

Atomoxetine Improves ADHD, Anxiety Disorder

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WASHINGTON — The attention-deficit hyperactivity drug atomoxetine does not appear to improve comorbid depression in adolescents, but it does appear to reduce comorbid anxiety in children and adolescents, according to data from two studies presented at the annual meeting of the Pediatric Academic Societies.

Both trials were sponsored by Eli Lilly

& Co., maker of atomoxetine (Strattera).

In the first study, patients aged 8-17 years, who met the DSM-IV diagnostic criteria for both attention-deficit hyperactivity disorder (ADHD) and anxiety disorder (generalized anxiety, separation anxiety, or social phobia disorder), were randomized to receive either atomoxetine (87 patients) or placebo (89 patients) in a 12-week trial.

The mean age of the patients was roughly 12 years, and boys outnumbered girls 3-1. The target dose of atomoxetine

was 1.2 mg/kg per day (split and given twice a day), said Calvin Sumner, M.D., of Eli Lilly.

ADHD symptoms were assessed using the ADHD Rating Scale (ADHDRS). The Pediatric Anxiety Rating Scale total score and the Multidimensional Anxiety Scale for Children (which allows children to rate their own anxiety) were used to assess anxiety symptoms. The last observations were carried forward.

As a way to minimize any placebo effect,

those randomized to receive atomoxetine actually received placebo for the first 2 weeks of the trial. Any patients who had a 25% reduction in anxiety score during that period were allowed to finish the trial but not included in the final analysis.

For the analysis that excluded patients with less than 25% improvement in anxiety during the first 2 weeks of the trial, those on atomoxetine (55 patients) had a significant improvement in ADHD scores from baseline to the end point, compared with those on placebo (58 patients). When all patients were considered, there was a significant improvement in ADHD scores for patients on atomoxetine, compared with those on placebo.

In the smaller analysis, there also was a significant improvement in anxiety scores for those on atomoxetine, compared with those on placebo. Among all patients, a significant improvement in anxiety scores was seen for those on atomoxetine, compared with those on placebo.

Decreased appetite was the only adverse event that occurred more frequently in the atomoxetine group.

In the second trial, adolescents had to meet the clinical definition of both ADHD and major depressive disorder. “These were kids who really had major depression,” Dr. Sumner said.

The patients, aged 12-18 years, were randomized to receive 9 weeks of treatment with atomoxetine (72 patients) or placebo (70 patients). Boys outnumbered girls 3-1. The target atomoxetine dose was 1.2 mg/kg each day, though patients could go up to a dose of 1.8 mg/kg each day. Both placebo and atomoxetine were given once a day.

The response of ADHD symptoms was measured using the 18-question ADHDRS. Depressive symptoms were measured using the Children’s Depression Rating Scale. Patients were assessed using the Young Mania Rating Scale, as a way of determining whether the depression experienced by these adolescents was a heralding event for bipolar disorder or true depression.

The ADHD and depression scores at 9 weeks were analyzed as change from baseline, with last observation carried forward. Treatment emergent mania was described as a patient who started with a score of less than 15 on the mania scale, and at the end point the score was 15 or greater.

“Atomoxetine really helped depression. There was a considerable reduction in the depressive rating scales. The other side of the story is, so did placebo,” Dr. Sumner said. Placebo showed a very strong effect on depressive symptoms that was independent of its effect on ADHD.

“So this was inconclusive. There was no evidence—that was separable from placebo—that atomoxetine had any benefit in reducing depressive symptoms,” he said.

Two patients in each group had treatment emergent mania, a result that was not interpretable. In terms of adverse events, nausea and decreased appetite were more common in the atomoxetine group. Importantly, there were no adverse events involving suicidal ideation or suicidal behavior in either group.

References: 1. Data on file. Pfizer Inc., New York, NY. 2. IMS Health Inc; May 2004.

LIPITOR® (Atorvastatin Calcium) Tablets
Brief Summary of Prescribing Information
CONTRAINDICATIONS: Active liver disease or unexplained persistent elevations of serum transaminases. Hypersensitivity to any component of this medication. **Pregnancy and Lactation** — Atherosclerosis is a chronic process and discontinuation of lipid-lowering drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia. Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). Since HMG-CoA reductase inhibitors decrease cholesterol synthesis and possibly the synthesis of other biologically active substances derived from cholesterol, they may cause fetal harm when administered to pregnant women. Therefore, HMG-CoA reductase inhibitors are contraindicated during pregnancy and in nursing mothers. **ATORVASTATIN SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS.** If the patient becomes pregnant while taking this drug, therapy should be discontinued and the patient apprised of the potential hazard to the fetus.
WARNINGS: Liver Dysfunction — HMG-CoA reductase inhibitors, like some other lipid-lowering therapies, have been associated with biochemical abnormalities of liver function. **Persistent elevations (>3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.** One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated with jaundice or other clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels returned to or near pretreatment levels without sequelae. Eighteen of 30 patients with persistent LFT elevations continued treatment with a reduced dose of atorvastatin. **It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of therapy and any elevation of dose, and periodically (eg, semiannually) thereafter.** Liver enzyme changes generally occur in the first 3 months of treatment with atorvastatin. Patients who develop increased transaminase levels should be monitored until the abnormalities resolve. Should an increase in ALT or AST of >3 times ULN persist, reduction of dose or withdrawal of atorvastatin is recommended. Atorvastatin should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to the use of atorvastatin (see CONTRAINDICATIONS). **Skeletal Muscle** — **Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin and with other drugs in this class.** Uncomplicated myalgia has been reported in atorvastatin-treated patients (see ADVERSE REACTIONS). Myopathy, defined as muscle aches or muscle weakness in conjunction with increases in creatine phosphokinase (CPK) values >10 times ULN, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report promptly unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever. Atorvastatin therapy should be discontinued if markedly elevated CPK levels occur or myopathy is diagnosed or suspected. The risk of myopathy during treatment with drugs in this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, erythromycin, niacin, or azole antifungals. Physicians considering combined therapy with atorvastatin and fibric acid derivatives, erythromycin, immunosuppressive drugs, azole antifungals, or lipid-lowering doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tenderness, or weakness, particularly during the initial months of therapy and during any periods of upward dosage titration of either drug. Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but there is no assurance that such monitoring will prevent the occurrence of severe myopathy. **Atorvastatin therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (eg, severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).**
PRECAUTIONS: General — Before instituting therapy with atorvastatin, an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, and weight reduction in obese patients, and to treat other underlying medical problems (see INDICATIONS AND USAGE in full prescribing information). **Information for Patients** — Patients should be advised to report promptly unexplained muscle pain, tenderness, or weakness, particularly if accompanied by malaise or fever. **Drug Interactions** — The risk of myopathy during treatment with drugs of this class is increased with concurrent administration of cyclosporine, fibric acid derivatives, niacin (nicotinic acid), erythromycin, azole antifungals (see WARNINGS, **Skeletal Muscle**). **Antacid:** When atorvastatin and Maalox® TC suspension were coadministered, plasma concentrations of atorvastatin decreased approximately 35%. However, LDL-C reduction was not altered. **Antipyrine:** Because atorvastatin does not affect the pharmacokinetics of antipyrine, interactions with other drugs metabolized via the same cytochrome isozymes are not expected. **Colestipol:** Plasma concentrations of atorvastatin decreased approximately 25% when colestipol and atorvastatin were coadministered. However, LDL-C reduction was greater when atorvastatin and colestipol were coadministered than when either drug was given alone. **Cimetidine:** Atorvastatin plasma concentrations and LDL-C reduction were not altered by coadministration of cimetidine. **Digoxin:** When multiple doses of atorvastatin and digoxin were coadministered, steady-state plasma digoxin concentrations increased by approximately 20%. Patients taking digoxin should be monitored appropriately. **Erythromycin:** In healthy individuals, plasma concentrations of atorvastatin increased approximately 40% with coadministration of atorvastatin and erythromycin, a known inhibitor of cytochrome P450 3A4 (see WARNINGS, **Skeletal Muscle**). **Oral Contraceptives:** Coadministration of atorvastatin and an oral contraceptive increased AUC values for norethindrone and ethinyl estradiol by approximately 30% and 20%. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin. **Warfarin:** Atorvastatin did not significantly alter prothrombin time when administered to patients receiving chronic warfarin treatment. **Endocrine Function** — HMG-CoA reductase inhibitors interfere with cholesterol synthesis and theoretically might blunt adrenal and/or gonadal steroid production. Clinical studies have shown that atorvastatin does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if an HMG-CoA reductase inhibitor is administered concomitantly with drugs that may decrease the levels or activity of endogenous steroid hormones, such as ketoconazole, spironolactone, and cimetidine. **CNS Toxicity** — Brain hemorrhage was seen in a female dog treated for 3 months at 120 mg/kg/day. Brain hemorrhage and optic nerve vacuolation were seen in another female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure approximately 16 times the human plasma area-under-the-curve (AUC, 0-24 hours) based on the maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after chronic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) the human AUC (0-24) based on the maximum recommended human dose of 80 mg/day. CNS vascular lesions, characterized by perivascular hemorrhages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with other members of this class. A chemically similar drug in this class produced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose that produced plasma drug levels about 30 times higher than the mean drug level in humans taking the highest recommended dose. **Carcinogenesis, Mutagenesis, Impairment of Fertility** — In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, there was a rhabdomyosarcoma and, in another, there was a fibrosarcoma. This dose represents a plasma AUC (0-24) value of approximately 16 times the mean human plasma drug exposure after an 80 mg oral dose. A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0-24) values of approximately 6 times the mean human plasma drug exposure after an 80 mg oral dose. **In vitro**, atorvastatin was not mutagenic or clastogenic in the following tests with and without metabolic activation: the Ames test with *Salmonella typhimurium* and *Escherichia coli*; the HGPRT forward mutation assay in Chinese hamster lung cells, and the chromosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in the *in vivo* mouse micronucleus test. Studies in rats performed at doses up to 175 mg/kg (15 times the human exposure) produced no changes in fertility. There was oligospermia and aspermia in the epididymis of 2 of 10 rats treated with 100 mg/kg/day of atorvastatin for 3 months (16 times the human AUC at the 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or reproductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years. **Pregnancy — Pregnancy Category X: See CONTRAINDICATIONS.** Safety in pregnant women has not been established. Atorvastatin crosses the rat placenta and reaches a level in fetal liver equivalent to that of maternal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) the human exposure based on surface area (mg/m²). In a study in rats given 20, 100, or 225 mg/kg/day, from gestation day 7 through to lactation day 21 (weaning), there was decreased pup survival at birth, neonate, weaning, and maturity in pups of mothers dosed with 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mothers dosed at 100 mg/kg/day; pup body weight was decreased at birth and at days 4, 21, and 91 at 225 mg/kg/day. Pup

development was delayed (rotorod performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) the human AUC at 80 mg/day. Rare reports of congenital anomalies have been received following intrauterine exposure to HMGC-CoA reductase inhibitors. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (VATER association) in a baby born to a woman who took lovastatin with dextroamphetamine sulfate during the first trimester of pregnancy. **LIPITOR** should be administered to women of child-bearing potential only when such patients are highly unlikely to conceive and have been informed of the potential hazards. If the woman becomes pregnant while taking **LIPITOR**, it should be discontinued and the patient advised again as to the potential hazards to the fetus. **Nursing Mothers** — Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of that in their mother's milk. Because of the potential for adverse reactions in nursing infants, women taking **LIPITOR** should not breast-feed (see CONTRAINDICATIONS). **Pediatric Use** — Safety and effectiveness in patients 10-17 years of age with heterozygous familial hypercholesterolemia have been evaluated in a controlled clinical trial of 6 months duration in adolescent boys and postmenarcheal girls. Patients treated with **LIPITOR** had an adverse experience profile generally similar to that of patients treated with placebo, the most common adverse experiences observed in both groups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In this limited controlled study, there was no detectable effect on growth or sexual maturation in boys or on menstrual cycle length in girls (see CLINICAL PHARMACOLOGY, *Clinical Studies* section in full prescribing information). **ADVERSE REACTIONS**, Pediatric Patients (ages 10-17 years); and **DOSAGE AND ADMINISTRATION**, *Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10-17 years of age)* in full prescribing information. Adolescent females should be counseled on appropriate contraceptive methods while on **LIPITOR** therapy (see CONTRAINDICATIONS and PRECAUTIONS, *Pregnancy*). **LIPITOR has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.** Clinical efficacy with doses up to 80 mg/day for 1 year have been evaluated in an uncontrolled study of patients with homozygous FH including 8 pediatric patients (see CLINICAL PHARMACOLOGY, *Clinical Studies: Homozygous Familial Hypercholesterolemia* in full prescribing information). **Geriatric Use** — The safety and efficacy of atorvastatin (10-80 mg) in the geriatric population (>65 years of age) was evaluated in the ACCESS study. In this 54-week open-label trial, 1,958 patients initiated therapy with atorvastatin 10 mg. Of these, 835 were elderly (>65 years) and 1,123 were non-elderly. The mean change in LDL-C from baseline after 6 weeks of treatment with atorvastatin 10 mg was -38.2% in the elderly patients versus -34.6% in the non-elderly group. The rates of discontinuation due to adverse events were similar between the two age groups. There were no differences in clinically relevant laboratory abnormalities between the age groups.

ADVERSE REACTIONS: **LIPITOR** 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. The most frequent adverse events thought to be related to atorvastatin 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 the following table.

Adverse Events in Placebo-Controlled Studies (% of Patients)					
BODY SYSTEM	Placebo	Atorvastatin	Atorvastatin	Atorvastatin	Atorvastatin
Adverse Event	N = 270	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 (see CLINICAL PHARMACOLOGY, *Clinical Studies* in full prescribing information) involving 10,305 participants treated with **LIPITOR** 10 mg daily (n=5,168) or placebo (n=5,137), the safety and tolerability profile of the group treated with **LIPITOR** 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, chelitis, 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** — Adverse events associated with **LIPITOR** 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 **LIPITOR** 10 to 20 mg daily was generally similar to that of placebo (see CLINICAL PHARMACOLOGY, *Clinical Studies* section in full prescribing information and PRECAUTIONS, *Pediatric Use*).

OVERDOSAGE: 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.

Please see full prescribing information for additional information about LIPITOR.

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