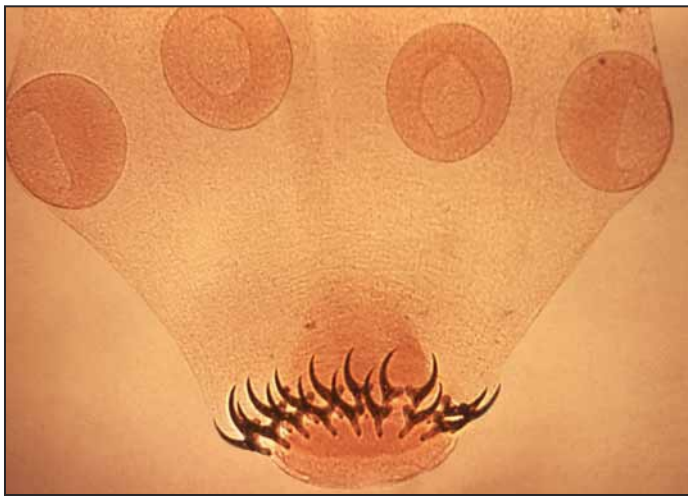


In the human intestine, the cysticercus (larval stage) develops over 2 months into an adult tapeworm, which can survive for years. The parasite attaches to and resides in the small intestine by using the suckers and hooks located in its head region, or scolex.



Parasite May Be at Root Of New-Onset Seizures

BY DAMIAN McNAMARA
Miami Bureau

MIAMI BEACH — Public health officials are stepping up efforts to combat cysticercosis, a parasitic infection with dire neurologic consequences that is on the rise in the United States, according to James H. Maguire, M.D., chief of the parasitic diseases branch of the National Center for In-

fectious Diseases at the Centers for Disease Control and Prevention, Atlanta.

Each year in the United States, there are an estimated 1,000 new cases of cysticercosis, a leading cause of adult-onset epilepsy in endemic areas such as Central America and Africa, Dr. Maguire said at the annual meeting of the American Society of Tropical Medicine and Hygiene.

Cysticercosis is acquired after accidental ingestion of the eggs of the pork tapeworm *Taenia solium*. Infected people shed the eggs in their feces; infection spreads through contaminated food, water, or surfaces. Once the eggs hatch in the stomach, they penetrate the intestine and travel through the bloodstream. The eggs produce characteristic cysts anywhere in the body; cysts in the brain cause neurocysticercosis and produce seizures and other neurologic sequelae, according to Dr. Maguire.

"The real message is if someone comes in with seizures and they have a single lesion on CT or MRI, it could be cysticercosis," Dr. Maguire said. Physicians need a high index of suspicion; an accurate diagnosis could spare a patient neurosurgery.

If a central nervous system cyst blocks the flow of cerebrospinal fluid, hydrocephalus can ensue. Surgery or shunt placement is indicated in some of these patients, but in most cases the cysts resolve on their own. Other neurologic sequelae include a permanent, stroke-like syndrome. Even the scar left behind by a former cyst can become the focus for future seizures, Dr. Maguire warned.

Patients are generally treated with antiparasitic drugs in combination with anti-inflammatory agents.

Infection typically comes from eating contaminated pork, fruits, and vegetables, but *T. solium* is also spread through contact with infected people or fecal matter. Federal standards for the U.S. pork industry protect most Americans, Dr. Maguire said.

Larval stage infection with *T. solium* leads to symptomatic cysticercosis, but people with an adult tapeworm can be unknowing sources of infection. Four cases of neurocysticercosis in New York City among Orthodox Jews—who do not eat pork—were initially puzzling to investigators (N. Engl. J. Med. 1992;327:692-5).

Only one had traveled to an endemic area. Of six domestic employees tested; one was found to have an active infection and another had a positive serologic test. "If a person is infected by someone with an adult tapeworm, contact tracing becomes very important," Dr. Maguire said.

Cysticercosis is becoming increasingly recognized in U.S.-born residents, although it is still primarily a disease of immigrants from countries such as Mexico, Central America, sub-Saharan Africa, India, and East Asia, Dr. Maguire said.

Increasingly, prevalence of cysticercosis is reported in New Mexico, New York, and especially California, states with a large number of immigrants. However, "We saw 6-12 cases per year in Boston when I worked there—not a hotbed of immigration," he added.

with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome (see WARNINGS, Monoamine Oxidase Inhibitors). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine and/or its metabolites are excreted into the milk of lactating rats. It is unknown whether or not duloxetine and/or its metabolites are excreted into human milk, but nursing while on Cymbalta is not recommended.

Pediatric Use—Safety and efficacy in pediatric patients have not been established (see WARNINGS, Clinical Worsening and Suicide Risk).

Geriatric Use—Of the 2418 patients in clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1074 patients in the DPN studies, 33% (357) were 65 years of age or over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

ADVERSE REACTIONS: Cymbalta has been evaluated for safety in 2418 patients diagnosed with MDD who participated in multiple-dose premarketing trials, representing 1099 patient-years of exposure. Among these 2418 Cymbalta-treated patients, 1139 patients participated in eight 8- or 9-week, placebo-controlled trials at doses ranging from 40 to 120 mg/day, while the remaining 1279 patients were followed for up to 1 year in an open-label safety study using flexible doses from 80 to 120 mg/day. Two placebo-controlled studies with doses of 80 and 120 mg/day had 6-month maintenance extensions. Of these 2418 patients, 993 Cymbalta-treated patients were exposed for at least 180 days and 445 Cymbalta-treated patients were exposed for at least 1 year. Cymbalta has also been evaluated for safety in 1074 patients with diabetic peripheral neuropathy representing 472 patient-years of exposure. Among these 1074 Cymbalta-treated patients, 568 patients participated in two 12- to 13-week, placebo-controlled trials at doses ranging from 20 to 120 mg/day. An additional 449 patients were enrolled in an open-label safety study using 120 mg/day for a duration of 6 months. Another 57 patients, originally treated with placebo, were exposed to Cymbalta for up to 12 months at 60 mg twice daily in an extension phase. Among these 1074 patients, 484 had 6 months of exposure to Cymbalta, and 220 had 12 months of exposure. For both MDD and DPN clinical trials, adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Clinical investigators recorded adverse events using descriptive terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals experiencing adverse events, grouping similar types of events into a smaller number of standardized event categories is necessary. MedDRA terminology was used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Events reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

Adverse Events Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—**Major Depressive Disorder**—Approximately 10% of the 1139 patients who received Cymbalta in the MDD placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (Cymbalta 1.4%, placebo 0.1%) was the only common adverse event reported as reason for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo). **Diabetic Peripheral Neuropathic Pain**—Approximately 14% of the 568 patients who received Cymbalta in the DPN placebo-controlled trials discontinued treatment due to an adverse event, compared with 7% of the 223 patients receiving placebo. Nausea (Cymbalta 3.5%, placebo 0.4%), dizziness (Cymbalta 1.6%, placebo 0.4%), somnolence (Cymbalta 1.6%, placebo 0%) and fatigue (Cymbalta 1.1%, placebo 0%) were the common adverse events reported as reasons for discontinuation and considered to be drug-related (ie, discontinuation occurring in at least 1% of the Cymbalta-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Cymbalta-Treated Patients in Placebo-Controlled Trials—**Major Depressive Disorder**—Treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the acute phase of MDD placebo-controlled trials (N=1139 Cymbalta; N=777 placebo) with an incidence greater than placebo were: **Gastrointestinal Disorders**—nausea, dry mouth, constipation, diarrhea, vomiting; **Metabolism and Nutrition Disorders**—appetite decreased (includes anorexia); **Investigations**—weight decreased; **General Disorders and Administration Site Conditions**—fatigue; **Nervous System Disorders**—dizziness, somnolence, tremors; **Skin and Subcutaneous Tissue Disorders**—sweating increased; **Vascular Disorders**—hot flushes; **Eye Disorders**—vision blurred; **Psychiatric Disorders**—insomnia (includes middle insomnia), anxiety, libido decreased, orgasm abnormal (includes anorgasmia); **Reproductive System and Breast Disorders**—males only: erectile dysfunction, ejaculation delayed, ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure).

The following events were reported by at least 2% of patients treated with Cymbalta for MDD and had an incidence \leq placebo: upper abdominal pain, palpitations, dyspepsia, back pain, arthralgia, headache, pharyngitis, cough, nasopharyngitis, and upper respiratory tract infection.

The most commonly observed adverse events in Cymbalta-treated MDD patients (incidence \geq 5% and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

Diabetic Peripheral Neuropathic Pain—Treatment emergent adverse events that occurred in 2% or more of patients treated with Cymbalta in the acute phase of DPN placebo-controlled trials (N=225 Cymbalta 60 mg BID; N=228 Cymbalta 60 mg QD; N=115 Cymbalta 20 mg QD; N=223 placebo) with an incidence greater than placebo were: **Gastrointestinal Disorders**—nausea, constipation, diarrhea, dry mouth, vomiting, dyspepsia, loose stools; **General Disorders and Administration Site Conditions**—fatigue, asthenia, pyrexia; **Infections and Infestations**—nasopharyngitis; **Metabolism and Nutrition Disorders**—decreased appetite, anorexia; **Musculoskeletal and Connective Tissue Disorders**—muscle cramp, myalgia; **Nervous System Disorders**—somnolence, headache, dizziness, tremor; **Psychiatric Disorders**—insomnia; **Renal and Urinary Disorders**—pollakiuria; **Reproductive System and Breast Disorders**—erectile dysfunction; **Respiratory, Thoracic and Mediastinal Disorders**—cough, pharyngolaryngeal pain; **Skin and Subcutaneous Tissue Disorders**—hyperhidrosis.

The following events were reported by at least 2% of patients treated with Cymbalta for DPN and had incidence \leq placebo: edema peripheral, influenza, upper respiratory tract infection, back pain, arthralgia, pain in extremity, and pruritus.

The most commonly observed adverse events in Cymbalta-treated DPN patients (incidence \geq 5% and at least twice the incidence in placebo patients) were: nausea; somnolence; dizziness; constipation; dry mouth hyperhidrosis; decreased appetite; and asthenia.

Adverse events seen in men and women were generally similar except for effects on sexual function (described below). Clinical studies of Cymbalta did not suggest a difference in adverse event rates people over or under 65 years of age. There were too few non-Caucasian patients studied to determine these patients responded differently from Caucasian patients.

Effects on Male and Female Sexual Function—Although changes in sexual desire, sexual performance and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be consequence of pharmacologic treatment. 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 the actual incidence. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking Cymbalta in MDD placebo-controlled trials were: Males (N=378 Cymbalta; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculate failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 Cymbalta; N=494 placebo): orgasm abnormal, libido decreased.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sex Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo measured by ASEX total score. These studies did not, however, include an active control drug with known effects on female sexual dysfunction, so that there is no evidence that its effects differ from those of antidepressants. Physicians should routinely inquire about possible sexual side effects. See Table 4 in PI for specific ASEX results.

Urinary Hesitation—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related. **Laboratory Changes**—Cymbalta treatment, for up to 9-weeks in MDD or 13-weeks in DPN placebo-controlled clinical trials, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients (see PRECAUTIONS). **Vital Sign Changes**—Cymbalta treatment, for up to 9-weeks in MDD placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, average 2 mm Hg systolic and 0.5 mm Hg diastolic compared to placebo and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg (see PRECAUTIONS). Cymbalta treatment for up to 9-weeks in MDD placebo-controlled clinical trials and for up to 13-weeks in DPN placebo-controlled trials caused a small increase in heart rate compared to placebo of about 2 beats per minute.

Weight Changes—In MDD placebo-controlled clinical trials, patients treated with Cymbalta for up to 9-weeks experienced a mean weight loss of approximately 0.5 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In DPN placebo-controlled clinical trials, patients treated with Cymbalta for up to 13-weeks experienced a mean weight loss of approximately 1.1 kg, compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. **Electrocardiogram Change:** Electrocardiograms were obtained from 321 Cymbalta-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8-weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for QT, PR, and QRS intervals between Cymbalta-treated and placebo-treated patients. Electrocardiograms were obtained from 528 Cymbalta-treated patients with DPN and 205 placebo-treated patients in clinical trials lasting up to 13-weeks. The rate-corrected QT (QTc) interval in Cymbalta-treated patients did not differ from that seen in placebo-treated patients. No clinically significant differences were observed for PR, QRS, or QTc measurements between Cymbalta-treated and placebo-treated patients.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class—Duloxetine is not a controlled substance. **Physical and Psychological Dependence**—In animal studies, duloxetine did not demonstrate barbiturate-(depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While Cymbalta has not been systematically studied in humans for its potential for abuse, there was indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse; follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: There is limited clinical experience with Cymbalta overdose in humans. In premarket clinical trials, as of October 2003, no cases of fatal acute overdose of Cymbalta have been reported. F non-fatal acute ingestions of Cymbalta (300 to 1400 mg), alone or in combination with other drugs, have been reported. **Management of Overdose**—There is no specific antidote to Cymbalta. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug.

DOSE AND ADMINISTRATION: Major Depressive Disorder—Cymbalta should be administered at a total dose of 40 mg/day (given as 20 mg BID) to 60 mg/day (given either once a day or as 30 mg BID) with regard to meals. There is no evidence that doses greater than 60 mg/day confer any additional benefit. **Diabetic Peripheral Neuropathic Pain**—Cymbalta should be administered at a total dose of 60 mg/day given once a day, without regard to meals. While a 120 mg/day dose was shown to be safe and effective, there is no evidence that doses higher than 60 mg confer additional significant benefit, and the higher doses clearly less well tolerated. For patients for whom tolerability is a concern, a lower starting dose may be considered. Since diabetes is frequently complicated by renal disease, a lower starting dose and gradual increase in dose should be considered for patients with renal impairment.

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