

Adverse Event	amlodipine		Placebo	
	M=% (N=1218)	F=% (N=512)	M=% (N=914)	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 $\leq 1\%$ 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:** hyposesthesia, 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 $\leq 0.1\%$ 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 $\geq 2\%$ 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	20 mg N=36	40 mg N=79	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 $\geq 2\%$ 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:** Echinomycosis, 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 postmenarcheal 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/m² 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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Studies Backing Drug Use For Autism Are Limited

BY JEFF EVANS
Senior Writer

NEW YORK — The body of data for using newer pharmacotherapeutic agents to treat autistic symptoms is struggling to keep up with the use of such drugs in practice, Lawrence Scahill, Ph.D., said at a psychopharmacology update sponsored by the American Academy of Child and Adolescent Psychiatry.

"An evidence-based discussion of autism is relatively brief, because we don't have a lot of evidence, unfortunately," said Dr. Scahill, director of the research unit on pediatric psychopharmacology at the Yale Child Study Center, New Haven, Conn.

Some medications have proven to be useful in treating target symptoms of autism, such as hyperactivity, tantrums, aggression, self-injury, and anxiety, he said.

In a survey of medication patterns in patients with autism or pervasive developmental disorder (PDD) in North Carolina, the use of any medication to treat the conditions rose from 31% in 1992-1993 to 45% in 2001, Dr. Scahill noted (J. Child Adolesc. Psychopharmacol. 2005;15:116-26).

The use of several classes of drugs rose during that period, including antipsychotics (from 12% to 17%), antidepressants (from 6% to 21%), and stimulants (from 7% to 14%). For antipsychotics and antidepressants, these changes reflect switches to atypicals and SSRIs, said Dr. Scahill, who disclosed that he serves as a consultant for Janssen Pharmaceutica N.V., which manufactures risperidone (Risperdal), and Pfizer Inc., which manufactures fluoxetine.

SSRIs for Repetitive Behavior, Anxiety
SSRIs such as fluoxetine have been used in PDD to treat repetitive behavior, anxiety, and aggression, as well as to improve socialization, Dr. Scahill said. Liquid fluoxetine proved to be more effective in treating repetitive behaviors than placebo in a randomized, double-blind, crossover study of 39 children and adolescents with autistic spectrum disorders. In the first phase of the trial, patients who received fluoxetine improved their scores on a clinician-rated instrument focused on repetitive behavior (the Children's Yale-Brown Obsessive Compulsive Scale-PDD) by 10%, compared with placebo patients who improved by 4%. The second phase of the study, in which the patients switched treatments, yielded similar results.

Adverse events occurred at a rate similar to that of placebo. The average dose of fluoxetine was 10 mg/day, beginning with 2.5 mg/day for the first week. "In terms of benefit, if you're aiming [SSRIs] at repetitive behavior, I don't say 'Don't do it,' but don't expect big effects," he said.

Aggression, Tantrums, Self-Injury

Risperidone is the atypical antipsychotic that has been studied most extensively in PDD, with open and controlled trials involving a total of 223 patients.

The FDA previously declared risperidone as nonapprovable for the treatment

of autism in children, but it is now being submitted for approval for the treatment of tantrums, aggression, and self-injury, Dr. Scahill said.

In an 8-week, randomized, double-blind trial, risperidone significantly reduced aggressive behavior, tantrums, and self-injurious behavior by 57% in 49 children, compared with 14% in 52 children on placebo, according to the parent-rated irritability subscale of the Aberrant Behavior Checklist. Clinician ratings yielded similar results. The patients averaged 1.8 mg/day (N. Engl. J. Med. 2002;347:314-21).

During a 4-month open-label extension of the study for 63 responders to risperidone, irritability scores did not worsen, and patients did not require more risperidone to maintain their response (Am. J. Psychiatry 2005;162:1361-9). These responders gained an average of 5.6 kg during a total of 6 months of treatment with risperidone (Am. J. Psychiatry 2004;161:1125-7).

In a 2-month, randomized, double-blind discontinuation of risperidone, patients who continued to receive risperidone had a significantly lower rate of relapse (2 of 16) than those who gradually replaced risperidone with placebo (10 of 16).

ADHD Symptoms

Even though hyperactivity is a common problem in children and adolescents with PDD, "the evidence to support the use of methylphenidate in this population is frightfully little," Dr. Scahill said.

Until recently, methylphenidate had been studied in only two investigations of 10 children with PDD and ADHD. On the Conners Hyperactivity Index, teachers reported an 11% improvement at a dose of 10-20 mg twice daily (J. Autism Dev. Disord. 1995;25:283-94), 32% improvement at 0.3 mg/kg per dose, and 47% improvement at 0.6 mg/kg per dose (J. Am. Acad. Child Adolesc. Psychiatry 1999;38:805-12).

In a more rigorous study of 66 children with PDD and hyperactivity conducted by Dr. Scahill and his colleagues, methylphenidate improved hyperactivity significantly but less than it would in typically developing children with ADHD, according to teacher and parent ratings (Arch. Gen. Psychiatry 2005;62:1266-74). Children in the randomized, double-blind, crossover trial tolerated three dose levels of the drug in a 7-day test dose period and then received placebo for 1 week, followed by 3 weeks of the three methylphenidate doses in random order.

Thirty-four patients who responded to treatment based on a less conservative definition of response later received 8 weeks of open-label methylphenidate at an individually determined best dose.

Adverse events such as decreased appetite and increased repetitive behavior and stereotypies occurred mainly with the highest dose, even though it was "not really that high" (0.5-0.6 mg/kg per dose), Dr. Scahill said. Few adverse events occurred in the 38% (25 of 66) of patients who responded to either the low dose (0.125-0.18 mg/kg per dose) or the medium dose (0.25-0.35 mg/kg per dose). ■