FDA APPROVES DULOXETINE FOR THE TREATMENT OF MAJOR DEPRESSIVE DISORDER

The United States Food and Drug Administration approved duloxetine hydrochloride (Cymbalta, Eli Lilly), a selective serotonin and norepinephrine reuptake inhibitor, for the treatment of major depressive disorder (MDD) in August.

The new indication is based on four randomized, double-blind, placebo-controlled, fixed-dose studies establishing the efficacy of duloxetine for MDD. All four studies were 8–9 weeks in duration and involved adult outpatients 18–83 years of age who met *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, criteria for MDD. Subjects in the first and second studies received duloxetine 60 mg/day or placebo; subjects in the third study received duloxetine 20 or 40 mg BID or placebo; and subjects in the fourth study received duloxetine 40 or 60 mg BID or placebo.

In all four studies, duloxetine was superior to placebo. Superiority was measured by improvement on 17-item Hamilton Rating Scale for Depression scores. Results show that duloxetine should be administered at doses of 40 mg/day (20 mg BID) up to 60 mg/day (60 mg/day or 30 mg BID). Dosages >60 mg/day showed no additional benefit. Treatment beyond 9 weeks has not been studied extensively. There is also insufficient evidence available as to how long patients should remain on duloxetine; it is recommended that patients on extended treatment be periodically evaluated for efficacy.

The most common side effects of duloxetine (ie, adverse effects with an incidence of >5% and at least twice the incidence in placebo-treated patients) were nausea, dry mouth, constipation, decreased appetite, fatigue, somnolence, and increased sweating. Patients on monoamine oxidase inhibitors should not take duloxetine. *–EJR*

FDA APPROVES ZIPRASIDONE FOR THE TREATMENT OF ACUTE BIPOLAR MANIA

The United States Food and Drug Administration approved ziprasidone (Geodon, Pfizer) for the treatment of acute bipolar mania, including manic and mixed episodes.

The approval came after two double-blind trials of 416 hospitalized patients suffering from acute mania. Treatment was initiated at 80 mg/day, in the first study the dosage was increased to 160 mg/day on day 2 and in the second study this increase occurred on day 3. During treatment in both studies, ziprasidone improved the symptoms of acute mania suffered by patients. These improvements were sustained during each study's duration (3 weeks). Unlike previously approved atypical antipsychotics, ziprasidone was not found to either increase a patient's weight or affect lipid production. The initial dosage of ziprasidone is 40 mg/day BID taken with food. The maximum daily dosage is 80 mg BID.

The most frequent adverse events seen in these studies were somnolence, dizziness, and extrapyramidal symptoms. A few cases of hyperglycemia were reported during treatment with ziprasidone and patients should be carefully monitored for these symptoms. Ziprasidone is contraindicated in patients with a history of QT prolongation, recent myocardial infarction, or uncompensated heart failure. Patients taking QT-prolonging agents should not take ziprasidone. *–EJR*

RESEARCHERS REVISE INTERNATIONAL CLASSIFICATION CRITERIA FOR HEADACHE DISORDERS

According to the National Institute of Neurological Disorders and Stroke, ~90% of headache patients can be successfully treated. Physicians have depended on the diagnostic criteria of the International Headache Society (IHS) to recognize and treat headaches since 1988. The second edition of the *International Classification of Headache Disorders* (*ICHD-II*), which was initially released in January of this year, has been recently revised by Richard B. Lipton, MD, of the Albert Einstein College of Medicine in Bronx, New York, and members of the IHS classification committee.

The updated edition includes new subtypes and previously undefined disorders. The classification divides headaches into primary and secondary disorders. Primary headaches are separated into four categories (migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias [TACs], and other primary headaches). Each subtype is then further separated by subtype.

Secondary disorders are divided into eight categories. There is also a third classification for causes of facial pain and other headaches. Secondary headaches include those attributed to head/neck injury, to infection, to a psychiatric condition, and to cranial or cervical vascular disorder.

The third class of headaches, "cranial neuralgias, central and primary facial pain, and other headaches," has two subtypes: cranial neuralgias and central causes of facial pain and other headache, cranial neuralgia, central or primary facial pain.

The new *ICHD-II* edition added a subtype for "chronic migraine," which is defined as a migraine lasting ≥15 days/month for ≥3 months without overuse of medication. The most frequently reported headache, tension-type, was revised into three subcategories: infre-

https://doi.org/10.1017/S1092852900001899 Published online by Cambridge University Press

quent episodic, frequent episodic, and chronic. Tension-type headaches can last anywhere from 30 minutes to 7 days and are characterized by a lack of nausea or vomiting, though anorexia may be present, as may only one photo- or phonophobia be present. They cannot be intensified by daily activity such as walking.

TACs were included for the first time in the revised *ICHD-II*. They were added to cluster headaches, which are defined as a sharp, drilling, or stabbing pain. Episodic paroxysmal hemicranias were also added to cluster headaches. They are characterized by ≥20 brief but and severe attacks within a few days, followed by an attack-free span ≥1 month. Among the revised "other primary headaches" are hypnic headaches, brief attacks of nocturnal head pain, and daily-persistent headaches, daily, ever-present head pains lasting >3 months. The *ICHD-II* also presents a step-by-step algorithm to determine if a secondary headache is due to an underlying disorder.

The genetic component of headaches is also discussed in the revised second edition, specifically in subtypes of familial hemiplegic migraine, which was elucidated via recent studies. This means that headaches such as familial hemiplegic migraine can be defined in terms of a genetic mutation.

Headache is a common complaint reported by patients. Lipton and colleagues believe a uniformed terminology and the classification of the wide-range of disorders concomitant with headache necessitate an instrument such as the *ICHD-II*. This can lead to improved clinical management and clearer direction for future research.

(*Neurology*. 2004;63:427-435) –*JRR*

MEXICAN AMERICANS MAY RUN A HIGHER RISK OF STROKE THAN NON-HISPANIC WHITES

Mexican Americans have a much greater risk of suffering a stroke than non-Hispanic whites (NHWs), according to findings from the Brain Attack Surveillance in Corpus Christi, Texas study. Lewis B. Morgenstern, MD, director of the University of Michigan Stroke Program in Ann Arbor, led the multicenter study.

There are more than 700,000 incidences of stroke annually in the United States. Stroke is the third leading cause of death in the US, causing more serious long-term disabilities than any other disease. Nearly three-quarters of all strokes occur in people over 65 years of age and the risk of having a stroke more than doubles each decade after 55 years of age.

Morgenstern and colleagues compared the incidences of stroke among Mexican Americans and NHWs in a population-based study in Nueces County, Texas. Validated stroke and near-stroke reports (N=2,350) were collected from the year 2000 to 2002. From those reports, the researchers studied 402 cases of stroke. The subjects were divided into Mexican Americans (n=207) and NHWs (n=195). The mean age of the Mexican Americans was 70.3 years, while the NHWs had a mean age of 74.8 years. Both groups had a *P*-value of <.001. The majority of patients were women.

Subjects were also separated into stroke subtype (Table). Mexican Americans showed a higher incidence of risk factors compared with NHWs. The researchers noted that 75% of Mexican Americans had a history of hypertension versus 71% of NHWs. Diabetes was reported in 56% of Mexican Americans versus 30% of NHWs. Also, 74 Mexican Americans had coronary artery disease compared with 68 NHWs, and 75 (36%) Mexican Americans reported a previous stroke compared with 66 (34%) NHWs.

Data analysis showed that of completed strokes, 53% were found in the Mexican American population. Crude cumulative incidence was 168/10,000 in Mexican Americans and 136/10,000 in NHWs. There was a greater cumulative incidence for ischemic stroke in Mexican Americans (45–59 years of age: risk ratio=2.04, 95% CI 1.55–2.69; 60–74 years of age: risk ratio=1.58, 95% CI 1.31–1.91; >75 years of age: risk ratio=1.12, 95% CI 1.24–2.16). Intracerebral hemorrhage was also more prevalent in Mexican Americans (risk ratio=1.63, 95% CI 1.24–2.16). The researchers reported no difference between Mexican Americans and NHWs in small-vessel infarction and stroke outcome.

TABLE. STUDY POPULATION BY STROKE SUBTYPE*

	Mexican Americans		Non-Hispanic Whites	
Stroke Subtype	n	Percent	n	Percent
Cardioembolism	34	16%	50	26%
Large artery atherosclerosis	29	14%	29	15%
Nonlacunar stroke of unknown etiology	52	25%	39	20%
Small-vested occlusion	43	21%	34	17%
Ischemic stroke of other determined etiology	4	2%	1	1%
Ischemic stroke of undetermined etiology	45	22%	42	22%

* *P*=.62

CNS Spectr. Vol 9, No 9. 2004.

https://doi.org/10.1017/S1092852900001899 Published online by Cambridge University Press

Morgenstern and colleagues believe that these results suggest that Mexican Americans have a significantly higher risk of stroke than NHWs. Hispanics are the largest minority group in the US, with Mexican Americans being the largest sub-group. With a growing and aging Mexican American population, the researchers note that stroke prevention for this group is critical.

(*Am J Epidemiol.* 2004;160:376-383; *Neurology.* 2004;63:574-576) –*JRR*

NEW RESEARCH FURTHER HIGHLIGHTS THE BIOLOGICAL BASIS OF DEPRESSION VULNERABILITY

Patients with major depressive disorder (MDD) require long-term treatment to maintain remission due to the chronicity of MDD. To further understand the relationship between MDD and the brain, researchers recently investigated brain serotonin function through tryptophan depletion and measured neural and behavioral responses.

Alexander Neumeister, MD, and colleagues at the National Institute of Mental Health in Bethesda, Maryland, studied 27 unmedicated patients with remitted MDD (18 women, 9 men; mean age=39.8 years) and 19 controls (10 women, 9 men; mean age=34.4 years) in a randomized, double-blind, crossover study at an outpatient clinic. Data were gathered over 3 weeks for single subjects. The entire length of the study was 2 years. To induce tryptophan depletion, researchers administered oral capsules containing an amino acid mixture without serotonin-precursor tryptophan. Antidepressants elevate serotonin levels; to achieve the reverse effect, the mixture lowered levels of tryptophan. Sham depletion used identical capsules containing hydrous lactose.

Six hours after tryptophan depletion, positron emission tomography studies were performed to study the neural effects of sham depletion and tryptophan depletion. Magnetic resonance images were obtained for all participants. Depressive behavior was assessed using a modified (24-item) version of the Hamilton Rating Scale for Depression.

Neumeister and colleagues found that tryptophan depletion induced a transient return of depressive symptoms in remitted MDD patients (60%) but not in controls ($P<.001$). In contrast to sham depletion, tryptophan depletion was associated with an increase in regional cerebral glucose utilization in front and center brain regions associated with depression, including the orbitofrontal cortex, medial thalamus, anterior and posterior cingulate cortices, and ventral striatum in remitted MDD patients. In remitted MDD patients who did not feel any symptoms, 40% had similar brain activity. None of the controls showed this pattern of brain activity, even when tryptophan levels were lowered. Neumeister and colleagues believe that this brain pattern suggests that tryptophan depletion unmasks a serotonin system-related trait dysfunction and identifies a circuit that likely plays a key role in MDD. This circuit can stay turned on even when remitted patients are not feeling depressed, suggesting that medication cannot alter its biology.

"The results provide further evidence that the biological basis of MDD is a continuing vulnerability factor and that people with MDD have to address this issue probably best by having maintenance treatment for the disorder," Dr. Neumeister said. "Medications obviously compensate for the underlying deficit but they do not correct it, and this explains the high relapse rate if patients who have been successfully treated discontinue their medications. Our results provide more evidence for the biological basis of this vulnerability."

Dr. Neumeister is currently conducting genetic research to determine which groups of people are generally vulnerable to depression.

"The primary motivation for this study was to add an obviously important piece of knowledge to the existing literature on MDD by studying remitted, unmedicated patients with a history of MDD," Dr. Neumeister said. "They are the most valuable group of people if we want to understand vulnerability factors for MDD, and if we try to understand the underlying biology of MDD."

Funding for this research was provided by the National Institute of Mental Health.

(*Arch Gen Psychiatry.* 2004;61:765-773) –*SW*

SELEGILINE AND OTHER MAOBI MAY REDUCE DISABILITY AMONG PATIENTS WITH EARLY PARKINSON'S DISEASE

The treatment of patients in the early stages of Parkinson's disease is critical to slow disease progression. To quantify the benefits and risks of monoamine oxidase type B inhibitors (MAOBIs) such as selegiline, Keith Wheatley, PhD, and colleagues of the University of Birmingham in England, reviewed 17 randomized trials involving 3,525 patients using data on mortality, motor complications, side effects, treatment compliance, and clinician-rated disability.

The researchers systemically searched trial literature from 1966 to December 2003. Eligible studies were randomized trials in early Parkinson's disease comparing an MAOBI (selegiline, lazabemide, or rasagiline), with or without levodopa versus placebo, levodopa, or both, with all other aspects of treatment being the same. Patients with Parkinson's disease have depleted

levels of dopamine; levodopa is the precursor required by the brain to produce dopamine and is used to reduce symptoms of Parkinson's disease.

Early disease was defined as patients with idiopathic Parkinson's disease who had no history of motor complications and were untreated or had received limited (generally <12 months) exposure to antiparkinsonian drugs. Data was combined using standard meta-analytic methods.

Wheatley and colleagues found that MAOBIs reduce disability, the need for levodopa, and the incidence of motor fluctuations without substantial side effects or increased mortality. A previous UK study in 1995 reported that MAOBIs increased mortality, however, the researchers suggest that this was probably a chance finding due to subsequent randomized trials.

The researchers found that there was no significant difference in mortality between patients on MAOBIs and controls (OR: 1.13, 95% CI 0.94–1.34; P=.2). The former group had significantly better total scores, motor scores, and activities of daily living scores on the unified Parkinson's disease rating scale at 3 months compared with patients taking placebo. They were also less likely to need levodopa (OR: 0.57, 95% CI 0.480–0.67; P<.00001) or to develop motor fluctuations (OR: 0.75, 95% CI 0.59–0.95; P=.02). No difference in side effects or patient withdrawals were observed between groups.

The researchers indicate that MAOBIs could be one of the most clinically effective and cost-effective treatments available for early Parkinson's disease. They also note that, due to the limited amount of data available comparing the risks and benefits of MAOBIs with other agents, additional large, long-term comparative trials, including patient-rated quality of life measures, are warranted to clarify their results.

(*BMJ*. doi:10.1136/bmj.38184.606169.AE) –*SW*

SERTRALINE MAY HELP TREAT BULIMIA NERVOSA

Bulimia nervosa (BN) is estimated to affect ~10% of college-aged women in the United States and presents with binge eating followed by purging (eg, vomiting, fasting, enemas, excessive employment of laxatives and diuretics, or compulsive exercising). BN is also often comorbid with depression. A recent study by Denise M. Sloan, PhD, of the Department of Psychology at Temple University in Philadelphia and colleagues suggests that the selective serotonin reuptake inhibitor sertraline may be helpful in the treatment of BN.

The 8-week study followed 18 BN outpatient women (mean age=30 years; SD=9) who were administered sertraline. At the beginning of the study, subjects were administered sertraline 50 mg. The dosage was then increased each week to a maximum dosage of 200 mg. Throughout the trial's first 4 weeks, dosages could be decreased in 50-mg increments due to high adverse events. All subjects were aware they were receiving sertraline. Prior to beginning the study, all of the women measured above the threshold for probable BN on the semi-structured Eating Disorders Examination (EDE). For diagnostic purposes, the Bulimia Test-Revised (BULTI-R) was also employed.

The researchers found no significant weight gain, although they did notice a decrease in the weight of the women. At baseline, pretreatment mean weight for the women was 131.2 lbs (SD=5.0). At endpoint, the mean weight of the subjects decreased to 129.7 lbs (SD=5.1). At trial completion, four subjects had withdrawn for undefined reasons. Two of the 14 remaining women showed no change on binging-purging symptoms. Of those who completed the study, 50% had ceased binging and purging.

"Six women remained above the threshold for probable bulimia but had improved from their baseline scores," Dr. Sloan said. "For example, they may have binged 6 times a week at the beginning of the study, but at the end they were purging only twice."

Follow-up analysis of variance showed that subjects had significant reductions from baseline to posttreatment in BULIT-R score ($F_{(1,17)}$=17.44, P<.001) and EDE total score $F_{(1,17)}$=13.43, P<.01).

Sloan and colleagues believe the improvement of BN symptoms may have been due to expectations of improvement. Therefore, although promising, there is no proof that sertraline is efficacious in treating BN. Adverse effects most commonly reported by patients were nausea, headache, diarrhea, and jitteriness. Dr. Sloan believes that future research should concentrate on double-blind, placebo-controlled studies in order to determine whether the current findings with sertraline can be replicated.

Funding for this research was provided by Pfizer.

(*Int J Eat Disord*. 2004;36:48-54). –*JRR* CNS

–Clinical Updates in Neuropsychiatry is compiled and written by José R. Ralat, Emil J. Ross, and Shelley Wong

CORRECTION

In the June issue of *CNS Spectrums*, Peter Kalina, MD, is listed as the director of pediatric neurology and developmental medicine in the Department of Pediatrics at Maimonides Medical Center. He is a neuroradiologist at the Mayo Clinic in Rochester, MN.