

Obstructive Apnea May Cause Cognitive Deficits

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FORT LAUDERDALE, FLA. — Although some children with sleep-disordered breathing experience significant cognitive deficits, not all do, and identification of those at risk remains a clinical challenge, according to a sleep medicine expert.

There is a wide range in individual susceptibility, Dr. David Gozal said. "A child can have a mild [sleep] disturbance and be af-

ected or have severe sleep apnea and be unaffected cognitively." Together with apnea severity and environmental factors, individual differences in susceptibility complete the triple-risk model of obstructive sleep apnea morbidity, said Dr. Gozal, professor and vice chair of research, department of pediatrics, University of Louisville (Ky.).

In general, increased apnea severity is associated with greater impairments in cognition. For example, Dr. Gozal and colleagues found significant neurocognitive

deficits with higher apnea/hypopnea index (AHI) scores in snoring children (J. Sleep Res. 2004;13:165-72).

With increases in AHI severity, a child's IQ can decrease, Dr. Gozal said at a pediatric pulmonology meeting sponsored by the American College of Chest Physicians. For children with an AHI of 5 or more, for example, there is average loss of 6-8 IQ points. "If you are born with an IQ of 100, that can be the difference between going to college or not."

At any AHI level in the study, however, there were children without any cognitive deficit, again pointing to the individual variability, said Dr. Gozal, who is also a respiratory/sleep physiologist in the division of sleep medicine at Kosair Children's Hospital Research Institute, also in Louisville.

Specifically, significantly higher impairments in phonological processing, visual and auditory attention, and social problems were found among children with an AHI greater than 5, compared with those scoring 5 or less. High scorers also had significantly worse thought problems, delinquent or oppositional behavior, aggressiveness, externalizing of problems, and deficits in verbal comprehension ability.

In another study of 297 poorly performing first graders, there was a 6- to 9-fold increase in sleep apnea, compared with the general population (Pediatrics 1998;102:616-20).

The good news is that apnea treatment reversed some learning deficits. Some parents thank Dr. Gozal for improvements in their children's ability to learn following adenotonsillectomy.

In terms of potential misdiagnosis, there is some overlap between children with attention-deficit/hyperactivity disorder (ADHD) symptoms and those with obstructive sleep apnea (OSA) who demonstrate intrinsic daytime sleepiness. These patients can benefit from stimulant treatment, Dr. Gozal said.

The diagnosis of sleep apnea may be completely overlooked, since these patients improve with stimulants, similarly to children with ADHD who also are intrinsically sleepy. However, children with a formal diagnosis of ADHD-inattentive type

who are not sleepy will be more likely to improve with addition of a norepinephrine reuptake inhibitor to treat their prefrontal cortex executive dysfunction, he said.

The way a child lives affects the way the sleep-disordered breathing affects them, Dr. Gozal said. "Physical activity is actually protective of our children when they have sleep apnea." For example, a walk in the park 30 minutes per day, 5 days a week, can prevent the onset of morbid consequences of apnea. In addition, higher home literacy levels are associated with a lesser likelihood of learning and behavioral deficits among children with sleep apnea, he said.

Given such individual variability in risk of adverse cognitive outcomes in these children, Dr. Gozal and his associates are searching for a prognostic marker. They found that elevated plasma C-reactive protein levels, an indicator of increased systemic inflammation, might indicate children with OSA are at greater neurocognitive risk (Am. J. Respir. Crit. Care Med. 2007;176:188-93).

They assessed 278 children and found high-sensitivity C-reactive protein (hsCRP) levels almost triple among children with cognitive deficits, compared with those without. Participants were 5- to 7-year-old children recruited from the community.

The mean hsCRP was 0.48 plus or minus 0.12 mg/dL in children with OSA and cognitive deficits, compared with 0.21 plus or minus 0.08 mg/dL in children with the condition and normal cognitive scores. This difference was statistically significant.

"We show in a community-based study of snoring and nonsnoring school-aged children, that children with OSA have increased levels of hsCRP and also exhibit decreased cognitive performances compared with control children," Dr. Gozal and his associates wrote. "Furthermore, hsCRP levels are significantly increased among patients with OSA and cognitive dysfunction, and this phenomenon persists even when after the severity of OSA is matched for the two cognitive function groups. Thus, hsCRP variation emerges as a predictive measure of risk for OSA-induced cognitive deficits in children." ■

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION

(5% and 4%); Fatigue (5% and 2%). **Psychiatric Disorders:** Insomnia (9% and 4%); Somnolence (6% and 2%); Appetite Decreased (3% and 1%); Libido Decreased (3% and 1%). **Respiratory System Disorders:** Rhinitis (5% and 4%); Sinusitis (3% and 2%). **Urogenital:** Ejaculation Disorder* (9% and <1%); Impotence* (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 > Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflicted injury, anxiety. *Primarily ejaculatory delay. †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* (Percentage of Patients Reporting Event) Body System/Adverse Event (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%); Insomnia (12% and 6%); Libido Decreased (7% and 2%); Dreaming Abnormal (3% and 2%); Appetite Decreased (3% 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 > Lexapro: inflicted 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=247 Lexapro; N=232 placebo). **Dose Dependency of Adverse Events** The potential dose dependency of common adverse events (defined as an incidence rate of ≥ 5% in either the 10 mg or 20 mg Lexapro groups) was examined 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=125); 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%, 6%); Indigestion (1%, 2%, 6%).** *Adverse events with an incidence rate of at least 5% in either 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 cause such untoward sexual experiences. 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: Adverse Event: 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 (3% 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=51), and placebo (N=527) 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, tic, 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 flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, syncope, malaise, anaphylaxis, fall. **Hemic and Lymphatic Disorders - Frequent:** 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:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, broomism, carbohydrate craving, confusion, depersonalization, 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, lipoma, 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 spontaneous and clinical trial experience and were not observed during the premarketing evaluation of escitalopram: Blood and Lymphatic System Disorders: hemolytic anemia, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, cardiac failure, myocardial infarction, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma. Gastrointestinal Disorders: gastrointestinal hemorrhage, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait, Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction. Investigations: electrocardiogram QT prolongation, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hypoglycemia, hypokalemia. Musculoskeletal and Connective Tissue Disorders: rhabdomyolysis. Nervous System Disorders: akathisia, choreoathetosis, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, neuroleptic malignant syndrome, nystagmus, seizures, serotonin syndrome, tardive dyskinesia. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, anger, delirium, delusion, nightmare, paranoia, visual hallucinations. Renal and Urinary Disorders: acute renal failure. Reproductive System and Breast Disorders: priapism. Respiratory, Thoracic and Mediastinal Disorders: pulmonary embolism. Skin and Subcutaneous Tissue Disorders: angioedema, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, hypotension, orthostatic hypotension, phlebitis thrombosis. Forest Pharmaceuticals, Inc. Subsidiary of Forest Laboratories, Inc. 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Follow-Up Care for Lung Cancer Survivors Viewed as Less Than Ideal

HOLLYWOOD, FLA. — Cure rates for locally advanced lung cancer are increasing, but obtaining good follow-up care remains a challenge for the growing number of lung cancer survivors, Dr. Mark G. Kris told attendees at the annual conference of the National Comprehensive Cancer Network.

Lung cancer survivors are at very high risk—from 1% to 5% per year—for developing another primary cancer. As a result, they need careful surveillance and should be asked about their smoking status, which should be documented in the medical record at each follow-up office visit, said Dr. Kris, chief of the thoracic oncology service at Memorial

Sloan-Kettering Cancer Center in New York.

Survivors of lung cancer are also at risk for other smoking-related illnesses, such as chronic obstructive pulmonary disease and heart disease, he continued, and should be followed accordingly. In addition, radiation to the chest accelerates cardiovascular disease. As a result, lung cancer survivors need careful cardiac monitoring, including stress testing and lipid monitoring.

Radiation also accelerates osteoporosis, for which Dr. Kris said lung cancer survivors need to be prospectively treated, regardless of their general bone density, to protect against bone loss.

—Fran Lowry