

Antipsychotics Tied to Adverse Metabolic Events

BY MARY ANN MOON
Contributing Writer

Antipsychotic medications are associated with adverse metabolic and cardiovascular events in children and adolescents who are treated in usual-care settings, according to a report.

In a retrospective cohort study, children who are treated with antipsychotics, particularly those who were also receiving antidepressants or mood stabilizers, were

two to three times more likely than those not taking the drugs to develop metabolic disruption and cardiovascular abnormalities, notably obesity, type 2 diabetes, cardiomegaly, nonspecified heart disease, tachycardia, nonspecified arrhythmia, and orthostatic hypotension/syncope, reported Dr. Roger S. McIntyre of the University of Toronto and his associates.

When assessing the risk-benefit profile of this class of drugs, physicians “need to give careful consideration to possible

metabolic disruptions or cardiovascular toxic effects, especially in individuals with comorbid metabolic conditions and those receiving concomitant psychotropic medications,” the investigators said.

They examined adverse events among children and adolescents who were included in the South Carolina Medicaid database in 1996-2005. In all, 4,140 patients were prescribed atypical or conventional antipsychotics (aripiprazole, ziprasidone, quetiapine, risperidone,

olanzapine, haloperidol, or fluphenazine). A random sample of 4,500 children who were not treated with antipsychotics served as controls.

The treated children and adolescents had primary diagnoses of ADHD, conduct disorder, oppositional-defiant disorder, major affective disorder, schizophrenia, and other psychotic disorders. Comorbid conditions included convulsions, CNS disorder, organic brain syndrome, severe mental retardation, substance-related disorder, and congenital heart defects. Nearly 80% of these patients were concomitantly taking antidepressants that can induce weight gain, and many were taking psychostimulants, SSRIs, and mood stabilizers.

Compared with controls, the patients who were treated with antipsychotics were more likely to develop obesity (odds ratio, 2.13), type 2 diabetes (OR, 3.23), cardiovascular conditions (OR, 2.70), and orthostatic hypotension (OR, 1.64). Girls, adolescents, and patients on combination therapy were at highest risk of these adverse effects, Dr. McIntyre and his associates said (*Arch. Pediatr. Adolesc. Med.* 2008;162:929-35).

“Of major public health concern is that, by the end of the study period, 25% of the sample had [one to three] comorbid chronic medical conditions (metabolic and cardiovascular) in addition to their psychiatric disorder,” they added.

“We can speculate that the antipsychotic treatment may have predisposed or exacerbated metabolic changes subsequently leading to cardiovascular events. Other hypothetical mechanisms could be ECG changes (such as QT-interval prolongation), procoagulation effects, or direct effects on blood pressure via adrenoceptor antagonism,” the investigators noted.

The study findings show that “psychiatric and primary care practitioners need to familiarize themselves with the potential for cardiometabolic toxic effects associated with antipsychotics in pediatric populations, and use them sparingly in children displaying early-onset risk factors,” Dr. McIntyre and his colleagues said.

Dr. McIntyre has received research grants from, served on advisory boards of, served on speakers bureaus of, and participated in CME activities of Eli Lilly & Co., the Stanley Medical Research Institute, the National Alliance for Research on Schizophrenia and Depression, AstraZeneca, Biovail Corp., Bristol-Myers Squibb Co., the France Foundation, GlaxoSmithKline, Janssen-Ortho Inc., Organon, Lundbeck, Pfizer Inc., Solvay/Wyeth, Shire PLC, 13CME, and Physicians Postgraduate Press Inc. ■

adverse effects in chronic use (see **WARNINGS—Clinical Worsening and Suicide Risk**). Safety and effectiveness in the pediatric population other than pediatric patients with OCD have not been established (see **BOXED WARNING** and **WARNINGS—Clinical Worsening and Suicide Risk**). Anyone considering the use of LUVOX CR in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use:** Approximately 230 patients and 5 patients participating in controlled premarketing studies with IR fluvoxamine maleate and LUVOX CR, respectively, were 65 years of age or over. No overall differences in safety were observed between these patients and younger patients. Other reported clinical experience has not identified differences in response between the elderly and younger patients. However, SSRIs and SNRIs, including LUVOX CR, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this AE (see **PRECAUTIONS—Hyponatremia**). Furthermore, the clearance of fluvoxamine is decreased by about 50% in elderly compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY**), and greater sensitivity of some older individuals also cannot be ruled out. Consequently, LUVOX CR should be slowly titrated during initiation of therapy. **ADVERSE REACTIONS—Associated with Discontinuation of Treatment:** Of the 279 patients with SAD and 124 patients with OCD treated with LUVOX CR in controlled clinical trials, 26% and 19% discontinued treatment due to an AE. The most common AEs ($\geq 1\%$) associated with discontinuation and considered to be drug related (ie those events associated with dropout at a rate at least twice that of placebo) were as follows: *In patients with SAD—Body as a Whole:* asthenia (4%), headache (3%), abdominal pain (1%); *Digestive:* nausea (8%), diarrhea (3%), anorexia (2%); *Nervous System:* insomnia (5%), somnolence (5%), anxiety (4%), dizziness (4%), abnormal thinking (2%), nervousness (2%), depression (1%), agitation (1%), paresthesia (1%), tremor (1%); *Skin and Appendages:* sweating (1%). *In patients with OCD—Body as a Whole:* asthenia (2%), pain (2%); *Digestive:* nausea (6%), diarrhea (6%), dyspepsia (2%); *Nervous System:* insomnia (5%), somnolence (4%), anxiety (2%), dizziness (3%). **Commonly Observed AEs:** LUVOX CR has been studied in 2 controlled trials of SAD (n=279) and 1 trial of OCD (n=124). In general, AE rates were similar in the 2 data sets as well as in a study of pediatric patients with OCD treated with IR fluvoxamine maleate. The most commonly observed AEs associated with the use of LUVOX CR and likely to be drug-related (incidence $\geq 5\%$ and at least twice that for placebo) were nausea, somnolence, asthenia, diarrhea, anorexia, abnormal ejaculation, tremor, sweating, and anorgasmia. In addition, the following AEs occurred in the SAD population: insomnia, dizziness, dyspepsia, yawn. In the OCD population, the following additional events occurred: decreased libido, anxiety, pharyngitis, vomiting, myalgia, and accidental injury. **AEs Occurring at an Incidence of 2%:** The following AEs occurred in adults at a frequency of $\geq 2\%$, and were more frequent than in the placebo group, among adult patients with SAD (n=279) treated once-daily with 100 to 300 mg/day LUVOX CR in two 12-week controlled trials: *Body as a Whole:* headache (35%), asthenia (24%), abdominal pain (5%), chest pain (3%); *Cardiovascular:* palpitation (3%), vasodilation (2%); *Digestive:* nausea (39%), diarrhea (14%), anorexia (14%), dyspepsia (10%), constipation (6%), liver function test abnormal (2%); *Nervous System:* insomnia (32%), somnolence (26%), dizziness (15%), dry mouth (11%), nervousness (10%), decreased libido (6%) [male (8%), female (4%)], anxiety (8%), tremor (8%), abnormal thinking (3%), abnormal dreams (3%), agitation (3%), hypertonia (2%), paresthesia (3%); *Respiratory System:* yawn (5%), bronchitis (2%); *Skin and Appendages:* sweating (6%); *Special Senses:* taste perversion (2%); *Urogenital:* abnormal ejaculation (11%), anorgasmia (5%) [male (4%), female (5%)], sexual function abnormal (3%) [male (2%), female (3%)], urinary tract infection (2%). The following AEs occurred at a frequency of $\geq 2\%$, and were more frequent than in the placebo group, among adult patients with OCD (n=124) treated once daily with 100 to 300 mg/day LUVOX CR in one 12-week controlled trial: *Body as a Whole:* headache (32%), asthenia (26%), pain (10%), accidental injury (5%), viral infection (2%); *Cardiovascular:* hypertension (2%); *Digestive:* nausea (34%), diarrhea (18%), anorexia (13%), dyspepsia (8%), constipation (4%), vomiting (6%), tooth disorder (2%), gingivitis (2%); *Hemic and Lymphatic:* ecchymosis (4%); *Metabolic and Nutritional Disorders:* weight loss (2%); *Musculoskeletal:* myalgia (5%); *Nervous System:* insomnia (35%), somnolence (27%), dizziness (12%), dry mouth (10%), decreased libido (6%) [male (10%), female (4%)], anxiety (6%), tremor (6%), abnormal thinking (3%), agitation (2%), apathy (3%), neurosis (2%), twitching (2%); *Respiratory System:* pharyngitis (6%), yawn (2%), laryngitis (3%), epistaxis (2%); *Skin:* sweating (7%), acne (2%); *Special Senses:* taste perversion (2%), amblyopia (2%); *Urogenital:* abnormal ejaculation (10%), anorgasmia (5%) [male (4%), female (5%)], menorrhagia (3%), sexual function abnormal (2%) [male (4%), female (0%)], polyuria (2%). These lists include the percentages of patients in each group who had at least 1 occurrence of an event during treatment. Reported AEs were classified using a COSTART-based Dictionary terminology. **Other AEs in OCD Pediatric Population:** In pediatric patients (n=57) treated with IR fluvoxamine maleate, the overall profile of AEs was generally similar to that seen in adult studies, as shown above. However, the following AEs, not shown above, were reported in 2 or more of the pediatric patients and were more frequent with IR fluvoxamine maleate than with placebo: cough increase, dysmenorrhea, emotional lability, fever, flatulence, flu syndrome, hyperkinesia, infection, manic reaction, rash, rhinitis, and sinusitis. **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 and with aging, 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 health care providers 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. The following sexual side effects were reported by $\geq 2\%$ of patients taking LUVOX CR in placebo-controlled trials of SAD and OCD: abnormal ejaculation (11%), anorgasmia [male (4%), female (5%)], impotence (2%), decreased libido [male (8%), female (4%)], sexual function abnormal [male (3%), female (2%)]. Fluvoxamine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae and upon discontinuation of fluvoxamine. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, health care providers should routinely inquire about such possible side effects. **Changes in Weight, Vital Signs, and Laboratory Tests:** No statistically significant differences in weight gain or loss were found between patients treated with LUVOX CR or placebo. Comparisons of IR fluvoxamine maleate or LUVOX CR versus placebo groups in separate short-term trials on (1) median change from baseline and on (2) incidence of patients meeting criteria for potentially important changes from baseline showed no important differences on various vital signs variables or serum chemistry, hematology, and urinalysis variables. **ECG Changes:** Comparisons of IR fluvoxamine maleate or LUVOX CR and placebo groups in separate pools of short-term OCD and depression trials on (1) mean change from baseline on various ECG variables and on (2) incidence of patients meeting criteria for potentially important changes from baseline on various ECG variables revealed no important differences. **Postmarketing Reports:** Voluntary reports of AEs in patients taking IR fluvoxamine maleate that have been received since market introduction and are of unknown causal relationship to fluvoxamine include acute renal failure, agranulocytosis, amenorrhea, anaphylactic reaction, angioedema, aplastic anemia, bullous eruption, Henoch-Schoenlein purpura, hepatitis, hyponatremia, ileus, laryngismus, neuropathy, pancreatitis, porphyria, priapism, serotonin syndrome, severe akinesia with fever when fluvoxamine was co-administered with anti-psychotic medication, Stevens-Johnson syndrome, toxic epidermal necrolysis, vasculitis, and ventricular tachycardia (including torsades de pointes). **DRUG ABUSE AND DEPENDENCE: Controlled Substance Class—LUVOX CR** is not a controlled substance. **Physical and Psychological Dependence:** The potential for abuse, tolerance, and physical dependence with IR fluvoxamine maleate has been studied in a nonhuman primate model. No evidence of dependency phenomena was found. The discontinuation effects of LUVOX CR were not systematically evaluated in controlled clinical trials. LUVOX CR was not systematically studied in clinical trials for potential for abuse, but there was no indication of drug-seeking behavior in clinical trials. It should be noted, however, that patients at risk for drug dependency were systematically excluded from investigational studies of IR fluvoxamine maleate. Generally, it is not possible to predict on the basis of preclinical or premarketing clinical experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, health care providers should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of LUVOX CR misuse or abuse (ie development of tolerance, incrementation of dose, drug-seeking behavior). **OVERDOSAGE: Human**

Experience: Exposure to IR fluvoxamine maleate includes over 45,000 patients treated in clinical trials and an estimated exposure of 50,000,000 patients treated during worldwide marketing experience (end of 2005). Of the 539 cases of deliberate or accidental overdose involving fluvoxamine reported from this population, there were 55 deaths. Of these, 9 were in patients thought to be taking IR fluvoxamine alone, and the remaining 46 were in patients taking fluvoxamine along with other drugs. Among nonfatal overdose cases, 404 patients recovered completely. Five patients experienced adverse sequelae of overdose, to include persistent mydriasis, unsteady gait, hypoxic encephalopathy, kidney complications (from trauma associated with overdose), bowel infarction requiring a hemicolectomy, and vegetative state. In 13 patients, the outcome was provided as abating at the time of reporting. In the remaining 62 patients, the outcome was unknown. The largest known ingestion of fluvoxamine IR involved 12,000 mg (equivalent to 2 to 3 months' dosage). The patient fully recovered. However, ingestions as low as 1,400 mg have been associated with lethal outcome, indicating considerable prognostic variability. In the controlled clinical trials with 403 patients treated with LUVOX CR, there was 1 nonfatal intentional overdose. Commonly ($\geq 5\%$) observed AEs associated with fluvoxamine maleate overdose include GI complaints (nausea, vomiting, and diarrhea), coma, hypokalemia, hypotension, respiratory difficulties, somnolence, and tachycardia. Other notable signs and symptoms seen with IR fluvoxamine maleate overdose (single or multiple drugs) include bradycardia, ECG abnormalities, (such as heart arrest, QT interval prolongation, first degree atrioventricular block, bundle branch block, and junctional rhythm), convulsions, dizziness, liver function disturbances, tremor, and increased reflexes. **Management of Overdose:** Treatment should consist of those general measures employed in the management of overdose with any antidepressant. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients. Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for fluvoxamine are known. A specific caution involves patients taking, or recently having taken, fluvoxamine maleate who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and/or an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see **Tricyclic Antidepressants (TCAs)** under **PRECAUTIONS**). In managing overdose, consider the possibility of multiple drug involvement. The health care provider should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference*. **DOSAGE AND ADMINISTRATION: SAD and OCD—**The recommended starting dose for LUVOX CR in adults is 100 mg qd. LUVOX CR should be administered, with or without food, as a single daily dose at bedtime. The dose should be increased in 50 mg increments every week, as tolerated, until maximum therapeutic benefit is achieved, not to exceed 300 mg per day. Capsules should not be crushed or chewed. **Special Populations—Dosage for Elderly or Hepatically Impaired Patients:** Elderly patients and those with hepatic impairment have been observed to have a decreased clearance of fluvoxamine maleate. Consequently, it may be appropriate to titrate slowly following the initial dose of 100 mg in these patient groups. **Treatment of Pregnant Women During the Third Trimester:** No neonates have been exposed to LUVOX CR. Neonates exposed to IR fluvoxamine maleate and other SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see **PRECAUTIONS**). When treating pregnant women with LUVOX CR during the third trimester, the health care provider should carefully consider the potential risks and benefits of treatment. The health care provider may consider tapering LUVOX CR in the third trimester. **Maintenance/Continuation of Extended Treatment:** Although the efficacy of LUVOX CR beyond 12 weeks of dosing for SAD and OCD has not been documented in controlled trials, SAD and OCD are chronic conditions, and it is reasonable to consider continuation for a responding patient. Dose adjustments should be made to maintain the patient on the lowest effective dose, and patients should be periodically reassessed to determine the need for continued treatment. **Switching Patients To or From a Monoamine Oxidase Inhibitor:** At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with LUVOX CR. Similarly, at least 14 days should be allowed after stopping LUVOX CR before starting an MAOI. **Discontinuation of Treatment with LUVOX CR:** Symptoms associated with discontinuation of other SSRIs or SNRIs have been reported (see **PRECAUTIONS**). Patients should be monitored for these symptoms when discontinuing treatment. 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 health care provider may continue decreasing the dose but at a more gradual rate.

HOW SUPPLIED: Storage: LUVOX CR Capsules should be protected from high humidity and stored at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature]. Avoid exposure to temperatures above 30°C (86°F). Dispense in tight containers. **Keep out of reach of children.**

Lotronex™ is a trademark of GlaxoSmithKline. LUVOX® is a registered trademark of Solvay Pharmaceuticals, Inc. ©2008 Jazz Pharmaceuticals, Inc. Printed in U.S.A. LCR-BPI-01 Rev 0208

References: 1. Davidson J, Yaryura-Tobias J, DuPont R, et al. Fluvoxamine-controlled release formulation for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol.* 2004;24:118-125. 2. Westenberg HGM, Stein DJ, Yang H, et al. A double-blind placebo-controlled study of controlled release fluvoxamine for the treatment of generalized social anxiety disorder. *J Clin Psychopharmacol.* 2004;24:49-55. 3. Hollander E, Koran LM, Goodman WK, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. *J Clin Psychiatry.* 2003;64:640-647. 4. LUVOX CR Prescribing Information. Jazz Pharmaceuticals, Inc., Palo Alto, CA; 2008.

LUVOX CR
fluvoxamine maleate extended-release capsules