

irregularity, extrasystoles, skin discoloration, urticaria, skin dryness, alopecia, dermatitis, muscle weakness, twitching, ataxia, hypertension, migraine, cold and clammy skin, apathy, agitation, anorexia, 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, urea 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 (% of Patients):** Adverse experiences reported in ≥2% of patients in placebo-controlled clinical studies of atorvastatin, regardless of causality assessment, are shown in Table 10.

Table 10. Adverse Events in Placebo-Controlled Studies (% of Patients)

Body System/ Adverse Event	Placebo N=270	10 mg N=863	atorvastatin 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

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, 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:** 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 CLINICAL PHARMACOLOGY, Clinical Studies section and PRECAUTIONS, Pediatric Use).

OVERDOSAGE: There is no information on overdose 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 nonresponsive; the third (105 mg) was hospitalized and had hypotension (90/50 mm Hg) 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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Rev 0 January 2004

St. John's Wort Equals Paroxetine in Study

BY NANCY WALSH

New York Bureau

EXETER, ENGLAND — A proprietary formulation of St. John's wort was equivalent in efficacy to paroxetine for moderate to severe depression in a prospective, randomized, multicenter study, Stephan Klement, M.D., reported at a symposium on alternative and complementary therapies sponsored by the universities of Exeter and Plymouth.

A group of 101 German patients whose Hamilton Rating Scale for Depression (HAM-D) scores exceeded 22 points were randomized to receive standardized hypericum extract WS 5570 (Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) in an initial daily dose of 900 mg/day, or paroxetine (Paxil) in an initial dose of 20 mg/day.

Patients whose initial response was insufficient could increase the dose of hypericum extract to 1,800 mg/day or of paroxetine to 40 mg/day. Response was considered to be a reduction of 50% or greater on the HAM-D, and remission was defined as a HAM-D end point total score below 10, said Dr. Klement of Schwabe Pharmaceuticals.

In a preplanned interim analysis at 6 weeks, response rates were 60% in the hypericum group and 63% in the paroxetine group, while remission rates were 46.6% with hypericum and 42.9% with paroxetine. The rates in the two groups were comparable, he said in a poster session.

Adverse events when calculated as incidence densities were 0.039/day of exposure for hypericum and 0.056/day of exposure for paroxetine. This represents a 43.6% advantage for hypericum based on ratio.

These findings differ from those seen in another randomized trial that compared a different extract of St. John's wort (LI 160, Lichtwer Pharma, Berlin) with sertraline and placebo. In that study, performed in the United States by the Hypericum Depression Trial Study Group, neither sertraline nor the hypericum extract was sig-

nificantly different from placebo in a group of 340 patients with major depression (JAMA 2002;287:1807-14).

"The major differences between the two trials can be attributed to different patient populations and the missing assay sensitivity in the [JAMA] trial," Dr. Klement told FAMILY PRACTICE NEWS.

Patients in the American trials were recruited from tertiary care clinics, and patients who had not responded to adequate trials of two antidepressant trials were included. The depressive episode had already persisted for more than 2 years in roughly one-third of patients, and for between 6 months and 2 years in a further third. This suggests that many of the patients were chronically depressed and some may have been treatment resistant, Dr. Klement said.

In the German study, patients were limited to only one previous adequate antidepressant therapy trial, "probably limiting the number of treatment-resistant patients," he said. The mean duration of the current depressive episode was significantly shorter in the German trial, suggesting that fewer patients were chronically depressed, and patients had sought care spontaneously in primary or secondary care settings.

The major drawback of the American study was its lack of assay sensitivity, Dr. Klement said. "Sertraline, a proven synthetic antidepressant, served as a positive control to check the sensitivity of the study. Neither St. John's wort extract nor sertraline differed significantly from placebo in the primary target criteria, which were reduction of the Hamilton depression total score and the number of patients showing complete remission."

The trial therefore did not have the assay sensitivity to document an antidepressant drug effect and thus does not appear to be useful for estimating the therapeutic potential of either St. John's wort or sertraline, he said, adding that in the German study, "no placebo group was included as it would have been unethical to give placebo to patients suffering from severe depression."

Expert Commentary

FAMILY PRACTICE NEWS asked David Spiegel, M.D., to comment on the new hypericum trial.

Dr. Spiegel, the Jack, Lulu, and Sam Willson Professor in the School of Medicine and associate chair of psychiatry and behavioral sciences, Stanford (Calif.) University, had this to say:

"This is an interesting study, well conducted but with the obvious drawbacks that it has no placebo control group. Also, it is always harder to prove statistically the absence of a difference (between hypericum and paroxetine) than the presence of a difference.

"The author is right that the JAMA study suffered because placebo pa-

tients actually did slightly better than those randomized to either hypericum or sertraline. Unfortunately, they used rather low doses of sertraline (50 or 100 mg) when one can prescribe up to 200 mg. Thus, neither treated group did especially well. They might have been treatment resistant, as the author suggests.

"This new study does provide suggestive, but not definitive, evidence that hypericum works as well for mild to moderate depression as paroxetine, but it does not rule out the possibility that this group of patients had transient depressive symptoms that are really responding to a placebo effect or the passage of time."