

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:** hypoaesthesia, neuropathy peripheral, paresthesia, tremor, vertigo. **Gastrointestinal:** anorexia, constipation, dyspepsia, dysphagia, diarrhea, flatulence, pancreatitis, vomiting, agitation, 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, 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
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, hypertension. **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:** 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/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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Menopausal Change Linked To Depression Symptoms

BY MARY ANN MOON
Contributing Writer

The “changing hormonal milieu” of menopause is strongly associated with new-onset major depression as well as depressive symptoms in women with no history of mood disturbance, reported Ellen W. Freeman, Ph.D., of the departments of ob.gyn. and psychiatry at the University of Pennsylvania, Philadelphia, and her associates in the Penn Ovarian Aging Study.

Women are significantly more likely to develop a depressive disorder when their levels of estradiol fluctuate, levels of FSH and LH increase, and levels of inhibin B decrease, as happens during the transition to menopause. It appears that the hormonal changes characteristic of ovarian aging produce “destabilizing effects” that contribute to depression, the investigators said.



depressive disorders on two consecutive assessments and four had them on three or more consecutive assessments.

A total of 108 women (47%) showed no depressive symptoms on either measure, the researchers said (Arch. Gen. Psychiatry 2006;63:375-82).

Changes in individual women’s levels of FSH, LH, and inhibin B were significantly associated with depressive symptoms and with major depression.

Similarly, variability in a woman’s mean levels of estradiol, FSH, and LH also were linked to depression and depressive symptoms.

“On average, the women were 4.58 times more likely to have higher FSH levels ... 3 times more likely to have higher LH levels ... and 63% more likely to have lower inhibin B levels ... at the time of high [depression] scores” compared with the time before high scores, the investigators said.

After the data were adjusted for several other depression risk factors, including change in employment status or marital status, the researchers found that a woman was, on average, more than five times “more likely to be in menopausal transition at the time of reporting high [depression] scores than she was before the onset of depressive symptoms.”

The “strongest risk factor for the new onset of diagnosed depressive disorders was the increased variability of estradiol (around the woman’s own mean levels) at the time of the diagnosed disorder,” Dr. Freeman and her associates said.

However, other health and demographic factors also significantly affected depression risk, “confirming ... the multifactorial nature of depressive symptoms.” These factors included hot flashes, body mass index, smoking status, and the presence or absence of PMS.

The researchers also observed that onsets of both major depression and depressive symptoms were more common in the earlier years of their study, raising the question of “whether [depressed] women entered the menopausal transition at an earlier age.” The study couldn’t answer that question because it was “designed to examine all women starting at a similar premenopausal baseline,” they noted. ■

VERBATIM

“The very low RDA for vitamin D is the main problem regarding issues of vitamin D and health.”

Dr. Edward Giovannucci, p. 24

This finding should make a substantial contribution to what has been only “limited evidence” in the literature about mood symptoms in the perimenopausal years. “Whether mood symptoms increase in the perimenopausal years and whether the occurrence of depressed mood is independently associated with ovarian changes or is secondary to vasomotor or other bothersome symptoms” has been controversial, they noted.

Dr. Freeman and her associates examined the issue by assessing fluctuations in reproductive hormone levels in 231 premenopausal women aged 35-47 years at baseline who were followed for 8 years. During that interval, 43% of the women entered the transition to menopause.

Hormone assays were conducted in 10 assessment periods, the first 6 at 8-month intervals. Blood samples were collected at the start of menstrual cycles, and subjects also were interviewed concerning their overall health, demographic factors, and menopausal symptoms.

Depressive symptoms were assessed using the CES-D (Center for Epidemiological Studies–Depression) scale; either the PRIME-MD (Primary Care Evaluation of Mental Disorders) or the PHQ (Patient Health Questionnaire) was used to detect major depressive disorder.

A total of 116 women (50%) was found to have depressive symptoms on the CES-D during follow-up.

Of these, 16 women had depressive symptoms on two consecutive assessments and 35 had them on three or more consecutive assessments.

Of the 231 women, 59 (26%) were found to have depressive disorders on the PRIME-MD or PHQ; 26 had major depressive disorder and 33 had other depressive disorders. Nine of the women had