

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:** hyposthesia, 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. **Hematologic:** 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, hypertension, 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
<b>BODY AS A WHOLE</b>					
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
<b>DIGESTIVE SYSTEM</b>					
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
<b>RESPIRATORY SYSTEM</b>					
Sinusitis	2.6	2.8	0.0	2.5	6.4
Pharyngitis	1.5	2.5	0.0	1.3	2.1
<b>SKIN AND APPENDAGES</b>					
Rash	0.7	3.9	2.8	3.8	1.1
<b>MUSCULOSKELETAL SYSTEM</b>					
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, myositis, tendon 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:** Echinomiasis, 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<sup>2</sup> 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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# Endocrine Society Urges Caution With Androgen

BY CHRISTINE KILGORE

Contributing Writer

The Endocrine Society is sounding a strong word of caution on the topic of androgen therapy with a new clinical practice guideline that recommends against diagnosing and treating androgen deficiency in women.

The guideline, published in the October issue of the *Journal of Clinical Endocrinology and Metabolism*, cites the "lack of a well-defined clinical syndrome" and the "lack of normative data on total or free testosterone levels across the life span" as reasons why a diagnosis should not be made.

On the issue of treatment, the document acknowledges "evidence for short-term efficacy of testosterone in selected populations, such as surgically menopausal women," but says that inadequate indications and insufficient evidence of long-term safety means that the "generalized use of testosterone in women" cannot be recommended.

"Based on [our literature review], we felt that at this time, we could not, as a committee and a society, recommend either for making the diagnosis or for treatment," said Dr. Margaret E. Wierman, the endocrinologist who chaired the seven-member task force that developed the guidelines.

"The quality of the literature was just not up to a standard [needed] to make a global recommendation," said Dr. Wierman, who serves as chief of endocrinology at the Veterans Affairs Medical Center in Denver and professor of medicine, physiology, and biophysics at the University of Colorado, Denver. "The sort of hype that testosterone has been given is not yet based on a lot of scientific fact."

The guideline, which also details basic research that must be done and calls for the development of more sensitive and specific assays for testosterone and free testosterone in women, has a tone and reach that differs from the less conservative "androgen deficiency" section in the American Association of Clinical Endocrinologists' recently updated menopause guidelines.

As observers—and even Dr. Wierman—see it, the guideline is bound to intensify debate about an already controversial issue. And if Dr. André Guay is any indication, it is endocrinologists who specialize in sexual dysfunction who may take issue with the guidelines most passionately.

"This isn't a guideline at all," said Dr. Guay, director of the Center for Sexual Function at the Lahey Clinic in Peabody, Mass. "I was hoping they would say, 'we don't have all the answers, but here are the answers we do have, and here is the best we can do,' just as we say with men—that I'll buy."

"But there's nothing in here that shows you how to deal with the problem given the knowledge we currently have. ... It's a disservice," said Dr. Guay, who has argued for years in articles and at meetings that evidence supports off-label androgen therapy in women.

Not so, said Dr. Neil Goodman, professor of medicine at the University of Miami. The guideline is "excellently done" by "leading people in the field," he said. "They went through the literature systematically and documented levels of evidence ... and they do point out the one area where there is good positive data—in the surgically menopausal group."

"I see it as a request for action," said Dr. Goodman, also a private-practice endocrinologist specializing in reproductive medicine. "It's a plea for better work to be done."

The guideline recommends that researchers use particular "human model systems" to study the benefits and risks of androgen therapy (for instance, it says that women with hypopituitarism can be used to study the physiological replacement of ovarian and adrenal androgen precursors).

It also recommends that particular end points—from appearance of or change in hirsutism to effects in the breast and alterations in the endometrium with and without estrogen coadministration—be considered in safety and risk assessments of androgen administration (*J. Clin. Endocrinol. Metab.* 2006;91:3697-710).

Dr. Wierman said she also hopes that the new guideline—as well as a document to be released by the Endocrine Society in the next 18-24 months on problems with sex steroid assays for both men and women—will drive development of more sensitive and specific assays. "I think the assay issue will soon be improved," she said.

Physicians also must appreciate the fact that the findings on estrogen from the Women's Health Initiative had some impact on the task force, Dr. Wierman said.

"At this point, we felt that the Endocrine Society needs to act as the word of caution so we're not coming back 5 years from now and saying, 'Why weren't we cautious? Why didn't we push our colleagues across academia to do the studies to better understand [androgens], so that patients will benefit and won't be harmed?'" she said.

Dr. Steven Petak, president of the American Association of Clinical Endocrinologists (AACE), said his organization took a different approach last year as they addressed the issue of androgen therapy when updating their menopause guidelines.

"We also were quite cautious, and we agree that long-term safety issues need to be clarified," he said. "But we still went on and stated that there are some criteria for diagnosis, and we gave some recommendations [for use of androgen]."

The Endocrine Society's guidelines "don't do much for patients whose therapies are being considered now," said Dr. Petak of the Texas Institute for Reproduction and Endocrinology. "The Endocrine Society's recommendations for further basic and clinical research in the field are of prime importance and we agree wholeheartedly."

Dr. Goodman cautioned against comparing the guidelines of the two organizations. "The Endocrine Society is looking at the entire, broader issue. They take a more universal kind of approach," he said. ■