| 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/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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# Screen Obese, Diabetic Women for Incontinence

BY MIRIAM E. TUCKER
*Senior Writer*

WASHINGTON — Obese female patients should be screened for urinary incontinence, particularly if they have diabetes, Jean M. Lawrence, Sc.D., reported in a poster at the annual scientific sessions of the American Diabetes Association.

A community-based survey of 4,237 women aged 25-84 years revealed significantly increased rates of three major forms of incontinence among women who were obese and had diabetes, reported Dr. Lawrence, of Kaiser Permanente Southern California, Pasadena, and her associates.

The women had a median age of 58 years. They were 60% white, 20% Hispanic, 10% black, 8% Asian, and 2% race unknown. Overall, 15% had stress urinary incontinence (SUI), 13% had overactive bladder (OAB), and 25% had anal incontinence (AI). In addition, 11% had diabetes, of whom 21% used insulin. The women with diabetes were older (64.6 years vs. 56.1 years), were more likely to be menopausal (85.8% vs. 64.4%), and to be obese (54.9% vs. 23.8%).

Of the 472 women with diabetes, 23.2% had SUI, compared with 14.1% of the 3,765 women without diabetes. OAB was also significantly more common among those with diabetes (21.6% vs. 12.4%), as was AI (32.4% vs. 24.3%).

Women who were both obese and had diabetes had adjusted odds ratios of 3.2 for SUI, 3.1 for OAB, and 1.8 for AI, compared with women who did not have either condition. Women who were obese but did not have diabetes had the next highest risk, with odds ratios of 2.45 for SUI, 2.79 for OAB, and 1.45 for AI. Among the nonobese women with diabetes (both insulin users and nonusers), the only significantly elevated risk was for SUI, with an odds ratio of 1.55, Dr. Lawrence and her associates reported. ■

# *Oral Medications Stop Acute Nongestational Uterine Bleeding*

BY FRAN LOWRY
*Orlando Bureau*

WASHINGTON — Oral medroxyprogesterone acetate and oral contraceptives are equally effective in stopping nongestational acute uterine bleeding, according to a small randomized controlled trial presented at the annual meeting of the American College of Obstetricians and Gynecologists.

Cessation of bleeding occurred in 88% of the women randomized to oral contraceptives and in 76% of the women randomized to medroxyprogesterone. The mean time to cessation in the oral contraceptive group was 3.2 days vs. 3.8 days in the medroxyprogesterone group, reported Dr. Malcolm G. Munro, professor of obstetrics and gynecology at the University of California, Los Angeles, and chairman of the abnormal uterine bleeding working group for Kaiser Permanente, Southern California.

**Oral contraceptives are the most commonly used treatment in North America, but their efficacy has not been tested.**

**DR. MUNRO**

Women with nongestational acute uterine bleeding are seen frequently, and yet there has been a paucity of research on how best to treat them. Oral contraceptives are the most commonly used treatment in North America, but their efficacy for this indication has not been scientifically tested, Dr. Munro said.

Only two studies of acute uterine bleeding have been reported in the literature. The first, a study of unopposed estrogen given intravenously in 32 women, was published in the early 1980s, and the second, a study of medroxyprogesterone acetate in 24 women, was published in 1997.

In an open-label trial, Dr. Munro and his colleagues at Kaiser Permanente randomized 40 women with acute uterine bleeding, defined as excessively heavy or prolonged bleeding that was not related to pregnancy, to receive either medroxyprogesterone acetate, 20 mg three times a day for 7 days, followed by 20 mg a day for 3 weeks, or combination oral contraceptive treatment with norethindrone, 1 mg, and ethinyl estradiol, 35 mcg, in one tablet three times a day for 7 days, followed by one tablet a day for 3 weeks.

At the end of the study, 33 of the original 40 patients remained, and in these patients both treatments were "roughly equivalent" with respect to efficacy and time to bleeding cessation. Patient satisfaction in both groups was high. There was a trend toward more nausea in the oral contraceptive group, and this trend may have been significant if we had a larger sample size, Dr. Munro said.

One patient in the oral contraceptive group required an emergency procedure, compared with none in the medroxyprogesterone acetate group. "All of the women in the study had been bleeding for more than 10 days. They were the type of patient who is often taken to the operating room. At the very least, they needed emergent intervention, and only one required an emergent intervention in this study," he added. ■