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ORIGINAL RESEARCH

Neural Dysfunction in Postpartum Depression: An fMRI Pilot Study

M.E. Silverman, H. Loudon, M. Safier, X. Protopopescu, G. Leiter, X. Liu, and M. Goldstein

REVIEW ARTICLE

Update: New Uses for Lithium and Anticonvulsants

J.M. Rosenberg and C. Salzman

CASE REPORTS

Risperidone-Induced Polydipsia and Polyphagia Associated with Galactorrhea, Abdominal Pain, and Rapid Weight Gain in an Adolescent Hispanic Female

K.I. Afzal, D.F. Briones, and C. DeVargas

Hypersexuality in Inpatient Children and Adolescents: Recognition, Differential Diagnosis, and Evaluation

F. El-Gabalawi and R.A. Johnson

Immunodeficiency Presenting with Subacute Cognitive Decline: Recent Illustrative Cases

D. Costello, J. Davis, and N. Venna

PEARLS IN CLINICAL NEUROSCIENCE

Social Anxiety Disorder: Psychobiological and Evolutionary Underpinnings

D.J. Stein and B. Vythilingum

COMMUNIQUE

Chronic Psychotic Disorder Due to Steroid-Responsive Encephalopathy Associated with Hashimoto's Thyroiditis

NEW SECTION IN SESSION

Newer Antipsychotics and the Differences Between Clinical Experiences and Clinical Trials

S.R. Marder

Yvyasse™ (lisdexamfetamine dimesylate)

Cl

Rx Only

BRIEF SUMMARY: Consult the full Prescribing Information for complete product information.

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY BE ADDICTIVE. DEPENDENT ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

INDICATIONS AND USAGE

Yvyasse is indicated for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD). The efficacy of Yvyasse in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12, who met DSM-IV criteria for ADHD, not DSM-IV-TR criteria. A diagnosis of Attention-Deficit/Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, in social, academic, or occupational functioning, and are present in two or more settings, e.g., at school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the inattentive type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/caresless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the hyperactive-impulsive type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go"; excessive talking; blurting answers; can't wait turn; intrusive. The Combined type requires both inattentive and hyperactive-impulsive criteria to be met. **Special Diagnostic Considerations:** Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of not only medical but of special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program: Yvyasse is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome. Drug treatment may not be indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When medical measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the child's symptoms.

Long-Term Use: The effectiveness of Yvyasse for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Yvyasse for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced atherosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma.

Agitated states.

Patients with a history of drug abuse.

During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result).

WARNINGS

Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products have not been used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug (see CONTRAINDICATIONS).

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should not be treated with stimulant drugs (see CONTRAINDICATIONS).

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm), and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for increases in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia (see CONTRAINDICATIONS).

Assessing Cardiovascular Status Before Treatment with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as palpitations, chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD patients with comorbid bipolar disorder because of concern for possible exacerbation of mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months of treatment, indicated that children (i.e., treatment for 7 days per week throughout the year) had a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d to l enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs, and -2.8 lbs, respectively, for placebo and amphetamine (d to l enantiomer ratio of 3:1). Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. In a controlled trial of lisdexamfetamine in children ages 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.3, and -2.5 lb, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of lisdexamfetamine, compared to a 1 to 1.5 weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received lisdexamfetamine over 12 months suggested that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a slowing in growth rate measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile of -13.4 over 1 year (average percentile at baseline and 12 months, were 60.6 and 47.2, respectively). Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizure. In patients with prior EEG abnormalities in absence of seizures, and very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

PRECAUTIONS

General: The least amount of Yvyasse feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdose. Yvyasse should be used with caution in patients who use other sympathomimetic drugs.

Tics: Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications.

Information for Patients: Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly.

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with lisdexamfetamine and should counsel them in its appropriate use. A patient Medication Guide is available for Yvyasse. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Drug Interactions:

Urinary acidifying agents—These agents (ammonium chloride, sodium acid phosphate, etc.) increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines.

Adrenergic blockers—Adrenergic blockers are inhibited by amphetamines.

Antidepressants, tricyclic—Amphetamines may enhance the activity of tricyclic antidepressants or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly by other tricyclic drugs cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated.

MAO inhibitors—MAO antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headache and other signs of hypertensive crisis. A variety of toxic neurological effects and malignant hyperpyrexia can occur, sometimes with fatal results.

Antihistamines—Amphetamines may counteract the sedative effect of antihistamines.

Antihypertensives—Amphetamines may antagonize the hypotensive effects of antihypertensives.

Chlorpromazine—Chlorpromazine may antagonize the hypotensive effects of norepinephrine receptors, thus inhibiting the central stimulant effects of amphetamines and can be used to treat amphetamine poisoning.

Ethosuximide—Amphetamines may delay intestinal absorption of ethosuximide.

Haloperidol—Haloperidol may delay intestinal absorption of amphetamines.

Lithium carbonate—The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate.

Meprobamate—Amphetamines potentiate the analgesic effect of meprobamate.

Methanamine therapy—Urinary excretion of amphetamines is increased, and efficacy is reduced by acidifying agents used in methanamine therapy.

Norepinephrine—Amphetamines enhance the adrenergic effect of norepinephrine.

Phenothiazines—Amphetamines may delay intestinal absorption of phenothiazine; co-administration of phenobarbital may produce a synergistic anticonvulsant action.

Phenytoin—Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action.

Propoxyphene—In cases of propoxyphene overdose, amphetamine CNS stimulation is potentiated and fatal convulsions can occur.

Veratrum alkaloids—Amphetamines inhibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is dose- and time-dependent. Amphetamines may interfere with urinary steroid determinations.

Carcinogenesis/Mutagenesis and Impairment of Fertility: Carcinogenicity studies of lisdexamfetamine have not been performed.

No evidence of carcinogenicity was found in studies in which d,l-amphetamine (enantiomer ratio of 1:1) was administered to male rats in the diet for 2 years at doses of up to 30 mg/kg/day in male mice, 10 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. Lisdexamfetamine dimesylate was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* and *S. typhimurium* components of the Ames test and in the L5178Y/TK⁺ mouse lymphoma assay *in vitro*.

Amphetamine (d to l enantiomer ratio of 3:1) did not adversely affect fertility or early embryonic development in the rat at doses of up to 20 mg/kg/day.

Pregnancy: Pregnancy Category C. Reproduction studies of lisdexamfetamine have not been performed.

Amphetamine (d to l enantiomer ratio of 3:1) had no apparent effects on embryofetal morphological development or survival when orally administered to pregnant rats and rabbits throughout the period of organogenesis at doses of up to 6 and 10 mg/kg/day, respectively. Fetal malformations and death have been reported in mice following parental administration of dextroamphetamine doses of 50 mg/kg/day or greater to pregnant animals. Administration of these doses was also associated with severe maternal toxicity. A number of studies in rodents indicate that prenatal or early postnatal exposure to amphetamine (d- or l- or d,l-) at doses similar to those used clinically can result in long term neurochemical and behavioral alterations. Reported behavioral effects include learning and memory deficits, altered locomotor activity, and changes in sexual function.

There are no adequate and well-controlled studies in pregnant women. There has been one report of severe congenital bony deformity, tracheo-esophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with other medications during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefits justify the potential risk to the fetus.

Nonteratogenic Effects: Infants born to mothers dependent on amphetamine have an increased risk of premature delivery and low birth weight. Also, infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude.

Use in Nursing Mothers: Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use: Yvyasse is indicated for use in children aged 6 to 12 years.

A study with 30 pediatric patients received oral doses of 4, 10, or 40 mg/kg/day of lisdexamfetamine from day 7 to day 63 of age. At these doses it was approximately 0.7, 2.7, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m² basis. Dose-related decreases in food consumption, bodyweight gain, and crown-rump length were seen, after a four week drug-free recovery period bodyweights and crown-rump lengths had significantly recovered in females but were still substantially reduced in males. Time to vaginal opening was delayed in females at the highest dose, but there were no drug effects on fertility when the animals were mated beginning on day 85 of age.

In a study in which juvenile dogs received lisdexamfetamine for 6 months beginning at 10 weeks of age, decreased bodyweight gain was seen at all doses tested (2, 5, and 12 mg/kg/day, which are approximately 0.5, 1, and 3 times the maximum recommended human daily dose of 70 mg on a mg/m² basis). The effect partially or fully reversed during a four week drug-free recovery period.

Use in Children under Six Years of Age: Lisdexamfetamine dimesylate has not been studied in 3-5 year olds. Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use: Yvyasse has not been studied in the geriatric population.

ADVERSE EVENTS

The premarketing development program for Yvyasse included exposures in a total of 404 participants in clinical trials (348 pediatric patients and 56 healthy adult subjects). Of these, 348 pediatric patients (ages 6 to 12) were evaluated in two controlled clinical studies (one parallel-group and one crossover), one open-label extension study, and one single-dose clinical pharmacology study. The information included in this section is based on data from the 4-week parallel-group controlled clinical trial in pediatric patients with ADHD. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, and ECGs.

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and listings that follow, MedRA terminology has been 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.

Adverse events associated with discontinuation of treatment: Ten percent (21/218) of Yvyasse-treated patients discontinued due to adverse events compared to 1% (1/72) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e., leading to discontinuation in at least 1% of Yvyasse-treated patients and at a rate at least twice that of placebo) were dizziness, decreased appetite, irritability, dry mouth, vomiting, postural hypotension, insomnia, and rash (2/18 each, 1%).

Adverse events occurring in a controlled trial: Adverse events reported in a 4-week clinical trial in pediatric patients treated with Yvyasse or placebo are presented in the table below.

The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual clinical practice, and that adverse events may occur with Yvyasse and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigations. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of the drug to the adverse events that occurred in at least 5% of the Yvyasse patients and at a rate twice that of the placebo group (Table 1). Upper abdominal pain, decreased appetite, dizziness, dry mouth, irritability, insomnia, nausea, vomiting, and decreased weight.

The following additional adverse reactions have been associated with the use of amphetamine. Amphetamine (d to l enantiomer ratio of 3:1), or Yvyasse.

Cardiovascular: Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System: Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal: Dryness of the mouth, unpleasant taste, diarrhea, constipation.

Allergic: Urticaria, hypersensitivity reactions including angioedema and anaphylaxis. Serious reactions including Stevens Johnson Syndrome and toxic epidermal necrolysis have been reported.

Endocrine: Impotence, changes in libido.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: Yvyasse is classified as a Schedule II controlled substance.

Amphetamines have been extensively abused. Tolerance, extreme psychological dependence and severe social disability have occurred. There are reports of patients who have increased the dosage to levels many times higher than recommended. Abuse resulting in prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines may include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia.

In a human abuse liability study, when equivalent oral doses of 100 mg lisdexamfetamine dimesylate and 40 mg immediate release d-amphetamine sulfate were administered to individuals with a history of drug abuse, lisdexamfetamine 100 mg produced subjective responses on a scale of "Drug Liking Effects," "Amphetamine Effects," and "Stimulant Effects" that were significantly less than 40 mg immediate release d-amphetamine sulfate. "Amphetamine Effects" and "Benzidine Effects" that were greater than placebo but less than those produced by an equivalent dose (20 mg) of intravenous d-amphetamine.

Animal Studies: Lisdexamfetamine produced behavioral effects qualitatively similar to those of the CNS stimulant d-amphetamine in monkeys trained to self-administer cocaine; intravenous lisdexamfetamine maintained self-administration at a rate that was statistically less than for cocaine, but greater than that of placebo.

OVERDOSAGE

Individual response to amphetamines varies widely. Toxic symptoms may occur idiosyncratically at low doses.

Symptoms/Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central nervous system stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse.

General clinical symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma.

Treatment: Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and supportive care. Inadequate or inappropriate treatment may result in permanent sequelae. In the regard Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute severe hypertension complicates amphetamine overdose, administration of intravenous phentolamine has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication.

The prolonged release of Yvyasse in the body should be considered when treating patients with overdose.

Manufactured for: New River Pharmaceuticals Inc., Blacksburg, VA 24060. Made in USA.

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Rev 02/07 104A 04 LDXBS1



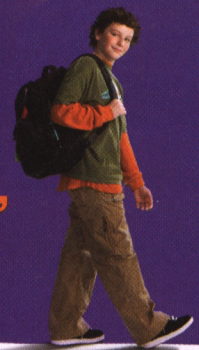
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INTRODUCING



VyvanseTM 
(lisdexamfetamine
dimesylate) capsules
The First Prodrug Stimulant

**Significant efficacy
throughout the day,
even at 6 PM¹**



IMPORTANT SAFETY INFORMATION

Vyvanse should not be taken by patients who have advanced arteriosclerosis; symptomatic cardiovascular disease; moderate to severe hypertension; hyperthyroidism; known hypersensitivity or idiosyncrasy to sympathomimetic amines; agitated states; glaucoma; a history of drug abuse; or during or within 14 days after treatment with monoamine oxidase inhibitors (MAOIs).

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses in ADHD. Physicians should take a careful patient history, including family history, and physical exam, to assess the presence of cardiac disease. Patients who report symptoms of cardiac disease such as exertional chest pain and unexplained syncope should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate.

New psychosis, mania, aggression, growth suppression, and visual disturbances have been associated with the use of stimulants. Use with caution in patients with a history of psychosis, seizures or EEG abnormalities, bipolar disorder, or depression. Growth monitoring is advised during prolonged treatment.

Amphetamines have a high potential for abuse. Administration of amphetamines for prolonged periods of time may lead to drug dependence. Particular attention should be paid to the possibility of subjects obtaining amphetamines for non-therapeutic uses or distribution to others and the drugs should be prescribed or dispensed sparingly. Misuse of amphetamine may cause sudden death and serious cardiovascular adverse events.

The most common adverse events reported in clinical studies of Vyvanse were loss of appetite, insomnia, abdominal pain, and irritability.

Please see Brief Summary of Prescribing Information, including Boxed Warning, on adjacent page.

Reference: 1. Biederman J, Krishnan S, Zhang Y, et al. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: a phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. *Clin Ther.* 2007;29:450-463.

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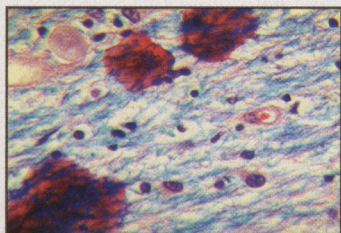
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EDITOR'S LETTER**798 New Uses for Old Drugs and New Circuits for Old Disorders**

Eric Hollander, MD, *Mount Sinai School of Medicine*

CASE REPORTS**818 Immunodeficiency Presenting with Subacute Cognitive Decline: Recent Illustrative Cases**

Khalid I. Afzal, MD, David F. Briones, MD, and Cecilia DeVargas, MD, *Texas Tech University Health Sciences Center-El Paso*

821 Hypersexuality in Inpatient Children and Adolescents: Recognition, Differential Diagnosis, and Evaluation

Fayez El-Gabalawi, MD, and Robert Arnold Johnson, MD, *Thomas Jefferson University Hospital*

842 Risperidone-Induced Polydipsia and Polyphagia Associated with Galactorrhea, Abdominal Pain, and Rapid Weight Gain in an Adolescent Hispanic Female

Daniel Costello, MD, MRCPI, *Harvard Medical School*; John Davis, MD, PhD, *Massachusetts General Hospital*; and Nagagopal Venna, MD, MRCPI, MRCP (UK), *Harvard Medical School*

REVIEW ARTICLE**831 Update: New Uses for Lithium and Anticonvulsants**

Jennifer M. Rosenberg, MD, MPH, *Front Range Clinical Research*; and Carl Salzman, MD, *Harvard Medical School*

ORIGINAL RESEARCH**853 Neural Dysfunction in Postpartum Depression: An fMRI Pilot Study**

Michael E. Silverman, PhD, Holly Loudon, MD; Michal Safier, BA, *Mount Sinai School of Medicine*; Xenia Protopopescu, PhD, *Weill Medical College of Cornell University*; Gila Leiter, MD, Xun Liu, PhD, and Martin Goldstein, MD, *Mount Sinai School of Medicine*

CNS Spectrums (ISSN 1092-8529) is published monthly by MBL Communications, Inc. 333 Hudson Street, 7th Floor, New York, NY 10013.

One-year subscription rates: domestic \$120; foreign \$195; in-training \$85. For subscriptions: Tel: 212-328-0800; Fax: 212-328-0600; Web: www.cns-spectrums.com. Single issues: \$15 – e-mail ks@mbldcommunications.com

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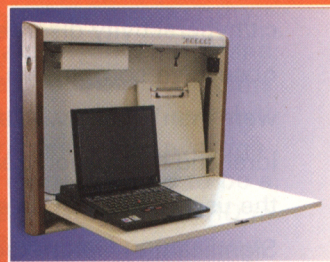
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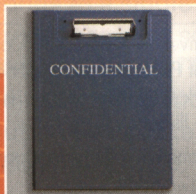
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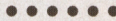
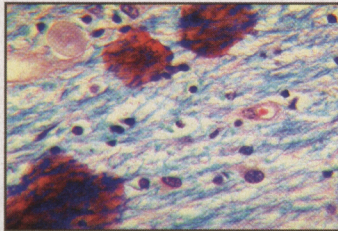
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COMMUNIQUE

- 801 Chronic Psychotic Disorder Due to Steroid-Responsive Encephalopathy Associated with Hashimoto's Thyroiditis**

CLINICAL UPDATES IN NEUROPSYCHIATRY

- 803 News From the Field of Neuroscience**
- *Longitudinal Study Tracks Autism Symptom and Behavior Changes Through Adulthood*
 - *Gene Abnormality Tied to Early-Onset Parkinson's Disease*
 - *Comprehensive Depression Treatment Program Improves Employee Health and Productivity*
 - *Brain Imaging Results May Lead to Early Diagnosis of Alzheimer's Disease*

PEARLS IN CLINICAL NEUROSCIENCE

- 806 Social Anxiety Disorder: Psychobiological and Evolutionary Underpinnings**

Dan J. Stein, MD, PhD, and Bavanisha Vythilingum, MB ChB, *University of Cape Town*

IN SESSION

- 812 Stephen R. Marder, MD**

- *Newer Antipsychotics and the Differences Between Clinical Experiences and Clinical Trials*

EXPERT ROUNDTABLE SUPPLEMENT

Case Studies in Bipolar Depression: Best Practices for the Hospitalized Patient

Paul E. Keck, Jr, MD, Mark A. Frye, MD, and Michael E. Thase, MD

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CNS Spectrums' editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients via original research, review articles, and case reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.

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*Because I don't want to lose
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The voices in his head are back.
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ZYPREXA
Olanzapine

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The labeling for ZYPREXA includes a boxed warning:

- Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo.
- ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

ZYPREXA is approved for the treatment of schizophrenia, acute bipolar mania, and for maintenance treatment in bipolar disorder.

For Important Safety Information, including boxed warning, see adjacent page and accompanying Brief Summary of Prescribing Information.

Lilly

Important Safety Information for ZYPREXA® (Olanzapine)

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ZYPREXA is not approved for the treatment of elderly patients with dementia-related psychosis.

Cerebrovascular adverse events (CVAE), including stroke, in elderly patients with dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of ZYPREXA in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of CVAE in patients treated with ZYPREXA compared to patients treated with placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and diabetes mellitus—Hyperglycemia, in some cases associated with ketoacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including ZYPREXA. All patients taking atypicals should be monitored for symptoms of hyperglycemia. Persons with diabetes who are started on atypicals should be monitored regularly for worsening of glucose control; those with risk factors for diabetes should undergo baseline and periodic fasting blood glucose testing. Patients who develop symptoms of hyperglycemia during treatment should undergo fasting blood glucose testing.

Neuroleptic malignant syndrome (NMS)—As with all antipsychotic medications, a rare and potentially fatal condition known as NMS has been reported with olanzapine. If signs and symptoms appear, immediate discontinuation is recommended. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis and cardiac dysrhythmia). Additional signs may include elevated creatinine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

Tardive dyskinesia (TD)—As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of TD. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic increase. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Medication dispensing and prescribing errors have occurred between ZYPREXA® (olanzapine) and Zyrtec® (cetirizine HCl). These errors could result in unnecessary adverse events or potential relapse in patients suffering from schizophrenia or bipolar disorder. To reduce the potential for dispensing errors, please write ZYPREXA clearly.

The most common treatment-emergent adverse event associated with ZYPREXA (vs placebo) in 6-week acute-phase schizophrenia trials was somnolence (26% vs 15%). Other common events were dizziness (11% vs 4%), weight gain (6% vs 1%), personality disorder (COSTART term for nonaggressive objectionable behavior; 8% vs 4%), constipation (9% vs 3%), akathisia (5% vs 1%), and postural hypotension (5% vs 2%).

The most common treatment-emergent adverse event associated with ZYPREXA (vs placebo) in 3- and 4-week bipolar mania trials was somnolence (35% vs 13%). Other common events were dry mouth (22% vs 7%), dizziness (18% vs 6%), asthenia (15% vs 6%), constipation (11% vs 5%), dyspepsia (11% vs 5%), increased appetite (6% vs 3%), and tremor (6% vs 3%).

For complete safety profile, see the full Prescribing Information.

ZYPREXA is a registered trademark of Eli Lilly and Company.
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ZYPREXA® (Olanzapine Tablets)

ZYPREXA® ZYDIS® (Olanzapine Orally Disintegrating Tablets)

ZYPREXA® IntraMuscular (Olanzapine for Injection)

Brief Summary: Please consult package insert for complete prescribing information.

WARNING

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks) in these patients revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (eg, heart failure, sudden death) or infectious (eg, pneumonia) in nature. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS AND USAGE: ZYPREXA and ZYPREXA Zydis are indicated for short- and long-term treatment of schizophrenia, for acute manic and mixed episodes of bipolar I disorder, and for maintenance treatment in bipolar disorder. The use of ZYPREXA for extended periods should be periodically re-evaluated as to the long-term usefulness of the drug for the individual patient. ZYPREXA IntraMuscular is indicated for treatment of agitation associated with schizophrenia and bipolar I mania.

CONTRAINDICATIONS: Known hypersensitivity to olanzapine.

WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. ZYPREXA is not approved for the treatment of patients with dementia-related psychosis (see BOX WARNING).

In placebo-controlled clinical trials of elderly patients with dementia-related psychosis, the incidence of death in olanzapine-treated patients (3.5%) was significantly greater than placebo-treated patients (1.5%).

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients with Dementia—Cerebrovascular adverse events (eg, stroke, transient ischemic attack), including fatalities, were reported in patients in trials of olanzapine in elderly patients with dementia-related psychosis. In placebo-controlled trials, there was a significantly higher incidence of cerebrovascular adverse events in patients treated with olanzapine compared to patients treated with placebo. Olanzapine is not approved for the treatment of patients with dementia-related psychosis.

Hyperglycemia and Diabetes Mellitus—Hyperglycemia, in some cases associated with ketacidosis, coma, or death, has been reported in patients treated with atypical antipsychotics including olanzapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Patients diagnosed with diabetes who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes who are starting treatment with atypicals should have fasting blood glucose (FBG) testing at baseline and periodically during treatment. Any patient treated with atypicals should be monitored for symptoms of hyperglycemia. Patients who develop symptoms of hyperglycemia during treatment with atypicals should undergo FBG testing.

Neuroleptic Malignant Syndrome (NMS)—Potentially fatal NMS has been reported in association with administration of antipsychotic drugs, including olanzapine. See complete prescribing information for information on management of NMS. Patients requiring antipsychotic drug treatment after recovery from NMS should be carefully monitored since recurrences have been reported.

Tardive Dyskinesia (TD)—Potentially irreversible TD may develop in patients treated with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients are more likely to develop the syndrome. If signs and symptoms of TD appear, consider drug discontinuation.

PRECAUTIONS: Hemodynamic Effects—Olanzapine may induce orthostatic hypotension associated with dizziness; tachycardia; and in some patients, syncope. Hypotension, bradycardia with/without hypotension, tachycardia, and syncope were also reported during the clinical trials with intramuscular olanzapine for injection. Incidence of syncope was 0.6%, 15/2500 with oral olanzapine in phase 2-3 trials and 0.3%, 2/722 with intramuscular olanzapine for injection in clinical trials. Three normal volunteers in phase 1 studies with intramuscular olanzapine experienced hypotension, bradycardia, and sinus pauses of up to 6 seconds that spontaneously resolved (in 2 cases the events occurred on intramuscular olanzapine, and in 1 case, on oral olanzapine). The risk for this sequence of events may be greater in nonpsychiatric patients compared to psychiatric patients who are possibly more adapted to certain effects of psychotropic drugs. Patients should remain recumbent if drowsy or dizzy after injection with intramuscular olanzapine for injection until examination has indicated they are not experiencing postural hypotension, bradycardia, and/or hypotension. Olanzapine should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications) where the occurrence of syncope, or hypotension and/or bradycardia might put them at increased medical risk. Caution is necessary in patients receiving treatment with other drugs having effects that can induce hypotension, bradycardia, respiratory or CNS depression (see Drug Interactions). Concomitant administration of intramuscular olanzapine and parenteral benzodiazepine has not been studied and is not recommended. If such combination treatment is considered, careful evaluation of clinical status for excessive sedation and cardiorespiratory depression is recommended.

Seizures—During premarketing testing, seizures occurred in 0.9% (22/2500) of olanzapine-treated patients, regardless of causality. Use cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold.

Hyperprolactinemia—Like other drugs that antagonize dopamine D₂ receptors, olanzapine elevates prolactin levels; a modest elevation persists during chronic administration. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro. However, neither clinical nor epidemiologic studies have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is inconclusive.

Transaminase Elevations—In placebo-controlled studies, clinically significant ALT (SGPT) elevations (≥3 times the upper limit of normal) were observed in 2% (6/243) of patients exposed to olanzapine compared to no (0/115) placebo patients. None of these patients experienced jaundice. Among about 2400 patients with baseline SGPT ≤90 IU/L, 2% (50/2381) had asymptomatic SGPT elevations to >200 IU/L. Most were transient changes that tended to normalize while olanzapine treatment was continued. Among 2500 patients in oral olanzapine trials, about 1% (23/2500) discontinued treatment due to transaminase increases. Rare postmarketing reports of hepatitis have been received. Very rare cases of cholestatic or mixed liver injury have also been reported in the postmarketing period. Exercise caution in patients who have signs and symptoms of hepatic impairment; preexisting conditions associated with limited hepatic functional reserve; or concomitant treatment with potentially hepatotoxic drugs (see Laboratory Tests, below).

Potential for Cognitive and Motor Impairment—Somnolence was a commonly reported, dose-related adverse event in premarketing trials (olanzapine 26% vs placebo 15%). Somnolence led to discontinuation in 0.4% (9/2500) of patients in the oral premarketing database.

Body Temperature Regulation—Use appropriate care when prescribing olanzapine for patients who will be experiencing conditions that may contribute to an elevation in core body temperature.

Dysphagia—Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's disease. Olanzapine and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide—The possibility of a suicide attempt is inherent in schizophrenia and in bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for olanzapine should be written for the smallest quantity of tablets consistent with good patient management.

Use in Patients with Concomitant Illnesses—Olanzapine should be used with caution in patients with clinically significant prostatic hypertrophy, narrow angle glaucoma, or a history of paralytic ileus.

In 5 placebo-controlled studies in elderly patients with dementia-related psychosis (N=1184), these treatment-emergent adverse events were reported with olanzapine at an incidence of ≥2% and significantly greater than with placebo: falls, somnolence, peripheral edema, abnormal gait, urinary incontinence, lethargy, increased weight, asthenia, pyrexia, pneumonia, dry mouth, visual hallucinations. Discontinuation due to adverse events was significantly greater with olanzapine than placebo (13% vs 7%). Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat this patient population, vigilance should be exercised (see BOX WARNING and WARNINGS).

Because of the risk of orthostatic hypotension with olanzapine, use caution in cardiac patients (see Hemodynamic Effects).

Information for Patients—See full prescribing information for information to discuss with patients taking olanzapine.

Laboratory Tests—Periodic assessment of transaminases is recommended in patients with significant hepatic disease.

Drug Interactions—Use caution when olanzapine is taken in combination with other centrally acting drugs and alcohol. Olanzapine may enhance the effects of certain antihypertensive agents. Olanzapine may antagonize the effects of levodopa and dopamine agonists. Agents that induce CYP1A2 or glucuronyl transferase enzymes (eg, omeprazole, rifampin) may cause an increase in olanzapine clearance. Inhibitors of CYP1A2 could potentially inhibit olanzapine clearance. Although olanzapine is metabolized by multiple enzyme systems, induction or inhibition of a single enzyme may appreciably alter olanzapine clearance. A dosage adjustment may need to be considered with specific drugs.

Activated charcoal (1 g) reduced the C_{max} and AUC of oral olanzapine by about 60%. Single doses of cimetidine (800 mg) or aluminum- and magnesium-containing antacids did not affect the oral bioavailability of olanzapine. Carbamazepine (200 mg bid) causes an approximately 50% increase in the clearance of olanzapine. Higher daily doses of carbamazepine may cause an even greater increase in olanzapine clearance. Neither ethanol (45 mg/70 kg single dose) nor warfarin (20 mg single dose) had an effect on olanzapine pharmacokinetics. Fluoxetine at 60 mg (single or multiple doses) causes a small increase in the C_{max} of olanzapine and a small decrease in olanzapine clearance; however, the impact of this factor is small in comparison to the overall variability between individuals, and dose modification is not routinely recommended. Fluvoxamine decreases the clearance of olanzapine; lower doses of olanzapine should be considered in patients receiving fluvoxamine concomitantly. In vitro data suggest that a clinically significant pharmacokinetic interaction between olanzapine and valproate is unlikely.

Olanzapine is unlikely to cause clinically important drug interactions mediated by the enzymes CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A. Single doses of olanzapine did not affect the pharmacokinetics of imipramine/desipramine or warfarin. Multiple doses of olanzapine did not influence the kinetics of diazepam/N-desmethyldiazepam, lithium, ethanol, or biperiden. However, coadministration of either diazepam or ethanol potentiated the orthostatic hypotension observed with olanzapine. Multiple doses of olanzapine did not affect the pharmacokinetics of theophylline or its metabolites. Co-administration of intramuscular lorazepam and intramuscular olanzapine for injection added to the somnolence observed with either drug alone (see Hemodynamic Effects).

Carcinogenesis, Mutagenesis, Impairment of Fertility—The incidence of liver hemangiomas and hemangiosarcomas in female mice was significantly increased in one carcinogenicity study at 2 times the maximum human daily oral dose (MHDD) but not in another study at 2-5 times the MHDD (mg/m² basis). In this study there was a high incidence of early mortalities in males in the 30/20 mg/kg/d group. The incidence of mammary gland adenomas and adenocarcinomas was significantly increased in female mice and rats given olanzapine at 0.5 and 2 times the MHDD respectively (mg/m² basis). In other studies, serum prolactin measurements of olanzapine showed elevations up to 4-fold in rats at the same doses used in the carcinogenicity studies. The relevance for human risk of the finding of prolactin mediated endocrine tumors in rodents is unknown. No evidence of mutagenic potential for olanzapine has been found.

In rats, fertility (females) and mating performance (males and females) were affected at doses 1.5-11 times the MHDD (mg/m² basis). Diestrous was prolonged and estrous delayed at 0.6 times the MHDD (mg/m² basis); therefore, olanzapine may produce a delay in ovulation.

Pregnancy Category C—There are no adequate and well-controlled studies in pregnant women. Olanzapine should be used in pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery, Nursing Mothers—Parturition in rats was not affected by olanzapine; its effect on labor and delivery in humans is unknown. In a study in lactating, healthy women, olanzapine was excreted in breast milk. Mean infant dose at steady state was estimated to be 1.8% of the maternal dose. It is recommended that women receiving olanzapine should not breast-feed.

Use in Pediatric and Geriatric Patients—Safety and effectiveness in pediatric patients have not been established. In premarketing clinical trials in patients with schizophrenia, there was no indication of any different tolerability of olanzapine in the elderly compared to younger patients. Studies in elderly patients with dementia-related psychosis have suggested there may be a different tolerability profile in these patients. Elderly patients with dementia-related psychosis treated with olanzapine are at an increased risk of death compared to placebo. Olanzapine is not approved for treatment of patients with dementia-related psychosis. If the prescriber elects to treat these patients, vigilance should be exercised. Consider a lower starting dose for any geriatric patient in the presence of factors that might decrease pharmacokinetic clearance or increase the pharmacodynamic response to olanzapine (see BOX WARNING, WARNINGS, and PRECAUTIONS).

ADVERSE REACTIONS: The following findings are based on a clinical trial database consisting of 8661 patients with approximately 4165 patient-years of exposure to oral olanzapine and 722 patients with exposure to intramuscular olanzapine for injection, including patients with schizophrenia, bipolar mania, or Alzheimer's disease (oral olanzapine trials) and patients with agitation associated with schizophrenia, bipolar I disorder (manic or mixed episodes), or dementia (intramuscular olanzapine for injection trials). See the full prescribing information for details on these trials. Certain portions of the discussion below relating to dose-dependent adverse events, vital sign changes, weight gain, laboratory changes, and ECG changes are derived from studies in patients with schizophrenia and have not been duplicated for bipolar mania or agitation; however, this information is also generally applicable to bipolar mania and agitation.

Associated with Discontinuation—Overall there was no difference in discontinuations due to adverse events in placebo-controlled oral olanzapine trials (olanzapine vs placebo: schizophrenia, 5% vs 6%; bipolar mania monotherapy, 2% vs 2%; bipolar mania cotherapy, 1% [olanzapine plus lithium or valproate] vs 2% [lithium or valproate alone]); or in placebo-controlled intramuscular olanzapine for injection trials (olanzapine for injection, 0.4%; placebo 0%). Discontinuations in oral schizophrenia trials due to increases in SGPT were considered to be drug related (olanzapine 2% vs placebo 0%; see PRECAUTIONS).

Commonly Observed Adverse Events—In 6-week, placebo-controlled, premarketing schizophrenia trials, the most common treatment-emergent adverse events associated with oral olanzapine (incidence ≥5% and olanzapine incidence at least twice that for placebo) were: postural hypotension, constipation, weight gain, dizziness, personality disorder (COSTART term for nonaggressive objectionable behavior), and akathisia. In 3- and 4-week placebo-controlled bipolar mania monotherapy trials, the most common treatment-emergent adverse events associated with oral olanzapine were: asthenia, dry mouth, constipation, dyspepsia, increased appetite, somnolence, dizziness, and tremor. In short-term bipolar mania combination therapy trials, the most common treatment-emergent adverse events observed with olanzapine plus lithium or valproate were dry mouth, weight gain, increased appetite, dizziness, back pain, constipation, speech disorder, increased salivation, anorexia, and paresthesia. In 24-hour placebo-controlled trials of intramuscular olanzapine for injection for agitation associated with schizophrenia or bipolar mania, somnolence was the one adverse event observed at an incidence of ≥5% and at least twice that for placebo (olanzapine for injection 6%, placebo 3%).

Adverse Events with an Incidence ≥2% in Oral Monotherapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥2.5 mg/d), and at a greater incidence with olanzapine than with placebo in short-term placebo-controlled trials (olanzapine N-532, placebo N-294):

Body as a Whole—accidental injury, asthenia, fever, back pain, chest pain; **Cardiovascular**—postural hypotension, tachycardia, hypertension; **Digestive**—dry mouth, constipation, dyspepsia, vomiting, increased appetite; **Hemic and Lymphatic**—ecchymosis; **Metabolic and Nutritional**—weight gain, peripheral edema; **Musculoskeletal**—extremity pain (other than joint), joint pain; **Nervous System**—somnolence, insomnia, dizziness, abnormal gait, tremor, akathisia, hypertonia, articulation impairment; **Respiratory**—rhinitis, cough increased, pharyngitis; **Special Senses**—amblyopia; **Urogenital**—urinary incontinence, urinary tract infection.

Adverse Events with an Incidence ≥2% in Oral Combination Therapy Trials—The following treatment-emergent events were reported at an incidence of ≥2% with oral olanzapine (doses ≥5 mg/d) plus lithium or valproate (N=229), and at a greater incidence than with placebo plus lithium or valproate (N=115) in short-term placebo-controlled trials: **Body as a Whole**—asthenia, back pain, accidental injury, chest pain; **Cardiovascular**—hypertension; **Digestive**—dry mouth, increased appetite, thirst, constipation, increased salivation; **Metabolic and Nutritional**—weight gain, peripheral edema, edema; **Nervous System**—somnolence, tremor, depression, dizziness, speech disorder, amnesia, paresthesia, apathy, confusion, euphoria, incoordination; **Respiratory**—pharyngitis, dyspnea; **Skin and Appendages**—sweating, acne, dry skin; **Special Senses**—amblyopia, abnormal vision; **Urogenital**—dysmenorrhea, vaginitis.

Adverse Events with an Incidence ≥1% in Intramuscular Trials—The following treatment-emergent adverse events were reported at an incidence of ≥1% with intramuscular olanzapine for injection (2.5-10 mg/injection) and at incidence greater than placebo in short-term, placebo-controlled trials in agitated patients with schizophrenia or bipolar mania: **Body as a Whole**—asthenia; **Cardiovascular**—hypotension, postural hypotension; **Nervous System**—somnolence, dizziness, tremor.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials—Extrapyramidal Symptoms: In an acute-phase controlled clinical trial in schizophrenia, there was no significant difference in ratings scales incidence between any dose of oral olanzapine (5±2.5, 10±2.5, or 15±2.5 mg/d) and placebo for parkinsonism (Simpson-Angus Scale total score >3) or akathisia (Barnes Akathisia global score ≥2). In the same trial, only akathisia events (spontaneously reported COSTART terms akathisia and hyperkinesia) showed a statistically significantly greater adverse events incidence with the 2 higher doses of olanzapine than with placebo. The incidence of patients reporting any extrapyramidal event was significantly greater than placebo only with the

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highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales incidence or spontaneously reported adverse events.

Other Adverse Events: Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (see PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (see PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. **Body as a Whole—***Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. **Cardiovascular—***Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. **Digestive—***Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. **Endocrine—***Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. **Hemic and Lymphatic—***Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. **Metabolic and Nutritional—***Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesterolemia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. **Musculoskeletal—***Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. **Nervous System—***Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. **Respiratory—***Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. **Skin and Appendages—***Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. **Special Senses—***Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. **Urogenital—***Frequent:* vaginitis; *Infrequent:* abnormal ejaculation, amenorrhea, breast pain, cystitis, decreased menstruation, dysuria, female lactation, glycosuria, gynecomastia, hematuria, impotence, increased menstruation, menorrhagia, metrorrhagia, polyuria, premenstrual syndrome, pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged, vaginal hemorrhage; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

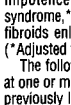
The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. **Body as a Whole—***Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. **Cardiovascular—***Infrequent:* AV block, heart block, syncope. **Digestive—***Infrequent:* diarrhea, nausea. **Hemic and Lymphatic—***Infrequent:* anemia. **Metabolic and Nutritional—***Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. **Musculoskeletal—***Infrequent:* twitching. **Nervous System—***Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. **Skin and Appendages—***Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

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Literature revised November 30, 2006

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https://doi.org/10.1017/S1092852900015480 Published online by Cambridge University Press