

Civilian TBI Data Show Dire Long-Term Outcomes

BY HEIDI SPLETE
Senior Writer

WASHINGTON — Long-term data from a registry of civilians with traumatic brain injury may yield information that is relevant to the care of injured veterans returning from Iraq and Afghanistan, said Jean A. Langlois, Sc.D., at a meeting on traumatic brain injuries sponsored by the Institute of Medicine.

During her presentation, Dr. Langlois

noted that there are relatively few long-term cohort studies of blast-induced TBI and the possible combined effects of these injuries and posttraumatic stress disorder (PTSD). The data she presented showed that civilian survivors of TBI often develop costly disabilities. More aggressive treatment might make a difference. "I think we will be seeing several directions for interventions, including electrical brain stimulation," Dr. Langlois said.

Approximately 124,000 civilians in the United States are hospitalized each year with TBI, and about 40% of these patients will experience long-term disabilities, said Dr. Langlois, an epidemiologist at the Centers for Disease Control and Prevention.

Findings from previous studies have shown that even uninjured military personnel who return from combat are at increased risk of psychosocial and psychiatric problems, including PTSD, major depression, suicide, impaired social function, and limited ability to work, she noted.

She reviewed data from four population-based studies using the South Carolina Traumatic Brain Injury Follow-up Registry that included patients with TBI who required hospitalization. The TBI was severe in 45% of patients, moderate in 15%, and mild in 40%. Patients were aged 15 years or older, 60% were male, and 75% were white.

The first of the four studies evaluated psychosocial health in 2,118 patients 1 year after TBI. Based on the scores from a validated social function scale, 29% of the TBI patients reported poor psychosocial health 1 year after their injuries, which is more than one standard deviation below the population norms, Dr. Langlois said.

"We found almost double the rate of psychosocial health problems [compared with the rate in] the general population, but only 36% reported receiving any mental health care after TBI," she said (Arch. Phys. Med. Rehabil. 2006;87:953-61).

Factors associated with poor psychosocial health 1 year after TBI included female gender, preinjury or postinjury psychiatric conditions, inadequate social support, physical limitations for activities of daily living, and preinjury drug or alcohol abuse problems.

Surprisingly, adults with TBI were less likely to report heavy alcohol consumption 1 year after injury, based on data from 1,606 patients.

The researchers used the CDC's Behavioral Risk Factor Surveillance summary questions to assess drinking habits. They found that 94% of the patients reported drinking the same amount or less alcohol 1 year after TBI than they did before TBI. And 50% of those who called themselves heavy drinkers reported drinking less. Heavy drinking was defined as an average of five or more drinks per occasion, or 22 or more drinking days within a month (J. Int. Neuropsychol. Soc. 2005;11:322-30).

But compared with the general population, the TBI population was more likely to binge drink (defined as five or more drinks on one occasion), and almost twice as likely to have five or more occasions to binge drink. Factors associated with heavy drinking were male gender, younger age, lack of support, diagnosis of depression since TBI, and self-reported fair to moderate (vs. excellent) mental health.

Also, research has shown that substance abuse problems may surface in later years after TBI, rather than immediately following the injury, said Dr. Langlois, citing a review of evidence that, on average, the quantities of alcohol consumed by TBI patients increased over time after their injuries (Arch. Phys. Med. Rehabil. 1995;76:302-9).

Clinical implications of heavy drinking include decreased recovery from TBI, increased impulsivity, exacerbation of cognitive problems, increased risk for seizures, and increased risk for additional brain injuries, Dr. Langlois added.

A third study focused on employment 1 year after TBI. These findings may have unique implications for returning military personnel who may not be able to redeploy and who will need to rejoin the civil-

ian work force, Dr. Langlois said. The employment study included patients from the South Carolina database, plus data on people with TBI who were not in the South Carolina registry, for a total of 3,444 patients (2,487 men and 957 women).

At 1 year after TBI, a majority (41%) of the patients had stopped working, 36% had kept the same hours, 13% were working fewer hours, and 10% were working

more hours, Dr. Langlois said.

Factors associated with not working included a longer hospital stay, nonwhite race, and having Medicaid or workers' compensation.

When the patients were divided by gender, men aged 20-24 years were the most likely to be working after 1 year, possibly because they tended to be the primary wage earners, whereas older men may have better disability or health benefits, Dr. Langlois noted. By contrast, women aged 18-24 years were most likely to be not working 1 year after TBI, possibly because they tend to be caring for children at home or because they may have complications if their injuries resulted from domestic violence, Dr. Langlois said.

Dr. Langlois concluded with a study of mortality within 1 year of TBI based on the South Carolina population data from 3,679 persons hospitalized with TBI (J. Head Trauma Rehab. 2005;20:257-69). Overall, the risk for all-cause mortality was seven times higher, compared with the U.S. death rate, and 80% of these deaths were reported as being related to the TBI, Dr. Langlois said.

Patients with severe TBI were significantly more likely to die within 15 months, compared with mild or moderate cases. Other factors associated with mortality from TBI included older age (75 years or older) and more comorbid conditions (three or more). The most common comorbidities were heart disease (48%), hypertension (29%), and fluid/electrolyte imbalance (21%).

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 > 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* (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 (15% 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%); Urge/Urge: Ejaculation Disorder^{1,2} (14% and 2%); Anorgasmia³ (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 Events¹ 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: 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=720) and Placebo (N=636); Libido Decreased (2% and 1%); Anorgasmia (3% and <1%) There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priligam 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=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 1/1,000 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 - 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, bruising, 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 experience and were not observed during the premarketing evaluation of escitalopram: abnormal gait, acute renal failure, aggression, akathisia, allergic reaction, anger, angioedema, atrial fibrillation, chorea, choreoathetosis, delirium, delusion, diplopia, dysarthria, dyskinesia, dystonia, echymosis, 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, prolactinemia, 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.

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Cigarette Smoking Reduces Parkinson's Risk

BY MARY ANN MOON
Contributing Writer

A pooled analysis of 11 clinical studies has confirmed that cigarette smoking protects against Parkinson's disease in a dose-dependent manner.

Many studies have suggested that smoking may play a protective role in PD, but most have been too small to provide definitive answers. Dr. Beate Ritz of the University of California, Los Angeles, and associates conducted a pooled analysis of eight case-control studies and three cohort studies involving 2,816 subjects who had PD and 8,993 controls. This large data set "enabled us to investigate aspects of cigarette smoking and subgroup-specific associations that could not be addressed ad-

equately in previous studies," they noted.

The risk of developing PD decreased as pack-years of cigarette smoking increased, so that the average relative risk for the disease dropped 5%-8% for every 10 pack-years of smoking. This dose-response pattern was seen in both men and women, and it was not affected by subjects' educational status.

There was also a strong dose-response trend for the number of years that had elapsed since smoking cessation. Current smokers and smokers who had recently quit showed the lowest risk for PD. People who had quit smoking in the past had a higher risk for PD, but their risk was still lower than that of people who had never smoked (Arch. Neurol. 2007;64:990-7).

Two possible mechanisms for this pro-

TECTIVE effect have been proposed. Substances such as nicotine in tobacco smoke may promote the survival of dopaminergic neurons, or smoking may alter the activity of metabolic enzymes and thus the production of toxic metabolites.

It is also possible that the same genetic or constitutional traits that raise susceptibility to PD may also deter subjects from smoking. Such traits could be a common cause for both smoking behavior and PD, Dr. Ritz and associates noted.

Tobacco's protective effect appeared to wane in subjects aged 75 and older, another finding that has been reported in previous studies. This is consistent with the hypothesis that smoking delays rather than prevents the onset of PD, the researchers added.