

Nicotine in Breast Milk Is Disruptive to Infant Sleep

BY TIMOTHY F. KIRN
Sacramento Bureau

A mother who smokes and breast-feeds appears to be giving her infant a dose of nicotine that significantly interferes with the baby's sleep, according to the results of a study.

Infants spent an average of about a third less time sleeping after their mothers smoked just prior to breast-feeding, compared with when the mothers refrained,

wrote Julie A. Mennella, Ph.D., and her associates at the Monell Chemical Senses Center in Philadelphia.

Nicotine is not listed as a drug that is contraindicated during breast-feeding because the benefits of breast-feeding are considered to be so great, they noted.

But the presence of nicotine in breast milk could have many adverse consequences. Mothers who smoke are known to wean their children earlier than are mothers who do not. It might be that sleep-deprived infants tend to be fussier and, if the sleep deprivation occurs because of smoking, the fussiness may stop when the mother stops breast-feeding. That in turn may reinforce a smoking mother's decision to wean. Sleep also is known to be important for learning and development, and therefore disruption of sleep caused by

smoking could have lasting consequences. Lastly, adolescents whose mothers smoked during their early life are more likely to smoke, and this may sometimes be because they recognize the flavors from breast milk and come to appreciate them.

The study was conducted with 15 volunteer mother-infant pairs. The average age of the infants was 4 months. The mothers were brought into a testing center twice, and told to refrain from smoking for 12 hours before each testing session, with the last breast-feeding done about 2.5 hours before the session. During one testing session, they were allowed to smoke at least one cigarette, in a separate room from the infant, and during one session they were not (Pediatrics 2007;120:497-502).

Nicotine levels in breast milk were measured at baseline and after smoking. The

infants' sleep and awake times were monitored using an ambulatory monitor for 3.5 hours. Nicotine stored in breast milk reaches peak levels about 30-60 minutes after smoking, then declines fairly rapidly.

During the smoking session, the estimated dose of nicotine delivered to the infants was a mean of 549 ng/kg, compared with 127 ng/kg during the nonsmoking session. During the nonsmoking session, the infants slept a mean of 84.5 minutes, compared with 53.4 minutes during the smoking session. All but two of the infants slept less during the smoking session.

Both active sleep and quiet sleep were reduced with smoking, and the duration of the longest bout of sleep declined from a mean of 60 minutes during the nonsmoking session to a mean of 37 minutes during the smoking session. ■

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 B: Lexapro: headache, upper respiratory tract infection, back pain, pharyngitis, inflamed 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* (Lexapro (N=429) and Placebo (N=427)).

Autonomic Nervous System Disorders: Dry Mouth (3% 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 B: 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=247 Lexapro; N=232 placebo). ¶Dose Dependency of Adverse Events

The potential dose dependency of common adverse events (defined as an incidence rate of 15% 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** (6%, 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 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 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: 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. Praprius 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=27) 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 Pre-marketing Evaluation of Lexapro** Following is a list of **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 pre-marketing 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 flushes, chest pain. **Infrequent:** edema of extremities, chills, tightness of chest, leg pain, asthenia, 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:** jitteriness, panic reaction, agitation, apathy, forgetfulness, depression aggravated, nervousness, restlessness aggravated, suicide attempt, amnesia, anxiety attack, bruxism, 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= 305 Respiratory System Disorders - Frequent: shortness of breath, 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 nodules. **Special Senses - Frequent:** vision blurred, linnitus. **Infrequent:** taste alteration, sarcoma, 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 pre-marketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, chorea, chorea-thetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, ecchymosis, erythema multiforme, extrapyramidal disorders, fulminant hepatitis, hepatic failure, hypoaesthesia, hypoglycemia, hypokalemia, INR increased, gastrointestinal hemorrhage, glaucoma, grand mal seizures (or convulsions), hemolytic anemia, hepatic necrosis, hepatitis, hypotension, leucopenia, myocardial infarction, myoclonus, neuroleptic malignant syndrome, nightmare, nystagmus, orthostatic hypotension, pancreatitis, paranoia, photosensitivity reaction, priapism, proctriaemia, prothrombin decreased, pulmonary embolism, QT prolongation, rhabdomyolysis, seizures, serotonin syndrome, SIADH, spontaneous abortion, Stevens Johnson Syndrome, tardive dyskinesia, thrombocytopenia, thrombosis, torsade de pointes, toxic epidermal necrolysis, ventricular arrhythmia, ventricular tachycardia and visual hallucinations.

BY DIANA MAHONEY
New England Bureau

Prenatal Smoking Tied to Irritability in Girls

BOSTON — Prenatal smoking exposure is associated with significant increases in irritability in newborn girls but not boys, according to a study presented at a meeting of the Society for Research in Child Development.

The fact that significant differences were not evident in male infants in the large, epidemiologic sample might suggest early links to later sex differences in behavioral outcomes, said Rachel L. Paster, a research assistant in the Centers for Behavioral and Preventive Medicine, Brown University, Providence, R.I.

All of the infants exposed to prenatal smoking exhibited increases in muscle tension, compared with unexposed infants, she said in a poster presentation.

Using data from the New England Cohort of the National Collaborative Perinatal Project (NCPP), Ms. Paster and colleagues examined the effects of smoking during pregnancy on the neurobehavior of male and female newborns in a sample of 991 healthy mother-infant pairs recruited between 1959 and 1962.

As part of the NCPP, smoking was mea-

sured prospectively at each prenatal visit and newborn neurobehavior was assessed using the Graham-Rosenblith behavioral examination. For the current investigation, the participants were classified as nonsmokers, moderate smokers (between 1 and 19 cigarettes per day), and heavy smokers (20 or more cigarettes per day).

"We found significant differences between smoking groups for irritability in females, but not in males," Ms. Paster reported. "Tests revealed significant differences between the heavy smoking group and both the moderate and no smoking groups only for female infants, while significant effects of maternal smoking group on muscle tone emerged for both male and female infants."

The tests also showed different patterns of effects for males and females with respect to muscle tone. "For females, the heavy smoking group was significantly dif-



Fussiness among newborns whose mothers smoked while pregnant could indicate an infant withdrawal syndrome.

ferent from both the moderate and no smoking groups, whereas for males, the moderate smoking group differed significantly from the no smoking and heavy smoking groups," said Ms. Paster.

Regarding the irritability findings, excessive irritability could indicate an infant withdrawal syndrome, Ms. Paster noted. Additionally, "irritability could potentially affect bonding and attachment with caregivers and may represent an early link to emotional dysregulation," she said. ■

Raynaud's of the Nipples Can Impede Breast-Feeding

SAN FRANCISCO — With only a handful of case reports in the medical literature, Raynaud's phenomenon of the nipples isn't the first thing that physicians think of when a breast-feeding mother complains of nipple pain.

If there are no signs of infection and no cracks or fissures on the nipples, one should consider this rare cause of nipple pain, especially if the woman has a history of Raynaud's syndrome, Sharon R. Wiener said at a meeting on antepartum and intrapartum management sponsored by the University of California, San Francisco.

The pain from this vasospasm of the nipples while breast-feeding usually is bilateral, severe, and has a spasm-like throb.

The nipple usually turns white but may be blue, purple, or red, said Ms. Wiener, a certified nurse-midwife at the university.

This problem has been misdiagnosed as a candidal infection. Of 12 women in a 2004 case report who were diagnosed with Raynaud's phenomenon of the nipples, 8 had been treated for candidiasis of the breast.

A recent patient seen by Ms. Wiener said she had been diagnosed with Raynaud's syndrome about 5 years before her pregnancy. She complained of episodes in which her nipples would become cold and then go into spasms for many hours.

Sending patients in whom you suspect this problem to a lactation consultant to identify poor latch can support the diag-

nosis. Alternatively, try applying a cold compress or ice to the nipple to see if it triggers the phenomenon.

The treatment of choice is the calcium channel blocker nifedipine, 5 mg b.i.d. for 2 weeks. It's a quick acting vasodilator, she said. "[Those] I have treated have responded very well and didn't need a repeat of the prescription." In mild cases, warm compresses or warm showers may suffice as treatment. Topical nitroglycerine appears to be effective treatment in half of cases.

Raynaud's phenomenon of the nipples has been associated with rheumatologic diseases, endocrine diseases, autoimmune diseases, cigarettes, and caffeine.

—Sherry Boschert