

Screen ADHD Patients First, Heart Group Says

BY DAMIAN McNAMARA
Miami Bureau

The new recommendation calling for electrocardiogram screening for children with attention-deficit/hyperactivity disorder before initiating pharmacologic treatment is not based on data, according to an expert in child and adolescent psychiatry.

Dr. David Fassler said that at this point, there is no evidence that such screening

would enhance safety or reduce the risk of rare but potentially serious heart-related problems.

"The best advice is for parents to talk to their child's doctor," Dr. Fassler, clinical professor of psychiatry at the University of Vermont, Burlington, said when asked about the recommendations. "They can then decide together what, if any, additional evaluation may be warranted."

Under the recommendations, issued in April by the American Heart Association, if patient history, family history, clinical examination, and/or ECG results suggest a higher risk, a referral to a pediatric cardiologist is warranted.

For patients currently taking methylphenidate, amphetamine, or another treatment for ADHD, a comprehensive assessment of cardiac risk is reasonable if deemed necessary, according to the AHA scientific statement published in *Circulation*, available at circ.ahajournals.org (Circulation 2008 April 21 [doi:10.1161/circulation.aha.107.189473]).

The AHA recommendations, offered by Dr. Victoria L. Vetter of the Children's Hospital of Philadelphia and her colleagues, say it is important to pay particular attention to symptoms such as palpitations, near syncope, or syncope that might indicate a cardiac condition.

Consider all other medications taken by a pediatric patient, including over-the-counter agents, according to the recommendations, titled "Cardiovascular Monitoring of Children and Adolescents With Heart Disease Receiving Stimulant Drugs."

Cardiac risk assessment of all children before prescribing ADHD medications, ongoing monitoring, and specific guidelines for children with known structural heart disease or other heart conditions are outlined in the statement.

In 1999, the AHA addressed concerns about potential adverse cardiac effects of psychotropic medications in children, but made no specific recommendations about stimulants. However, "since that time, a constellation of circumstances has come together, necessitating a second look at this complicated issue," the authors of the current statement wrote.

The authors note that ADHD might be more prevalent among children with heart

disease than the estimated 4%-16% of the general population. One study, for example, indicated that 45% of children with heart disease had abnormal attention scores and 39% had abnormal hyperactivity scores (*Pediatrics* 2000;105:1082-9).

The recommendation for selective ECG screening is new. The writing group suggested the testing will increase the likelihood of identifying significant cardiac conditions such as hypertrophic cardiomyopathy, long QT syndrome, and Wolff-Parkinson-White syndrome that might place the child at risk.

"We recognize that the ECG cannot identify all children with these conditions but will increase the probability," wrote Dr. Vetter and the six other experts on the American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Young and the Council on Cardiovascular Nursing.

"The use of selective ECG screening in this population is thought to be medically indicated and of reasonable cost." Dr. Vetter, the majority of writing group members, and the four physician reviewers had no relevant financial disclosures.

A physician familiar with interpretation of pediatric ECG should assess results, according to the recommendations. A repeat ECG might be useful after initiation of ADHD medication if there is a change in relevant family history or, if the first ECG was performed before the age of 12, after the child turns 12 years old.

Initial assessment of a child with ADHD should include personal history of fainting or dizziness, particularly with exercise; seizures; rheumatic fever; chest pain or shortness of breath with exercise; an unexplained, noticeable change in exercise tolerance; palpitations, increased heart rate, or extra/skipped heartbeats; history of hypertension; and other factors.

Relevant family history includes sudden or unexplained death of someone young, sudden cardiac death or myocardial infarction before age 35 years, sudden death

during exercise, and cardiac arrhythmias.

During physical examination, assess the child for an abnormal heart murmur and other cardiovascular abnormalities, including hypertension. It also is important to assess the child for irregular or rapid heart rhythm, as well as findings suggestive of Marfan syndrome.

Refer any patient with significant findings to a pediatric cardiologist for further evaluation, because a routine physician examination might miss some conditions associated with sudden cardiac death, the authors recommended. Pediatricians should perform ongoing assessment of patients identified at risk at each subsequent visit, according to the guidelines. A physical examination including blood pressure and pulse assessment is suggested. "There are no clinical studies or data indicating that children with most types of congenital heart disease are at significant risk for sudden cardiac death while on these [ADHD] medications," the authors wrote. Nevertheless, the authors addressed cardiovascular monitoring of children with known structural heart disease or other heart conditions.

"It is reasonable to consider the use of stimulant medication in patients with congenital heart disease that is not repaired or repaired but without current hemodynamic or arrhythmic concerns or congenital heart disease that is considered to be stable by the patient's pediatric cardiologist unless the patient's pediatric cardiologist has specific concerns."

Dr. Fassler thinks that more large-scale, long-term research on stimulants and other medications used to treat child and adolescent psychiatric disorders are needed. "Such studies will ultimately help us determine who is most likely to respond to specific interventions, and if there are particular groups of kids who may be at increased risk for certain side effects," he said. Future studies are warranted, the authors wrote, to assess the true risk of sudden cardiac death associated with use of stimulant drugs in children and adolescents with and without heart disease. ■

Atomoxetine Not Effective for ADHD/ODD

Atomoxetine had no enduring effect on oppositional defiant disorder symptoms in a new report of manufacturer data from children with both ODD and attention-deficit/hyperactivity disorder.

The findings from the 8-week, multicenter, placebo-controlled trial run counter to the results of a previous study that suggested atomoxetine (Strattera) could improve symptoms in patients with both disorders. Atomoxetine, a norepinephrine reuptake inhibitor, was approved in 2002 as the first nonstimulant medication for attention-deficit/hyperactivity disorder (ADHD). ODD is thought to be present in 40%-60% of children with ADHD.

In the study, 156 children with both disorders received 1.2 mg/kg per day of atomoxetine for 8 weeks, and 70 received placebo. The subjects, aged 6-12 years, came from 17 centers in Europe. Improvement was measured on the Swanson, Nolan, and Pelham Rating Scale-Revised, which has 18 items used to grade ADHD symptoms and 8 used to grade ODD symptoms.

ADHD symptoms were significantly improved on the rating scale, but ODD symptoms were no better at week 8. Although those given the active treatment had improved ratings relative to placebo-treated children at weeks 2 and 5 of the trial, "it remains uncertain whether atom-

oxetine exerts a specific and enduring effect on ODD symptoms," said Dr. Mark E. Bangs of Lilly Research Laboratories, Indianapolis, and his colleagues in the Atomoxetine ADHD/ODD Study Group (*Pediatrics* 2008;121:e314-20).

"Patients with ADHD and ODD will not be disadvantaged by treatment with atomoxetine, but additional pharmacologic or psychological strategies may be needed to address the ODD symptoms, they said. Dr. Bangs and several of his coinvestigators are employees and shareholders of Eli Lilly & Co., which funded the study and manufactures Strattera.

—Timothy F. Kirm

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(3% and <1%), Anorgasmia (2% and <1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed injury, anxiety. †Denominator used was for males only (N=225 Lexapro; N=188 placebo). ‡Denominator used was for females only (N=490 Lexapro; N=404 placebo). Generalized Anxiety Disorder Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients. The most commonly observed adverse events in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia (see TABLE 3). TABLE 3: Treatment-Emergent Adverse Events: Incidence in Placebo-Controlled Clinical Trials for Generalized Anxiety Disorder* (Lexapro (N=429) and Placebo (N=427)).

Autonomic Nervous System Disorders: Dry Mouth (9% and 5%); Sweating Increased (4% and 1%); Central & Peripheral Nervous System Disorders: Headache (24% and 17%); Paresthesia (2% and 1%); Gastrointestinal Disorders: Nausea (18% and 8%); Diarrhea (8% and 6%); Constipation (5% and 4%); Indigestion (3% and 2%); Vomiting (3% and 1%); Abdominal Pain (2% and 1%); Flatulence (2% and 1%); Toothache (2% and 0%). General: Fatigue (8% and 2%); Influenza-like symptoms (5% and 4%); Musculoskeletal: Neck/Shoulder Pain (3% and 1%). Psychiatric Disorders: Somnolence (13% and 7%); Decreased Libido (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (2% and 1%); Lethargy (3% and 1%); Yawning (2% and 1%). Urogenital: Ejaculation Disorder[†] (14% and 2%); Anorgasmia[‡] (6% and <1%); Menstrual Disorder (2% and 1%). *Events reported by at least 2% of patients treated with Lexapro are reported, except for the following events which had an incidence on placebo \geq Lexapro: inflamed injury, dizziness, back pain, upper respiratory tract infection, rhinitis, pharyngitis. †Primarily ejaculatory delay. ‡Denominator used was for males only (N=182 Lexapro; N=195 placebo). †Denominator used was for females only (N=470 Lexapro; N=232 placebo). Dose Dependency of Adverse Events: The potential dose dependency of common adverse events (defined as an incidence rate of \geq 25% in either the 10 mg or 20 mg Lexapro groups) on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse events that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group. TABLE 4: Incidence of Common Adverse Events* in Patients with Major Depressive Disorder Receiving Placebo (N=311), 10 mg/day Lexapro (N=310), 20 mg/day Lexapro (N=312); Insomnia (4%, 7%, 14%); Diarrhea (5%, 6%, 14%); Dry Mouth (3%, 4%, 9%); Somnolence (1%, 4%, 9%); Dizziness (2%, 4%, 7%); Sweating Increased (<1%, 3%, 8%); Constipation (1%, 3%, 6%); Fatigue (2%, 2%, 2%); Indigestion (1%, 2%, 6%). *Adverse events with an incidence rate of at least 5% in either of the Lexapro groups and with an incidence rate in the 20 mg/day Lexapro group that was approximately twice that of the 10 mg/day Lexapro group and the placebo group. Male and Female Sexual Dysfunction with SSRIs: Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can potentially cause sexual dysfunction. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence. Table 5 shows the incidence rates of sexual side effects in patients with major depressive disorder and GAD in placebo-controlled trials. TABLE 5: Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials (In Males Only: Lexapro (N=407) and Placebo (N=383)); Ejaculation Disorder (primarily ejaculatory delay) (12% and 1%); Libido Decreased (6% and 2%); Impotence (2% and <1%). In Females Only: Lexapro (N=737) and Placebo (N=636)); Libido Decreased (3% and 1%); Anorgasmia (1% and <1%). There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligis has been reported with all SSRIs.

While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. Vital Sign Changes: Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. Weight Changes: Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. Laboratory Changes: Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. ECG Changes: Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=327) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. Other Events Observed During the Premarketing Evaluation of Lexapro: Following is a list of WHO terms that reflect treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. All reported events are included except those already listed in Tables 2 & 3, those occurring in only one patient, event terms that are so general as to be uninformative, and those that are unlikely to be drug related. It is important to emphasize that although the events reported occurred during treatment with Lexapro, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on one or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in less than 1/100 patients but at least 1/1000 patients; Cardiovascular - Frequent: palpitation, hypertension, infrequent: bradycardia, tachycardia, ECG abnormal, flushing, varicose vein. Central and Peripheral Nervous System Disorders - Frequent: light-headed feeling, migraine, infrequent: tremor, vertigo, restless legs, shaking, twitching, dysequilibrium, tics, carpal tunnel syndrome, muscle contractions involuntary, sluggishness, coordination abnormal, faintness, hyperreflexia, muscular tone increased. Gastrointestinal Disorders - Frequent: heartburn, abdominal cramp, gastroenteritis. Infrequent: gastroesophageal reflux, bloating, abdominal discomfort, dyspepsia, increased stool frequency, belching, gastritis, hemorrhoids, gagging, polyposis gastric, swallowing difficult. General - Frequent: allergy, pain in limb, fever, hot flashes, chest pain. Infrequent: edema of extremities, chills, lightness of chest, leg pain, asthma, syncope, malaise, anaphylaxis, fall. Hemic and Lymphatic Disorders - Infrequent: bruise, anemia, nosebleed, hematoma, lymphadenopathy cervical. Metabolic and Nutritional Disorders - Frequent: increased weight. Infrequent: decreased weight, hyperglycemia, thirst, bilirubin increased, hepatic enzymes increased, gout, hypercholesterolemia. Musculoskeletal System Disorders - Frequent: arthralgia, myalgia. Infrequent: jaw stiffness, muscle cramp, muscle stiffness, arthritis, muscle weakness, back discomfort, arthropathy, jaw pain, joint stiffness. Psychiatric Disorders - Frequent: appetite increased, lethargy, irritability, concentration impaired. Infrequent: flatulence, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, anorexia, anxiety attack, bruxism, carbohydrate craving, confusion, depression/agitation, disorientation, emotional lability, feeling unreal, tremulousness nervous, crying abnormal, depression, excitability, auditory hallucination, suicidal tendency. Reproductive Disorders/Female* - Frequent: menstrual cramps, menstrual disorder. Infrequent: menorrhagia, breast neoplasm, pelvic inflammation, premenstrual syndrome, spotting between menses. *% based on female subjects only. N= 905 Respiratory System Disorders - Frequent: bronchitis, sinus congestion, coughing, nasal congestion, sinus headache. Infrequent: asthma, breath shortness, laryngitis, pneumonia, tracheitis. Skin and Appendages Disorders - Frequent: rash. Infrequent: pruritus, acne, alopecia, eczema, dermatitis, dry skin, folliculitis, impo, furunculosis, dry lips, skin nodule. Special Senses - Frequent: vision blurred, tinnitus. Infrequent: taste alteration, earache, conjunctivitis, vision abnormal, dry eyes, eye irritation, visual disturbance, eye infection, pupils dilated, metallic taste. Urinary System Disorders - Frequent: urinary frequency, urinary tract infection. Infrequent: urinary urgency, kidney stone, dysuria, blood in urine. Events Reported Subsequent to the Marketing of Escitalopram: Although no causal relationship to escitalopram treatment has been found, the following adverse events have been reported to have occurred in patients and to be temporally associated with escitalopram treatment during post marketing experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, alkalosis, allergic reaction, anger, angioedema, atrial fibrillation, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypospadias, hypoglycemia, hypokalemia, IRR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leukopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, procloniaemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, tonsils de pinnules, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

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