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 ≤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	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 ≥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/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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Avoid Diagnostic Pitfalls For Parkinson's Disease

BY HEIDI SPLETE
Senior Writer

BALTIMORE — Be sure to reevaluate a diagnosis of Parkinson's disease in a patient at every visit, Dr. Stephen G. Reich advised at a meeting sponsored by the American Geriatrics Society and Johns Hopkins University.

The false-positive rate for a Parkinson's disease (PD) diagnosis is about 35% at the initial diagnosis and 24% at final diagnosis, according to data from several autopsy studies. Autopsy results remain the preferred method for confirming a diagnosis of PD, noted Dr. Reich, professor of neurology at the University of Maryland and codirector of its Maryland Parkinson's Disease and Movement Disorders Center.

In a study of more than 470,000 U.S. nursing-home residents, the three best predictors of PD were the presence of a resting tremor, a unilateral onset of symptoms, and a beneficial and sustained response to levodopa, the investigators noted (Pharmacotherapy 1999;19:1321-7).

The false-positive rate for a PD diagnosis is about 35% at the initial diagnosis and 24% at the final diagnosis, according to data from several autopsy studies.

Not everyone with PD has a resting tremor, but many do, and this tremor improves with movement. Classic PD starts on one side of the body, unrelated to right- or left-handedness. Some patients with Parkinson's-like syndromes (rather than Parkinson's disease) have an initial response to levodopa, but it won't be sustained.

Based on his research and experience, Dr. Reich listed the top 10 pitfalls of PD diagnosis. The first six are false positives:

► **Essential tremor (ET).** This is the condition most often misdiagnosed as PD. "The best way to distinguish ET from PD is the history and physical," Dr. Reich said. Patients presenting with ET usually report that the tremor has been present for years. But most tremor patients with PD present to a primary care physician within about 6 months of the initiation of symptoms.

Also, ask tremor patients about their responses to alcohol. About 60% or more of patients with ET notice that a little alcohol temporarily alleviates the problem, he said.

When conducting the physical exam, remember that PD is a resting tremor and thus tends to improve with movement, but essential tremor worsens with movement. A strictly unilateral tremor is probably PD. "Essential tremor, although it might be asymmetrical, is almost always bilateral," he said. Tremor of the head or voice is usually an essential tremor, he added.

Handwriting in patients with PD tends to be micrographic but is not tremulous, even if patients have tremor at rest. Patients with ET have full-sized handwriting, but it looks shaky. Patients with PD also may have cogwheel rigidity, a masked face, and trouble rising from a chair.

► **Lower-half Parkinsonism.** "These are the patients geriatricians see day in and day out. They are disproportionately fine from the waist up," Dr. Reich said. This is not PD. It appears clinically as a shuffling, broad-based gait, difficulty rising from a seated position, with impaired posture and balance. Most patients with this condition present at an age older than 70 years, and the symptoms occur below the waist.

Some of these patients respond well to shunts for normal-pressure hydrocephalus, he noted.

► **Drug-induced Parkinsonism.** This condition often goes unrecognized because it might take up to 1 year to resolve after taking a particular drug. "You have to ask what medicines patients have taken in the past," Dr. Reich said.

Check hospital records to confirm medications, and be cautious about diagnosing PD—especially if patients have taken antipsychotics, metoclopramide, or dopamine depleters such as reserpine, because the PD symptoms might resolve with time.

► **Parkinson's disease vs. Parkinson's syndrome.** Red flags that differentiate a Parkinson's syndrome (such as progressive supranuclear palsy or multiple system atrophy) from PD include impaired downward gaze, little or no response to levodopa, early hallucinations, early dementia, and falls early in the course, as well as symmetric onset and absence of tremor.

► **Alzheimer's disease presenting as Parkinsonism.** "The physical symptoms of Parkinsonism, such as lack of balance, may bring the patient to your office, but if it is accompanied by dementia, it is probably Parkinsonism rather than clinical PD," Dr. Reich said.

► **Parkinsonism of "normal aging."** PD tends to peak at about 60 years of age, so be cautious about diagnosing it after age 75 years, he said.

The last four pitfalls of PD diagnoses are false negatives:

► **Sensory or pain presentation of PD.** Dr. Reich said he often sees patients who have recovered from a frozen shoulder, for example, but they still have trouble moving one hand. Foot pain, particularly in young-onset PD patients, as well as tingling or numbness, fibromyalgia, or restless legs syndrome, can be symptoms of PD.

► **Young-onset PD.** PD is often not recognized in patients in their 30s and 40s. "You can be too old for PD but not too young," Dr. Reich said. "It is uncommon, but it is out there," he said.

► **Unilateral lower extremity presentation.** "When a patient presents with one lower-extremity symptom, even if he or she complains of pain or weakness, don't discount PD," Dr. Reich said.

► **Atremulous PD.** Patients with atremulous PD are most often misdiagnosed with stroke, but the fact that only half the body is affected by stiffness or balance problems is a tip-off that the problem might be PD instead, Dr. Reich said. ■