New Treatments Are Emerging to Beat Smoking

BY CARL SHERMAN
Contributing Editor

NEW YORK — With a fuller understanding of the neurobiology of tobacco dependence, potential therapeutic targets have emerged that suggest novel treatments for this devastating health problem, Robert Anthenelli, M.D., said at the annual conference of the Association for Research in Nervous and Mental Disease.

Of particular promise are drugs that target nicotinic receptor subtypes, endocannabinoid antagonists, and selective MAO inhibitors, said Dr. Anthenelli, director of the substance dependence program at the Veterans Affairs Medical Center in Cincinnati.

Tobacco is more likely than alcohol or cocaine to produce dependence in users and is responsible for enormous amounts of mortality and morbidity worldwide, but there are only two approved drug treatment modalities—nicotine replacement and bupropion—and neither is terribly effective, he said.

Neurobiologic research has shown that the acetylcholine system plays a key role in nicotine response and dependence. Nicotinic receptors, which bind acetylcholine, are present on almost all neurons and mediate attention, arousal, and cognition.

Diversity of subunit composition allows nicotinic receptors to be involved in a number of different processes. It appears that two subtypes, α4 β2, which predominates in the brain, and α7, are key players in tobacco dependence, he explained.

Initially, nicotine stimulates these receptors (and through them, the firing of dopaminergic neurons), producing tobacco's desired effects. Over time, though, exposure pushes the receptors into a desensitized state that promotes tolerance. Their consequent upregulation contributes to withdrawal symptoms that make smoking cessation difficult, Dr. Anthenelli said at the meeting, which was cosponsored by the New York Academy of Medicine.

Partial agonists to the α4 β2 nicotinic receptor are currently under development. In the presence of nicotine, these drugs work like antagonists, blocking the drug's reinforcing effect; in its absence, they ameliorate withdrawal.

Of particular promise are drugs that target nicotinic receptor subtypes, endocannabinoid antagonists, and selective MAO inhibitors.

In a phase IIa study, almost half of smokers taking one such drug, varenicline, successfully quit after 7 weeks, compared with 16% taking placebo and one-third taking bupropion. In this and other studies, the drug's side effect profile appeared to be benign, Dr. Anthenelli said.

Other compounds in this class also are under investigation, he said.

Another intriguing target for novel interventions is the endocannabinoid system, which acts in the mesolimbic area of the brain and regulates appetite and other functions. Nicotine stimulates the release of endocannabinoids in the limbic forebrain.

Rimonabant, the first compound developed to modulate this system, works through its influence on one type of receptor (cannabinoid-1). It has aroused great interest for its effects on weight and lipid metabolism but appears to be promising as an aid to smoking cessation as well, Dr. Anthenelli said.

In a phase III trial, rimonabant (20 mg/day) achieved significantly greater abstinence rates than did placebo, as measured during the last 4 weeks of a 10-week trial: 27.6% vs. 15.6% by intent-to-treat analysis, 36% vs. 20% among completers. A lower dosage of the drug (5 mg/day) was no more effective than placebo.

It is particularly encouraging, since weight gain is an important obstacle for many who try to quit smoking, that weight changed little for those on the drug: a mean gain of 0.6 kg, compared with 7.3 kg on placebo, Dr. Anthenelli said.

Selective MAO inhibitors also are being investigated for this application. Cigarette smoke inhibits MAO activity, possibly through components other than nicotine, and the selective MAO inhibitor selegiline reduced craving and smoking in a laboratory study. In a controlled trial, 25% of patients who added selegiline to nicotine replacement achieved abstinence after a year, compared with 11% of those who used nicotine replacement and placebo. ■

CYMBALTA® (duloxetine hydrochloride)

Brief Summary. Consult the package insert for complete prescribing information.

INDICATIONS AND USAGE: Cymbalta is indicated for the treatment of major depressive disorder (MDD).

CONTRAINDICATIONS: Hypersensitivity—Known hypersensitivity to the product.

Monoamine Oxidase Inhibitors (MAOIs)—Concomitant use with Cymbalta is contraindicated (*see* WARNINGS). **Uncontrolled Narrow-Angle Glaucoma**—In clinical trials, duloxetine use was associated with an increased risk of mydriasis; therefore, its use is not recommended in patients with uncontrolled narrow-angle glaucoma.

WARNINGS: Clinical Worsening and Suicide Risk—Patients with MDD, both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality), whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Although there has been a long-standing concern that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients, a causal role for antidepressants in inducing such behaviors has not been established. **Patients being treated with antidepressants should be observed closely for clinical worsening and suicidality, especially at the beginning of a course of drug therapy, or at the time of dose changes, either increases or decreases.** Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or whose emergent suicidality is severe, abrupt in onset, or was not part of the patient's presenting symptoms. The following symptoms—anxiety, agitation, panic attacks, insomnia, irritability, hostility (aggressiveness), impulsivity, akathisia, hypomania, and mania—have been reported in adult and pediatric patients being treated with antidepressants for MDD as well as for other indications, both psychiatric and nonpsychiatric. **Families and caregivers of patients being treated with antidepressants for MDD or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers.** Prescriptions should be written for the smallest quantity of capsules consistent with good patient management and to reduce the risk of overdose. If discontinuing treatment, the medication should be tapered.

MAOIs—In patients receiving a serotonin reuptake inhibitor (SSRI) in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRIs and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. The effects of combined use of duloxetine and MAOIs have not been evaluated in humans or animals. Therefore, because duloxetine is an inhibitor of both serotonin and norepinephrine reuptake, it is recommended that duloxetine not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of duloxetine, at least 5 days should be allowed after stopping duloxetine before starting an MAOI.

PRECAUTIONS: General—Hepatotoxicity—Duloxetine increases the risk of elevation of serum transaminase levels. Liver transaminase elevations resulted in the discontinuation of 0.3% (27/8454) of duloxetine-treated patients. In these patients, the median time to detection of the transaminase elevation was about two months. In controlled trials in MDD, elevations of alanine transaminase (ALT) to > 3 times the upper limit of normal occurred in 0.9% (8/930) of duloxetine-treated patients and in 0.3% (2/652) placebo-treated patients. In the full cohort of placebo-controlled trials in any indication, 1% (39/3732) of duloxetine-treated patients had a > 3 times the upper limit of normal elevation of ALT compared to 0.2% (6/2568) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose-response relationship for ALT and AST elevation of > 3 times the upper limit of normal and > 5 times the upper limit of normal, respectively.

The combination of transaminase elevations and elevated bilirubin, without evidence of obstruction, is generally recognized as an important predictor of severe liver injury. Three duloxetine patients had elevations of transminases and bilirubin, but also had elevation of alkaline phosphatase, suggesting an obstructive process; in these patients, there was evidence of heavy alcohol use and this may have contributed to the abnormalities seen. Because it is possible that duloxetine and alcohol may interact to cause liver injury, duloxetine should ordinarily not be prescribed to patients with substantial alcohol use. Effect on Blood Pressure—In clinical trials, duloxetine treatment was associated with mean increases in blood pressure, averaging 2 mm Hg systolic and 0.5 mm Hg diastolic and an increase in the incidence of at least one measurement of systolic blood pressure over 140 mm Hg compared to placebo. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment (*see* ADVERSE REACTIONS, Vital Sign Changes). Activation of Mania/Hypomania—In placebo-controlled trials in patients with MDD, activation of mania or hypomania was reported in 0.1% (1/1139) of duloxetine-treated patients and 0.1% (1/777) of placebo-treated patients. Activation of mania/hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of MDD. As with these other agents, duloxetine should be used cautiously in patients with a history of mania. Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials in patients with MDD, seizures occurred in 0.1% (1/1139) of duloxetine-treated patients and 0% (0/777) of placebo-treated patients. Like other drugs in the treatment of MDD, duloxetine should be prescribed with care in patients with a history of a seizure disorder. Controlled Narrow-Angle Glaucoma—In clinical trials, duloxetine was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma. (*see* CONTRAINDICATIONS, Uncontrolled Narrow-Angle Glaucoma). Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking Cymbalta. Following abrupt discontinuation in placebo-controlled clinical trials of up to 9-weeks duration, the following symptoms occurred at a rate greater than or equal to 2% and a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness; nausea; headache; paresthesia; vomiting; irritability; and nightmare.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate.

Use in Patients With Concomitant Illness—Clinical experience with duloxetine in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of duloxetine's enteric coating. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using duloxetine in patients with conditions that may slow gastric emptying. Duloxetine has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. However, the electrocardiograms of 321 patients who received duloxetine in placebo-controlled clinical trials and had qualitatively normal ECGs at baseline were evaluated; duloxetine was not associated with the development of clinically significant ECG abnormalities (*see* ADVERSE REACTIONS, Electrocardiogram Changes). Increased plasma concentrations of duloxetine, and especially of its metabolites, occur in patients with end stage renal disease (ESRD) and severe renal impairment (creatinine clearance <30 mL/min). For this reason, duloxetine is not recommended for patients with ESRD.

Markedly increased exposure to duloxetine occurs in patients with hepatic insufficiency and duloxetine should not be administered to these patients.

Laboratory Tests—No specific laboratory tests are recommended.

Drug Interactions—*Potential for Other Drugs to Affect Duloxetine*—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism. Inhibitors of CYP1A2—Concomitant use of duloxetine with fluvoxamine, an inhibitor of CYP1A2, results in approximately a 6-fold increase in AUC and about a 2.5- fold increase in C_{max} of duloxetine. Some quinolone antibiotics would be expected to have similar effects and these combinations should be avoided. Inhibitors of CYP2D6—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 may result in higher concentrations of duloxetine. Paroxetine (20 mg QD) increased the concentration of duloxetine (40 mg QD) by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (eg, fluoxetine, quinidine). *Potential for Duloxetine to Affect Other Drugs—Drugs Metabolized by CYP1A2—In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity, and it is unlikely to have a clinically significant effect on the metabolism of CYP1A2 substrates. Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg BID) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold. Therefore, co-administration of duloxetine with other drugs that are extensively metabolized by this isozyme and which have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines and Type 1C arrhythmics (eg, propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with duloxetine. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, duloxetine and thioridazine should not be co-administered.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. *Duloxetine May Have a Clinically Important Interaction With the Following Other Drugs*—Alcohol—When duloxetine and ethanol were administered several hours apart so that peak concentrations of each would coincide, duloxetine did not increase the impairment of mental and motor skills caused by alcohol. In the duloxetine clinical trials database, three duloxetine-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen. (see PRECAUTIONS, Hepatotoxicity) CNS Acting Drugs—Given the primary CNS effects of duloxetine, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action. Potential for Interaction With Drugs That Affect Gastric Acidity—Duloxetine has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, duloxetine, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Drugs that raise the gastrointestinal pH may lead to an earlier release of duoloxetine. However, co-administration of duloxetine with aluminum- and magnesium-containing antacids (51 mEq) or duloxetine with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40-mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption.

Monoamine Oxidase Inhibitors—*See* CONTRAINDICATIONS *and* WARNINGS.

Carcinogenesis, Mutagenesis, Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at dietary doses of approximately 140 mg/kg/day (11 times the maximum recommended human dose [MRHD] of 60 mg/day on a mg/m² basis), there was an increased incidence of hepatocellular adenomas and carcinomas; the no-effect level was approximately 50 mg/kg (4 times the MRHD on a mg/m² basis). Tumor incidence was not increased in male mice receiving duloxetine at dietary doses up to approximately 100 mg/kg/day (8 times the MRHD on a mg/m² basis). In rats, dietary doses of duloxetine up to approximately 27 mg/kg/day in females (4 times the MRHD on a mg/m² basis) or approximately 36 mg/kg/day in males (6 times the MRHD on a mg/m² basis) did not increase the incidence of tumors. Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an in vitro mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*. Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at daily doses up to 45 mg/kg (7 times the MRHD on a mg/m² basis) did not alter mating or fertility.

Pregnancy—Pregnancy—Nonteratogenic Effects—Neonates exposed to SSRIs or 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, MAOIs). When treating a pregnant woman with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment.

Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development. When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 and 15 times the MRHD on a mg/m² basis, in rats and rabbits, respectively). However, fetal weights were decreased at this dose, with a no-effect level of 10 mg/kg (2 and 3 times the MRHD on a mg/m² basis). When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased following maternal exposure to 30 mg/kg/day (5 times the MRHD on a mg/m² basis), with a no-effect level of 10 mg/kg. Furthermore, behaviors consistent 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.

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 duloxetine 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 duloxetine, 5.9% (143) 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: Duloxetine 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 duloxetine-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 duloxetine-treated patients were exposed for at least 180 days and 445 duloxetine-treated patients were exposed for at least 1 year. 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 adverse events represent 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—Approximately 10% of the 1139 patients who received duloxetine in the placebo-controlled trials discontinued treatment due to an adverse event, compared with 4% of the 777 patients receiving placebo. Nausea (duloxetine 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 duloxetine-treated patients and at a rate of at least twice that of placebo).

Adverse Events Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Treatment-emergent adverse events that occurred in 2% or more of patients treated with duloxetine in the acute phase of MDD placebo-controlled trials (N=1139 duloxetine; 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, tremor; *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 duloxetine and had an incidence ≤ 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 duloxetine-treated MDD patients (incidence ≥5% and at least twice the incidence in placebo patients) were: nausea; dry mouth; constipation; decreased appetite; fatigue; somnolence; and increased sweating.

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 in people over or under 65 years of age. There were too few non-Caucasian patients studied to determine if 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 a 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 their actual incidence. Sexual side effects spontaneously reported by at least 2% of either male or female patients taking duloxetine in placebo-controlled trials were: Males (N=378 duloxetine; N=247 placebo): orgasm abnormal (includes anorgasmia), ejaculatory dysfunction (includes ejaculation disorder and ejaculation failure), libido decreased, erectile dysfunction, ejaculation delayed. Females (N=761 duloxetine; N=530 placebo): orgasm abnormal (includes anorgasmia), libido decreased.

Because adverse sexual events are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 placebo-controlled trials. In these trials, patients treated with duloxetine 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 duloxetine experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on duloxetine than on placebo as 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 other antidepressants. Physicians should routinely inquire about possible sexual side effects. See Table 3 in full PI for specific ASEX results.

Urinary Hesitation—Duloxetine is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with duloxetine, consideration should be given to the possibility that they might be drug-related. Laboratory Changes—Duloxetine treatment, for up to 9 weeks in 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 duloxetine-treated patients when compared with placebo-treated patients (*see* PRECAUTIONS). Vital Sign Changes—Duloxetine treatment, for up to 9 weeks in placebo-controlled clinical trials of 40 to 120 mg daily doses caused increases in blood pressure, averaging 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). Duloxetine treatment, for up to 9 weeks in placebo-controlled clinical trials caused a small increase in heart rate compared to placebo of about 2 beats per minute. Weight Changes—In placebo-controlled clinical trials, patients treated with duloxetine 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. Electrocardiogram Changes—Electrocardiograms were obtained from 321 duloxetine-treated patients with MDD and 169 placebo-treated patients in clinical trials lasting up to 8 weeks. The rate-corrected QT (QTc) interval in duloxetine-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 duloxetine-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-like (depressant) abuse potential. In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

While duloxetine has not been systematically studied in humans for its potential for abuse, there was no 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 and follow such patients closely, observing them for signs of misuse or abuse of duloxetine (eg, development of tolerance, incrementation of dose, drug-seeking behavior).

OVERDOSAGE: There is limited clinical experience with duloxetine overdose in humans. In premarketing clinical trials, as of November 2002, no cases of fatal acute overdose of duloxetine have been reported. Four nonfatal acute ingestions of duloxetine (300 to 1400 mg), alone or in combination with other drugs, have been reported. ***Management of Overdose***—There is no specific antidote to duloxetine. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug effective in the treatment of MDD.

DOSAGE AND ADMINISTRATION: 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) without regard to meals.

There is no evidence that doses greater than 60 mg/day confer any additional benefits.

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