weighed 30 kg or more.

The results of the study were assessed using the school and home ADHD Rating Scale-IV total score change from baseline to last treatment visit.

After 1 week, the 125 modafinil-treated patients had significantly greater improvements in school scores, compared with the 64 placebo patients, and those results were maintained through week 7.

On the school scale, patients on modafinil experienced a 17.2-point drop in symptoms, compared with an 8.2-point drop for patients on placebo. Modafinil also significantly improved total scores from parents, compared with placebo.

The side effects included insomnia and appetite decrease. Overall, the side effects were generally mild and occurred at initiation of the treatment. There were two serious adverse events not associated with the trial, said Dr. Biederman, who is an advisory board member for Cephalon and receives research/grant support from the company.

The researchers also assessed ADHD symptoms and physical/emotional response after rapid discontinuation. During the 2-week withdrawal phase, there were no reported symptom rebounds, no adverse events related to withdrawal, and no physical or emotional responses.

Modafinil appears to work like a gentler stimulant, Dr. Biederman told this newspaper. The findings present possible new treatment options, he said. Although stimulants are effective, they are not universally effective. About 30%-40% of patients are nonresponsive to stimulants, and some patients also have tolerability problems.

Stimulants have the potential for acute deterioration and symptom rebound if treatment is interrupted or discontinued without tapering, he said.

In the second study, researchers considered the effect of a flexible dose of modafinil in children and adolescents.

The study included 198 patients aged 6-17 years who were started on a dose of 85 mg/day of modafinil, which was titrated over 22 days based on clinical effectiveness. The maximum dose was 425 mg/day with once-daily dosing, said James Swanson, Ph.D., of the University of California at Irvine Child Development Center, who was the lead investigator.

The results were assessed using the school and home ADHD Rating Scale-IV, the Clinical Global Impression of Improvement (CGI-I), and Test Variables of Attention (TOVA).

The home score showed a mean drop of 17.6 points in symptoms for the 131 patients receiving modafinil at a mean stable dose of 361 mg/day, compared with a 7.5-point drop in symptoms for the 67 patients on placebo. The improvement in the total school score was also significantly greater for modafinil patients, Dr. Swanson said.

Modafinil was shown to significantly improve inattention and hyperactivity/impulsivity, and there was an improvement in overall clinical condition and in the TOVA measurements of ADHD.

The researchers focused not only on decreasing symptoms of ADHD, but on increasing positive interaction and social skills, and they saw an increase in positive behaviors, he said.

The side effects included insomnia, headache, and appetite problems, which are similar to the side effects for stimulants, said Dr. Swanson, who is an advisory board member with Cephalon, receives research/grant support from the company, and is a member of the company's speakers' bureau. ■