Observed During the Premarketing Evaluation of GEODON: Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesteremia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesteremia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal syndrome, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **Other Events Observed During Post-marketing Use:** Adverse event reports not listed above that have been received since market introduction include rare occurrences of the following (no causal relationship with ziprasidone has been established): *Cardiac Disorders:* Tachycardia, torsade de pointes (in the presence of multiple confounding factors - see **WARNINGS**); *Digestive System Disorders:* Swollen tongue; *Nervous System Disorders:* Facial droop, neuroleptic malignant syndrome, serotonin syndrome (alone or in combination with serotonergic medicinal products), tardive dyskinesia; *Psychiatric Disorders:* Insomnia, mania/hypomania; *Reproductive System and Breast Disorders:* Galactorrhea, priapism; *Skin and subcutaneous Tissue Disorders:* Allergic reaction (such as allergic dermatitis, angioedema, orofacial edema, urticaria), rash; *Urogenital System Disorders:* Enuresis, urinary incontinence; *Vascular Disorders:* Postural hypotension, syncope. **DRUG ABUSE AND DEPENDENCE — *Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE —** In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

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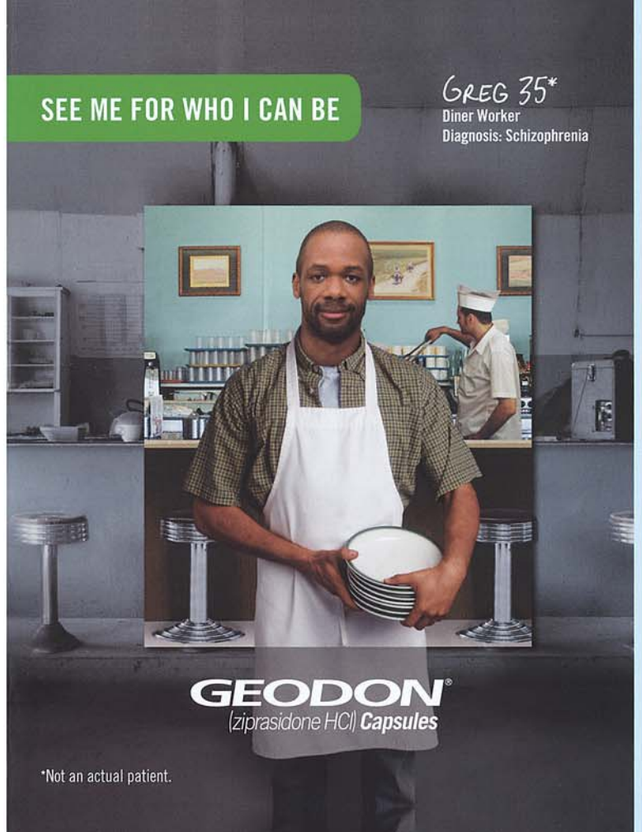

GEODON is indicated for the treatment of schizophrenia.

Important Safety Information

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

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with certain other QT-prolonging drugs. GEODON has a greater capacity to prolong the QT_c interval than several antipsychotics. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. In many cases this would lead to the conclusion that other drugs should be tried first. Hypokalemia may increase the risk of QT prolongation and arrhythmia.

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

In short-term schizophrenia trials, the most commonly observed adverse events associated with GEODON at an incidence of ≥5% and at least twice the rate of placebo were somnolence and respiratory tract infection.

Please see brief summary of prescribing information on adjacent page.

For more information, please visit www.pfizerpro.com/GEODON

BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON® (ziprasidone HCl) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

INDICATIONS—GEODON Capsules are indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

CONTRAINDICATIONS —*QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS —*Increased Mortality in Elderly Patients with Dementia-Related Psychosis:*** **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING). *QT Prolongation and Risk of Sudden Death:*** **GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. *Neuroleptic Malignant Syndrome (NMS):*** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS —*General:*** **Leukopenia, Neutropenia and Agranulocytosis —** *Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia and agranulocytosis have been reported temporally related to antipsychotic agents. Possible risk factors for leukopenia/neutropenia include preexisting low white blood cell count (WBC) and history of drug induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of GEODON should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue GEODON and have their WBC followed until recovery. Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING. WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).** Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** **in WARNINGS** and Orthostatic Hypotension **in PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimuriumin* the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m² basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m² basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m² basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS —*Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash; including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash, and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathesia Scale did not generally show a difference between GEODON and placebo. ***Dystonia:*** Prolonged abnormal contractions of muscle groups may occur in susceptible individuals during first few days of treatment. Dystonia may occur at any dose level but with greater frequency and severity with high potency and at higher doses of first generation antipsychotic drugs. Elevated risk is observed in males and younger age groups. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (<23) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events***

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inside

PERIODICALS:
TIME-SENSITIVE MATERIALS

Credit: Josephine Zeitlin

Psychiatrist and jazz pianist Denny Zeitlin, M.D., found his passion for his two vocations early in life and believes each one enriches the other. Above, he is shown working in a recording studio. **See story on page 17.**

Pfizer Pays Record Settlement In Marketing-Violation Case

This marks the fourth time in the past decade that the world's largest pharmaceutical company has agreed to pay the government after charges of unlawful marketing practices were filed.

BY JUN YAN

Pfizer Inc. will pay $2.3 billion in a massive settlement of civil and criminal charges for illegally promoting prescription drugs for unapproved indications and bribing physicians with kickbacks, the U.S. Department of Justice (DOJ) announced on September 2.

Federal prosecutors alleged that Pfizer and Pharmacia and Upjohn, a company Pfizer acquired, promoted four of their drugs—valdecoxib, ziprasidone, pregabalin, and linezolid—to health care professionals for unapproved indications and thus violated the federal False Claims Act.

In addition to promoting off-label indications, a practice prohibited by the Food, Drug, and Cosmetic Act, Pfizer was alleged to have induced physicians to prescribe the company's products by flying them to resort locations under the guise of consultant meetings and giving them lavish gifts and entertainments.

Pharmacia and Upjohn pleaded guilty to a criminal charge for "misbranding Bextra [valdecoxib] with the intent to defraud or mislead," according to the DOJ announcement. Prosecutors alleged that valdecoxib, a nonsteroidal anti-inflammatory medication, was illegally promoted for indications and dosages that the Food and Drug Administration (FDA) had previously declined to approve because of safety concerns.

Valdecoxib was withdrawn from the market in 2005 at the FDA's request as evidence emerged about serious and potentially fatal adverse events associated with the drug, including cardiovascular events and severe skin reactions. Valdecoxib was initially approved in 2001. Its annual sales in 2004 amounted to $1.3 billion.

Federal authorities said this is the fourth settlement in the past decade between Pfizer and the government regarding Pfizer's unlawful marketing and promotional practices. In a previous case, Pfizer paid $450 million and pleaded to felony charges for illegally promoting off-label uses of gabapentin (Neurontin)—an activ-

please see ***Settlement*** *on page 42*

Norris, Oldham Vie to Become President-Elect

Two psychiatrists whose contributions extend across multiple areas are nominated to be APA's next president-elect, while one officer will no longer be responsible for the duties of secretary and treasurer.

BY KEN HAUSMAN

The Nominating Committee has chosen two psychiatrists who have made extensive contributions to the field to vie in next year's election for the post of APA president-elect, in which Wellesley, Mass., psychiatrist Donna Norris, M.D., will face off against John Oldham, M.D., of Houston in the 2010 election.

Norris, a private practitioner of child, adolescent, and forensic psychiatry, is on the Harvard volunteer faculty and is chair of the Ethics Committee of the Massachusetts Psychiatric Society. Previously she was APA secretary-treasurer, Area 1 trustee, and speaker of the Assembly.

Oldham is senior vice president and chief of staff at the Menninger Clinic and a professor of psychiatry at Baylor. He is on the APA Council on Research and Quality Care, editor of the *Journal of Psychiatric Practice*, and president-elect of the American College of Psychiatrists.

In next year's election the position of secretary-treasurer will be split into two positions. Competing to be secretary are Fred Gottlieb, M.D., of Los Angeles, and Roger Peele, M.D., of Rockville, Md. Gottlieb is a former speaker of the Assembly and APA treasurer. Peele, also a former

please see ***Election*** *on page 42*

Petition Candidates

Any member wishing to be nominated by petition is urged to contact Ricardo Juarez immediately by phone at (888) 35-PSYCH, ext. 8527, or (703) 907-8527 or by e-mail at rjuarez@psych.org. Signatures of 400 voting members (100 for area trustee and member-in-training trustee-elect) supporting the nomination must be filed with the APA secretary-treasurer by **October 15.** Biographical and campaign materials for publication in *Psychiatric News* and for distribution with the ballot are also due by this deadline from all candidates.

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Misuse Rises With Number Of ADHD Prescriptions

The number of calls to poison control centers that were related to prescription amphetamine abuse by teenagers rose sharply from 1998 to 2005.

BY JUN YAN

Data from poison control centers throughout the United States suggest that, over the past decade, more teens misused prescription drugs intended to treat attention-deficit/hyperactivity disorder (ADHD), and some did it with serious consequences.

A study published in the July *Pediatrics* examined information on ADHD-drug-related calls to poison control centers throughout the United States from 1998 to 2005. Jennifer Setlik, M.D., and colleagues at the Cincinnati Children's Hospital Medical Center, analyzed the trends of intentional abuse or misuse of prescription drugs indicated for ADHD treatment among people aged 13 to 19 years. The study findings were derived from the National Poison Data System, a database maintained by the American Association of Poison Control Centers and containing data on calls to 61 regional poison control centers throughout the United States.

The number of calls related to prescription ADHD medication abuse for nonmedical reasons by 13- to 19-year-olds increased by 76 percent from 1998 to 2005 as recorded in the database. The rate of increase in this category was far steeper than that for the total of all substance-abuse-related calls for the general public and the teenaged population. During the same period, ADHD prescriptions for youth aged 10 to 19 nationwide increased by 80 percent, suggesting a parallel between access and abuse.

The rising trend in ADHD medication abuse, at least cases that were serious enough to result in a call to a poison control center, was primarily driven by prescription amphetamine/dextroamphetamine medications. These calls increased more than fivefold—from 71 calls in 1998 to 409 in 2005. Calls related to illicit amphetamine use and amphetamine prescriptions for non-ADHD reasons were excluded from the study. Meanwhile, the number of prescriptions for amphetamine salts to treat ADHD increased from 1.5 million to 3.6 million for teenagers.

The number of methylphenidate-related calls to poison control centers decreased from 246 in 1998 to 172 to 2005 while the total number of prescriptions for methylphenidate saw a relatively modest growth from 2.7 million in 1998 to 4.3 million in 2005.

Among the ADHD-medication-related calls, 65 percent contained information about patients' outcomes. In 42 percent of these cases, the teenagers experienced clinically significant events, including the deaths of three females and one male.

Because poison control centers record only the cases reported to them by individuals or health care professionals who are seeking information or advice, the rates in this study do not reflect the true rates of abuse and do not include serious cases treated in emergency rooms, the authors acknowledged. However, the trends of increased stimulant abuse represent a broad trend in the teen population, particularly regarding amphetamine salts. The authors speculated that this observation may be the result of either the increased number of abusers or increased severity of abuse, or both.

Surveys have indicated that many teenagers share their prescription drugs for ADHD with their friends and schoolmates, the authors noted, which could account for the growing abuse as more prescriptions are written.

An abstract of "Adolescent Prescription ADHD Medication Abuse Is Rising Along With Prescriptions for These Medications" is posted at <pediatrics.aappublications.org/cgi/content/abstract/124/3/875>. ■

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Board of Trustees Endorses HR 3200

BY ALAN F. SCHATZBERG, M.D.

APA's Board of Trustees meeting on September 11 and 12 was highly productive. We discussed a number of key issues for the organization, and I will be highlighting some of the discussions and decisions over the next few issues. Of particular note, we spent considerable time discussing what APA's positions on health care reform should be, particularly whether we should support HR 3200, America's Affordable Health Choices Act. Previously we had sent a letter commenting to the key House committees on aspects of the proposed legislation. At the Board meeting, we formally and unanimously voted to endorse the bill, including the so-called public option.

Although no bill is perfect and there may be elements that may be less attractive to one or another constituency, we recognized that overall HR 3200 offers many positive benefits for psychiatrists and other physicians and, most importantly, for our patients. Among these benefits:

• Requiring a basic benefit package for all qualified health benefit plans in the Health Insurance Exchange proposed in HR 3200. Of particular note, mental health and substance-use disorder treatment is included within the basic benefit package, and this coverage requirement would be extended to all health insurance plans within five years.

The Health Insurance Exchange would be a grouping of health insurance plans for individuals, families, and certain small employers offering a choice of plans in a competitive environment. Uninsured or underinsured Americans would be pooled together to balance the risk of illness and cost of coverage across a large number of individuals. The exchange also could be used to ensure access to affordable, portable health insurance coverage.

• Blocking insurance discrimination based on individuals' health status and preexisting conditions.

• Requiring a public health insurance option in the exchange. We were particularly pleased that the bill as amended by the Energy and Commerce Committee clarifies that physician participation in the public plan is voluntary and that no penalties may be levied for not participating.

• Establishing meaningful requirements for employers and individuals to obtain qualified health insurance coverage.

• Eliminating the pending 21 percent reduction in the Medicare payment update and addressing the flawed sustainable growth rate formula that is used to determine physician reimbursement fees each year.

• Preserving the recent advances in parity for mental health and substance-use disorder treatment, as well as extending the physician fee schedule mental health add-on as enacted in the Medicare Improvements for Patients and Providers Act of 2008. Under this act, the discriminatory 50 percent copay for psychiatric services is being phased out so that patients will have the same 20 percent copay for such care as they do other types of medical care.

As you can see, the bill preserves the gains we have made in regard to parity and provides major benefits for our patients, including prior illness protection and the elimination of proposed reductions in Medicare reimbursement.

We joined a number of major medical societies, including the AMA, in supporting both the bill and a public plan. We also commended the AMA Board of Trustees and advocacy staff for showing leadership in ensuring that APA has an active role in crafting meaningful solutions to the country's health insurance crisis.

In our Board discussions last month, it was clear that the Board believes that a public option can provide a competitive force in the marketplace, and many of our patients are already covered under existing public plans. The Board was clear, however, that our members' participation in a public plan should be purely on a voluntary basis.

We were aided in the discussion by the presence of Dr. Bob Cabaj, the chair of APA's Council on Advocacy and Government Relations. One key action of the Board was to clarify its oversight on responses to proposed legislation that often come at short notice. The president, president-elect, and the council chair will be consulted by Dr. Jay Scully, APA's medical director, and APA's Government Relations staff. This will allow for more rapid responses on key issues. The Executive Committee and full Board will continue to be consulted as needed.

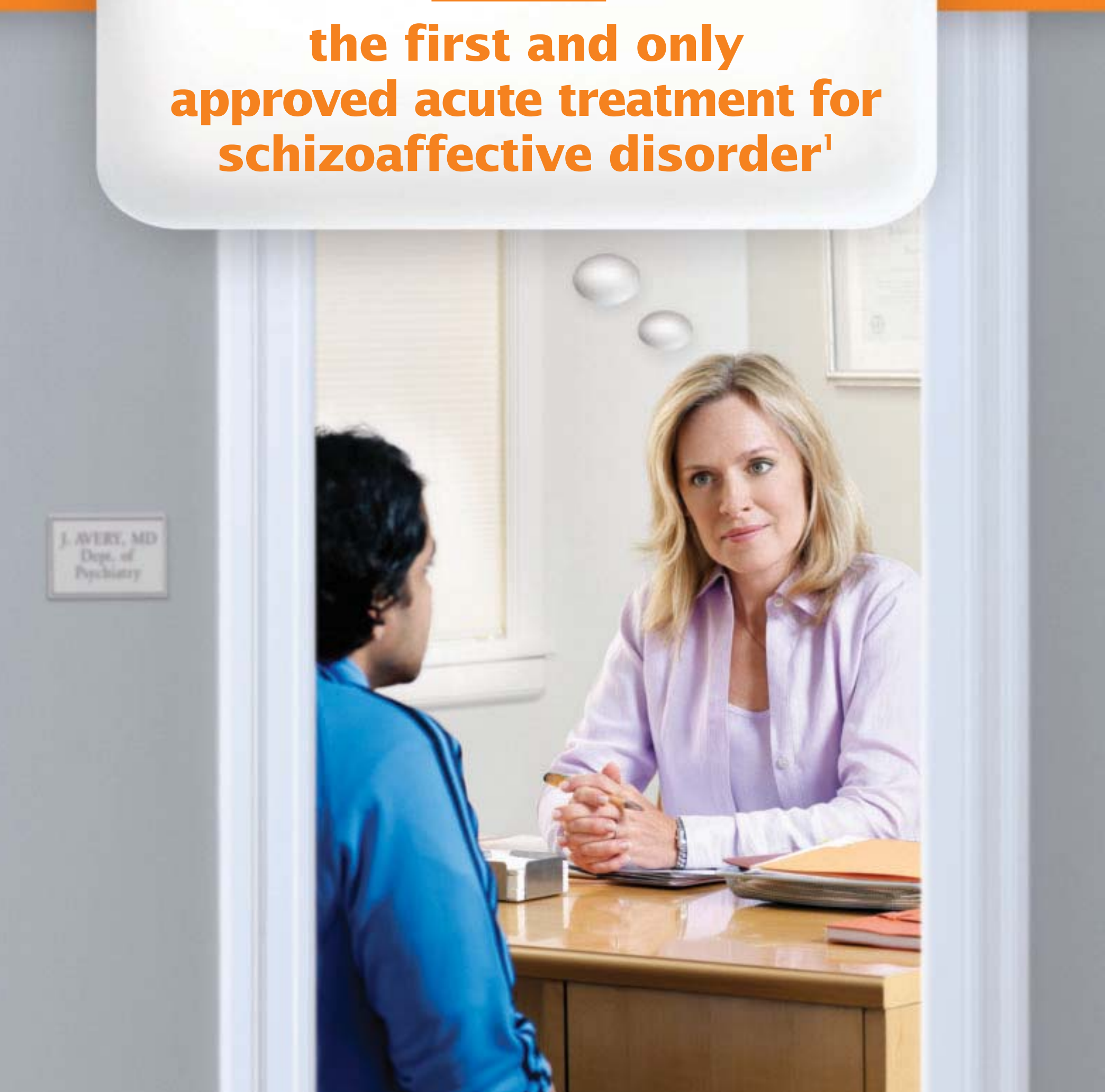
We expect to be involved with our coalition partners in sending Congress numerous letters and other communications over the next few months as work on health care reform unfolds. For example, since the Board met, we sent a letter to the Senate Finance Committee on its bill commending Sens. Max Baucus (D-Mont.), chair of the committee, and Charles Grassley (R-Iowa), ranking minority member, for including coverage of mental illness and substance-use disorders within the basic required benefit package under the Health Insurance Exchange. However, we also pointed out serious concerns we have about the bill, such as its failure to include a long-term fix to Medicare's physician payment formula and issues related to the new federal parity law. The letter is posted at <www.psych.org/dgr/apasfhcrltr>.

We will keep you informed of APA's progress with regard to health care reform in *Psychiatric News* and on APA's Web site under "Advocacy." ■

For my patients with schizoaffective disorder,
one treatment comes to mind:

INVEGA®
(paliperidone)

the first and only approved acute treatment for schizoaffective disorder[1]



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- acute and maintenance treatment of schizophrenia[1]
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- acute treatment of schizoaffective disorder as an adjunct to mood stabilizers and/or antidepressants*[1]

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PALIPERIDONE
Extended-Release Tablets

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*In 2 clinical studies, the most commonly used mood stabilizers were valproate and lithium. The most commonly used antidepressants were SSRIs and SNRIs. Use of MAOIs was excluded.[1]

For more information, including study designs and clinical data, please contact your Janssen® representative.

IMPORTANT SAFETY INFORMATION FOR INVEGA®

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® (paliperidone) is not approved for the treatment of patients with dementia-related psychosis.

Hypersensitivity: Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone, which is a metabolite of risperidone, therefore paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA®.

Cerebrovascular Adverse Events (CAEs): CAEs, including fatalities and stroke, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. INVEGA® is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and close medical monitoring, and treatment of any concomitant serious medical problems.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.

Tardive Dyskinesia (TD): TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly women patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD. Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Hyperglycemia and Diabetes: Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including INVEGA®. Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, INVEGA® elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.

Orthostatic Hypotension and Syncope: INVEGA® may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. INVEGA® should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension.

Leukopenia, Neutropenia and Agranulocytosis have been reported with antipsychotics, including paliperidone. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a decline in WBC and in the absence of other causative factors, discontinuation of INVEGA® should be considered. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA®. INVEGA® has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® does not affect them adversely, and should use caution when operating machinery.

Seizures: INVEGA® should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold.

Suicide: The possibility of suicide attempt is inherent in schizophrenia. Close supervision of high-risk patients should accompany drug therapy.

Maintenance Treatment: Physicians who elect to use INVEGA® for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient.

Commonly Observed Adverse Reactions: The most commonly observed adverse reactions in clinical trials occurring at an incidence of ≥5% and at least 2 times placebo were: schizophrenia—extrapyramidal symptoms, tachycardia, and akathisia; schizoaffective disorder—extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

Reference: 1. INVEGA® (paliperidone) [Prescribing Information]. Titusville, NJ., Ortho-McNeil-Janssen Pharmaceuticals, Inc.

Please see brief summary of full Prescribing Information for INVEGA® on adjacent page.

Janssen®
Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.

 October 2009 01JN09092A

INVEGA®

(paliperidone) Extended-Release Tablets

Brief Summary

BEFORE PRESCRIBING INVEGA®, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® (paliperidone) Extended-Release Tablets is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions]*

INVEGA® (paliperidone) Extended-Release Tablets are indicated for the acute and maintenance treatment of schizophrenia *[see Clinical Studies (14) in full PI*].

CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. INVEGA® (paliperidone) is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA®.

WARNINGS AND PRECAUTIONS

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. INVEGA® (paliperidone) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients With Dementia-Related Psychosis: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. INVEGA® was not marketed at the time these studies were performed. INVEGA® is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions]*.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate-release was more than twice the exposure observed with the maximum recommended 12 mg dose of INVEGA® (C_{max} ss = 113 ng/mL and 45 ng/mL, respectively, when administered with a standard breakfast). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which C_{max} ss = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose. None of the subjects had a change exceeding 60 msec or a QTcLD exceeding 500 msec at any time during this study.

For the three fixed-dose efficacy studies in subjects with schizophrenia, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the INVEGA® 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec). No subject receiving INVEGA® had a QTcLD exceeding 500 msec at any time in any of these three studies.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA®, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA®. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because INVEGA® was not marketed at the time these studies were performed, it is not known if INVEGA® is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Hyperprolactinemia: Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1) in full PI]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Potential for Gastrointestinal Obstruction: Because the INVEGA® tablet is non-deformable and does not appreciably change in shape in the gastrointestinal tract, INVEGA® should ordinarily not be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, "short gut" syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in non-deformable controlled-release formulations. Because of the controlled-release design of the tablet, INVEGA® should only be used in patients who are able to swallow the tablet whole *[see Dosage and Administration (2.3) and Patient Counseling Information (17.8) in full PI]*.

A decrease in transit time, e.g., as seen with diarrhea, would be expected to decrease bioavailability and an increase in transit time, e.g., as seen with gastrointestinal neuropathy, diabetic gastroparesis, or other causes, would be expected to increase bioavailability. These changes in bioavailability are more likely when the changes in transit time occur in the upper GI tract.

Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. In pooled results of the three placebo-controlled, 6-week, fixed-dose trials in subjects with schizophrenia, syncope was reported in 0.8% (7/850) of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) compared to 0.3% (1/355) of subjects treated with placebo. INVEGA® should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: *Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including INVEGA®. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment: Somnolence was reported in subjects treated with INVEGA® *[see Adverse Reactions]*. Antipsychotics, including INVEGA®, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures: During premarketing clinical trials in subjects with schizophrenia (the three placebo-controlled, 6-week, fixed-dose studies and a study conducted in elderly schizophrenic subjects), seizures occurred in 0.22% of subjects treated with INVEGA® (3 mg, 6 mg, 9 mg, 12 mg) and 0.25% of subjects treated with placebo. Like other antipsychotic drugs, INVEGA® should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

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 dementia. INVEGA® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for INVEGA® should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Priapism: Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Priapism has been reported with INVEGA® during postmarketing surveillance. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): No cases of TTP were observed during clinical studies with paliperidone. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA® to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Antiemetic Effect: An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Use in Patients with Concomitant Illness: Clinical experience with INVEGA® in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3) in full PI]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA® has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA®, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions]*.

Monitoring: Laboratory Tests: No specific laboratory tests are recommended.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions]*
- QT prolongation *[see Warnings and Precautions]*
- Tardive dyskinesia *[see Warnings and Precautions]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions]*
- Hyperprolactinemia *[see Warnings and Precautions]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*
- Dysphagia *[see Warnings and Precautions]*
- Suicide *[see Warnings and Precautions]*
- Priapism *[see Warnings and Precautions]*
- Thrombotic thrombocytopenic purpura (TTP) *[see Warnings and Precautions]*
- Disruption of body temperature regulation *[see Warnings and Precautions]*
- Antiemetic effect *[see Warnings and Precautions]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions]*

The most common adverse reactions in clinical trials in subjects with schizophrenia (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate in any of the dose groups) were extrapyramidal symptoms, tachycardia, and akathisia. The most common adverse reactions in clinical trials in patients with schizoaffective disorder (reported in 5% or more of subjects treated with INVEGA® and at least twice the placebo rate) were extrapyramidal symptoms, somnolence, dyspepsia, constipation, weight increased, and nasopharyngitis.

The most common adverse reactions that were associated with discontinuation from clinical trials in subjects with schizophrenia (causing discontinuation in 2% of INVEGA®-treated subjects) were nervous system disorders. The most common adverse reactions that were associated with discontinuation from clinical trials in subjects with schizoaffective disorder were gastrointestinal disorders, which resulted in discontinuation in 1% of INVEGA®-treated subjects. *[See Adverse Reactions]*.

The safety of INVEGA® was evaluated in 1205 adult subjects with schizophrenia who participated in three placebo-controlled, 6-week, double-blind trials, of whom 850 subjects received INVEGA® at fixed doses ranging from 3 mg to 12 mg once daily. The information presented in this section was derived from pooled data from these three trials. Additional safety information from the placebo-controlled phase of the long-term maintenance study, in which subjects received INVEGA® at daily doses within the range of 3 mg to 15 mg (n=104), is also included.

The safety of INVEGA® was also evaluated in 622 adult subjects with schizoaffective disorder who participated in two placebo-controlled, 6-week, double-blind trials. In one of these trials, 206 subjects were assigned to one of two dose levels of INVEGA®: 6 mg with the option to reduce to 3 mg (n = 108) or 12 mg with the option to reduce to 9 mg (n = 98) once daily. In the other study, 214 subjects received flexible doses of INVEGA® (3-12 mg once daily). Both studies included subjects who received INVEGA® either as monotherapy or as an adjunct to mood stabilizers and/or antidepressants. Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of INVEGA® (adverse drug reactions) based on the comprehensive assessment of the available adverse event information. A causal association for INVEGA® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizophrenia: *Table 1* enumerates the pooled incidences of adverse reactions reported in the three placebo-controlled, 6-week, fixed-dose studies, listing those that occurred in 2% or more of subjects treated with INVEGA® in any of the dose groups, and for which the incidence in INVEGA®-treated subjects in any of the dose groups was greater than the incidence in subjects treated with placebo.

Table 1. Adverse Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizophrenia in Three Short-Term, Fixed-Dose, Placebo-Controlled Clinical Trials *: Body System or Organ Class Dictionary-Derived Term followed by **Percent of Patients Reporting Event Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: **Total percentage of subjects with adverse reactions:** 37, 48, 47, 53, 59; **Cardiac disorders:** Atrioventricular block first degree 1, 2, 0, 2, 1; Bundle branch block 2, 3, 1, 3, <1; Sinus arrhythmia 0, 2, 1, 1, <1; Tachycardia 7, 14, 12, 12, 14; **Gastrointestinal disorders:** Abdominal pain upper 1, 1, 3, 2, 2; Dry mouth 1, 2, 3, 1, 3; Salivary hypersecretion<10<114; **General disorders:** Asthenia 1, 2, <1, 2, 2; Fatigue 1, 2, 1, 2, 2; **Nervous system disorders:** Akathisia 4, 4, 3, 8, 10; Dizziness 4, 6, 5, 4, 5; Extrapyramidal symptoms 8, 10, 7, 20, 18; Headache 12, 11, 12, 14, 14; Somnolence 7, 6, 9, 10, 11; **Vascular disorders:** Orthostatic hypotension 1, 2, 1, 2, 4.* Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from three studies; one study included once-daily INVEGA® doses of 3 mg and 9 mg, the second study included 6 mg, 9 mg, and 12 mg, and the third study included 6 mg and 12 mg *[see Clinical Studies (14) in full PI]*. Extrapyramidal symptoms includes the terms dyskinesia, dystonia, extrapyramidal disorder, hypertonia, muscle rigidity, oculogyration, parkinsonism, and tremor. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. Adverse reactions for which the INVEGA® incidence was equal to or less than placebo are not listed in the table, but included the following: vomiting.

Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials – Schizoaffective Disorder: *Table 2* enumerates the pooled incidences of adverse reactions reported in the two placebo-controlled 6-week studies, listing those that occurred in 2% or more of subjects treated with INVEGA® and for which the incidence in INVEGA®-treated subjects was greater than the incidence in subjects treated with placebo.

INVEGA® (paliperidone) Extended-Release Tablets

Table 2. Adverse Drug Reactions Reported by ≥ 2% of INVEGA®-Treated Subjects with Schizoaffective Disorder in Two Double-Blind, Placebo-Controlled Clinical Trials: Body System or Organ Class Dictionary-Derived Term followed by **Placebo (N=202)** first, **INVEGA® 3-6 mg once-daily fixed-dose range (N=108)** second, **INVEGA® 9-12 mg once-daily fixed-dose range (N=98)** third, **INVEGA® 3-12 mg once-daily flexible dose (N=214)** fourth: **Total percentage of subjects with adverse reactions:** 32, 48, 50, 43; **Cardiac disorders:** Tachycardia 2, 3, 1, 2; **Gastrointestinal disorders:** Abdominal discomfort/Abdominal pain upper 1, 1, 0, 3; Constipation 2, 4, 5, 4; Dyspepsia 2, 5, 6, 6; Nausea 6, 8, 8, 5; Stomach discomfort 1, 0, 1, 2; **General disorders:** Asthenia 1, 3, 4, <1; **Infections and Infestations:** Nasopharyngitis 1, 2, 5, 3; Rhinitis 0, 1, 3, 1; Upper respiratory tract infection 1, 2, 2, 2; **Investigations:** Weight increased 1, 5, 4, 4; **Metabolism and nutrition disorders:** Decreased appetite <1, 1, 0, 2; Increased appetite <1, 3, 2, 2; **Musculoskeletal and connective tissue disorders:** Back pain 1, 1, 1, 3; Myalgia <1, 2, 4, 1; **Nervous system disorders:** Akathisia 4, 4, 6, 6; Dysarthria 0, 1, 4, 2; Extrapyramidal symptoms 8, 20, 17, 12; Somnolence 5, 12, 12, 8; **Psychiatric disorders:** Sleep disorder <1, 2, 3, 0; **Respiratory, thoracic and mediastinal disorders:** Cough 1, 1, 3, 1; Pharyngolaryngeal pain <1, 0, 2, 1. * Table includes adverse reactions that were reported in 2% or more of subjects in any of the INVEGA® dose groups and which occurred at greater incidence than in the placebo group. Data are pooled from two studies. One study included once-daily INVEGA® doses of 6 mg (with the option to reduce to 3 mg) and 12 mg (with the option to reduce to 9 mg). The second study included flexible once-daily doses of 3 to 12 mg. Among the 420 subjects treated with INVEGA®, 230 (55%) received INVEGA® as monotherapy and 190 (45%) received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. Somnolence includes the terms sedation and somnolence. Tachycardia includes the terms tachycardia, sinus tachycardia, and heart rate increased. All EPS-related terms are grouped under "extrapyramidal symptoms".

Monotherapy versus Adjunctive Therapy: The designs of the two placebo-controlled, 6-week, double-blind trials in subjects with schizoaffective disorder included the option for subjects to receive antidepressants (except monoamine oxidase inhibitors) and/or mood stabilizers (lithium, valproate, or lamotrigine). In the subject population evaluated for safety, 230 (55%) subjects received INVEGA® as monotherapy and 190 (45%) subjects received INVEGA® as an adjunct to mood stabilizers and/or antidepressants. When comparing these 2 subpopulations, only nausea occurred at a greater frequency (≥ 3% difference) in subjects receiving INVEGA® as monotherapy.

Other Adverse Reactions Observed During Premarketing Evaluation of INVEGA®: The following additional adverse reactions occurred in < 2% of INVEGA®-treated subjects in the above schizophrenia and schizoaffective disorder clinical trial datasets.

Cardiac disorders: bradycardia, palpitations

Eye disorders: vision blurred

Gastrointestinal disorders: abdominal pain, small intestinal obstruction, swollen tongue

General disorders: edema

Immune system disorders: anaphylactic reaction

Nervous system disorders: dizziness postural, grand mal convulsion, lethargy, syncope

Psychiatric disorders: nightmare

Reproductive system and breast disorders: amenorrhea, breast discharge, breast engorgement, breast pain, erectile dysfunction, galactorrhea, gynecomastia, menstruation irregular

Vascular disorders: hypotension, ischemia

Discontinuations Due to Adverse Reactions: Schizophrenia Trials:The percentages of subjects who discontinued due to adverse reactions in the three schizophrenia placebo-controlled, 6-week, fixed-dose studies were 3% and 1% in INVEGA®- and placebo-treated subjects, respectively. The most common reasons for discontinuation were nervous system disorders (2% and 0% in INVEGA®- and placebo-treated subjects, respectively).

Schizoaffective Disorder Trials: The percentages of subjects who discontinued due to adverse reactions in the two schizoaffective disorder placebo-controlled 6-week studies were 1% and <1% in INVEGA®- and placebo-treated subjects, respectively. The most common reasons for discontinuation were gastrointestinal disorders (1% and 0% in INVEGA®- and placebo-treated subjects, respectively).

Dose-Related Adverse Reactions: Schizophrenia Trials: Based on the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, among the adverse reactions that occurred with a greater than 2% incidence in the subjects treated with INVEGA®, the incidences of the following adverse reactions increased with dose: somnolence, orthostatic hypotension, akathisia, dystonia, extrapyramidal disorder, hypertonia, parkinsonism, and salivary hypersecretion. For most of these, the increased incidence was seen primarily at the 12 mg dose, and, in some cases, the 9 mg dose.

Schizoaffective Disorder Trials: In a placebo-controlled, 6-week, high- and low-dose study in subjects with schizoaffective disorder, akathisia, dystonia, dysarthria, myalgia, nasopharyngitis, rhinitis, cough, and pharyngolaryngeal pain occurred more frequently (i.e., a difference of at least 2%) in subjects who received higher doses of INVEGA® compared with subjects who received lower doses.

Demographic Differences: An examination of population subgroups in the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia and in the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder did not reveal any evidence of clinically relevant differences in safety on the basis of gender or race alone; there was also no difference on the basis of age *[see Use in Specific Populations]*.

Extrapyramidal Symptoms (EPS): Pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS *(Table 3)*, and (4) incidence of spontaneous reports of EPS *(Table 4)*. For the Simpson-Angus Scale, spontaneous EPS reports and use of anticholinergic medications, there was a dose-related increase observed for the 9 mg and 12 mg doses. There was no difference observed between placebo and INVEGA® 3 mg and 6 mg doses for any of these EPS measures.

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Ratings Scales and Use of Anticholinergic Medication – Schizophrenia Studies: EPS Group followed by **Percentage of Patients Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: Parkinsonism[a] 9, 11, 3, 15, 14; Akathisia[b] 6, 6, 4, 7, 9; Use of anticholinergic medications[c] 10, 10, 9, 22, 22. a: For Parkinsonism, percent of patients with Simpson-Angus global score > 0.3 (Global score defined as total sum of items score divided by the number of items); b: For Akathisia, percent of patients with Barnes Akathisia Rating Scale global score ≥ 2; c: Percent of patients who received anticholinergic medications to treat emergent EPS

Table 4. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizophrenia Studies: EPS Group followed by **Percentage of Patients Placebo (N=355)** first, **INVEGA® 3 mg once daily (N=127)** second, **6 mg once daily (N=235)** third, **9 mg once daily (N=246)** fourth, **12 mg once daily (N=242)** fifth: Overall percentage of patients with EPS-related AE 11, 13, 10, 25, 26; Dyskinesia 3, 5, 3, 8, 9; Dystonia 1, 1, 1, 5, 5; Hyperkinesia 4, 4, 3, 8, 10; Parkinsonism 2, 3, 3, 7, 6; Tremor 3, 3, 3, 4, 3.

Dyskinesia group includes: Dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms, oculogyration, trismus

Hyperkinesia group includes: Akathisia, hyperkinesia

Parkinsonism group includes: Bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism

Tremor group includes: Tremor

Compared to data from the studies in schizophrenia, pooled data from the two placebo-controlled 6-week studies in subjects with schizoaffective disorder showed similar types and frequencies of EPS as measured by rating scales, anticholinergic medication use, and spontaneous reports of EPS-related adverse events. For subjects with schizoaffective disorder, there was no dose-related increase in EPS observed for parkinsonism with the Simpson-Angus scale or akathisia with the Barnes Akathisia Rating Scale. There was a dose-related increase observed with spontaneous EPS reports of hyperkinesia and dystonia and in the use of anticholinergic medications.

Table 5 shows the EPS data from the pooled schizoaffective disorder trials.

Table 5. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term – Schizoaffective Disorder Studies: EPS Group followed by **Percentage of Patients Placebo (N=202)** first, **INVEGA® 3-6 mg once-daily fixed-dose range (N=108)** second, **9-12 mg once-daily fixed-dose range (N=98)** third, **3-12 mg once-daily flexible dose (N=214):** Overall percentage of patients with EPS-related AE 11, 23, 22, 17; Dyskinesia 1, 3, 1, 1; Dystonia 1, 2, 3, 2; Hyperkinesia 5, 5, 8, 7; Parkinsonism 3, 14, 7, 7; Tremor 3, 12, 11, 5.

Dyskinesia group includes: Dyskinesia, muscle twitching

Dystonia group includes: Dystonia, muscle spasms, oculogyration

Hyperkinesia group includes: Akathisia, hyperkinesia, restlessness

Parkinsonism group includes: Bradykinesia, drooling, hypertonia, muscle rigidity, muscle tightness, musculoskeletal stiffness, parkinsonian gait, parkinsonism

Tremor group includes: Tremor

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia and from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, between-group comparisons revealed no medically important differences between INVEGA® and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® was associated with increases in serum prolactin *[see Warnings and Precautions]*.

Weight Gain: Schizophrenia Trials: In the pooled data from the three placebo-controlled, 6-week, fixed-dose studies in subjects with schizophrenia, the proportions of subjects meeting a weight gain criterion of ≥7% of body weight were compared, revealing a similar incidence of weight gain for INVEGA® 3 mg and 6 mg (7% and 6%, respectively) compared with placebo (5%), and a higher incidence of weight gain for INVEGA® 9 mg and 12 mg (9% and 9%, respectively).

Schizoaffective Disorder Trials: In the pooled data from the two placebo-controlled, 6-week studies in subjects with schizoaffective disorder, a higher percentage of INVEGA®-treated subjects (5%) had an increase in body weight of ≥ 7% compared with placebo-treated subjects (1%). In the study that examined high- and low-dose groups, the increase in body weight of ≥ 7% was 3% in the low-dose group, 7% in the high-dose group, and 1% in the placebo group.

Other Findings Observed During Clinical Trials: The safety of INVEGA® was also evaluated in a long-term trial designed to assess the maintenance of effect with INVEGA® in adults with schizophrenia *[see Clinical Studies (14) in full PI]*. In general, adverse reaction types, frequencies, and severities during the initial 14-week open-label phase of this study were comparable to those observed in the 6-week, placebo-controlled, fixed-dose studies. Adverse reactions reported during the long-term double-blind phase of this study were similar in type and severity to those observed in the initial 14-week open-label phase.

Postmarketing Experience: The following adverse reaction has been identified during postapproval use of INVEGA®; because this reaction was reported voluntarily from a population of uncertain size, it is not possible to reliably estimate its frequency: priapism.

Adverse Reactions Reported With Risperidone: Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with risperidone can be found in the ADVERSE REACTIONS section of the risperidone package insert.

DRUG INTERACTIONS

Potential for INVEGA® to Affect Other Drugs: Given the primary CNS effects of paliperidone *[see Adverse Reactions]*, INVEGA® should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA® is administered with other therapeutic agents that have this potential *[see Warnings and Precautions]*.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

In a clinical study, subjects on a stable dose of valproate showed comparable valproate average plasma concentrations when 3-15 mg of INVEGA® was added to their existing valproate treatment.

Potential for Other Drugs to Affect INVEGA®: Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of INVEGA® 6 mg once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA® should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology (12.3) in full PI]*. In an interaction study in healthy subjects in which a single 3 mg dose of INVEGA® was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

Co-administration of a single dose of INVEGA® 12 mg with divalproex sodium extended-release tablets (two 500 mg tablets once daily) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Dosage reduction for INVEGA® should be considered when INVEGA® is co-administered with valproate after clinical assessment.

Pharmacokinetic interaction between lithium and INVEGA® is unlikely.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.: There are no adequate and well controlled studies of INVEGA® in pregnant women. INVEGA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

INVEGA® (paliperidone) Extended-Release Tablets

In animal reproduction studies, there were no increases in fetal abnormalities when pregnant rats and rabbits were treated during the period of organogenesis with up to 8 times the maximum recommended human dose of paliperidone (on a mg/m² basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, there were increases in pup deaths seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m² basis (see risperidone package insert).

Nursing Mothers: Paliperidone is 9-hydroxyrisperidone, the active metabolite of risperidone. In animal studies, risperidone and 9-hydroxyrisperidone were excreted in milk. Risperidone and 9-hydroxyrisperidone are also excreted in human breast milk. Caution should be exercised when INVEGA® is administered to a nursing woman. The known benefits of breastfeeding should be weighed against the unknown risks of infant exposure to paliperidone.

Pediatric Use: Safety and effectiveness of INVEGA® in patients < 18 years of age have not been established.

Geriatric Use: The safety, tolerability, and efficacy of INVEGA® were evaluated in a 6-week placebo-controlled study of 114 elderly subjects with schizophrenia (65 years of age and older, of whom 21 were 75 years of age and older). In this study, subjects received flexible doses of INVEGA® (3 mg to 12 mg once daily). In addition, a small number of subjects 65 years of age and older were included in the 6-week placebo-controlled studies in which adult schizophrenic subjects received fixed doses of INVEGA® (3 mg to 15 mg once daily) *[see Clinical Studies (14) in full PI]*. There were no subjects ≥ 65 years of age in the schizoaffective disorder studies.

Overall, of the total number of subjects in schizophrenia clinical studies of INVEGA® (n = 1796), including those who received INVEGA® or placebo, 125 (7.0%) were 65 years of age and older and 22 (1.2%) were 75 years of age and older. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in response between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with moderate to severe renal impairment *[see Clinical Pharmacology (12.3) in full PI]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5) in full PI]*.

Renal Impairment: Dosing must be individualized according to the patient's renal function status *[see Dosage and Administration (2.5) in full PI]*.

Hepatic Impairment: No dosage adjustment is required in patients with mild to moderate hepatic impairment. INVEGA® has not been studied in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: INVEGA® (paliperidone) is not a controlled substance.

Abuse: Paliperidone has not been systematically studied in animals or humans for its potential for abuse. It is not possible to predict the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of INVEGA® misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

Dependence: Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

OVERDOSAGE

Human Experience: While experience with paliperidone overdose is limited, among the few cases of overdose reported in pre-marketing trials, the highest estimated ingestion of INVEGA® was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and somnolence, tachycardia and hypotension, and QT prolongation.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the extended-release nature of the product when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Inactive ingredients are carnauba wax, cellulose acetate, hydroxyethyl cellulose, propylene glycol, polyethylene glycol, polyethylene oxides, povidone, sodium chloride, stearic acid, butylated hydroxytoluene, hypromellose, titanium dioxide, and iron oxides. The 3 mg tablets also contain lactose monohydrate and triacetin.

Manufactured by:
ALZA Corporation, Vacaville, CA 95688 *OR*
Janssen Cilag Manufacturing, LLC, Gurabo, Puerto Rico 00778

Manufactured for:
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.,
Titusville, NJ 08560

Revised: July 2009
10105905B

Treat today with NAMENDA

Proven efficacy and tolerability

- Improves function, delays onset of behavioral symptoms, and provides benefits in cognition[1-3]
- Proven safety and tolerability with low risk of gastrointestinal side effects may lead to therapy persistence[4,5]
- Reduces caregiving time, cost, and caregiver distress[3,6,7]
- Effective first-line and in combination with an acetylcholinesterase inhibitor[1,2]

Broad patient access–covered on 98% of Medicare Part D formularies[4]

Namenda® memantine HCl

Extending memory and function

NAMENDA® (memantine HCl) is indicated for the treatment of moderate to severe Alzheimer's disease.

NAMENDA is contraindicated in patients with known hypersensitivity to memantine HCl or any excipients used in the formulation. The most common adverse events reported with NAMENDA vs placebo (≥5% and higher than placebo) were dizziness, confusion, headache, and constipation. In patients with severe renal impairment, the dosage should be reduced.

References: 1. Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, Möbius HJ, for the Memantine Study Group. Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med.* 2003;348:1333-1341. **2.** Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, Gergel I, for the Memantine Study Group. Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA.* 2004;291:317-324. **3.** Cummings JL, Schneider E, Tariot PN, Graham SM, for the Memantine MEM-MD-02 Study Group. Behavioral effects of memantine in Alzheimer disease patients receiving donepezil treatment. *Neurology.* 2006;67:57-63. **4.** Data on file. Forest Laboratories, Inc. **5.** NAMENDA® (memantine HCl) Prescribing Information. Forest Pharmaceuticals, Inc., St Louis, Mo. **6.** Wimo A, Winblad B, Stöffler A, Wirth Y, Möbius HJ. Resource utilisation and cost analysis of memantine in patients with moderate to severe Alzheimer's disease. *Pharmacoeconomics.* 2003;21:327-340. **7.** Winblad B, Poritis N. Memantine in severe dementia: results of the ³M-BEST Study (Benefit and efficacy in severely demented patients during treatment with memantine). *Int J Geriatr Psychiatry.* 1999;14:135-146.

Forest Pharmaceuticals, Inc.

For more details, please visit **www.namenda.com**.

Please see brief summary of Prescribing Information on the adjacent page.

62-1014307R R2 03/09

Namenda
memantine HCl ®

Tablets/Oral Solution
Rx Only

Brief Summary of Prescribing Information.

For complete details, please see full Prescribing Information for Namenda.

INDICATIONS AND USAGE
Namenda (memantine hydrochloride) is indicated for the treatment of moderate to severe dementia of the Alzheimer's type.

CONTRAINDICATIONS
Namenda (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

PRECAUTIONS
Information for Patients and Caregivers: Caregivers should be instructed in the recommended administration (twice per day for doses above 5 mg) and dose escalation (minimum interval of one week between dose increases).

Neurological Conditions
Seizures: Namenda has not been systematically evaluated in patients with a seizure disorder. In clinical trials of Namenda, seizures occurred in 0.2% of patients treated with Namenda and 0.5% of patients treated with placebo.

Genitourinary Conditions
Conditions that raise urine pH may decrease the urinary elimination of memantine resulting in increased plasma levels of memantine.

Special Populations
Hepatic Impairment
Namenda undergoes partial hepatic metabolism, with about 48% of administered dose excreted in urine as unchanged drug or as the sum of parent drug and the N-glucuronide conjugate (74%). No dosage adjustment is needed in patients with mild or moderate hepatic impairment. Namenda should be administered with caution to patients with severe hepatic impairment.

Renal Impairment
No dosage adjustment is needed in patients with mild or moderate renal impairment. A dosage reduction is recommended in patients with severe renal impairment (see CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION in Full Prescribing Information).

Drug-Drug Interactions
N-methyl-D-aspartate (NMDA) antagonists: The combined use of Namenda with other NMDA antagonists (amantadine, ketamine, and dextromethorphan) has not been systematically evaluated and such use should be approached with caution.

Effects of Namenda on substrates of microsomal enzymes: In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) showed minimal inhibition of these enzymes by memantine. In addition, *in vitro* studies indicate that at concentrations exceeding those associated with efficacy, memantine does not induce the cytochrome P450 isoenzymes CYP1A2, CYP2C9, CYP2E1, and CYP3A4/5. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected.

Effects of inhibitors and/or substrates of microsomal enzymes on Namenda: Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine.

Acetylcholinesterase (AChE) inhibitors: Coadministration of Namenda with the AChE inhibitor donepezil HCl did not affect the pharmacokinetics of either compound. In a 24-week controlled clinical study in patients with moderate to severe Alzheimer's disease, the adverse event profile observed with a combination of memantine and donepezil was similar to that of donepezil alone.

Drugs eliminated via renal mechanisms: Because memantine is eliminated in part by tubular secretion, coadministration of drugs that use the same renal cationic system including hydrochlorothiazide (HCTZ), triamterene (TA), metformin, cimetidine, ranitidine, quinidine, and nicotine, could potentially result in altered plasma levels of both agents. However, coadministration of Namenda and HCTZ/TA did not affect the bioavailability of either memantine or TA, and the bioavailability of HCTZ decreased by 20%. In addition, coadministration of memantine with the antihyperglycemic drug Glucovance® (glyburide and metformin HCl) did not affect the pharmacokinetics of memantine, metformin, and glyburide. Furthermore, memantine did not modify the serum glucose lowering effect of Glucovance®.

Drugs that make the urine alkaline: The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate), and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions.

Carcinogenesis, Mutagenesis and Impairment of Fertility
There was no evidence of carcinogenicity in a 113-week oral study in mice at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (20 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks.

Memantine produced no evidence of genotoxic potential when evaluated in the *in vitro S. typhimurium* or *E. coli* reverse mutation assay, an *in vitro* chromosomal aberration test in human lymphocytes, an *in vivo* cytogenetics assay for chromosome damage in rats, and the *in vivo* mouse micronucleus assay. The results were equivocal in an *in vitro* gene mutation assay using Chinese hamster V79 cells.

No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males.

Pregnancy
Pregnancy Category B: Memantine given orally to pregnant rats and pregnant rabbits during the period of organogenesis was not teratogenic up to the highest doses tested (18 mg/kg/day in rats and 30 mg/kg/day in rabbits, which are 9 and 30 times, respectively, the maximum recommended human dose [MRHD] on a mg/m² basis).

Slight maternal toxicity, decreased pup weights and an increased incidence of non-ossified cervical vertebrae were seen at an oral dose of 18 mg/kg/day in a study in which rats were given oral memantine beginning pre-mating and continuing through the postpartum period. Slight maternal toxicity and decreased pup weights were also seen at this dose in a study in which rats were treated from day 15 of gestation through the post-partum period. The no-effect dose for these effects was 6 mg/kg, which is 3 times the MRHD on a mg/m² basis.

There are no adequate and well-controlled studies of memantine in pregnant women. Memantine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers
It is not known whether memantine is excreted in human breast milk. Because many drugs are excreted in human milk, caution should be exercised when memantine is administered to a nursing mother.

Pediatric Use
There are no adequate and well-controlled trials documenting the safety and efficacy of memantine in any illness occurring in children.

ADVERSE REACTIONS
The experience described in this section derives from studies in patients with Alzheimer's disease and vascular dementia.

Adverse Events Leading to Discontinuation: In placebo-controlled trials in which dementia patients received doses of Namenda up to 20 mg/day, the likelihood of discontinuation because of an adverse event was the same in the Namenda group as in the placebo group. No individual adverse event was associated with the discontinuation of treatment in 1% or more of Namenda-treated patients and at a rate greater than placebo.

Adverse Events Reported in Controlled Trials: The reported adverse events in Namenda (memantine hydrochloride) trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior and the types of patients treated may differ. Table 1 lists treatment-emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with Namenda than for those treated with placebo. No adverse event occurred at a frequency of at least 5% and twice the placebo rate.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving Namenda and at a Higher Frequency than Placebo-treated Patients

Body System Adverse Event	Placebo (N = 922) %	Namenda (N = 940) %
Body as a Whole		
Fatigue	1	2
Pain	1	3
Cardiovascular System		
Hypertension	2	4
Central and Peripheral Nervous System		
Dizziness	5	7
Headache	3	6
Gastrointestinal System		
Constipation	3	5
Vomiting	2	3
Musculoskeletal System		
Back pain	2	3
Psychiatric Disorders		
Confusion	5	6
Somnolence	2	3
Hallucination	2	3
Respiratory System		
Coughing	3	4
Dyspnea	1	2

Other adverse events occurring with an incidence of at least 2% in Namenda-treated patients but at a greater or equal rate on placebo were agitation, fall, inflicted injury, urinary incontinence, diarrhea, bronchitis, insomnia, urinary tract infection, influenza-like symptoms, abnormal gait, depression, upper respiratory tract infection, anxiety, peripheral edema, nausea, anorexia, and arthralgia.

The overall profile of adverse events and the incidence rates for individual adverse events in the subpopulation of patients with moderate to severe Alzheimer's disease were not different from the profile and incidence rates described above for the overall dementia population.

Vital Sign Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, diastolic blood pressure and weight) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. There were no clinically important changes in vital signs in patients treated with Namenda. A comparison of supine and standing vital sign measures for Namenda and placebo in elderly normal subjects indicated that Namenda treatment is not associated with orthostatic changes.

Laboratory Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Namenda treatment.

ECG Changes: Namenda and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with Namenda treatment.

Other Adverse Events Observed During Clinical Trials
Namenda has been administered to approximately 1350 patients with dementia, of whom more than 1200 received the maximum recommended dose of 20 mg/day. Patients received Namenda treatment for periods of up to 884 days, with 862 patients receiving at least 24 weeks of treatment and 387 patients receiving 48 weeks or more of treatment.

Treatment emergent signs and symptoms that occurred during 8 controlled clinical trials and 4 open-label trials were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using WHO terminology, and event frequencies were calculated across all studies.

All adverse events occurring in at least two patients are included, except for those already listed in Table 1, WHO terms too general to be informative, minor symptoms or events unlikely to be drug-caused, e.g., because they are common in the study population. Events are classified by body system and listed using the following definitions: frequent adverse events - those occurring in at least 1/100 patients; infrequent adverse events - those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to Namenda treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies.

Body as a Whole: *Frequent:* syncope. *Infrequent:* hypothermia, allergic reaction.

Cardiovascular System: *Frequent:* cardiac failure. *Infrequent:* angina pectoris, bradycardia, myocardial infarction, thrombophlebitis, atrial fibrillation, hypotension, cardiac arrest, postural hypotension, pulmonary embolism, pulmonary edema.

Central and Peripheral Nervous System: *Frequent:* transient ischemic attack, cerebrovascular accident, vertigo, ataxia, hypokinesia. *Infrequent:* paresthesia, convulsions, extrapyramidal disorder, hypertonia, tremor, aphasia, hypoesthesia, abnormal coordination, hemiplegia, hyperkinesia, involuntary muscle contractions, stupor, cerebral hemorrhage, neuralgia, ptosis, neuropathy.

Gastrointestinal System: *Infrequent:* gastroenteritis, diverticulitis, gastrointestinal hemorrhage, melena, esophageal ulceration.

Hemic and Lymphatic Disorders: *Frequent:* anemia. *Infrequent:* leukopenia.

Metabolic and Nutritional Disorders: *Frequent:* increased alkaline phosphatase, decreased weight. *Infrequent:* dehydration, hyponatremia, aggravated diabetes mellitus.

Psychiatric Disorders: *Frequent:* aggressive reaction. *Infrequent:* delusion, personality disorder, emotional lability, nervousness, sleep disorder, libido increased, psychosis, amnesia, apathy, paranoic reaction, thinking abnormal, crying abnormal, appetite increased, paronia, delirium, depersonalization, necrosis, suicide attempt.

Respiratory System: *Frequent:* pneumonia. *Infrequent:* apnea, asthma, hemoptysis.

Skin and Appendages: *Frequent:* rash. *Infrequent:* skin ulceration, pruritus, cellulitis, eczema, dermatitis, erythematous rash, alopecia, urticaria.

Special Senses: *Frequent:* cataract, conjunctivitis. *Infrequent:* macula lutea degeneration, decreased visual acuity, decreased hearing, tinnitus, blepharitis, blurred vision, corneal opacity, glaucoma, conjunctival hemorrhage, eye pain, retinal hemorrhage, xerophthalmia, diplopia, abnormal lacrimation, myopia, retina detachment.

Urinary System: *Frequent:* frequent micturition. *Infrequent:* dysuria, hematuria, urinary retention.

Events Reported Subsequent to the Marketing of Namenda, both US and Ex-US
Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment and are not described elsewhere in labeling: aspiration pneumonia, asthenia, atrioventricular block, bone fracture, carpal tunnel syndrome, cerebral infarction, chest pain, cholelithiasis, claudication, colitis, deep venous thrombosis, depressed level of consciousness (including loss of consciousness and rare reports of coma), dyskinesia, dysphagia, encephalopathy, gastritis, gastroesophageal reflux, grand mal convulsions, intracranial hemorrhage, hepatitis (including increased ALT and AST and hepatic failure), hyperglycemia, hyperlipidemia, hypoglycemia, ileus, increased INR, impotence, lethargy, malaise, myoclonus, neuroleptic malignant syndrome, acute pancreatitis, Parkinsonism, acute renal failure (including increased creatinine and renal insufficiency), prolonged QT interval, restlessness, sepsis, Stevens-Johnson syndrome, suicidal ideation, sudden death, supraventricular tachycardia, tachycardia, tardive dyskinesia, thrombocytopenia, and hallucinations (both visual and auditory).

ANIMAL TOXICOLOGY
Memantine induced neuronal lesions (vacuolation and necrosis) in the multipolar and pyramidal cells in cortical layers III and IV of the posterior cingulate and retrosplenial neocortices in rats similar to those which are known to occur in rodents administered other NMDA receptor antagonists. Lesions were seen after a single dose of memantine, in a study in which rats were given daily oral doses of memantine for 14 days, the no-effect dose for neuronal necrosis was 6 times the maximum recommended human dose on a mg/m² basis. The potential for induction of central neuronal vacuolation and necrosis by NMDA receptor antagonists in humans is unknown.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Class: Memantine HCl is not a controlled substance.

Physical and Psychological Dependence: Memantine HCl is a low to moderate affinity uncompetitive NMDA antagonist that did not produce any evidence of drug-seeking behavior or withdrawal symptoms upon discontinuation in 2,504 patients who participated in clinical trials at therapeutic doses. Post marketing data, outside the U.S., retrospectively collected, has provided no evidence of drug abuse or dependence.

OVERDOSAGE
Signs and symptoms associated with memantine overdosage in clinical trials and from worldwide marketing experience include agitation, confusion, ECG changes, loss of consciousness, psychosis, restlessness, slowed movement, somnolence, stupor, unsteady gait, visual hallucinations, vertigo, vomiting, and weakness. The largest known ingestion of memantine worldwide was 2.0 grams in a patient who took memantine in conjunction with unspecified antidiabetic medications. The patient experienced coma, diplopia, and agitation, but subsequently recovered.

Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. As in any cases of overdose, general supportive measures should be utilized, and treatment should be symptomatic. Elimination of memantine can be enhanced by acidification of urine.

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Rev. 04/07

Early Part D Access Problems May Not Be Resolved

The lead researcher of a recent study believes that the findings are relevant to the current Medicare Part D program because of continuing problems associated with re-randomizing patients to new plans.

BY MARK MORAN

Patients with serious mental illness enrolled in the Medicare Part D prescription drug program who experienced problems accessing medications in the 12 months following initiation of the program in January 2006 were significantly more likely to visit an emergency department during that period.

Forty-four percent of patients who were dually eligible for Medicare and Medicaid experienced a problem accessing medications in the transition from Medicaid to Part D coverage. Among this group, the average predicted probability of visiting an emergency department was significantly greater than among those who did not experience an access problem.

"Medication-access issues due to plan switching or changes in plan coverage rules are likely to still be an issue for a large number of dual eligibles."

"These findings are some of the first to look at the impact of Part D on dual-eligible patients with serious mental illnesses," lead author Haiden Huskamp, Ph.D., told *Psychiatric News*. "We found that many dual eligibles had problems accessing medications after being switched from Medicaid drug coverage to a Part D plan and that individuals who did were more likely to use psychiatric ED [emergency department] care, raising concerns about negative impacts of Part D on quality of care for these individuals.

"Clinicians treating dual-eligible patients with mental illness need to be aware of the potential problems in accessing medications that may be experienced by their patients who are automatically assigned to plans that may or may not meet their medication needs," she said.

Huskamp is an associate professor of health care policy at Harvard Medical School.

The findings were derived from a study of psychiatrists randomly selected from the AMA's master physician file and were reported in the September *Psychiatric Services*. The study analyzes data gathered by the American Psychiatric Institute for Research and Education (APIRE) on medication-access problems in the period January-December 2006. Darrel Regier, M.D, M.P.H., director of APIRE, and Joyce West, Ph.D., M.P.P., senior scientist with APIRE, are the coauthors.

(A previous study by APIRE on access problems based on Part D's first four months was published in the *American Journal of Psychiatry* in May 2007.)

In the new *Psychiatric Services* study, surveyed psychiatrists provided information on a final sample size of 908 dually eligible patients.

Each psychiatrist in the study was randomly assigned one of 21 start days and times to report on the next dually eligible patient treated during the psychiatrist's last typical workweek. For each patient included in the study on whom the psychiatrist reported, researchers obtained data on the patient's sociodemographic characteristics, treatment setting, diagnosis, and clinical characteristics and whether the patient experienced specific medication-access problems.

They also obtained information on emergency department visits related to the patient's psychiatric illness and psychiatric hospitalizations during the study period.

Individuals who did and did not experience medication-access problems were matched using "propensity score matching," a statistical method of creating pairs while adjusting for confounding factors. After creating a matched sample of individuals who did and individuals who did not experience a medication-access problem, the researchers estimated two variables: the likelihood of having any emergency department visits and any hospitalization days for a psychiatric illness in the 12 months after initiation of the Part D program in January 2006, and the number of emergency department visits and hospital days.

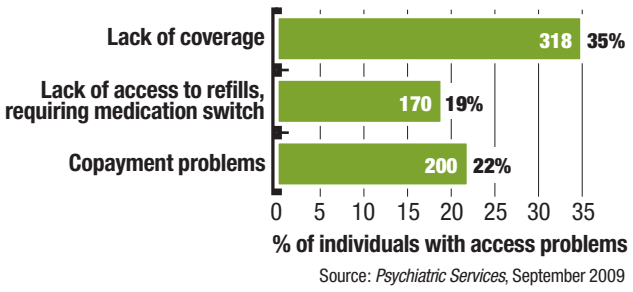
Three possible medication-access problems were assessed in the current study: being unable to access clinically indicated refills or new prescriptions because the drugs were not covered or approved, being stable on a clinically desired or indicated medication but switching to a different drug because refills were not covered or approved, and problems accessing medications because of copayments.

Huskamp and colleagues found that 400 patients, or 44 percent of the sample,

please see ***Access*** *on page 36*

Medication Access Problems Common Under Part D

In a study of patients eligible for Medicare and Medicaid who were enrolled in Medicare Part D in the program's first year (2006), medication-access problems were assessed in the three categories shown below.



Source: *Psychiatric Services*, September 2009

Some Part D Beneficiaries Could Face Difficulty Getting Psychiatric Drugs

Changes in Medicare Part D may mean new drug coverage plans for enrollees, including low-income beneficiaries with subsidized incomes, unless they take action.

BY RICH DALY

Most Medicare Part D beneficiaries are expected to encounter only small increases—an average of 6 percent—in their insurance premiums in 2010. However, some low-income participants could be shifted automatically to lower-cost plans if they don't indicate that they wish to remain with their current plan when Medicare officials notify them about the impending change.

The Centers for Medicare and Medicaid Services (CMS) announced in August that early plan bids indicated that the majority of beneficiaries enrolled in Part D prescription drug plans would have monthly premium increases that average only $2. That increase would bring the average monthly premium to $30 next year.

However, the changes could seriously affect some beneficiaries, particularly low-income subsidy (LIS) beneficiaries in plans with 2010 premiums that are higher than the subsidy the federal government will pay toward their coverage. In such cases, CMS automatically assigns beneficiaries to new lower-cost plans unless they ask not to be switched. Medicare officials estimate that about 800,000 LIS beneficiaries will need to move to a plan charging at or below the benchmark subsidy amount or face automatic reassignment. LIS beneficiaries can opt to stay in the same plan, but they must pay any costs above the subsidy amount.

Nearly 10 million beneficiaries receive prescription drug coverage through the LIS benefit, and it can amount to substantial financial assistance. Generally, Part D beneficiaries are responsible for paying monthly premiums, an annual deductible, and copayments. Those who qualify for full LIS assistance pay no deductible or monthly premiums, however, and they are not subject to falling into Part D's "donut hole"—the coverage gap in prescription-drug costs that begins when the beneficiary has paid $2,700 out of pocket and ends when the beneficiary reaches $4,350.

Any reassignment to a new plan could seriously impact Part D beneficiaries with mental illness because not all drug plans cover psychotropic medications equally.

CMS officials said they would release further details on Part D changes as well as on premiums and benefits for Medicare Advantage plans in late September.

"Although most Part D plans should have relatively stable premiums, all beneficiaries should compare their current coverage with the plans that will be offered in 2010 when information becomes available in October," said Jonathan Blum, acting director of CMS's Center for Health Plan Choices, in a written statement.

More information on 2010 Part D enrollment and related topics can be accessed at <www.medicare.gov>. ■

Home-Visitation Advocates Confront Chorus of Doubts

Critics cast doubt on the idea that federal funding for voluntary home-visitation programs nationwide would reduce the so-called epidemic of parental child abuse and neglect.

BY RICH DALY

A psychiatrist-legislator's little-noticed provision in one of the 1,000-plus-page health care reform bills in Congress would create the first federally funded program for home visits to expectant mothers and families with children under age 6. However, the program has drawn criticism from some "family rights" groups over concerns about its efficacy and appropriateness.

The legislation to establish a regular funding stream for such a voluntary program was sponsored by Rep. Jim McDermott (D-Wash.), a child psychiatrist. He and other supporters said that existing nonfederal home-visitation programs have provided critical supports to families in need.

"Home-visitation programs have a proven track record of increasing the chances that a child will have a safer, healthier, and more productive life," said McDermott in a written statement in July. Home-visitation programs generally entail various types of health care workers—including nurses and mental health counselors—surveying the homes of families over many months or years and offering parenting advice.

Home-visitation programs, which have existed in various forms for several decades, have long received funding from state and local governments and private entities. The programs have functioned with a variety of purposes, but they are fre-

please see ***Home Visitation*** *on page 36*

Cost Pressures Increase Odds That Health Reform Will Pass

Despite contentious developments over the summer with regard to health care reform, the current system's spiraling costs have kept payers united in pushing for reform legislation this year.

BY RICH DALY

Although the exact size and scope of a final health care overhaul measure remains unclear, many experts continue to view as inevitable enactment of some type of reform legislation this year.

The ability of President Obama and Democratic leaders in Congress to get a health care reform measure passed this year was cast into doubt because of massive cost estimates released in July by the Congressional Budget Office and raucous town-hall meetings in August dominated by constituents opposed to reform proposals.

But those developments have not altered the basic realities that employees expect employers to provide health insurance and that health insurance is becoming increasingly unaffordable for both parties.

"When push comes to shove, even if it ends up just being the interest groups with the Democratic Party, I think you will in fact see something that is relatively comprehensive" this year, said Dallas Salisbury, president and CEO of the Employee Benefits Research Institute, at a forum sponsored by the Alliance for Health Reform last month in Washington, D.C.

His belief that Congress will enact some type of health reform was based on his research indicating that employers know their workers need insurance coverage but are increasingly unable to pay for it. For instance, he found that 35 percent of employees identify their employer's health insurance policy as the most important reason they sought their job.

The same inexorable cost pressures led Gail Wilensky, who once headed the agency now known as the Centers for Medicare and Medicaid Services, to agree that it is inevitable that Congress will pass a bill this year that not only reforms health insurance but also overhauls how health care is provided.

"We need expanded coverage and reforms of the health insurance market, but sustainability in spending and improving the quality and clinical appropriateness are even more important," she said.

Credit: Rich Daly

Kirsten Beronio, vice president for public policy and advocacy at Mental Health America, tells congressional staff at a September briefing that health care reform could help control the future growth in costs if the final measure includes the mental health and substance abuse prevention, detection, and treatment provisions of some bills under consideration.

Among the key reforms to reduce costs that Wilensky expects Congress to enact are incentives to reduce unnecessary hospital readmissions and cuts in "generous" Medicare nursing home reimbursement rates. Halving the number of unnecessary hospital readmissions—which demonstration projects have attained in some locations—would reduce Medicare spending by $100 billion over 10 years, according to Glen Thorpe, chair of the Department of Health Policy and Management at Emory University.

Thorpe also expects a reform measure to be passed this year; however, he suggested that an incremental approach is possible. It could take several years of passing small reform packages to meet the two general goals that have drawn broad consensus: universal insurance coverage and cost control to slow health care spending growth.

The two main cost-control approaches that Thorpe expects to be part of a reform law will aim to reduce the number of clinically obese Americans and improve care for people with chronic illness. He hailed several pilot programs to improve care coordination for Medicare beneficiaries with chronic illness, who now have almost no such integrated care, even though 95 percent have multiple chronic conditions. Effective reform would identify which approaches—such as programs that assign one physician as a patient's coordinator—are most effective and then

please see ***Health Reform*** *on page 36*

Psychiatrists Should Be Armed In War Against Smoking

Experts call on psychiatrists to do more to help patients with serious mental illnesses quit smoking and gain back 20 to 30 years of healthy life.

BY JUN YAN

People with mental illness lose decades of their lifespan compared with the general public, and cigarette smoking contributes substantially to this glaring disparity. Now, a wealth of tools and resources is at psychiatrists' fingertips to help them integrate smoking-cessation treatment into their daily practice.

Although tobacco use has been declining for several decades in the general public, the proportion of smokers remains high among those with psychiatric disorders. Research has shown that 75 percent to 85 percent of patients with serious mental illnesses, such as schizophrenia and bipolar disorder, use tobacco and that 44 percent of cigarettes sold in the United States are consumed by people with a mental illness.

"It is time for psychiatrists to integrate smoking cessation [interventions] into their practice," said Douglas Ziedonis, M.D., M.P.H., in an interview with *Psychiatric News*. "In the past 10 years, we have learned a lot more about the medical outcomes of [psychiatric] patients."

Ziedonis is chair of the Department of Psychiatry at the University of Massachusetts (UMass) Medical School and UMass Memorial Medical Center and an expert in tobacco dependence.

He pointed out that mentally ill patients are particularly vulnerable to cancers and cardiovascular diseases, not only because so many of them smoke, but also because the symptoms of their illnesses and the metabolic side effects of many pharmacotherapies compound the health risks that smoking aggravates.

A CDC analysis of 1997-2000 data from eight states showed that the relative risk of death for public mental health clients was higher than for state general populations. Deaths among public mental health clients ranged from 1.2 to 4.9 times higher than the expected number of deaths in those states. Using nationwide life-expectancy data, the study found that the average number of potential years of life lost by a deceased mental health client ranged from 14 years to 32 years in the eight states. The leading causes of death included heart disease, cancer, and cerebrovascular, respiratory, and lung diseases.

"Psychiatrists can do a lot in their practice," said Ziedonis. "They know how to assess patients' motivation [to quit smoking] and how to motivate them." Psychiatrists can integrate smoking cessation seamlessly into their routine screening and, if necessary, can do so with behavioral interventions for alcohol and substance use problems as well, he suggested.

Steven Schroeder, M.D., founder and director of the Smoking Cessation Leadership Center based at the University of San Francisco (UCSF), agreed. "Psychiatrists can become experts themselves," he told *Psychiatric News*.

Alternatively, psychiatrists can encourage and refer patients to treatment programs provided by health care systems such as Kaiser Permanente and the Mayo Clinic or to free smoking-cessation hot-

please see ***Smoking*** *on page 12*

Smoking-Cessation Resources for Health Professionals

- **APA Practice Guideline for the Treatment of Patients With Substance Use Disorders**
  <www.psych.org/MainMenu/EducationCareerDevelopment/LifeLongLearning/PracticeGuidelines/PGSubstanceUseDisorders.aspx>
- **Tobacco Cessation Leadership Network: Bringing Everyone Along**
  <www.tcln.org/bea/cme/index.aspx>
- **Smoking Cessation Leadership Center**
  <http://smokingcessationleadership.ucsf.edu/index.htm>
- **Food and Drug Administration Center for Tobacco Products**
  <www.fda.gov/TobaccoProducts/default.htm>
- **National Institute on Drug Abuse: Resources for Medical and Health Professionals**
  <www.drugabuse.gov/nidamed>
- **University of Medicine and Dentistry of New Jersey: Tobacco Dependence Program**
  <www.tobaccoprogram.org>

Smoking

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lines such as (800) QUIT-NOW, Schroeder suggested.

Both the UMass Medical Center and UCSF have incorporated tobacco-addiction treatment into psychiatric residency training, according to Ziedonis and Schroeder. For practicing psychiatrists, a vast number of resources are available online that can help them become experts in helping patients quit smoking (see box on page 11).

One of these online resources is "Bringing Everyone Along," a project funded by the American Legacy Foundation, a nonprofit organization created from the tobacco-industry legal settlement in 1999. Among the manuals, toolkits, resource guides, and pamphlets, the Web site offers an online continuing medical education module for physicians on treating tobacco addiction.

"It is time for psychiatrists to integrate smoking cessation [interventions] into their practice."

The Smoking Cessation Leadership Center's Web site also contains resources and educational materials, including training videos and Webcasts for health care professionals interested in learning to conduct tobacco screening and interventions. In January the center published a toolkit designed specifically for mental health providers titled "Smoking Cessation for Persons With Mental Illnesses."

Interventions Succeed

It is largely a myth that psychiatric patients are resistant to smoking cessation, said Ziedonis. The majority of smokers, including those with mental illness, do want to quit, but are often unsuccessful without professional intervention, according to Ziedonis and Schroeder.

Rather than expecting patients to quit on their own, physicians may find more success in helping patients stop smoking by combining behavioral interventions and medications. For example, Ziedonis noted, psychiatrists can integrate smoking cessation into their discussions with patients about self-destructive behaviors and help them implement behavioral changes, such as using a smoking log, that can lead patients to understand craving triggers and manage slips and relapses.

Two of the medications used to promote smoking cessation, bupropion and varenicline, are now subject to a boxed warning for increased risk of suicidal thoughts and behaviors. However, Ziedonis believes that

concerns about varenicline should not prevent psychiatrists from prescribing it for patients who want to try the treatment, as long as they are carefully monitored. Also, "psychiatrists are very comfortable with prescribing and monitoring bupropion," he said. In addition, five types of FDA-approved nicotine-replacement treatments can work for many patients. These include nicotine gums, transdermal patches, lozenges, nasal sprays, and inhalers.

"Nicotine replacement is far safer than smoking," said Ziedonis.

More Changes Are Coming

On June 22 the Food and Drug Administration (FDA) gained the right to regulate tobacco products after President Obama signed the Family Smoking Prevention and Tobacco Control Act into law. The agency has established a Center for Tobacco Products and is seeking public comments related to the writing of regulatory guidelines.

As mandated by the new law, tobacco manufacturers and importers will begin to report to the FDA the ingredients in their products by January 2010. Later in 2010, the companies will need FDA approval to use the terms "light," "low," or "mild" on their products. By October, warning labels for cigarettes will be strengthened.

Both Ziedonis and Schroeder urged psychiatrists to do more to help patients stop smoking.

Smoking cessation is a "health-disparity issue, a stigma issue" for mentally ill individuals, Ziedonis believes. He argues that it is long overdue for patients with mental illness to receive aggressive smoking interventions.

"If you want to help your patients get healthy, you need to take smoking as seriously as mental illnesses, because it is the most likely cause to kill your patients," Schroeder said.

The CDC study is posted at <www.cdc.gov/pcd/issues/2006/apr/05_0180.htm>. The Smoking Cessation Leadership Center's tookkit is posted at <http://smokingcessationleadership.ucsf.edu/Downloads/catolgue/MHtoolkitJan_2009.pdf>. ■

Medical Musicians Invited to Tour

The Medical Musical Group Symphony Orchestra and Chorale is seeking participants. The group will hold "Healing for the Nations" concerts in Washington, D.C., on November 4 and in London, November 11, in support of malaria eradication. Participants will have an opportunity to tour London and nearby sites as well as Cardiff, Wales.

More information may be obtained by calling (202) 797-0700, sending an e-mail to vanmmg@hotmail.com, or visiting <www.medicalmusical.org>. ■

Telepsychiatry Fulfills Promise In Rural Mississippi

A Mississippi psychiatrist has launched telepsychiatry in one of the poorest areas of America. He envisions having a seamless telepsychiatry system in place there in five years.

BY JOAN AREHART-TREICHEL

The Mississippi Delta—in northwest Mississippi—has its claims to fame. The Delta is the birthplace of playwright Tennessee Williams, actor Morgan Freeman, and a spate of blues musicians, but it also is home to some of the poorest and least visible people in America. Along with that poverty has been minimal access to psychiatric services—that is, until a year ago, when telepsychiatry arrived in the Delta.

The program was spearheaded by Grayson Norquist, M.D., chair of the Department of Psychiatry at the University of Mississippi Medical College (UMMC) in Jackson.

Two years ago, Norquist approached the Delta Health Alliance about setting up a telepsychiatry service in the Delta. The alliance, which was founded in 2001 to support community-based health care initiatives, liked the idea and gave him a grant to do it.

Norquist and his colleagues at UMMC decided to set up their telepsychiatry service between their psychiatry department in Jackson and community mental health centers in two small Delta towns—Clarksdale and Greenwood—which are more than 100 miles from Jackson. "But then we had to figure out how to do it," Norquist said in an interview.

The "major hassle," he said, was getting the phone company to put the requisite cables into place. But it was finally completed, and they got their telepsychiatry service up and running a year ago.

> **"We might be able to use [telepsychiatry communication] to reach elderly persons at home."**

At first adult patients were not especially comfortable with two-way live communication via a television screen,

Norquist said. However, "the kids adapted to it immediately," he reported. "They love it! They call us the TV docs."

And now a year later, adult patients indicate that they are happy with the system as well. In fact, it is so popular that Norquist and his team are having difficulty meeting the needs of their patients in Clarksdale and Greenwood, along with all of their other responsibilities at the University of Mississippi, but nonetheless they are working on an expansion.

"We hope to install telepsychiatry communication between community mental health centers in Clarksdale and Greenwood and the state hospital to improve the continuity of care of mentally ill patients from those regions. We hope to expand telepsychiatry communication to some other community mental health centers in the Delta as well. And if equipment could be set up for broadband wireless telepsychiatry communication, it would expand our capabilities even more. For instance, we might be able to use it to reach elderly persons at home."

In five years, in fact, he visualizes having a "seamless telepsychiatry system in place in the Delta." Also, he is making progress in working with the state on reimbursing psychiatrists for telepsychiatry services.

Another facet of their program, Norquist reported, is using telepsychiatry to train staff in the community mental health centers in Clarksdale and Greenwood to practice evidence-based medicine. "A psychologist is helping us conduct training in motivational interviewing," he said. "We are also using the telepsychiatry system to provide ongoing case supervision after the training to ensure fidelity to the practice."

Although there are a number of other telepsychiatry programs throughout the United States that deliver patient care and training, he said, this continued training through case supervision appears to be unusual among telepsychiatry programs. ■

Cassada Appointed to Head Up Mississippi Mental Health Board

Margaret Kea Cassada, M.D., of Greenville, Miss., was recently named chair of the Mississippi Board of Mental Health. She is the principal psychiatrist for the Cassada Psychiatric Clinic in Greenville and is the medical director of the Senior Care Unit, Senior Psychiatric Unit, and the Intensive Outpatient Program at Greenwood Leflore Hospital, Sharkey Issaquena County Hospital, and North Sunflower County Hospital. ■

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6 ADVERSE REACTIONS

The following adverse reactions are described in more detail in the *Warnings and Precautions* section of the label: Serious skin rashes *[see Warnings and Precautions (5.1)]*, Hypersensitivity reactions *[see Warnings and Precautions (5.2)]*, Acute multiorgan failure *[see Warnings and Precautions (5.3)]*, Blood dyscrasias *[see Warnings and Precautions (5.4)]*, Suicidal behavior and ideation *[see Warnings and Precautions (5.5)]*, Withdrawal seizures *[see Warnings and Precautions (5.9)]*, Status epilepticus *[see Warnings and Precautions (5.10)]*, Sudden unexplained death in epilepsy *[see Warnings and Precautions (5.11)]*.

6.1 Clinical Trials: Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. LAMICTAL has been evaluated for safety in patients with epilepsy and in patients with Bipolar I Disorder. Adverse reactions reported for each of these patient populations are provided below. Excluded are adverse reactions considered too general to be informative and those not reasonably attributable to the use of the drug.

Epilepsy: *Most Common Adverse Reactions in All Clinical Studies: Adjunctive Therapy in Adults With Epilepsy:* The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with LAMICTAL during adjunctive therapy in adults and not seen at an equivalent frequency among placebo-treated patients were: dizziness, ataxia, somnolence, headache, diplopia, blurred vision, nausea, vomiting, and rash. Dizziness, diplopia, ataxia, blurred vision, nausea, and vomiting were dose-related. Dizziness, diplopia, ataxia, and blurred vision occurred more commonly in patients receiving carbamazepine with LAMICTAL than in patients receiving other AEDs with LAMICTAL. Clinical data suggest a higher incidence of rash, including serious rash, in patients receiving concomitant valproate than in patients not receiving valproate *[see Warnings and Precautions (5.1)]*. Approximately 11% of the 3,378 adult patients who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (3.0%), dizziness (2.8%), and headache (2.5%). In a dose-response study in adults, the rate of discontinuation of LAMICTAL for dizziness, ataxia, diplopia, blurred vision, nausea, and vomiting was dose-related.

Monotherapy in Adults With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with the use of LAMICTAL during the monotherapy phase of the controlled trial in adults not seen at an equivalent rate in the control group were vomiting, coordination abnormality, dyspepsia, nausea, dizziness, rhinitis, anxiety, insomnia, infection, pain, weight decrease, chest pain, and dysmenorrhea. The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions associated with the use of LAMICTAL during the conversion to monotherapy (add-on) period, not seen at an equivalent frequency among low-dose valproate-treated patients, were dizziness, headache, nausea, asthenia, coordination abnormality, vomiting, rash, somnolence, diplopia, ataxia, accidental injury, tremor, blurred vision, insomnia, nystagmus, diarrhea, lymphadenopathy, pruritus, and sinusitis. Approximately 10% of the 420 adult patients who received LAMICTAL as monotherapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.5%), headache (3.1%), and asthenia (2.4%).

Adjunctive Therapy in Pediatric Patients With Epilepsy: The most commonly observed (≥5% for LAMICTAL and more common on drug than placebo) adverse reactions seen in association with the use of LAMICTAL as adjunctive treatment in pediatric patients 2 to 16 years of age and not seen at an equivalent rate in the control group were infection, vomiting, rash, fever, somnolence, accidental injury, dizziness, diarrhea, abdominal pain, nausea, ataxia, tremor, asthenia, bronchitis, flu syndrome, and diplopia. In 339 patients 2 to 16 years of age with partial seizures or generalized seizures of Lennox-Gastaut syndrome, 4.2% of patients on LAMICTAL and 2.9% of patients on placebo discontinued due to adverse reactions. The most commonly reported adverse reaction that led to discontinuation of LAMICTAL was rash. Approximately 11.5% of the 1,081 pediatric patients 2 to 16 years of age who received LAMICTAL as adjunctive therapy in premarketing clinical trials discontinued treatment because of an adverse reaction. The adverse reactions most commonly associated with discontinuation were rash (4.4%), reaction aggravated (1.7%), and ataxia (0.6%).

Controlled Adjunctive Clinical Studies in Adults With Epilepsy: Listed below are treatment-emergent adverse reactions that occurred in at least 2% of adult patients with epilepsy treated with LAMICTAL in placebo-controlled trials and were numerically more common in the patients treated with LAMICTAL. In these studies, either LAMICTAL or placebo was added to the patient's current AED therapy. Adverse reactions were usually mild to moderate in intensity. LAMICTAL was administered as adjunctive therapy to 711 patients; 419 patients received adjunctive placebo. Patients in these adjunctive studies were receiving 1 to 3 of the following concomitant AEDs (carbamazepine, phenytoin, phenobarbital, or primidone) in addition to LAMICTAL or placebo. Patients may have reported multiple adverse reactions during the study or at discontinuation; thus, patients may be included in more than one category.

Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Adult Patients With Epilepsy (Adverse events in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo): Body as a whole: Headache (29,19), flu syndrome (7,6), fever (6,4), abdominal pain (5,4), neck pain (2,1), reaction aggravated (seizure exacerbation) (2,1); **Digestive:** Nausea (19,10), vomiting (9,4), diarrhea (6,4), dyspepsia (5,2), constipation (4,3), anorexia (2,1); **Musculoskeletal:** Arthralgia (2,0); **Nervous:** Dizziness (38,13), ataxia (22,6), somnolence (14,7), incoordination (6,2), insomnia (6,2), tremor (4,1), depression (4,3), anxiety (4,3), convulsion (3,1), irritability (3,2), speech disorder (3,0), concentration disturbance (2,1); **Respiratory:** Rhinitis (14,9), pharyngitis (10,9), cough increased (8,6); **Skin and appendages:** Rash (10,5), pruritus (3,2); **Special senses:** Diplopia (28,7), blurred vision (16,5), vision abnormality (3,1); **Urogenital** (female patients only, n = 365, n = 207): Dysmenorrhea (7,6), vaginitis (4,1), amenorrhea (2,1).

Dose-Related Adverse Reactions From a Randomized, Placebo-Controlled Adjunctive Trial in Adults With Epilepsy: In a randomized, parallel study comparing placebo (n = 73) and 300 (n = 71) and 500 mg/day (n = 72) of LAMICTAL, some of the more common drug-related adverse reactions were dose-related. The following adverse reactions are listed by incidence in placebo first, LAMICTAL 300 mg dose second, and LAMICTAL 500 mg dose third: ataxia (10,10,28), blurred vision (10,11,25), diplopia (8,24,49), dizziness (27,31,54), nausea (11,18,25), vomiting (4,11,18). The overall adverse reaction profile for LAMICTAL was similar between females and males, and was independent of age. Because the largest non-Caucasian racial subgroup was only 6% of patients exposed to LAMICTAL in placebo-controlled trials, there are insufficient data to support a statement regarding the distribution of adverse reaction reports by race. Generally, females receiving either LAMICTAL as adjunctive therapy or placebo were more likely to report adverse reactions than males. The only adverse reaction for which the reports on LAMICTAL were greater than 10% more frequent in females than males (without a corresponding difference by gender on placebo) was dizziness (difference = 16.5%). There was little difference between females and males in the rates of discontinuation of LAMICTAL for individual adverse reactions.

Controlled Monotherapy Trial in Adults With Partial Seizures: Listed below are treatment-emergent adverse reactions that occurred in at least 5% of patients with epilepsy treated with monotherapy with LAMICTAL in a double-blind trial following discontinuation of either concomitant carbamazepine or phenytoin not seen at an equivalent frequency in the control group. Forty-three patients received monotherapy with LAMICTAL up to 500 mg/day; 44 received low-dose valproate monotherapy at 1,000 mg/day. Patients in these studies were converted to LAMICTAL or valproate monotherapy from adjunctive therapy with carbamazepine or phenytoin. Patients may have reported multiple adverse experiences during the study; thus, patients may be included in more than one category.

Treatment-Emergent Adverse Reaction Incidence in Adults With Partial Seizures in a Controlled Monotherapy Trial (Adverse reactions in at least 5% of patients treated with LAMICTAL and numerically more frequent than in the valproate group are listed by body system with the incidence for LAMICTAL followed by valproate): Body as a whole: Pain (5,0), infection (5,2), chest pain (5,2); **Digestive**: Vomiting (9,0), dyspepsia (7,2), nausea (7,2); **Metabolic and nutritional:** Weight decrease (5,2); **Nervous:** Coordination abnormality (7,0), dizziness (7,0), anxiety (5,0), insomnia (5,2); **Respiratory:** Rhinitis (7,2); **Urogenital** (female patients only (n=21), (n=28)): Dysmenorrhea (5 ,0).

Adverse reactions that occurred with a frequency of less than 5% and greater than 2% of patients receiving LAMICTAL and numerically more frequent than placebo were: **Body as a Whole:** Asthenia, fever. **Digestive:** Anorexia, dry mouth, rectal hemorrhage, peptic ulcer. **Metabolic and Nutritional:** Peripheral edema. **Nervous System:** Amnesia, ataxia, depression, hypesthesia, libido increase, decreased reflexes, increased reflexes, nystagmus, irritability, suicidal ideation. **Respiratory**: Epistaxis, bronchitis, dyspnea. **Skin and Appendages:** Contact dermatitis, dry skin, sweating. **Special Senses:** Vision abnormality. *Incidence in Controlled Adjunctive Trials in Pediatric Patients With Epilepsy:* Listed below are adverse reactions that occurred in at least 2% of 339 pediatric patients with partial seizures or generalized seizures of Lennox-Gastaut syndrome, who received LAMICTAL up to 15 mg/kg/day or a maximum of 750 mg/day. Reported adverse reactions were classified using COSTART terminology. LAMICTAL was administered as adjunctive therapy to 168 patients; 171 patients received adjunctive placebo.

Treatment-Emergent Adverse Reaction Incidence in Placebo-Controlled Adjunctive Trials in Pediatric Patients With Epilepsy (Adverse reactions in at least 2% of patients treated with LAMICTAL and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo): Body as a whole: Infection (20,17), fever (15,14), accidental injury (14,12), abdominal pain (10,5), asthenia (8,4), flu syndrome (7,6), pain (5,4), facial edema (2,1), photosensitivity (2,0); **Cardiovascular:** Hemorrhage (2,1); **Digestive:** Vomiting (20,16), diarrhea (11,9), nausea (10,2), constipation (4,2), dyspepsia (2,1), **Hemic and lymphatic:** Lymphadenopathy (2,1); **Metabolic and nutritional:** Edema (2,0) **Nervous system:** Somnolence (17,15), dizziness (14,4), ataxia (11,3), tremor (10,1), emotional lability (4,2), gait abnormality (4,2), thinking abnormality (3,2), convulsions (2,1), nervousness (2,1), vertigo (2,1); **Respiratory:** Pharyngitis (14,11), bronchitis (7,5), increased cough (7,6), sinusitis (2,1), bronchospasm (2,1); **Skin:** Rash (14,12), eczema (2,1), pruritus (2,1); **Special senses:** Diplopia (5,1), blurred vision (4,1), visual abnormality (2,0); **Urogenital:** (male and female patients) Urinary tract infection (3,0).

Bipolar Disorder: The most commonly observed (≥5%) treatment-emergent adverse reactions seen in association with the use of LAMICTAL as monotherapy (100 to 400 mg/day) in adult patients (≥18 years of age) with Bipolar Disorder in the 2 double-blind, placebo-controlled trials of 18 months' duration, and numerically more frequent than in placebo-treated patients are: **Treatment-Emergent Adverse Reaction Incidence in 2 Placebo-Controlled Trials in Adults With Bipolar I Disorder (Adverse reactions in at least 5% of patients treated with LAMICTAL as monotherapy and numerically more frequent than in the placebo group are listed by body system with the incidence for LAMICTAL followed by placebo.)** Patients in these studies were converted to LAMICTAL (100 to 400 mg/day) or placebo monotherapy from add-on therapy with other psychotropic medications. Patients may have reported multiple adverse reactions during the study; thus, patients may be included in more than one category **General**: Back pain (8,6); fatigue (8,5), abdominal pain (6,3); **Digestive:** Nausea (14,11), constipation (5,2), vomiting (5,2); **Nervous System:** Insomnia (10,6), somnolence (9,7), xerostomia (dry mouth) (6,4); **Respiratory:** Rhinitis (7,4), exacerbation of cough (5,3), pharyngitis (5,4); **Skin:** Rash (nonserious) (7,5). In the overall bipolar and other mood disorders clinical trials, the rate of serious rash was 0.08% (1 of 1,233) of adult patients who received LAMICTAL as initial monotherapy and 0.13% (2 of 1,538) of adult patients who received LAMICTAL as adjunctive therapy *[see Warnings and Precautions (5.1)]*. Adverse reactions that occurred in at least 5% of patients and were numerically more common during the dose-escalation phase of LAMICTAL in these trials (when patients may have been receiving concomitant medications) compared with the monotherapy phase were: headache (25%), rash (11%), dizziness (10%), diarrhea (8%), dream abnormality (6%), and pruritus (6%). During the monotherapy phase of the double-blind, placebo-controlled trials of 18 months' duration, 13% of 227 patients who received LAMICTAL (100 to 400 mg/day), 16% of 190 patients who received placebo, and 23% of 166 patients who received lithium discontinued therapy because of an adverse reaction. The adverse reactions which most commonly led to discontinuation of LAMICTAL were rash (3%) and mania/hypomania/mixed mood adverse reactions (2%). Approximately 16% of 2,401 patients who received LAMICTAL (50 to 500 mg/day) for Bipolar Disorder in premarketing trials discontinued therapy because of an adverse reaction; most commonly due to rash (5%) and mania/hypomania/mixed mood adverse reactions (2%). The overall adverse reaction profile for LAMICTAL was similar between females and males, between elderly and nonelderly patients, and among racial groups.

These adverse reactions were usually mild to moderate in intensity. Other reactions that occurred in 5% or more patients but equally or more frequently in the placebo group included: dizziness, mania, headache, infection, influenza, pain, accidental injury, diarrhea, and dyspepsia.

Adverse reactions that occurred with a frequency of less than 5% and greater than 1% of patients receiving LAMICTAL and numerically more frequent than placebo were: ***General:*** Fever, neck pain. ***Cardiovascular:*** Migraine. ***Digestive:*** Flatulence. **Metabolic and Nutritional:** Weight gain, edema. **Musculoskeletal:** Arthralgia, myalgia. ***Nervous System:*** Amnesia, depression, agitation, emotional lability, dyspraxia, abnormal thoughts, dream abnormality, hypoesthesia. ***Respiratory***: Sinusitis. ***Urogenital:*** Urinary frequency.

Adverse Reactions Following Abrupt Discontinuation: In the 2 maintenance trials, there was no increase in the incidence, severity or type of adverse reactions in Bipolar Disorder patients after abruptly terminating therapy with LAMICTAL. In clinical trials in patients with Bipolar Disorder, 2 patients experienced seizures shortly after abrupt withdrawal of LAMICTAL. However, there were confounding factors that may have contributed to the occurrence of seizures in these bipolar patients *[see Warnings and Precautions (5.9)]*.

Mania/Hypomania/Mixed Episodes: During the double-blind, placebo-controlled clinical trials in Bipolar I Disorder in which patients were converted to monotherapy with LAMICTAL (100 to 400 mg/day) from other psychotropic medications and followed for up to 18 months, the rates of manic or hypomanic or mixed mood episodes reported as adverse reactions were 5% for patients treated with LAMICTAL (n = 227), 4% for patients treated with lithium (n = 166), and 7% for patients treated with placebo (n = 190). In all bipolar controlled trials combined, adverse reactions of mania (including hypomania and mixed mood episodes) were reported in 5% of patients treated with LAMICTAL (n = 956), 3% of patients treated with lithium (n = 280), and 4% of patients treated with placebo (n = 803).

6.2 Other Adverse Reactions Observed in All Clinical Trials: LAMICTAL has been administered to 6,694 individuals for whom complete adverse reaction data was captured during all clinical trials, only some of which were placebo controlled. During these trials, all adverse reactions were recorded by the clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse reactions, similar types of adverse reactions were grouped into a smaller number of standardized categories using modified COSTART dictionary terminology. The frequencies presented represent the proportion of the 6,694 individuals exposed to LAMICTAL who experienced an event of the type cited on at least one occasion while receiving LAMICTAL. All reported adverse reactions are included except those already listed in the previous tables or elsewhere in the labeling, those too general to be informative, and those not reasonably associated with the use of the drug. Adverse reactions are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: frequent adverse reactions are defined as those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1,000 patients; rare adverse reactions are those occurring in fewer than 1/1,000 patients. **Body as a Whole:** *Infrequent:* Allergic reaction, chills, and malaise. **Cardiovascular System:** *Infrequent:* Flushing, hot flashes, hypertension, palpitations, postural hypotension, syncope, tachycardia, and vasodilation. **Dermatological:** *Infrequent:* Acne, alopecia, hirsutism, maculopapular rash, skin discoloration, and urticaria. *Rare:* Angioedema, erythema, exfoliative dermatitis, fungal dermatitis, herpes zoster, leukoderma, multiforme erythema, petechial rash, pustular rash, Stevens-Johnson syndrome, and vesiculobullous rash. **Digestive System:** *Infrequent:* Dysphagia, eructation, gastritis, gingivitis, increased appetite, increased salivation, liver function tests abnormal, and mouth ulceration. *Rare:* Gastrointestinal hemorrhage, glossitis, gum hemorrhage, gum hyperplasia, hematemesis, hemorrhagic colitis, hepatitis, melena, stomach ulcer, stomatitis, and tongue edema. **Endocrine System:** *Rare:* Goiter and hypothyroidism. **Hematologic and Lymphatic System:** *Infrequent:* Ecchymosis and leukopenia. *Rare:* Anemia, eosinophilia, fibrin decrease, fibrinogen decrease, iron deficiency anemia, leukocytosis, lymphocytosis, macrocytic anemia, petechia, and thrombocytopenia. **Metabolic and Nutritional Disorders:** *Infrequent:* Aspartate transaminase increased. *Rare:* Alcohol intolerance, alkaline phosphatase increase, alanine transaminase increase, bilirubinemia, general edema, gamma glutamyl transpeptidase increase, and hyperglycemia. **Musculoskeletal System:** *Infrequent:* Arthritis, leg cramps, myasthenia, and twitching. *Rare:* Bursitis, muscle atrophy, pathological fracture, and tendinous contracture. **Nervous System:** *Frequent:* Confusion and paresthesia. *Infrequent:* Akathisia, apathy, aphasia, CNS depression, depersonalization, dysarthria, dyskinesia, euphoria, hallucinations, hostility,

Govt. Hopes Loan Repayments Lure Psychiatrists to Rural Areas

More money is available to help psychiatrists and other mental health professionals reduce their debt load.

BY AARON LEVIN

Stimulus and response worked for Pavlov. Can it work as well for the U.S. government as it tries to place psychiatrists and mental health professionals where they are needed?

The Health Resources and Services Administration (HRSA) hopes that more psychiatrists will respond to offers of stimulus money and practice for two years in medically underserved areas, anywhere from Bethel, Alaska, to Brooklyn, N.Y.

The Obama administration's economic stimulus package—formally known as the American Recovery and Reinvestment Act—allots $300 million for the National Health Service Corps (NHSC), including $200 million to cover loan repayments for primary care clinicians who agree to work for two years in health professional shortage areas.

Psychiatry is considered an "approved primary care specialty" in the eyes of the NHSC.

The HRSA program does not pay salaries but offers up to $50,000 toward repayment of qualifying loans. The loan-repayments funds are exempt from income and employment taxes.

Wider Choice of Eligible Service Sites

New applicants to the program will have a wider choice of eligible service sites than before and a greater number of vacancies from which to choose, according to an agency statement. There are more than 7,000 health care jobs of all types currently listed by the agency.

Kofi Abadio, M.D., completed his NHSC service in 2008 after graduating from the University of Oklahoma Medical School and finishing residency in Norman, Okla. He worked for two years in private practice in Salina, Kan., a designated underserved area.

"I felt like I was helping in an area where help was needed," Abadio told *Psychiatric News*. "Psychiatry is psychiatry, wherever you go."

Private practice is just one alternative for psychiatrists taking part in the program. About half of NHSC clinicians fulfill their commitment at federally supported health centers. Others serve in rural health clinics, Indian Health Service clinics, public health department clinics, hospital-affiliated primary care practices, managed care networks, prisons, and U.S. Immigration, Customs, and Enforcement sites.

Health Professional Shortage Areas are designated by HRSA as having shortages of primary medical care, dental, or mental health providers and may be defined by geographic, demographic, or institutional criteria.

Abadio felt welcomed into the overall medical community in Salina once he began practice there. He noted that the NHSC does not pay a salary, so his compensation was the same as any other psychiatrist would receive in the same setting. The advantage was the reduction in medical-school debt, he said.

"If there was any drawback, it was the paperwork involved in documenting the numbers of patients you see, how many are on Medicare or Medicaid, and so on," he said.

Abadio enjoyed working in a rural area. He still lives in Salina, even after taking a full-time job as a civilian psychiatrist with the U.S. Army 40 miles away at Fort Riley.

Must Practice General Psychiatry

Psychiatrists in the NHSC must meet the same qualifications as other physicians but must serve in areas specifically designated as having mental health professional shortages. They must also agree to practice as general psychiatrists during their period of service, even if they have completed fellowships in subspecialties such as child or geriatric psychiatry.

They must be board certified in psychiatry or have completed a residency program in psychiatry and have a full, permanent medical license from the state where they intend to serve.

At least 21 hours of the 40-hour workweek must be spent providing direct patient counseling during normally scheduled office hours in an ambulatory outpatient care setting, according to agency information. The remaining hours must be spent providing clinical services in alternative settings or performing practice-related administrative activities.

More information on the National Health Service Corps is posted at <http://nhsc.hrsa.gov/index.htm>. ■

SEE ME FOR WHO I CAN BE

Lisa, 32*
Part-time Caterer
Diagnosis: Bipolar Disorder
Recent Episode: Mixed

*Not an actual patient.

Do you see your patients' full potential?

GEODON is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic symptoms.

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

GEODON is contraindicated in patients with a known history of QT prolongation, recent acute myocardial infarction, or uncompensated heart failure, and should not be used with certain other QT-prolonging drugs. **GEODON has been associated with prolongation of the QT_c interval. In some drugs, QT prolongation has been associated with torsade de pointes, a potentially fatal arrhythmia. Patients who are at risk for significant electrolyte disturbances should have baseline measurements performed before initiating GEODON. Patients on diuretics should be monitored.**

As with all antipsychotic medications, a rare and potentially fatal condition known as neuroleptic malignant syndrome (NMS) has been reported with GEODON. NMS can cause hyperpyrexia, muscle rigidity, diaphoresis, tachycardia, irregular pulse or blood pressure, cardiac dysrhythmia, and altered mental status. If signs and symptoms appear, immediate discontinuation, treatment, and monitoring are recommended.

Prescribing should be consistent with the need to minimize tardive dyskinesia (TD), a potentially irreversible dose- and duration-dependent syndrome. If signs and symptoms appear, discontinuation should be considered since TD may remit partially or completely.

Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia.

Precautions include the risk of rash, orthostatic hypotension, and seizures.

The most common adverse events associated with GEODON in bipolar mania were somnolence, extrapyramidal symptoms, dizziness, akathisia, and abnormal vision.

Please see brief summary of prescribing information on adjacent page.

For more information, please visit www.pfizerpro.com/GEODON

GEODON®
(ziprasidone HCl) Capsules

BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. Geodon (ziprasidone) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

INDICATIONS—GEODON Capsules is indicated for the treatment of schizophrenia and acute manic or mixed episodes associated with bipolar disorder with or without psychotic features. GEODON® (ziprasidone mesylate) for Injection is indicated for acute agitation in schizophrenic patients.

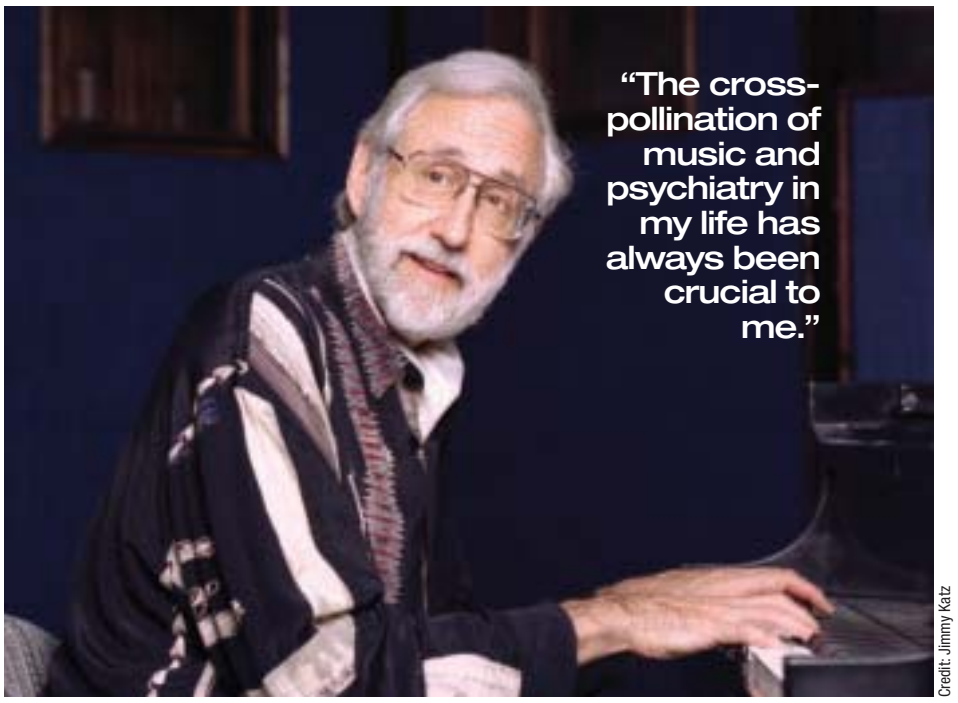
CONTRAINDICATIONS — *QT Prolongation:* Because of GEODON's dose-related prolongation of the QT interval and the known association of fatal arrhythmias with QT prolongation by some other drugs, GEODON is contraindicated in patients with a known history of QT prolongation (including congenital long QT syndrome), with recent acute myocardial infarction, or with uncompensated heart failure (see **WARNINGS**). Pharmacokinetic/pharmacodynamic studies between GEODON and other drugs that prolong the QT interval have not been performed. An additive effect of GEODON and other drugs that prolong the QT interval cannot be excluded. Therefore, GEODON should not be given with dofetilide, sotalol, quinidine, other Class Ia and III anti-arrhythmics, mesoridazine, thioridazine, chlorpromazine, droperidol, pimozide, sparfloxacin, gatifloxacin, moxifloxacin, halofantrine, mefloquine, pentamidine, arsenic trioxide, levomethadyl acetate, dolasetron mesylate, probucol, or tacrolimus. GEODON is also contraindicated with drugs that have demonstrated QT prolongation as one of their pharmacodynamic effects and have this effect described in the full prescribing information as a contraindication or a boxed or bolded warning (see **WARNINGS**). GEODON is contraindicated in individuals with a known hypersensitivity to the product. **WARNINGS — *Increased Mortality in Elderly Patients with Dementia-Related Psychosis*: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. GEODON (ziprasidone) is not approved for the treatment of patients with dementia-related psychosis (see BOXED WARNING). *QT Prolongation and Risk of Sudden Death*: GEODON use should be avoided in combination with other drugs that are known to prolong the QT_c interval. Additionally, clinicians should be alert to the identification of other drugs that have been consistently observed to prolong the QT_c interval. Such drugs should not be prescribed with GEODON. A study directly comparing the QT/QT_c-prolonging effect of GEODON with several other drugs effective in the treatment of schizophrenia was conducted in patient volunteers. The mean increase in QT_c from baseline for GEODON ranged from approximately 9 to 14 msec greater than for four of the comparator drugs (risperidone, olanzapine, quetiapine, and haloperidol), but was approximately 14 msec less than the prolongation observed for thioridazine. In this study, the effect of GEODON on QT_c length was not augmented by the presence of a metabolic inhibitor (ketoconazole 200 mg bid). In placebo-controlled trials, GEODON increased the QT_c interval compared to placebo by approximately 10 msec at the highest recommended daily dose of 160 mg. In clinical trials the electrocardiograms of 2/2988 (0.06%) GEODON patients and 1/440 (0.23%) placebo patients revealed QT_c intervals exceeding the potentially clinically relevant threshold of 500 msec. In the GEODON patients, neither case suggested a role of GEODON. Some drugs that prolong the QT/QT_c interval have been associated with the occurrence of torsade de pointes and with sudden unexplained death. The relationship of QT prolongation to torsade de pointes is clearest for larger increases (20 msec and greater) but it is possible that smaller QT/QT_c prolongations may also increase risk, or increase it in susceptible individuals, such as those with hypokalemia, hypomagnesemia, or genetic predisposition. Although torsade de pointes has not been observed in association with the use of GEODON at recommended doses in premarketing studies, experience is too limited to rule out an increased risk. A study evaluating the QT/QT_c prolonging effect of intramuscular GEODON, with intramuscular haloperidol as a control, was conducted in patient volunteers. In the trial, ECGs were obtained at the time of maximum plasma concentration following two injections of GEODON (20 mg then 30 mg) or haloperidol (7.5 mg then 10 mg) given four hours apart. Note that a 30 mg dose of intramuscular GEODON is 50% higher than the recommended therapeutic dose. The mean change in QT_c from baseline was calculated for each drug using a sample-based correction that removes the effect of heart rate on the QT interval. The mean increase in QT_c from baseline for GEODON was 4.6 msec following the first injection and 12.8 msec following the second injection. The mean increase in QT_c from baseline for haloperidol was 6.0 msec following the first injection and 14.7 msec following the second injection. In this study, no patient had a QT_c interval exceeding 500 msec. As with other antipsychotic drugs and placebo, sudden unexplained deaths have been reported in patients taking GEODON at recommended doses. The premarketing experience for GEODON did not reveal an excess of mortality for GEODON compared to other antipsychotic drugs or placebo, but the extent of exposure was limited, especially for the drugs used as active controls and placebo. Nevertheless, GEODON's larger prolongation of QT_c length compared to several other antipsychotic drugs raises the possibility that the risk of sudden death may be greater for GEODON than for other available drugs for treating schizophrenia. This possibility needs to be considered in deciding among alternative drug products. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QT_c interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QT_c interval; and (4) presence of congenital prolongation of the QT interval. GEODON should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias (see CONTRAINDICATIONS, and see *Drug Interactions* under PRECAUTIONS). It is recommended that patients being considered for GEODON treatment who are at risk for significant electrolyte disturbances, hypokalemia in particular, have baseline serum potassium and magnesium measurements. Hypokalemia (and/or hypomagnesemia) may increase the risk of QT prolongation and arrhythmia. Hypokalemia may result from diuretic therapy, diarrhea, and other causes. Patients with low serum potassium and/or magnesium should be repleted with those electrolytes before proceeding with treatment. It is essential to periodically monitor serum electrolytes in patients for whom diuretic therapy is introduced during GEODON treatment. Persistently prolonged QT_c intervals may also increase the risk of further prolongation and arrhythmia, but it is not clear that routine screening ECG measures are effective in detecting such patients. Rather, GEODON should be avoided in patients with histories of significant cardiovascular illness, eg, QT prolongation, recent acute myocardial infarction, uncompensated heart failure, or cardiac arrhythmia. GEODON should be discontinued in patients who are found to have persistent QT_c measurements >500 msec. *Neuroleptic Malignant Syndrome (NMS)*:** A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs. The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported. ***Tardive Dyskinesia (TD):*** A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients undergoing treatment with antipsychotic drugs. Although the prevalence of TD appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop TD. If signs and symptoms of TD appear in a patient on GEODON, drug discontinuation should be considered. ***Hyperglycemia and Diabetes Mellitus:*** Hyperglycemia-related adverse events, sometimes serious, have been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia or diabetes in patients treated with GEODON, and it is not known if GEODON is associated with these events. Patients treated with an atypical antipsychotic should be monitored for symptoms of hyperglycemia. **PRECAUTIONS — *General:*** Rash: In premarketing trials, about 5% of GEODON patients developed rash and/or urticaria, with discontinuation of treatment in about one-sixth of these cases. The occurrence of rash was dose related, although the finding might also be explained by longer exposure in higher-dose patients. Several patients with rash had signs and symptoms of associated systemic illness, e.g., elevated WBCs. Most patients improved promptly upon treatment with antihistamines or steroids and/or upon discontinuation of GEODON, and all patients were reported to recover completely. Upon appearance of rash for which an alternative etiology cannot be identified, GEODON should be discontinued. Orthostatic Hypotension: GEODON may induce orthostatic hypotension associated with dizziness, tachycardia, and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 0.6% of GEODON patients. GEODON should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions that would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications). Seizures: In clinical trials, seizures occurred in 0.4% of GEODON patients. There were confounding factors that may have contributed to seizures in many of these cases. As with other antipsychotic drugs, GEODON should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia, and GEODON and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **(See also Boxed WARNING, WARNINGS: Increased Mortality in Elderly Patients with Dementia-Related Psychosis).** Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, GEODON elevates prolactin levels in humans. Tissue culture experiments indicate that approximately one third of human breast cancers are prolactin dependent in vitro, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event in GEODON patients. In the 4- and 6-week placebo-controlled trials, somnolence was reported in 14% of GEODON patients vs 7% of placebo patients. Somnolence led to discontinuation in 0.3% of patients in short-term clinical trials. Since GEODON has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that GEODON therapy does not affect them adversely. Priapism: One case of priapism was reported in the premarketing database. Body Temperature Regulation: Although not reported with GEODON in premarketing trials, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Suicide: The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. GEODON prescriptions should be written for the smallest quantity of capsules consistent with good patient management to reduce overdose risk. Use in Patients with Concomitant Illness: Clinical experience with GEODON in patients with certain concomitant systemic illnesses is limited. GEODON has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of QT_c prolongation and orthostatic hypotension with GEODON, caution should be observed in cardiac patients (see ***QT Prolongation and Risk of Sudden Death*** in **WARNINGS** and Orthostatic Hypotension in **PRECAUTIONS**). ***Information for Patients:*** To ensure safe and effective use of GEODON, the information and instructions in the *Patient Information Section* should be discussed with patients. ***Laboratory Tests:*** Patients being considered for GEODON treatment who are at risk of significant electrolyte disturbances should have baseline serum potassium and magnesium measurements. Low serum potassium and magnesium should be repleted before treatment. Patients who are started on diuretics during GEODON therapy need periodic monitoring of serum potassium and magnesium. Discontinue GEODON in patients who are found to have persistent QT_c measurements >500 msec (see **WARNINGS**). ***Drug Interactions:*** (1) GEODON should not be used with any drug that prolongs the QT interval. (2) Given the primary CNS effects of GEODON, caution should be used when it is taken in combination with other centrally acting drugs. (3) Because of its potential for inducing hypotension, GEODON may enhance the effects of certain antihypertensive agents. (4) GEODON may antagonize the effects of levodopa and dopamine agonists. Effect of Other Drugs on GEODON: *Carbamazepine*, 200 mg bid for 21 days, resulted in a decrease of approximately 35% in the AUC of GEODON. *Ketoconazole*, a potent inhibitor of CYP3A4, 400 mg qd for 5 days, increased the AUC and C_{max} of GEODON by about 35%-40%. *Cimetidine*, 800 mg qd for 2 days, did not affect GEODON pharmacokinetics. Coadministration of 30 mL of *Maalox* did not affect GEODON pharmacokinetics. Population pharmacokinetic analysis of schizophrenic patients in controlled clinical trials has not revealed any clinically significant pharmacokinetic interactions with benztropine, propranolol, or lorazepam. Effect of GEODON on Other Drugs: In vitro studies revealed little potential for GEODON to interfere with the metabolism of drugs cleared primarily by CYP1A2, CYP2C9, CYP2C19, CYP2D6, and CYP3A4, and little potential for drug interactions with GEODON due to displacement. GEODON 40 mg bid administered concomitantly with *lithium* 450 mg bid for 7 days did not affect the steady-state level or renal clearance of lithium. GEODON 20 mg bid did not affect the pharmacokinetics of concomitantly administered *oral contraceptives*, ethinyl estradiol (0.03 mg) and levonorgestrel (0.15 mg). Consistent with in vitro results, a study in normal healthy volunteers showed that GEODON did not alter the metabolism of *dextromethorphan*, a CYP2D6 model substrate, to its major metabolite, dextrorphan. There was no statistically significant change in the urinary dextromethorphan/dextrorphan ratio. ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were conducted with GEODON in Long Evans rats and CD-1 mice. In male mice, there was no increase in incidence of tumors relative to controls. In female mice there were dose-related increases in the incidences of pituitary gland adenoma and carcinoma, and mammary gland adenocarcinoma at all doses tested. Increases in serum prolactin were observed in a 1-month dietary study in female, but not male, mice. GEODON had no effect on serum prolactin in rats in a 5-week dietary study at the doses that were used in the carcinogenicity study. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (see Hyperprolactinemia). Mutagenesis: There was a reproducible mutagenic response in the Ames assay in one strain of *S. typhimurium* in the absence of metabolic activation. Positive results were obtained in both the in vitro mammalian cell gene mutation assay and the in vitro chromosomal aberration assay in human lymphocytes. Impairment of Fertility: GEODON increased time to copulation in Sprague-Dawley rats in two fertility and early embryonic development studies at doses of 10 to 160 mg/kg/day (0.5 to 8 times the MRHD of 200 mg/day on a mg/m^2 basis). Fertility rate was reduced at 160 mg/kg/day (8 times the MRHD on a mg/m^2 basis). There was no effect on fertility at 40 mg/kg/day (2 times the MRHD on a mg/m^2 basis). The fertility of female rats was reduced. ***Pregnancy—Pregnancy Category C:*** There are no adequate and well-controlled studies in pregnant women. GEODON should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. ***Labor and Delivery:*** The effect of GEODON on labor and delivery in humans is unknown. ***Nursing Mothers:*** It is not known whether, and if so in what amount, GEODON or its metabolites are excreted in human milk. It is recommended that women receiving GEODON should not breast feed. ***Pediatric Use:*** The safety and effectiveness of GEODON in pediatric patients have not been established. ***Geriatric Use:*** Of the approximately 4500 patients treated with GEODON in clinical studies, 2.4% (109) were 65 years of age or over. In general, there was no indication of any different tolerability for GEODON or of reduced clearance of GEODON in the elderly compared to younger adults. Nevertheless, the presence of multiple factors that might increase the pharmacodynamic response to GEODON, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period for some elderly patients. **ADVERSE REACTIONS — *Adverse Findings Observed in Short-term, Placebo-Controlled Trials:*** The following findings are based on the short-term placebo-controlled premarketing trials for schizophrenia (a pool of two 6-week, and two 4-week fixed-dose trials) and bipolar mania (a pool of two 3-week flexible-dose trials) in which GEODON was administered in doses ranging from 10 to 200 mg/day. ***Adverse Events Associated with Discontinuation:*** Schizophrenia: Approximately 4.1% (29/702) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 2.2% (6/273) on placebo. The most common event associated with dropout was rash, including 7 dropouts for rash among GEODON patients (1%) compared to no placebo patients (see **PRECAUTIONS**). Bipolar Mania: Approximately 6.5% (18/279) of GEODON-treated patients in short-term, placebo-controlled studies discontinued treatment due to an adverse event, compared with about 3.7% (5/136) on placebo. The most common events associated with dropout in the GEODON-treated patients were akathisia, anxiety, depression, dizziness, dystonia, rash, and vomiting, with 2 dropouts for each of these events among GEODON patients (1%) compared to one placebo patient each for dystonia and rash (1%) and no placebo patients for the remaining adverse events. ***Adverse Events at an Incidence ≥5% and at Least Twice the Rate of Placebo:*** The most commonly observed adverse events associated with GEODON in schizophrenia trials were somnolence (14%) and respiratory tract infection (8%). The most commonly observed adverse events associated with the use of GEODON in bipolar mania trials were somnolence (31%), extrapyramidal symptoms (31%), dizziness (16%), akathisia (10%), abnormal vision (6%), asthenia (6%), and vomiting (5%). The following list enumerates the treatment-emergent adverse events that occurred during acute therapy, including only those events that occurred in 2% of GEODON patients and at a greater incidence than in placebo. Schizophrenia: Body as a Whole—asthenia, accidental injury, chest pain. Cardiovascular—tachycardia. Digestive—nausea, constipation, dyspepsia, diarrhea, dry mouth, anorexia. Nervous—extrapyramidal symptoms, somnolence, akathisia, dizziness. Respiratory—respiratory tract infection, rhinitis, cough increased. Skin and Appendages—rash, fungal dermatitis. Special Senses—abnormal vision. Bipolar Mania: Body as a Whole—headache, asthenia, accidental injury. Cardiovascular—hypertension. Digestive—nausea, diarrhea, dry mouth, vomiting, increased salivation, tongue edema, dysphagia. Musculoskeletal—myalgia. Nervous—somnolence, extrapyramidal symptoms, dizziness, akathisia, anxiety, hypesthesia, speech disorder. Respiratory—pharyngitis, dyspnea. Skin and Appendages—fungal dermatitis. Special Senses—abnormal vision. ***Dose Dependency:*** An analysis for dose response in the schizophrenia trials revealed an apparent relation of adverse event to dose for the following: asthenia, postural hypotension, anorexia, dry mouth, increased salivation, arthralgia, anxiety, dizziness, dystonia, hypertonia, somnolence, tremor, rhinitis, rash, and abnormal vision. ***Extrapyramidal Symptoms (EPS):*** The incidence of reported EPS for GEODON patients in the short-term, placebo-controlled schizophrenia trials was 14% vs 8% for placebo. Objectively collected data from those trials on the Simpson-Angus Rating Scale and the Barnes Akathisia Scale did not generally show a difference between GEODON and placebo. ***Dystonia:*** Prolonged abnormal contractions of muscle groups may occur in susceptible individuals during first few days of treatment. Dystonia may occur at any dose level but with greater frequency and severity with high potency and at higher doses of first generation antipsychotic drugs. Elevated risk is observed in males and younger age groups. ***Vital Sign Changes:*** GEODON is associated with orthostatic hypotension (see **PRECAUTIONS**). ***Weight Gain:*** In short-term schizophrenia trials, the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared, revealing a statistically significantly greater incidence of weight gain for GEODON patients (10%) vs placebo patients (4%). A median weight gain of 0.5 kg was observed in GEODON patients vs 0.0 kg in placebo patients. Weight gain was reported as an adverse event in 0.4% of both GEODON and placebo patients. During long-term therapy with GEODON, a categorization of patients at baseline on the basis of body mass index (BMI) showed the greatest mean weight gain and the highest incidence of clinically significant weight gain (>7% of body weight) in patients with a low BMI (*<23*) compared to normal (23-27) or overweight (>27) patients. There was a mean weight gain of 1.4 kg for patients with a "low" baseline BMI, 0.0 kg for patients with a "normal" BMI, and a 1.3 kg mean weight loss for patients with a "high" BMI. ***ECG Changes:*** GEODON is associated with an increase in the QT_c interval (see **WARNINGS**). In schizophrenia trials, GEODON was associated with a mean increase in heart rate of 1.4 beats per minute compared to a 0.2 beats per minute decrease among placebo patients. ***Other Adverse Events Observed During the Premarketing Evaluation of GEODON:*** Frequent adverse events are those occurring in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. Schizophrenia: Body as a Whole — *Frequent:* abdominal pain, flu syndrome, fever, accidental fall, face edema, chills, photosensitivity reaction, flank pain, hypothermia, motor vehicle accident. Cardiovascular System — *Frequent:* tachycardia, hypertension, postural hypotension; *Infrequent:* bradycardia, angina pectoris, atrial fibrillation; *Rare:* first-degree AV block, bundle branch block, phlebitis, pulmonary embolus, cardiomegaly, cerebral infarct, cerebrovascular accident, deep thrombophlebitis, myocarditis, thrombophlebitis. Digestive System — *Frequent:* anorexia, vomiting; *Infrequent:* rectal hemorrhage, dysphagia, tongue edema; *Rare:* gum hemorrhage, jaundice, fecal impaction, gamma glutamyl transpeptidase increased, hematemesis, cholestatic jaundice, hepatitis, hepatomegaly, leukoplakia of mouth, fatty liver deposit, melena. Endocrine — *Rare:* hypothyroidism, hyperthyroidism, thyroiditis. Hemic and Lymphatic System — *Infrequent:* anemia, ecchymosis, leukocytosis, leukopenia, eosinophilia, lymphadenopathy; *Rare:* thrombocytopenia, hypochromic anemia, lymphocytosis, monocytosis, basophilia, lymphedema, polycythemia, thrombocythemia. Metabolic and Nutritional Disorders — *Infrequent:* thirst, transaminase increased, peripheral edema, hyperglycemia, creatine phosphokinase increased, alkaline phosphatase increased, hypercholesterolemia, dehydration, lactic dehydrogenase increased, albuminuria, hypokalemia; *Rare:* BUN increased, creatinine increased, hyperlipemia, hypocholesterolemia, hyperkalemia, hypochloremia, hypoglycemia, hyponatremia, hypoproteinemia, glucose tolerance decreased, gout, hyperchloremia, hyperuricemia, hypocalcemia, hypoglycemic reaction, hypomagnesemia, ketosis, respiratory alkalosis. Musculoskeletal System — *Frequent:* myalgia; *Infrequent:* tenosynovitis; *Rare:* myopathy. Nervous System — *Frequent:* agitation, extrapyramidal symptoms, tremor, dystonia, hypertonia, dyskinesia, hostility, twitching, paresthesia, confusion, vertigo, hypokinesia, hyperkinesia, abnormal gait, oculogyric crisis, hypesthesia, ataxia, amnesia, cogwheel rigidity, delirium, hypotonia, akinesia, dysarthria, withdrawal syndrome, buccoglossal syndrome, choreoathetosis, diplopia, incoordination, neuropathy; *Infrequent:* paralysis; *Rare:* myoclonus, nystagmus, torticollis, circumoral paresthesia, opisthotonos, reflexes increased, trismus. Respiratory System — *Frequent:* dyspnea; *Infrequent:* pneumonia, epistaxis; *Rare:* hemoptysis, laryngismus. Skin and Appendages — *Infrequent:* maculopapular rash, urticaria, alopecia, eczema, exfoliative dermatitis, contact dermatitis, vesiculobullous rash. Special Senses — *Frequent:* fungal dermatitis; *Infrequent:* conjunctivitis, dry eyes, tinnitus, blepharitis, cataract, photophobia; *Rare:* eye hemorrhage, visual field defect, keratitis, keratoconjunctivitis. Urogenital System — *Infrequent:* impotence, abnormal ejaculation, amenorrhea, hematuria, menorrhagia, female lactation, polyuria, urinary retention, metrorrhagia, male sexual dysfunction, anorgasmia, glycosuria; *Rare:* gynecomastia, vaginal hemorrhage, nocturia, oliguria, female sexual dysfunction, uterine hemorrhage. **Adverse Finding Observed in Trials of Intramuscular GEODON:** In these studies, the most commonly observed adverse events associated with the use of intramuscular GEODON (≥5%) and observed at a rate on intramuscular GEODON (in the higher dose groups) at least twice that of the lowest intramuscular GEODON group were headache (13%), nausea (12%), and somnolence (20%). **Adverse Events at an Incidence >1% in Short-Term Fixed-Dose Intramuscular Trials:** The following list enumerates the treatment-emergent adverse events that occurred in ≥1% of GEODON patients (in the higher dose groups) and at least twice that of the lowest intramuscular GEODON group. Body as a Whole—headache, injection site pain, asthenia, abdominal pain, flu syndrome, back pain. Cardiovascular—postural hypotension, hypertension, bradycardia, vasodilation. Digestive—nausea, rectal hemorrhage, diarrhea, vomiting, dyspepsia, anorexia, constipation, tooth disorder, dry mouth. Nervous—dizziness, anxiety, insomnia, somnolence, akathisia, agitation, extrapyramidal syndrome, hypertonia, cogwheel rigidity, paresthesia, personality disorder, psychosis, speech disorder. Respiratory—rhinitis. Skin and Appendages—furunculosis, sweating. Urogenital—dysmenorrhea, priapism. **DRUG ABUSE AND DEPENDENCE — *Controlled Substance Class:*** GEODON is not a controlled substance. **OVERDOSAGE**—In premarketing trials in over 5400 patients, accidental or intentional overdosage of GEODON was documented in 10 patients. All patients survived without sequelae. In the patient taking the largest confirmed amount (3240 mg), the only symptoms reported were minimal sedation, slurring of speech, and transitory hypertension (BP 200/95).

Revised August 2008

Psychiatry and All That Jazz Are Parallel Passions

Improvisation and intellectual curiosity drive the professional success of a psychiatrist and acclaimed musician who finds balance in the things he loves.

BY EVE BENDER



Credit: Jimmy Katz

Denny Zeitlin presents his lecture-demonstration, "Unlocking the Creative Impulse: The Psychology of Improvisation."


Credit: Josephine Zeitlin

Zeitlin Trio, from left: Buster Williams, who plays bass; Denny Zeitlin, piano; and Matt Wilson, drums.

One might say that Denny Zeitlin, M.D., got an early jump on his dual career as a psychiatrist and jazz pianist.

His father was a radiologist who learned to play piano by ear, and his mother was a classically trained pianist. He can remember at the age of 2 climbing up on their respective laps and placing his little hands on theirs as they played on the Steinway in the living room so that he could "get a sense of what it was like to traverse the keyboard before I could sit there myself and play," he said in an interview with *Psychiatric News*.

Less than a year later, Zeitlin claimed the piano bench for himself and began creating melodies and improvising upon them.

The precocious boy from Highland Park, Ill., soon discovered that he possessed another gift.

"It wasn't too many years later that I began practicing psychotherapy on the playground, without a license," Zeitlin remarked.

State licensing boards need not be alarmed, however. Zeitlin, inspired by his uncle, who was a psychoanalyst, was merely listening to his elementary-school classmates who had entrusted him with problems relating to parents, siblings, and peers.

"I wanted to listen, understand, and be helpful to them," said Zeitlin, adding that he found the experience of guiding his peers through the pitfalls of their elementary-school years fascinating and gratifying.

He also voraciously read books with psychological theories or themes and was certain that he would eventually enter the helping profession.

Zeitlin received formal training first in music and then in medicine but never imagined that it would be impossible to have a successful career in both fields.

"The cross-pollination of music and psychiatry in my life has always been crucial to me," he remarked.

Playing With the Pros

When at age 6 Zeitlin began studying classical piano, he found that he was drawn to the modern composers. During this period of formal study, he said, he was less interested in reinterpreting the written page note for note as classical pianists do and more interested in studying how the music was structured and transforming it to make his own.

One of the defining moments in his life came during the eighth grade, when he first heard a jazz album by George Shearing, which was markedly different from anything Zeitlin had experienced up to that point. "I could tell that new music was being composed from moment to moment, and I was blown away by the rhythmic drive of the music," he said.

Zeitlin's discovery of jazz could not have come at a better place or time. Chicago in the early 1950s boasted a burgeoning jazz scene, and during his high-school years Zeitlin would sit in with jazz musicians at local clubs until the wee hours, an experience he called "an informal apprenticeship in the world of jazz."

He also formed a jazz trio of his own, and would play with other ensembles as well at cocktail parties or local jazz venues.

As an undergraduate at the University of Illinois and then as a medical student at Johns Hopkins, Zeitlin continued to play with seasoned jazz musicians. "I can recall studying for six hours each night in my monastic cell in the medical resident hall," Zeitlin said, "and then I'd drive to a local jazz club and sit in with some jazz musicians for several hours after that, just immersing myself in the music."

Recording Career Is Launched

Although he was interested in honing his musical skills, in light of his medical studies he had no plans to begin a recording career or even to make his music more public. That all changed when as a third-year medical student in 1963, he was offered a fellowship in psychiatry at Columbia University in the New York State Psychiatric Institute. During his 10-week stint there, he met with famed Columbia Records producer John Hammond, who was enthusiastic about Zeitlin's work, and together they went to work in the studio.

His first recording was as the featured pianist on "Flute Fever," an album by Jeremy Steig.

Between 1963 and 1967, four additional albums were released by Columbia, featuring the Denny Zeitlin Trio.

He has since released more than 30 recordings, maintained an international performing career, appeared frequently on network TV and radio, and twice won first place in the Down Beat International Jazz Critics Poll.

His two most recent releases showcase the span of his work over the years. One is a three-CD box set reissue from the 1960s called, "Denny Zeitlin: The Columbia Studio Trio Sessions," and the other is a CD featuring his current trio, titled, "Denny Zeitlin Trio in Concert Featuring Buster Williams and Matt Wilson."

Reviews of Zeitlin's work are often infused with praise for his inventiveness—for instance, a review in the *Los Angeles Times* referred to him as an "artist whose skills are so expansive that he can integrate everything he hears into the fabric of his soloing. In the best sense, in the manner that has always been true of jazz's finest improvisers, Zeitlin constantly stretches the creative envelope, measuring himself only against the infinite demands of his music."

Jazz historian Ted Gioia, looking back on Zeitlin's early work with Columbia Records, asked in one review, "And why is Denny Zeitlin important? There is the obvious matter of his formidable technical command of the instrument. His touch, his dynamics, and his clarity of execution are exemplary. But even more to the point, Zeitlin came to grips with virtually all of the pressing issues facing the jazz keyboardists of his generation."

Zeitlin's musical career was not limited to studio recordings and concerts; he was asked to compose the musical score for the 1978 remake of "Invasion of the Body Snatchers," starring Donald Sutherland and Brooke Adams. He also composed and performed music for the first season of the TV show "Sesame Street."

A Life Improvised

After graduating from medical school, Zeitlin moved to San Francisco in 1964 to intern at the University of California, San Francisco (UCSF), where he also completed a psychiatry residency in 1968 at the Langley Porter Psychiatric Institute and where he is now a clinical professor of psychiatry.

In addition, he has maintained a private practice out of his home in Marin County and an office on the UCSF campus, where he conducts psychotherapy with individuals, couples, and groups. He also consults to other psychotherapists' practices and conducts courses and workshops in psychotherapy.

Zeitlin's longtime mentor was Joseph Weiss, M.D., a psychoanalyst and founder of control-mastery theory with whom Zeitlin met each week from 1975 until Weiss's death in 2004. Control-mastery theory is a psychodynamic, cognitive, relational theory about how pathogenic beliefs stem from early traumatic events; the goal of the therapy is to help patients change their pathogenic beliefs.

He has been able to find a common thread throughout his work with patients and his music through a workshop he has developed titled "Unlocking the Creative Impulse: The Psychology of Improvisation."

Zeitlin has found in his work and life that the best way to unleash one's powers of creativity and to excel at creative or analytic pursuits is to blend the discipline of the craft—focusing on technical skill, for instance—with a more experiential approach in which one loses the "positional sense of oneself" and becomes one with the activity.

When this state is achieved while playing music, Zeitlin noted, he feels as if he is simply a conduit for his music, and he experiences the music not just in sound, but in color and texture.

He finds that in his work with patients, this state is achieved when he is able, on an intellectual and emotional level, to enter his patients' worlds "in the most deep and empathetic way so that I can more fully understand what it is that they are trying to describe."

Though his work with patients and music are major components of his life, Zeitlin refers to his wife of 40 years, Josephine, as the "hub" of his life. She is a landscape designer and actor whom Zeitlin describes as "the most naturally creative person I've ever known."

At age 70 Zeitlin has no plans to slow down and is excited about the future. "I have created a body of work over the years that feels authentic to me. My goal is to keep growing as an artist and keep finding new ways to stretch myself as a musician," he said, and the same holds true in his work as a psychiatrist: "I'm hoping to find new ways to be effective in my work with patients."

More information about Denny Zeitlin and his work is posted at <www.dennyzeitlin.com>. ■

Students Learn About Medical Career As Doctors Go 'Back to School'

BY JACQUELINE SMITH, M.D.

During APA's annual meeting in San Francisco in May, I had the great fortune of participating in a rewarding offering that was not part of the meeting's formal program. As a part of the AMA's "Doctors Back to School" program, I visited the School of Saint Leo the Great across the Bay in Oakland, Calif. The "Doctors Back to School" program encourages minority youth to attend college and then medical school.

APA participates in the program through the Commission to End Health Disparities, of which it is a member. APA's involvement in the program is in conjunction with major APA meetings such as the annual meeting and the Institute on Psychiatric Services. It represents a wonderful and unique opportunity for young students to learn about the rewarding and diverse field of psychiatry in particular and glean more general information about a career as a physician.

More than 60 students from the sixth through eighth grades attended the presentation. Also attending were Marilyn King from the APA Office of Minority and National Affairs, who coordinated the visit; child and adolescent psychiatry resident Dr. Aeva Gaymon-Doomes; recent medical school graduate Dr. Onisha Lawrence; and medical student Byron Young.

After we introduced ourselves, the students wasted no time asking questions.

They wanted to know what our high school and college course loads were and if any of us had ever goofed off in school or made mistakes. We told them about our own choices of courses; for example, I was a biology and psychology major in college. However, we also emphasized that they could choose whatever classes interested them, as long as they met basic requirements for college and then medical school matriculation.

Many of the students were particularly interested in what gross anatomy was like. When one youngster finally asked the question, a murmur rippled through the crowd. We of course gave them the basic spiel about using human bodies, learning the anatomy, and working with partners or as part of a team. But to satisfy their real question—was the course truly gross?—we gave a few more details about the odor in the rooms and what it was like to explore and handle all the organs.

We also discussed other topics such as how we chose our undergraduate colleges and medical schools. For many of us, we wanted to be in particular cities (New Orleans, Atlanta); for others, there were practicalities such as the course offerings or cost; and for some, there were more profound reasons such as where the school's athletic teams ranked and availability of student tickets!

We addressed the importance of balancing work and studies with fun. For my part, I was pretty straight-laced until college when I took time to be in the marching band, play intramural sports, and attend my fair share of parties. Dr. Gaymon-Doomes joined a sorority and met her husband in college.

In explaining why we chose psychiatry as our specialty, the responses included working with at-risk populations and being able to have a diversity of experiences. The two child and adolescent fellows were able to share our experiences as physicians and psychiatrists. We discussed working in settings such as hospitals, clinics, and schools; seeing patients with various diagnoses, such as depression or ADHD; and getting to work with parents. Dr. Gaymon-Doomes discussed the use of telepsychiatry to reach rural populations.

These young students were truly an enthusiastic and inquisitive group. One young man who sat in front asked the first question. Even though we made it clear we wanted to hear from everyone, he kept his hand raised almost the entire hour! He and some of the other students stayed and asked us questions after the formal program was over. They even asked to take a group picture with us. Who knew that a psychiatrist could feel like a rock star from time to time?

Though this is generally a program provided at national meetings, resident and medical student APA members should consider implementing the "Doctors Back to School" program in conjunction with local- and state-level meetings and conferences. It is easy to do and takes very little preparation other than setting up the visit. Ms. King and her office will help seek out the schools and set up visits. There is also a tool kit available at the Web site below.

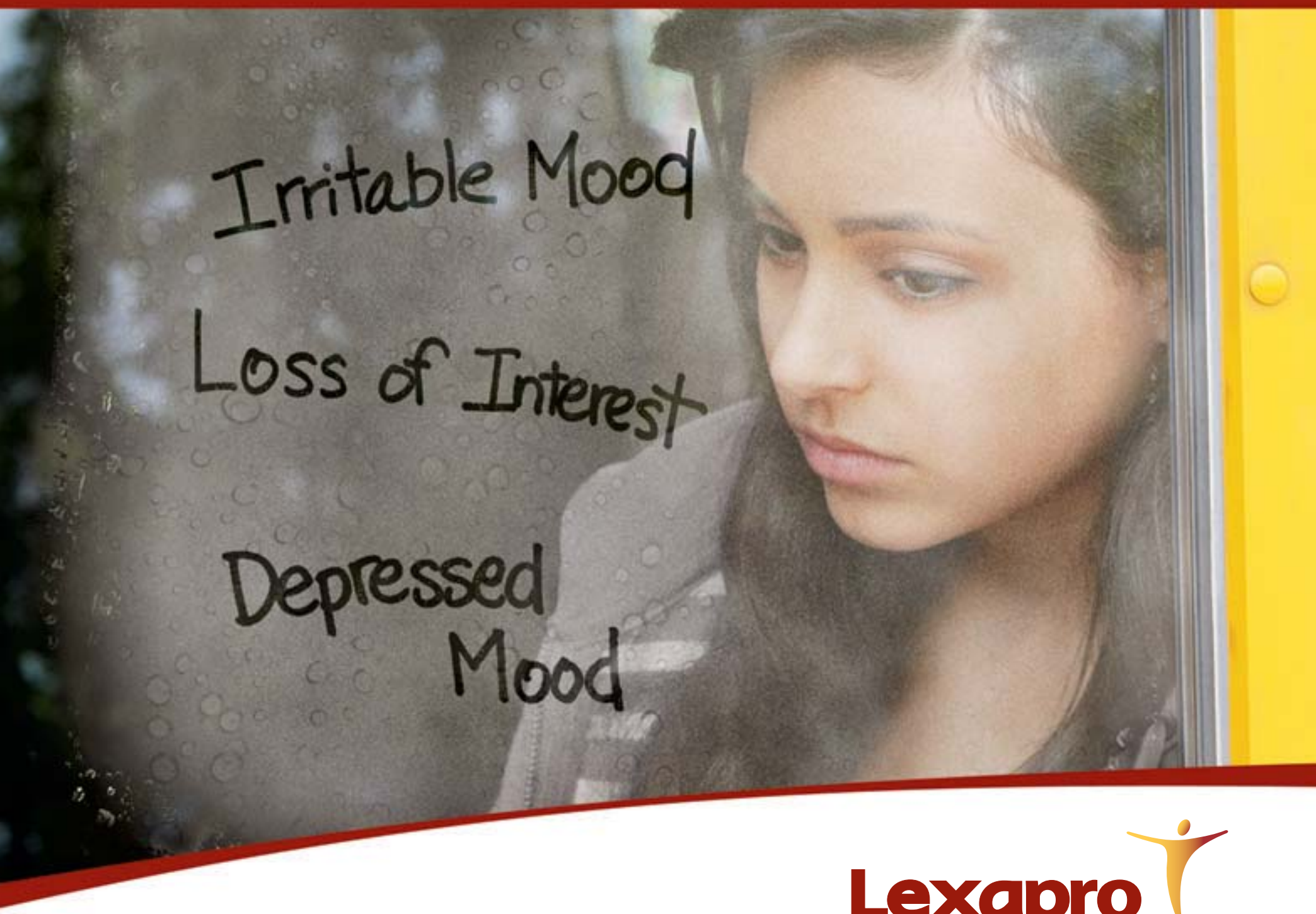
In short, it is fun and serves to inspire youth to believe that they too can become a physician and even a psychiatrist.

More information about the "Doctors Back to School Program" is posted at <www.ama-assn.org/ama/pub/physician-resources/public-health/eliminating-health-disparities/doctors-back-school/doctors-back-school-kit.shtml>. ■

Jacqueline Smith, M.D., is a PGY-5 child and adolescent psychiatry fellow at the University of North Carolina.

For Major Depressive Disorder (MDD)...

LEXAPRO IS NOW APPROVED for adolescents aged 12 to 17[1]



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DSM-IV-TR criteria for Major Depressive Episode: Five or more symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure in nearly all activities. In children and adolescents, depressed mood can be irritable mood.[2]

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age.

Please see additional Important Safety Information on following pages.

IMPORTANT SAFETY INFORMATION (continued)

Contraindications

- Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). There have been reports of serious, sometimes fatal, reactions with some cases resembling neuroleptic malignant syndrome (NMS) and serotonin syndrome. Features may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Serotonin syndrome was reported for two patients who were concomitantly receiving linezolid, an antibiotic which has MAOI activity. Lexapro should not be used in combination with an MAOI or within 14 days of discontinuing an MAOI. MAOIs should not be initiated within 14 days of discontinuing Lexapro.

- Lexapro is contraindicated in patients taking pimozide or with hypersensitivity to escitalopram or citalopram.

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, especially within the first few months of treatment or when changing the dose. Consideration should be given to changing the therapeutic regimen, including discontinuing medication, in patients whose depression is persistently worse, who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients treated with antidepressants should be alerted about the need to monitor patients daily for the emergence of agitation, irritability, unusual changes in behavior, or the emergence of suicidality, and report such symptoms immediately. Prescriptions for Lexapro should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

LEXAPRO provides symptom relief for adolescents with MDD

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for Major Depressive Disorder (MDD) in adolescents aged 12 to 17[1]

- **For acute and maintenance treatment[1]**
  - —Patients should be periodically reassessed to determine the need for maintenance treatment[1]
- **Significant improvement in CDRS-R scores starting at week 4[3]**
  - —Full antidepressant effect may take 4 to 6 weeks
- **Flexible dosing with a recommended dose of 10 mg/day[1]**
  - —Titration to 20 mg/day, if necessary, after a minimum of 3 weeks[1]

LEXAPRO is indicated as an integral part of a total treatment program for MDD. Drug treatment may not be indicated for all adolescents with this syndrome.

- A major depressive episode may be the initial presentation of bipolar disorder. In patients at risk for bipolar disorder, treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. Lexapro should be used cautiously in patients with a history of mania or seizure disorder. Lexapro is not approved for use in treating bipolar depression.
- The concomitant use of Lexapro with other SSRIs, SNRIs, triptans, tryptophan, antipsychotics or other dopamine antagonists is not recommended due to potential development of life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Reactions have been reported with SNRIs and SSRIs alone, including Lexapro, but particularly with drugs that impair metabolism of serotonin (including MAOIs). Management of these events should include immediate discontinuation of Lexapro and the concomitant agent and continued monitoring.
- Patients should be monitored for adverse reactions when discontinuing treatment with Lexapro. During marketing of Lexapro and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. A gradual dose reduction rather than abrupt cessation is recommended whenever possible.

Please see additional Important Safety Information on next page.

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escitalopram oxalate

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References: 1. LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2009. **2.** American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed (Text Revision). Washington, DC: APA; 2000. **3.** Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry.* 2009;48:721-729.

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION **Rx Only**

Brief Summary: For complete details, please see full Prescribing Information for Lexapro.

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age. *[See Warnings and Precautions: Clinical Worsening and Suicide Risk, Patient Counseling Information: Information for Patients, and Used in Specific Populations: Pediatric Use].*

INDICATIONS AND USAGE: Major Depressive Disorder-Lexapro (escitalopram) is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age [*see Clinical Studies*]. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. **Generalized Anxiety Disorder**-Lexapro is indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults [*see Clinical Studies*]. Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

CONTRAINDICATIONS: Monoamine oxidase inhibitors (MAOIs)-Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated [*see Warnings and Precautions*]. **Pimozide**-Concomitant use in patients taking pimozide is contraindicated [*see Drug Interactions*]. **Hypersensitivity to escitalopram or citalopram**-Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk-Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

TABLE 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration*]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers [*see also Patient Counseling Information*]. Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder**-A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with 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. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions**-The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Lexapro treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended. Treatment with Lexapro and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated. **Discontinuation of Treatment with Lexapro**-During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration*]. **Seizures**-Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. **Activation of Mania/Hypomania**-In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. **Hyponatremia**-Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Geriatric Use*]. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Abnormal Bleeding**-SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation. **Interference with Cognitive and Motor Performance**-In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. **Use in Patients with Concomitant Illness**-Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day [*see Dosage and Administration*]. Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients [*see Dosage and Administration*]. **Potential for Interaction with Monoamine Oxidase Inhibitors**-In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

ADVERSE REACTIONS: Clinical Trials Experience-Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Clinical Trial Data Sources; Pediatrics (6 -17 years)**-Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established. **Adults**-Adverse events information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. 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 tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment; Major Depressive Disorder; Pediatrics (6 -17 years)**-Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Lexapro and greater than placebo) associated with discontinuation was insomnia (1% Lexapro, 0% placebo). **Adults-**Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder; Adults**-Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials; Major Depressive Disorder; Pediatrics (6 -17 years)**-The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions (excluding those which appear in Table 2 and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion. **Adults**-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 2
Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Major Depressive Disorder

Adverse Reaction	Lexapro (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=225 Lexapro; N=188 placebo).
[3]Denominator used was for females only (N=490 Lexapro; N=404 placebo).

Generalized Anxiety Disorder; Adults-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia. Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 3
Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Generalized Anxiety Disorder

Adverse Reactions	Lexapro (N=429)	Placebo (N=427)
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 Lexapro; N=195 placebo).
[3]Denominator used was for females only (N=247 Lexapro; N=232 placebo).

Dose Dependency of Adverse Reactions-The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse reactions that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

TABLE 4
Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder

Adverse Reaction	Placebo (N=311)	10 mg/day Lexapro (N=310)	20 mg/day Lexapro (N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

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, 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 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

TABLE 5
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	Lexapro	Placebo
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes**-Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes**-Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Reactions Observed During the Premarketing Evaluation of Lexapro**-Following is a list of treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in Tables 2 & 3, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section. Cardiovascular - hypertension, palpitation. Central and Peripheral Nervous System Disorders - light-headed feeling, migraine. Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis. General - allergy, chest pain, fever, hot flushes, pain in limb. Metabolic and Nutritional Disorders - increased weight. Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness. Psychiatric Disorders - appetite increased, concentration impaired, irritability. Reproductive Disorders/Female - menstrual cramps, menstrual disorder. Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache. Skin and Appendages Disorders - rash. Special Senses - vision blurred, tinnitus. Urinary System Disorders - urinary frequency, urinary tract infection. **Post-Marketing Experience; Adverse Reactions Reported Subsequent to the Marketing of Escitalopram**-The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Ear and Labyrinth Disorders: vertigo Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance. Gastrointestinal Disorders: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction, anaphylaxis. Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia. Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis. Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency. Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention. Reproductive System and Breast Disorders: menorrhagia, priapism. Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn. Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

DRUG INTERACTIONS: Serotonergic Drugs-Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions*]. The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended. **Triptans**-There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions*]. **CNS Drugs**- Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. **Alcohol**-Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. **Monoamine Oxidase Inhibitors (MAOIs)**-[*see Contraindications and Warnings and Precautions*]. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)**-Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued. **Cimetidine**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. **Digoxin**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. **Lithium**-Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. **Pimozide and Celexa**-In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. **Sumatriptan**-There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. **Theophylline**-Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. **Warfarin**-Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. **Carbamazepine**-Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. **Triazolam**-Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. **Ketoconazole**-Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. **Ritonavir**-Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. **CYP3A4 and -2C19 Inhibitors**-*In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. **Drugs Metabolized by Cytochrome P4502D6**-*In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. **Metoprolol**-Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. **Electroconvulsive Therapy (ECT)**-There are no clinical studies of the combined use of ECT and escitalopram.

USE IN SPECIFIC POPULATIONS: Pregnancy; Pregnancy Category C-In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy-Nonteratogenic Effects-Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions*]. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery**-The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers**-Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman. **Pediatric Use**-Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [*see Clinical Studies*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. **Geriatric Use**-Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see *Hyponatremia*]. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration*]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence; Physical and Psychological Dependence-Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience-In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported. Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose. **Management of Overdose**-Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Lexapro. In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

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APA Honors Innovative Mental Health Programs

Award winners this year showcase the ability of psychiatric programs to transcend the traditional settings of hospital and clinic.

BY MARK MORAN

Call it "psychiatry without borders."

From psychiatric treatment for those receiving hospice care, to supported employment and smoking cessation for the seriously mentally ill people in the community, APA's 2009 Psychiatric Services Achievement Award winners are a showcase of innovative treatment programs providing psychiatric services outside the traditional settings of hospital and clinic.

The awards will be presented this year on Thursday, October 8, at APA's Institute on Psychiatric Services in New York. The goal of the awards, which were established in 1949, is to recognize national models of creative service delivery to mentally ill or disabled individuals.

Each program that applies for the award is graded by the Achievement Awards Committee on criteria that are spelled out in the application. The highest-ranking applications are selected for a site review to be written by a member of the district branch where the program is located.

The chair of the 2009 Psychiatric Services Achievement Awards Committee is Beatrice Kovasznay, M.D.

First-place, or Gold, awards are given to one program in two categories—academically or institutionally sponsored programs, and community-based programs. Both winners receive $10,000, with award funds being provided this year by Pfizer Inc.

Silver and Bronze awards are given to programs in either academic or community settings. The Silver Award winner receives $7,500 from Pfizer, while the Bronze Award winner receives $5,000.

Pfizer has been participating in the program since 1981.

This year's Gold Award winner for an institutionally sponsored program is the Palliative Care Psychiatric Program at San Diego Hospice and the Institute for Palliative Medicine.

According to the site review written by psychiatrist Alexander Green, M.D., the program investigates better assessments and treatments for depression, delirium, and other mental health concerns to improve outcomes for those with advanced life-threatening illnesses. It is directed by Scott Irwin, M.D., Ph.D.

"Although there were approximately 1.4 million patients under hospice care, in 4,300 programs worldwide, there were essentially no psychiatrists involved in direct, regular on-site clinical care," Green wrote of the genesis of the program. "A light bulb went on in the mind of this young professional [Irwin] at the beginning of his career. [He] volunteered his services to build a unit at the San Diego hospice, in the hope that funding would come. It did—he has received funding for the program from the National Institute of Mental Health, the National Palliative Care Research Center, the Arch Stone Foundation, and the John A. Hartford Center of Excellence in Geriatric Psychiatry at the University of California, San Diego."

Research in the Palliative Care Psychiatric Program has included alternative routes for pain-medication administration, alternatives to pain medication, the use of short-term stimulants in depression in the hospice setting, issues regarding voluntarily stopping oral intake, unrecognized cognitive impairments, new screening techniques for underrecognized depression and delirium, and psychiatry residency education in end-of-life issues.

The program also educates institute faculty, palliative medicine fellows, clinical staff, nurses, and international visitors. The team now includes five part-time psychiatrists.

The Gold Award for community-based programs this year goes to the Thresholds Supported Employment Program in Chicago.

"This innovative program is fully integrated within a mental health clinic that provides psychiatric treatment, case management, and psychosocial rehabilitation services to its patients," wrote psychiatrist Lisa Rone, M.D., in her site review of Thresholds. "The program helps with employment when members are recovering from their illness and desire to be employed. The Supported Employment Program is considered a direct recovery-focused therapy as well as a point of engagement for other services, such as dual-diagnosis treatment. . . .

"This program has a unique ability to work with employees that may not want to disclose their mental illness. Employment specialists discuss specific approaches a member may take in a job interview to prepare and rehearse them. The employment specialists also work directly with employers to reduce stigma regarding the chronically mentally ill by having employers that have employed Thresholds members meet with prospective new employers to discuss their experiences with the member employees."

A Silver Award for second place for either a community or institutional program will be presented to the CHOICES (Consumers Helping Others Improve Their Condition by Ending Smoking) Program of the Department of Psychiatry's Division of Addiction at the University of Medicine and Dentistry of New Jersey–Robert Wood Johnson Medical School, New Brunswick, N.J.

The award is in recognition of the program's creative approach to smoking cessation among seriously mentally ill people. Kovasznay noted that the program uses individuals who have experienced serious mental illness and have also been smokers to act as peer counselors in helping patients quit smoking.

"This program focuses on an important issue in an underserved population," wrote Jacob Jacoby, M.D., in his site review of CHOICES. "This is a population where cigarette smoking is the norm, but where a focus on stopping this potentially life-threatening addiction is either ignored or underemphasized to an alarming degree. . . . This program represents an early, perhaps pioneer development in sending counselors who themselves have been cigarette smokers . . . to interact in varying treatment modalities with other nicotine-using, psychiatrically affected patients."

A Bronze Award for third place goes to the Children and Adolescent Services Program at the South Bronx Mental Health Council Inc. (SBMHC) in New York. The program was recognized for its expansion of an evidence-based, culturally sensitive model for improving home and school life through promotion of positive behavioral changes and social skills development.

The evidence-based model employed by the program is the Community Parent Education Program (COPE).

"The SBMHC sought a model that would challenge [staff] to improve their skills and provide a critical service to the local children before they were identified as clinical cases," wrote psychiatrist L. Mark Russakoff, M.D., in his site review of the program. "In collaboration with five other outpatient programs in the Bronx, the SBMHC chose COPE as a means to help the parents of children who were coming to the attention of school officials or others. The program is a group intervention, which permits exceptional learning opportunities for the participants (including staff, patients, and parents) and the fiscal efficiencies associated with group programs. It has been cited as a model program by the New York State Office of Mental Health."

More information is posted at <www.psych.org/achievementawards>. ■

APA Announces New Member Benefits

→ Register to Receive Drug Alerts Online

APA has worked with the FDA, AMA, state medical societies, and liability carriers to bring a new service—the Health Care Notification Network (HCNN)—to APA members. The HCNN, which is a private network for physicians and health care professionals, provides secure online delivery of news about drug and medical-device recalls and patient-safety alerts, replacing the current paper process that is both slow and prone to error.

These are among other HCNN features:

- The HCNN is free to physicians and their staff members.
- A copy of alerts can be sent automatically to practice administrators and added to their physician account.
- Privacy is protected by the not-for-profit board that governs the HCNN.
- The HCNN does no advertising or selling.
- Recipients can opt out at any time.

Alerts sent through the HCNN are paid for by manufacturers who use the network for alert delivery.

APA members may enroll online at <www.hcnn.net/registration/apa/registration.aspx>. Additional information is available at <www.hcnn.net> or (866) 925-5155.

→ Get a Web Page on PsychSites.com

APA members are eligible for a personal Web page and directory listing on PsychSites.com. PsychSites.com is a starting place for members who have no Internet presence and provides increased visibility and links for members who already have Web sites.

Personal pages can be edited online and include online technical support. The page can include a 250-word profile, titles, office contact information, up to seven hyperlinks to other Web sites, and a photo. Participating members will be included in a database of mental health professionals that is searchable by location, specialty, and more than 150 mental health subspecialties.

More information can be accessed at <www.psych.org/Resources/Membership/MemberOnlyBenefitsServices.aspx> under "Professional Benefits."

→ Get a Financial Consult From Merrill Lynch

APA has entered into a partnership with Merrill Lynch to provide free financial consultations to APA members as a member benefit. Merrill Lynch is offering APA members convenient access to customized, actionable financial advice from one of the world's leading wealth-management firms. A dedicated, nationwide team of Merrill Lynch Financial Advisors is ready to assist APA members with developing strategies to meet their personal financial needs, supported by an illustrated report outlining specific investment strategies to help reach their goals.

APA members can call Merrill Lynch at 888-9ML-OFFER (965-6333) between 8 a.m. and 6 p.m. (ET), Monday through Friday.

Members should reference their APA partner code 1844 and ask about other benefits available to APA members who become clients.

Biomarker May Differentiate PTSD From Other Disorders

Researchers studying a possible biomarker for diagnosing PTSD will soon expand their study sample from dozens to hundreds of subjects.

BY AARON LEVIN

One of the realities of practicing psychiatry is the reliance on patients' subjective descriptions of their symptoms. How many psychiatrists have wished for the equivalent of the internist's minimally invasive blood or urine tests that reveal so much about the patient's heart, kidneys, lungs, or liver? An objective biochemical test that could provide a quantifiable measure to diagnose psychiatric illness and measure its response to treatment would be welcomed by researchers, clinicians, and patients alike.

Interest is especially high now in potential biomarkers for mild traumatic brain injury and posttraumatic stress disorder (PTSD) as a consequence of the wars in Iraq and Afghanistan. Such tests do not yet exist, but research teams have hypothesized that substances such as cortisol, GABA, or platelet serotonin might be markers for PTSD.

A team of researchers led by Lei Zhang, M.D., an assistant professor of psychiatry at the Uniformed Services University of the Health Sciences (USUHS) in Bethesda, Md., have proposed another candidate for such a biomarker for PTSD, a protein called p11. They reported their findings in the September *Journal of Psychiatric Research.*

Animal research has shown that stress and the stress-related hormone glucocorticoid increased expression of p11. Previous human research showed that p11 was down regulated in the cortex of patients with depression but that p11 mRNA was up regulated in the prefrontal cortex of those with PTSD, raising the possibility that the two conditions might be differentiated by p11 levels.

> **"The challenge of biomarkers in psychiatry is always blood versus brain."**

"The glucocorticoid receptor turns the p11 promoter on and off, allowing us to see how stress links to the molecular mechanism and thus to the disease," said Zhang in an interview. "The p11 peptide also interacts with serotonin 5HTI-B, which plays a role in depression."

Their next step was to seek any correlations between levels of p11 in the blood and PTSD, given the intricacies of the blood-brain barrier, said Robert Ursano, M.D., a professor of psychiatry at USUHS and a coauthor of Zhang's paper.

"The challenge of biomarkers in psychiatry is always blood versus brain," said Ursano.

In their current study, Zhang, Ursano, and coworkers examined 79 subjects: 13 diagnosed with PTSD, 16 with major depressive disorder, 24 with bipolar disorder, 12 with schizophrenia, and 14 nonpsychiatric controls. They were recruited though National Yang-Ming University and the Taipei Veterans General Hospital, both in Taipei, Taiwan, where several of Zhang's coauthors work.

The subjects were categorized by an examination of their records and through clinical interviews. About 77 percent of those with PTSD also had other psychiatric comorbidities. They gave samples of blood and salivary and serum cortisol.

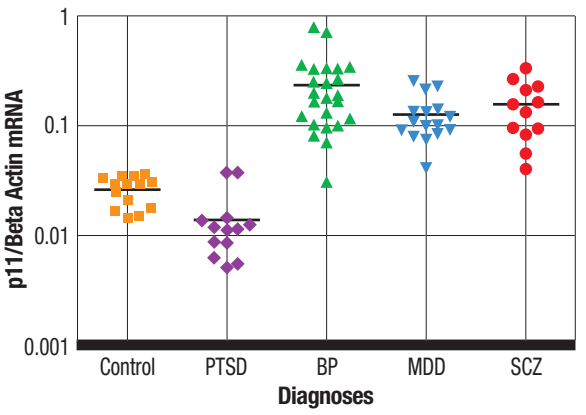
The researchers found that patients with PTSD could be separated from the others in the trial according to blood levels of p11.

Patients with PTSD had lower levels of p11 mRNA in their peripheral mononuclear blood cells than controls. Patients with bipolar disorder, major depression,

please see ***Biomarker*** *on page 44*

Protein Levels Differ By Diagnosis

Levels of p11 mRNA in patients with PTSD are significantly lower than in those with bipolar disorder ($p<0.01$), major depression ($p<0.01$), schizophrenia ($p<0.01$), or control subjects ($p<0.05$). Such differences may someday lead to diagnostic biomarkers.



Source: Lei Zhang, M.D., et al., *Journal of Psychiatric Research,* September 2009

Heroin Treatment May Help Difficult-to-Treat Opioid Addicts

The economic, social, and therapeutic context in different countries affects how health care providers prioritize and adopt treatments for opioid addiction.

BY JUN YAN

A Canadian study shows that heroin maintenance keeps some patients in drug treatment longer than methadone therapy and reduces illegal behaviors in certain difficult-to-treat patients with chronic relapsing opioid addiction. Meanwhile, clinicians and other addiction experts continue to debate the efficacy of various addiction treatment approaches.

The new study, known as the North American Opiate Medication Initiative (NAOMI), was conducted by Eugenia Oviedo-Joekes, Ph.D., and colleagues at the University of British Columbia and the Université de Montréal and published in the August 20 *New England Journal of Medicine*. It was funded by the Canadian Institutes of Health Research, Canada Foundation for Innovation, Canada Research Chairs Program, the universities of British Columbia and Montreal, and provincial government agencies.

From 2005 to 2008 in Montreal and Vancouver, patients who had *DSM-IV*-diagnosed opioid dependence, injected heroin daily, and had failed at least two previous treatments including at least one methadone treatment were recruited for the study. Participants were randomized to receive either oral methadone (n=111) or diacetylmorphine injection (n=115) treatment for 12 months in an open-label design. Diacetylmorphine is the active ingredient in heroin and was self-administered by participants under medical supervision at the study clinics.

Nearly 88 percent of heroin-treated patients remained in the treatment at the end of one year, statistically significantly higher than the 54 percent retention rate for the methadone-treated patients.

In addition, 67 percent of heroin-treated patients met the criteria for responders in terms of reduced illicit-drug use or illegal activities, compared with 48 percent of methadone-treated patients, also a statistically significant difference. Patients were considered responders if they had at least a 20 percent reduction from baseline in either the illicit-drug use or the illegal-activity subscales of the European Addiction Severity Index.

The study protocol allowed participants to self-administer diacetylmorphine at a maximum of three times a day, with a dose of no more than 1,000 mg/day. The actual dose used by participants averaged 392 mg/day. The mean dose of methadone given in the study was 96 mg/day.

Diacetylmorphine use was associated with more serious adverse events, including overdose in 10 patients, which required immediate treatment with naloxone, and seizure in six patients.

The findings from this study were not unexpected and were similar to those from several studies conducted in Germany, Switzerland, the Netherlands, and Spain since the 1990s on heroin-maintenance treatment in chronically addicted patients. The most recent was a German study by Christian Haasen, M.D., and colleagues at the University Medical Center Eppendorf in Hamburg and published in the July 2007 *British Journal of Psychiatry*.

In these studies patients who received heroin-maintenance treatment in a supervised environment were found to do better than patients who received methadone on a number of outcome indicators such as improvement in physical health and decreased criminal behaviors. The Canadian study, however, is the first heroin study published in a major U.S. medical journal.

These studies do not demonstrate that heroin-maintenance treatment is more efficacious than methadone, Charles O'Brien, M.D., Ph.D., told *Psychiatric News*. Rather, the findings are limited to a small segment of opioid-addicted patients. "The [heroin-maintenance] approach represents a second-class therapy for people who refuse to get methadone treatment," he said.

O'Brien is the Kenneth Appel Professor of Psychiatry at the University of Pennsylvania and chair of the *DSM-V* work group on areas related to addiction psychiatry. He also served as a consultant for the heroin-maintenance study in the Netherlands.

Commenting on the NAOMI study, O'Brien noted that the research protocol gave participants the option of a maximum of three injections of heroin a day. Maintaining opioid addicts on heroin as the Canadian researchers did "is a way of harm reduction, but [patients] were not motivated to change their lives," he said. "They get high three times a day, which interferes with normal life. . . . Methadone or buprenorphine treatment can enable rehabilitation."

Heroin maintenance is also prohibitively expensive, O'Brien emphasized. It would be unwise to adopt it widely in the U.S. health care context, where treatments for addiction, such as methadone and buprenorphine, are poorly funded in the first place. "We don't even have enough money for methadone therapy. We should put the funds into making methadone and buprenorphine treatment and proper counseling available to more people with opioid dependence, which will make a far bigger difference."

Trends in opioid addiction treatment "often owe more to the politics of the situation" and to "professional factors" than to research evidence, Virginia Berridge, Ph.D., a professor in history and public health policy analysis at the London School of Hygiene and Tropical Medicine, University of London, wrote in an accompanying editorial. She pointed out that in countries where the opioid-addiction studies were conducted, Switzerland and the Netherlands have chosen to adopt heroin maintenance as a treatment option, but Germany and Spain have not.

An abstract of "Diacetylmorphine Versus Methadone for the Treatment of Opioid Addiction" is posted at <content.nejm.org/cgi/content/abstract/361/8/777>. An abstract of "Heroin-Assisted Treatment for Opioid Dependence: Randomised Controlled Trial" is posted at <bjp.rcpsych.org/cgi/content/abstract/191/1/55>. ■

Data Reveal More About Link Of Depression, Heart Disease

To treat on not to treat depression in patients with heart disease is still the question, and the answer might be getting nearer.

BY AARON LEVIN

Patients with heart disease and depression continue to present a conundrum to cardiologists and psychiatrists.

Depression seems associated with increased risk of poor cardiac outcomes, while a heart attack or heart failure might reasonably induce reactive depression in the patient. About 15 percent to 20 percent of patients hospitalized for heart attacks meet *DSM-IV* criteria for depression, yet decades of research have revealed an association between the two conditions without proving conclusively which causes which. Both biological (heart rate variability, HPA axis dysfunction, increased inflammatory response) and behavioral (lack of exercise, poor medication adherence) factors have been proposed to link the two.

"Registry data can't define cause and effect, and there are too few animal experiments or large randomized controlled trials in humans to determine causation," said Karina Davison, Ph.D., in an interview. Davison is director of the cardiovascular behavioral health center and Herbert Irving Associate Professor of Medicine and Psychiatry in the College of Physicians and Surgeons at Columbia University. "That leaves us with only observational data," she said, although several proposals for such trials are under review at the National Institutes of Health.

Whether treating depression will significantly improve cardiovascular outcomes remains an open question. A cautiously worded science advisory from the American Heart Association in the October 2008 journal *Circulation* offered this conclusion:

"Depression is commonly present in patients with coronary heart disease (CHD) and is independently associated with increased cardiovascular morbidity and mortality. Screening tests for depressive symptoms should be applied to identify patients who may require further assessment and treatment."

One study, the Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), recently reported results from nearly seven years of follow-up among 361 of 369 patients hospitalized with acute coronary syndrome (ACS) who also had major depressive disorder (MDD) on screening. Of those, 75 died during the follow-up period.

Severity of depression was "strongly and significantly" associated with mortality during 6.7 years of follow-up, but depression prior to ACS and onset before or after hospitalization were not associated with death.

SADHART didn't clarify if treatment helped reduce mortality rates, but it did find that patients whose depression did not get better had twice the risk of dying as those who did improve, wrote Alexander Glassman, M.D., chief of clinical psychopharmacology at New York State Psychiatric Institute and a professor of psychiatry at the College of Physicians and Surgeons of Columbia University, and colleagues in the September *Archives of General Psychiatry*.

The SADHART researchers randomized patients to 24 weeks of sertraline treatment or placebo, and found that neither cohort showed any advantage in mortality. However, patients whose mood improved, whether or not they were treated, had a lower chance of dying. Only 15.6 percent of patients with a CGI-I score of 1 or 2 at six months died over the next 6.7 years, compared with 28.4 percent of patients whose depression did not improve.

SADHART's lack of success with conventional treatment may arise because not all patient behavior outside the trial's parameters can be controlled or because not all depression is the same, said Davison.

"A patient who exercised might also take omega-3 capsules, for instance," she said. "Or a patient's depression might be due to white matter hyperintensities, which would not respond to an SSRI."

Patients whose depression improved had better adherence to the antidepressant, which may be a marker for adherence to cardiovascular drugs, suggested the authors.

"Adherence to cardiovascular medications after ACS reduces mortality and could mediate the relationship between failure of MDD to improve substantially and long-term mortality," wrote Glassman and colleagues. "[D]epression impairs quality of life and needs to be treated. When patients with MDD after ACS do not respond to antidepressant treatment, a special effort should be made to promote lifestyle improvements and cardiovascular medication adherence."

The effect on medication adherence is not bidirectional, said Davison. Depressed patients who don't take their antidepressants are less likely to take their cardiovascular medications, but adherence to these medications does not influence use of antidepressants.

Failure to nail down a causal connection between the two conditions doesn't mean there hasn't been progress in recent years, said C. Barr Taylor, M.D., a professor of psychiatry and behavioral sciences and director of the Laboratory for the Study of Behavioral Medicine at Stanford University School of Medicine.

"In the last two decades, researchers have demonstrated the importance of depression in cardiovascular disease and the value of antidepressants and lifestyle

please see ***Depression*** *on page 43*

AHA Backs Depression Screening

The American Heart Association says it "supports a strategy of increased awareness and screening for depression in patients with CHD [coronary heart disease]," in light of the high prevalence of depression in those patients. APA has endorsed this science advisory.

These are among the recommendations:

- Routine screening for depression in patients with CHD should be available in various medical settings. The opportunity to screen for and treat depression in cardiac patients should not be missed, as effective depression treatment may improve health outcomes.
- Patients with positive screening results should be evaluated by a professional qualified in the diagnosis and management of depression.
- Patients with cardiac disease who are under treatment for depression should be carefully monitored for adherence to their medical care, drug efficacy, and safety with respect to their cardiovascular as well as mental health.
- Coordination of care between health care providers is essential in patients with combined medical and mental health diagnoses.

"Depression and Coronary Heart Disease: Recommendations for Screening, Referral, and Treatment" is posted at <http://circ.ahajournals.org/cgi/content/full/118/17/1768>.

All May Not Be Rosy In Oxytocin's Future

Since oxytocin is a documented social lubricant, one might expect it to quell envy and gloating. However, it seems to do just the opposite—increase such emotions.

BY JOAN AREHART-TREICHEL

Until now, the brain hormone oxytocin has been found to play a role in prosocial emotions and behaviors. Scientists have found that when given intranasally, it can enhance social interactions and the formations of attachments, increase people's trust in each other, and reduce social anxiety (*Psychiatric News*, November 21, 2008).

However, oxytocin's fortune may be turning. A new study has found that it also may have antisocial properties—it may increase people's envy and gloating.

This new study was conducted by Simone Shamay-Tsoory, Ph.D., of the University of Haifa in Israel, and her colleagues. Results were published online July 30 in *Biological Psychiatry*.

Fifty-nine individuals who responded to an ad posted at the University of Haifa participated in this double-blind, placebo-controlled, within-subject study. The subjects were aged 20 to 37; 33 were female and 26 male.

Subjects were randomly assigned to receive intranasal oxytocin or a placebo and then played a game of chance under three conditions. During the first condition, a fake opponent won more money than the subjects did (to make them envious). During the second condition, a fake opponent lost more money than the subjects did (to make them gloat). During the third condition, a fake opponent won the same amount of money the subjects did (to provoke neither envy nor gloating). After playing each of the games, subjects were rated on feelings of envy and gloating.

In a second experimental session, the subjects who had received oxytocin got a placebo, and subjects who had received a placebo got oxytocin, and they played under the same three conditions.

As expected, subjects experienced significantly more envy after playing the envy-provoking game than after playing the other two games. And also as expected, subjects experienced significantly more gloating after playing the gloating-provoking game than after playing the other two games.

Finally the researchers looked to see whether there was any link between the envy or gloating emotions that subjects had experienced and the treatment they had received before playing the games. The answer was yes. Subjects experienced significantly more envy after playing the envy-provoking game and more gloating after playing the gloating-provoking game if they had received oxytocin beforehand than if they had received a placebo beforehand.

Thus, the administration of oxytocin enhanced envy and gloating, the researchers concluded. But how to explain this apparently contradictory finding since oxytocin seems to promote positive social emotions and bonding between people? One possibility, the researchers speculated, is that oxytocin not only promotes positive social emotions, but also modulates social emotions in general. For instance, oxytocin could "result in more trustworthiness and generosity in positive contexts, while leading to more envy and *Schadenfreude* in competitive contexts," they suggested.

The study was funded by the Israel Ministry of Health.

An abstract of "Intranasal Administration of Oxytocin Increases Envy and Schadenfreude (Gloating)" can be accessed by clicking on <www.journals.elsevierhealth.com> then "Articles in Press." ■

Brain MRI May Pinpoint Those at High Psychosis Risk

Hyperactivity in an area of the hippocampus tracked positively with symptom severity, suggesting that MRI screening could potentially be used to identify patients likely to experience first-episode psychosis.

BY MARK MORAN

A region of the hippocampus appears to be uniquely activated during functional magnetic resonance imaging (MRI) among individuals who later go on to develop psychosis.

Using cerebral blood volume mapping, the region—known as the CA1 subfield of the hippocampus—was found to be hyperactive among those individuals who were at high risk of psychosis and who later developed a first-episode psychotic disorder. Moreover, hyperactivity in the CA1 subfield also tracked positively with increasing severity of delusional symptoms and with avolition and social withdrawal—two "negative" symptoms associated with worsening outcome.

The report appeared in the September *Archives of General Psychiatry*. The lead author is Scott Small, M.D., the Herbert Irving Associate Professor of Neurology in the Sergievsky Center and in the Taub Institute for Research on Alzheimer's Disease and the Aging Brain at Columbia University Medical Center.

"Functional imaging can tell you where in the brain something is happening, not what is happening," said first author Scott Schobel, M.D., an assistant professor of clinical psychiatry at Columbia University College of Physicians and Surgeons, in an interview with *Psychiatric News*. "But what this hyperactive state strongly suggests is an increase in metabolism that is plausibly linked to dysfunction in the glutamate system."

Though far from conclusive, the finding points to the possibility in the future of a screen for determining which high-risk (or "prodromal") patients are likely to go on to develop a first-episode psychosis. Using clinical criteria today, clinicians can reliably predict approximately 50 percent to 60 percent of high-risk individuals who will go on to develop a psychotic disorder.

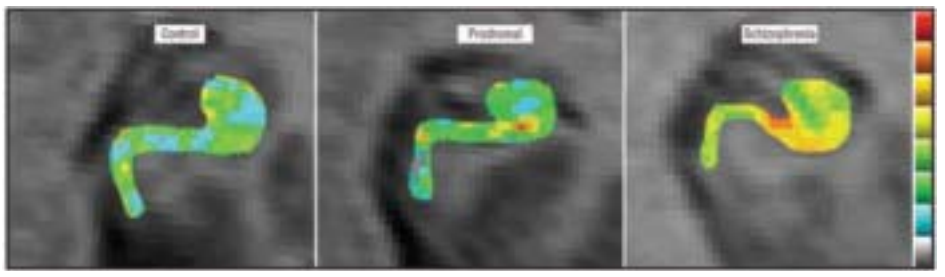
"The idea would be that one could use brain imaging as a snapshot of illness severity within the CA1 subfield," Schobel said. "It could potentially be used to identify those within the high-risk population who have abnormal activity above a certain threshold to selectively target this group with clinical treatments aimed at preventing illness progression, including potentially a glutamate-modulating therapy and/or cognitive therapy."

Schobel said the study relied on a new high-resolution MRI technique developed by Small. In the study, cerebral blood volume mapping with the new technique was used on 18 patients with schizophrenia, 18 age-matched, healthy control subjects, and 18 individuals with prodromal psychosis.

In a first between-group analysis comparing patients with schizophrenia and controls, abnormal cerebral blood volume (CBV) was found in the CA1 subfield and in the orbitofrontal cortex; abnormal decreases in CBV were found in the dorsolateral prefrontal cortex. In a second longitudinal analysis, abnormal CBV increases in the CA1 subfield predicted clinical progression to psychosis among the 18 prodromal individuals.

Functional MRI Identifies Brain Areas Involved In Early Stages of Schizophrenia

The warmer colors of yellow and red in these functional MRI images indicate higher cerebral blood volume in the CA1 subfield of the at-risk individual and the CA1 subfield of a patient with schizophrenia.



Credit: *Archives of General Psychiatry*, 66(9) 938-946 2009, © 2009 American Medical Association

Finally, a third analysis showed that CBV levels in the CA1 subfield correlated with severity of symptoms of psychosis.

"Progressive hyperfunctionality of the CA1 subfield was positively associated with worsening delusional severity," Schobel told *Psychiatric News*. "That was

please see ***Brain MRI*** *on page 36*

IMPORTANT SAFETY INFORMATION

INVEGA® SUSTENNA™ (paliperidone palmitate) extended-release injectable suspension is indicated for the acute and maintenance treatment of schizophrenia in adults.

IMPORTANT SAFETY INFORMATION FOR INVEGA® SUSTENNA™

WARNING: Increased Mortality in Elderly Patients with Dementia-Related Psychosis
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis.

- **Hypersensitivity:** Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone, which is a metabolite of risperidone. Therefore paliperidone is contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in INVEGA® SUSTENNA™.
- **Cerebrovascular Adverse Events (CAEs):** CAEs, including fatalities and stroke, have been reported in elderly patients with dementia-related psychosis taking oral risperidone in clinical trials. The incidence of CAEs with risperidone was significantly higher than with placebo. INVEGA® SUSTENNA™ is not approved for the treatment of patients with dementia-related psychosis.
- **Neuroleptic Malignant Syndrome (NMS):** NMS, a potentially fatal symptom complex, has been reported with the use of antipsychotic medications, including paliperidone. Clinical manifestations include muscle rigidity, fever, altered mental status and evidence of autonomic instability (see full Prescribing Information). Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and close medical monitoring, and treatment of any concomitant serious medical problems.
- **QT Prolongation:** Paliperidone causes a modest increase in the corrected QT (QTc) interval. Avoid the use of drugs that also increase QT interval and in patients with risk factors for prolonged QT interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias. Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval.
- **Tardive Dyskinesia (TD):** TD is a syndrome of potentially irreversible, involuntary, dyskinetic movements that may develop in patients treated with antipsychotic medications. The risk of developing TD and the likelihood that dyskinetic movements will become irreversible are believed to increase with duration of treatment and total cumulative dose, but can develop after relatively brief treatment at low doses. Elderly women patients appeared to be at increased risk for TD, although it is impossible to predict which patients will develop the syndrome. Prescribing should be consistent with the need to minimize the risk of TD. Discontinue drug if clinically appropriate. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.
- **Hyperglycemia and Diabetes:** Hyperglycemia, some cases extreme and associated with ketoacidosis, hyperosmolar coma or death has been reported in patients treated with atypical antipsychotics (APS), including INVEGA® SUSTENNA™. Patients starting treatment with APS who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing. Some patients require continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- **Weight Gain:** Weight gain has been observed with INVEGA® SUSTENNA™ and other atypical antipsychotic medications. Monitor weight gain.
- **Hyperprolactinemia:** As with other drugs that antagonize dopamine D_2 receptors, INVEGA® SUSTENNA™ elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to risperidone, which is associated with higher levels of prolactin elevation than other antipsychotic agents.
- **Orthostatic Hypotension and Syncope:** INVEGA® SUSTENNA™ may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period. Monitoring should be considered in patients for whom this may be of concern. INVEGA® SUSTENNA™ should be used with caution in patients with known cardiovascular disease, cerebrovascular disease or conditions that would predispose patients to hypotension.
- **Leukopenia, Neutropenia and Agranulocytosis** have been reported with antipsychotics, including paliperidone. Patients with a history of clinically significant low white blood cell count (WBC) or drug-induced leukopenia/neutropenia should have frequent complete blood cell counts during the first few months of therapy. At the first sign of a clinically significant decline in WBC and in the absence of other causative factors, discontinuation of INVEGA® SUSTENNA™ should be considered. Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count $<1000/mm^3$) should discontinue INVEGA® SUSTENNA™ and have their WBC followed until recovery.

ACT EARLIER
WITH NEW ONCE-MONTHLY INVEGA® SUSTENNA™

- Once-monthly dosing[3]
- Demonstrated safety and tolerability profile[†‡3]
- Significantly delayed time to relapse in the longer-term maintenance study[3]

[†]Reported in 4 fixed-dose, double-blind, placebo-controlled studies (N=1803).
[‡]Reported in the longer-term maintenance study (N=849).

- **Potential for Cognitive and Motor Impairment:** Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA® SUSTENNA™. INVEGA® SUSTENNA™ has the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that INVEGA® SUSTENNA™ does not affect them adversely, and should use caution when operating machinery.
- **Seizures:** INVEGA® SUSTENNA™ should be used cautiously in patients with a history of seizures or with conditions that potentially lower seizure threshold.
- **Suicide:** The possibility of suicide attempt is inherent in schizophrenia. Close supervision of high-risk patients should accompany drug therapy.
- **Administration:** For intramuscular injection only. Care should be taken to avoid inadvertent injection into a blood vessel.
- **Commonly Observed Adverse Reactions for INVEGA® SUSTENNA™:** The most common adverse reactions in clinical trials in patients with schizophrenia (≥5% and twice placebo) were injection site reactions, somnolence/sedation, dizziness, akathisia and extrapyramidal disorder.

References: 1. Mahmoud RA, Engelhart LM, Janagap CC, Oster G, Ollendorf D. Risperidone versus conventional antipsychotics for schizophrenia and schizoaffective disorder: symptoms, quality of life and resource use under customary clinical care. *Clin Drug Invest.* 2004;24:275-286. **2.** Keith SJ, Kane JM, Turner M, Conley RR, Nasrallah HA. Academic highlights: guidelines for the use of long-acting injectable atypical antipsychotics. *J Clin Psychiatry.* 2004;65:120-131. **3.** INVEGA® SUSTENNA™ [Prescribing Information]. Titusville, NJ: Ortho-McNeil-Janssen Pharmaceuticals, Inc. July 2009.

Please see accompanying brief summary of full Prescribing Information for INVEGA® SUSTENNA™.

Visit www.invegasustenna.com for more information.

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 September 2009 01PM09124

INVEGA® SUSTENNA™ (paliperidone palmitate)
Extended-Release Injectable Suspension

Brief Summary

BEFORE PRESCRIBING INVEGA® SUSTENNA™, PLEASE SEE FULL PRESCRIBING INFORMATION, INCLUDING BOXED WARNING.

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death 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 (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of patients with dementia-related psychosis. *[See Warnings and Precautions]*

INVEGA® SUSTENNA™ (paliperidone palmitate) is indicated for the acute and maintenance treatment of schizophrenia in adults *[see Clinical Studies (14) in full PI]*.

CONTRAINDICATIONS

Hypersensitivity reactions, including anaphylactic reactions and angioedema, have been observed in patients treated with risperidone and paliperidone. Paliperidone palmitate is converted to paliperidone, which is a metabolite of risperidone and is therefore contraindicated in patients with a known hypersensitivity to either paliperidone or risperidone, or to any of the excipients in the INVEGA® SUSTENNA™ formulation.

WARNINGS AND PRECAUTIONS

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. INVEGA® SUSTENNA™ (paliperidone palmitate) is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

Cerebrovascular Adverse Events, Including Stroke, in Elderly Patients With Dementia-Related Psychosis: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse events (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. Oral paliperidone and INVEGA® SUSTENNA™ were not marketed at the time these studies were performed and are not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions]*.

Neuroleptic Malignant Syndrome: A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs, including paliperidone. 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 creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases in which the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: (1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; (2) intensive symptomatic treatment and medical monitoring; and (3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient appears to require antipsychotic drug treatment after recovery from NMS, reintroduction of drug therapy should be closely monitored, since recurrences of NMS have been reported.

QT Prolongation: Paliperidone causes a modest increase in the corrected QT (QTc) interval. The use of paliperidone should be avoided in combination with other drugs that are known to prolong QTc including Class 1A (e.g., quinidine, procainamide) or Class III (e.g., amiodarone, sotalol) antiarrhythmic medications, antipsychotic medications (e.g., chlorpromazine, thioridazine), antibiotics (e.g., gatifloxacin, moxifloxacin), or any other class of medications known to prolong the QTc interval. Paliperidone should also be avoided in patients with congenital long QT syndrome and in patients with a history of cardiac arrhythmias.

Certain circumstances may increase the risk of the occurrence of torsade de pointes and/or sudden death in association with the use of drugs that prolong the QTc interval, including (1) bradycardia; (2) hypokalemia or hypomagnesemia; (3) concomitant use of other drugs that prolong the QTc interval; and (4) presence of congenital prolongation of the QT interval.

The effects of oral paliperidone on the QT interval were evaluated in a double-blind, active-controlled (moxifloxacin 400 mg single dose), multicenter QT study in adults with schizophrenia and schizoaffective disorder, and in three placebo- and active-controlled 6-week, fixed-dose efficacy trials in adults with schizophrenia.

In the QT study (n = 141), the 8 mg dose of immediate-release oral paliperidone (n=50) showed a mean placebo-subtracted increase from baseline in QTcLD of 12.3 msec (90% CI: 8.9; 15.6) on day 8 at 1.5 hours post-dose. The mean steady-state peak plasma concentration for this 8 mg dose of paliperidone immediate release ($C_{max\ ss}$ = 113 ng/mL) was more than 2-fold the exposure observed with the maximum recommended 234 mg dose of INVEGA® SUSTENNA™ administered in the deltoid muscle (predicted median $C_{max\ ss}$ = 50 ng/mL). In this same study, a 4 mg dose of the immediate-release oral formulation of paliperidone, for which $C_{max\ ss}$ = 35 ng/mL, showed an increased placebo-subtracted QTcLD of 6.8 msec (90% CI: 3.6; 10.1) on day 2 at 1.5 hours post-dose.

In the three fixed-dose efficacy studies of oral paliperidone extended release, electrocardiogram (ECG) measurements taken at various time points showed only one subject in the oral paliperidone 12 mg group had a change exceeding 60 msec at one time-point on Day 6 (increase of 62 msec).

In the four fixed-dose efficacy studies of INVEGA® SUSTENNA™, no subject experienced a change in QTcLD exceeding 60 msec and no subject had a QTcLD value of > 500 msec at any time point. In the maintenance study, no subject had a QTcLD change > 60 msec, and one subject had a QTcLD value of 507 msec (Bazett's QT corrected interval [QTcB] value of 483 msec); this latter subject also had a heart rate of 45 beats per minute.

Tardive Dyskinesia: A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to predict which patients will develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible appear to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase, but the syndrome can develop after relatively brief treatment periods at low doses, although this is uncommon.

There is no known treatment for established tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment itself may suppress (or partially suppress) the signs and symptoms of the syndrome and may thus mask the underlying process. The effect of symptomatic suppression on the long-term course of the syndrome is unknown.

Given these considerations, INVEGA® SUSTENNA™ should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that is known to respond to antipsychotic drugs. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient treated with INVEGA® SUSTENNA™, drug discontinuation should be considered. However, some patients may require treatment with INVEGA® SUSTENNA™ despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with all atypical antipsychotics. These cases were, for the most part, seen in post-marketing clinical use and epidemiologic studies, not in clinical trials, and there have been few reports of hyperglycemia or diabetes in trial subjects treated with INVEGA® SUSTENNA™. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Weight Gain: Weight gain has been observed with INVEGA® SUSTENNA™ and other atypical antipsychotics. In the 13-week study involving 234 mg initiation dosing, the proportion of subjects with an abnormal weight increase ≥ 7% showed a dose-related trend, with a 5% incidence rate in the placebo group compared with rates of 6%, 8%, and 13% in the INVEGA® SUSTENNA™ 39 mg, 156 mg, and 234 mg groups, respectively. In the two 13-week, fixed-dose, double-blind, placebo-controlled trials (pooled data), the proportions of subjects meeting a weight gain criterion of ≥ 7% of body weight were 6%, 9%, and 10% in the INVEGA® SUSTENNA™ 39 mg, 78 mg, and 156 mg groups, respectively, compared with 2% in the placebo group. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, 8% and 6% in the INVEGA® SUSTENNA™ 78 mg and 156 mg groups, respectively, met this criterion compared with 4% in the placebo group.

During the 33-week open-label period (9-week flexible-dose transition phase followed by a 24-week maintenance phase flexible-dose and minimum 12-week fixed dose) of the maintenance trial, 12% of INVEGA® SUSTENNA™-treated subjects met this criterion; the mean (SD) weight change from open-label baseline was +0.7 (4.79) kg. In the variable length double-blind phase, this criterion (weight gain of ≥ 7% from double-blind phase to endpoint) was met by 6% of INVEGA® SUSTENNA™-treated subjects compared with 3% of placebo-treated subjects; the mean weight change from double-blind baseline was +0.5 kg for INVEGA® SUSTENNA™ compared with –1.0 kg for placebo. Similar results were observed in the open-label extension phase of this study.

Hyperprolactinemia: Like other drugs that antagonize dopamine D_2 receptors, paliperidone elevates prolactin levels and the elevation persists during chronic administration. Paliperidone has a prolactin-elevating effect similar to that seen with risperidone, a drug that is associated with higher levels of prolactin than other antipsychotic drugs.

Hyperprolactinemia, regardless of etiology, may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotrophin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds. Long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both female and male subjects.

Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. An increase in the incidence of pituitary gland, mammary gland, and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats *[see Nonclinical Toxicology (13.1) in full PI]*. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Orthostatic Hypotension and Syncope: Paliperidone can induce orthostatic hypotension and syncope in some patients because of its alpha-blocking activity. Syncope was reported in < 1% (4/1293) of subjects treated with INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg in the four fixed-dose, double-blind, placebo-controlled trials compared with 0% (0/510) of subjects treated with placebo. In the four fixed-dose efficacy studies, orthostatic hypotension was reported as an adverse event by < 1% (2/1293) of INVEGA® SUSTENNA™-treated subjects compared to 0% (0/510) with placebo. Incidences of orthostatic hypotension and syncope in the long-term studies were similar to those observed in the short-term studies.

INVEGA® SUSTENNA™ should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction or ischemia, conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in patients who are vulnerable to hypotension.

Leukopenia, Neutropenia, and Agranulocytosis: *Class Effect:* In clinical trial and/or postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to antipsychotic agents, including INVEGA®, an oral form of paliperidone. Agranulocytosis has also been reported.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a history of a clinically significant low WBC or a drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and discontinuation of INVEGA® SUSTENNA™ should be considered at the first sign of a clinically significant decline in WBC in the absence of other causative factors.

Patients with clinically significant neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm^3) should discontinue INVEGA® SUSTENNA™ and have their WBC followed until recovery.

Potential for Cognitive and Motor Impairment: Somnolence, sedation, and dizziness were reported as adverse reactions in subjects treated with INVEGA® SUSTENNA™ *[see Adverse Reactions]*. Antipsychotics, including INVEGA® SUSTENNA™, have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that paliperidone therapy does not adversely affect them.

Seizures: In the four fixed-dose double-blind placebo-controlled studies, <1% (1/1293) of subjects treated with INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg experienced an adverse event of convulsion compared with <1% (1/510) of placebo-treated subjects who experienced an adverse event of grand mal convulsion.

Like other antipsychotic drugs, INVEGA® SUSTENNA™ should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

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 dementia. INVEGA® SUSTENNA™ and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high-risk patients should accompany drug therapy.

Priapism: Drugs with alpha-adrenergic blocking effects have been reported to induce priapism. Although no cases of priapism have been reported in clinical trials with INVEGA® SUSTENNA™, priapism has been reported with oral paliperidone during postmarketing surveillance. Severe priapism may require surgical intervention.

Thrombotic Thrombocytopenic Purpura (TTP): No cases of TTP were observed during clinical studies with oral paliperidone or INVEGA® SUSTENNA™. Although cases of TTP have been reported in association with risperidone administration, the relationship to risperidone therapy is unknown.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing INVEGA® SUSTENNA™ to patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Administration: INVEGA® SUSTENNA™ is intended for intramuscular injection, and care must be taken to avoid inadvertent injection into a blood vessel *[see Dosage and Administration (2.3) in full PI]*.

Antiemetic Effect: An antiemetic effect was observed in preclinical studies with paliperidone. This effect, if it occurs in humans, may mask the signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Use in Patients with Concomitant Illness: Clinical experience with INVEGA® SUSTENNA™ in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3) in full PI]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

INVEGA® SUSTENNA™ has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with INVEGA® SUSTENNA™, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions]*.

Monitoring: Laboratory Tests: No specific laboratory tests are recommended.

ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Increased mortality in elderly patients with dementia-related psychosis *[see Boxed Warning and Warnings and Precautions]*
- Cerebrovascular adverse events, including stroke, in elderly patients with dementia-related psychosis *[see Warnings and Precautions]*
- Neuroleptic malignant syndrome *[see Warnings and Precautions]*
- QT prolongation *[see Warnings and Precautions]*
- Tardive dyskinesia *[see Warnings and Precautions]*
- Hyperglycemia and diabetes mellitus *[see Warnings and Precautions]*
- Weight gain *[see Warnings and Precautions]*
- Hyperprolactinemia *[see Warnings and Precautions]*
- Orthostatic hypotension and syncope *[see Warnings and Precautions]*
- Leukopenia, neutropenia, and agranulocytosis *[see Warnings and Precautions]*
- Potential for cognitive and motor impairment *[see Warnings and Precautions]*
- Seizures *[see Warnings and Precautions]*
- Dysphagia *[see Warnings and Precautions]*
- Suicide *[see Warnings and Precautions]*
- Priapism *[see Warnings and Precautions]*
- Thrombotic Thrombocytopenic Purpura *[see Warnings and Precautions]*
- Disruption of body temperature regulation *[see Warnings and Precautions]*
- Avoidance of inadvertent injection into a blood vessel *[see Warnings and Precautions]*
- Antiemetic effect *[see Warnings and Precautions]*
- Increased sensitivity in patients with Parkinson's disease or those with dementia with Lewy bodies *[see Warnings and Precautions]*
- Diseases or conditions that could affect metabolism or hemodynamic responses *[see Warnings and Precautions]*

Throughout this section, a distinction is made between adverse events and adverse reactions. Adverse events are events reported by the clinician investigator and there is no attempt to assign causality to the study drug. Adverse reactions are adverse events that are considered to be reasonably associated with the use of INVEGA® SUSTENNA™ (adverse drug reactions) based on a predetermined method of assessment, e.g., a comparison of adverse event rates for drug and placebo groups for the event of interest. It is not possible to reliably establish causality by considering individual adverse event reports for drug-treated patients. Thus, the section overall is labeled Adverse Reactions, however, individual subsections are labeled adverse reactions or adverse events, depending on what is included in the subsection.

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The most common (at least 5% in any INVEGA® SUSTENNA™ group) and likely drug-related (adverse events for which the drug rate is at least twice the placebo rate) adverse reactions from the double-blind, placebo-controlled trials were injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder.

The data described in this section are derived from a clinical trial database (Phase 2 and 3) consisting of a total of 2770 subjects with schizophrenia who received at least one dose of INVEGA® SUSTENNA™ in the recommended dose range of 39 mg to 234 mg and a total of 510 subjects with schizophrenia who received placebo. Among the 2770 INVEGA® SUSTENNA™-treated subjects, 1293 received INVEGA® SUSTENNA™ in four fixed-dose, double-blind, placebo-controlled trials (one 9-week and three 13-week studies), 849 received INVEGA® SUSTENNA™ in the maintenance trial (of whom 205 continued to receive INVEGA® SUSTENNA™ during the double-blind placebo-controlled phase of this study), and 628 received INVEGA® SUSTENNA™ in two non-placebo controlled trials (a noninferiority active-comparator trial and an injection site [deltoid-gluteal] cross-over trial). One of the 13-week studies included a 234 mg INVEGA® SUSTENNA™ initiation dose followed by treatment with either 39 mg, 156 mg, or 234 mg every 4 weeks.

Adverse events during exposure to study treatment were obtained by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The majority of all adverse reactions were mild to moderate in severity.

Commonly-Observed Adverse Events in Double-Blind, Placebo-Controlled Clinical Trials: *Table 1* lists the adverse events reported in 2% or more of INVEGA® SUSTENNA™-treated subjects with schizophrenia in the four fixed-dose, double-blind, placebo-controlled trials.

Table 1. Incidence of Treatment Emergent Adverse Events in ≥ 2% of INVEGA® SUSTENNA™-Treated Subjects with Schizophrenia in Four Fixed-Dose, Double-Blind, Placebo-Controlled Trials: System Organ Class Adverse Event followed by **Placebo[a] (N=510)** first, **39 mg (N=130)** second, **78 mg (N=302)** third, **156 mg (N=312)** fourth, **234/39 mg[b] (N=160)** fifth, **234/156 mg[b] (N=165)** sixth, **234/234 mg[b] (N=163)** seventh: Total percentage of subjects with adverse event: 70, 75, 68, 69, 63, 60, 63; **Gastrointestinal disorders:** Abdominal discomfort/Abdominal pain upper 1, 0, 3, 3, 1, 2, 3; Constipation 5, 3, 5, 5, 2, 4, 1; Diarrhea 2, 0, 3, 2, 1, 2, 2; Dry mouth 1, 3, 1, 0, 1, 1, 1; Nausea 3, 4, 4, 3, 2, 2, 2; Toothache 1, 1, 1, 3, 1, 2, 3; Vomiting 4, 5, 4, 2, 3, 2, 2; **General disorders andadministration site conditions:** Asthenia 0, 2, 1, <1, 0, 1, 1; Fatigue 1, 1, 2, 2, 1, 2, 1; Injection site reactions 2, 0, 4, 6, 9, 7, 10; **Infections and infestations:** Nasopharyngitis 2, 0, 2, 2, 4, 2, 2; Upper respiratory tract infection 2, 2, 2, 2, 1, 2, 4; Urinary tract infection 1, 0, 1, <1, 1, 1, 2; **Injury, poisoning and procedural complications:** Skin laceration <1, 2, <1, 0, 1, 0, 0; **Investigations:** Alanine aminotransferaseincreased 2, 0, 2, 1, 1, 1, 1; Weight increased 1, 4, 4, 1, 1, 1, 2; **Musculoskeletal andconnective tissue disorders:** Back pain 2, 2, 1, 3, 1, 1, 1; Musculoskeletal stiffness 1, 1, <1, <1, 1, 1, 2; Myalgia 1, 2, 1, <1, 1, 0, 2; Pain in extremity 1, 0, 2, 2, 2, 3, 0; **Nervous system disorders:** Akathisia 3, 2, 2, 3, 1, 5, 6; Dizziness 1, 6, 2, 4, 1, 4, 2; Extrapyramidal disorder 1, 5, 2, 3, 1, 0, 0; Headache 12, 11, 11, 15, 11, 7, 6; Somnolence/sedation 3, 5, 7, 4, 1, 5, 5; **Psychiatric disorders:** Agitation 7, 10, 5, 9, 8, 5, 4; Anxiety 7, 8, 5, 3, 5, 6, 6; Insomnia 15, 15, 15, 13, 12, 10, 13; Nightmare <1, 2, 0, 0, 0, 0, 0; Suicidal ideation 2, 0, 1, 2, 2, 2, 1; **Respiratory, thoracic and mediastinal disorders:** Cough 1, 2, 3, 1, 0, 1, 1; **Vascular disorders:** Hypertension 1, 2, 1, 1, 1, 1, 0. Percentages are rounded to whole numbers. Table includes adverse events that were reported in 2% or more of subjects in any of the INVEGA® SUSTENNA™ dose groups and which occurred at greater incidence than in the placebo group. [a] Placebo group is pooled from all studies and included either deltoid or gluteal injection depending on study design. [b] Initial deltoid injection of 234 mg followed by either 39 mg, 156 mg, or 234 mg every 4 weeks by deltoid or gluteal injection. Other dose groups (39 mg, 78 mg, and 156 mg) are from studies involving only gluteal injection. [See Clinical Studies (14) in full PI]

Adverse events for which the paliperidone palmitate incidence was equal to or less than placebo are not listed in the table, but included the following: dyspepsia, psychotic disorder, schizophrenia, and tremor. The following terms were combined: somnolence/sedation, breast tenderness/breast pain, abdominal discomfort/abdominal pain upper, and tachycardia/sinus tachycardia/heart rate increased. All injection site reaction-related adverse events were collapsed and are grouped under "Injection site reactions".

Adverse Reactions Observed During the Premarketing Evaluation of INVEGA® SUSTENNA™ Not Listed in Table 1: The following additional adverse reactions occurred in INVEGA® SUSTENNA™-treated subjects in the above four fixed-dose, double-blind, placebo-controlled trials, in the double-blind phase of the maintenance trial, or in INVEGA® SUSTENNA™-treated subjects with schizophrenia who participated in other Phase 3 trials, and were not reported in Table 1. They were determined to be adverse reactions based upon reasons to suspect causality such as timing of onset or termination with respect to drug use, plausibility in light of the drug's known pharmacology, occurrence at a frequency above that expected in the treated population or occurrence of an event typical of drug-induced adverse reactions.

Cardiac disorders: bradycardia, bundle branch block, postural orthostatic tachycardia syndrome, tachycardia
Ear and labyrinth disorders: vertigo
Endocrine disorders: hyperprolactinemia
Eye disorders: oculogyric crisis, eye rolling, vision blurred
Gastrointestinal disorders: salivary hypersecretion, stomach discomfort
Investigations: blood cholesterol increased, blood glucose increased
Metabolism and nutrition disorders: decreased appetite, increased appetite
Nervous system disorders: convulsion, dizziness postural, drooling, dysarthria, dyskinesia, dystonia, hypertonia, lethargy, neuroleptic malignant syndrome, oromandibular dystonia, parkinsonism, psychomotor hyperactivity, syncope
Psychiatric disorders: restlessness
Reproductive system and breast disorders: amenorrhea, erectile dysfunction, galactorrhea, gynecomastia, menstruation irregular, sexual dysfunction
Skin and subcutaneous tissue disorders: pruritus generalized, rash
Vascular disorders: orthostatic hypotension

Discontinuations Due to Adverse Events: The percentages of subjects who discontinued due to adverse events in the four fixed-dose, double-blind, placebo-controlled trials were 5.0% and 7.8% in INVEGA® SUSTENNA™- and placebo-treated subjects, respectively.

Dose-Related Adverse Reactions: Based on the pooled data from the four fixed-dose, double-blind, placebo-controlled trials, among the adverse reactions that occurred at ≥ 2% incidence in the subjects treated with INVEGA® SUSTENNA™, only akathisia increased with dose. Hyperprolactinemia also exhibited a dose relationship, but did not occur at ≥ 2% incidence in INVEGA® SUSTENNA™-treated subjects from the four fixed-dose studies.

Demographic Differences: An examination of population subgroups in the double-blind placebo-controlled trials did not reveal any evidence of differences in safety on the basis of age, gender, or race alone; however, there were few subjects ≥ 65 years of age.

Extrapyramidal Symptoms (EPS): Pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials provided information regarding treatment-emergent EPS. Several methods were used to measure EPS: (1) the Simpson-Angus global score (mean change from baseline or score at the end of trial) which broadly evaluates Parkinsonism, (2) the Barnes Akathisia Rating Scale global clinical rating score (mean change from baseline or score at the end of trial) which evaluates akathisia, (3) use of anticholinergic medications to treat emergent EPS, (4) the Abnormal Involuntary Movement Scale scores (mean change from baseline or scores at the end of trial) *(Table 2)*, and (5) incidence of spontaneous reports of EPS *(Table 3)*.

Table 2. Treatment-Emergent Extrapyramidal Symptoms (EPS) Assessed by Incidence of Rating Scales and Use of Anticholinergic Medication: Scale followed by **Percentage of Subjects Placebo (N=262)** first, **INVEGA® SUSTENNA™ 39 mg (N=130)** second, **78 mg (N=223)** third, **156 mg (N=228)** fourth: Parkinsonism[a] 9, 12, 10, 6; Akathisia[b] 5, 5, 6, 5; Dyskinesia[c] 3, 4, 6, 4; Use of Anticholinergic Medications[d] 12, 10, 12, 11. [a]For Parkinsonism, percent of subjects with Simpson-Angus Total score > 0.3 at endpoint (Total score defined as total sum of items score divided by the number of items) [b]For Akathisia, percent of subjects with Barnes Akathisia Rating Scale global score ≥ 2 at endpoint [c]For Dyskinesia, percent of subjects with a score ≥ 3 on any of the first 7 items or a score ≥ 2 on two or more of any of the first 7 items of the Abnormal Involuntary Movement Scale at endpoint [d]Percent of subjects who received anticholinergic medications to treat emergent EPS

Table 3. Treatment-Emergent Extrapyramidal Symptoms (EPS)-Related Adverse Events by MedDRA Preferred Term: EPS Group followed by **Percentage of Subjects Placebo (N=262)** first, **INVEGA® SUSTENNA™ 39 mg (N=130)** second, **78 mg (N=223)** third, **156 mg (N=228)** fourth: Overall percentage of subjects with EPS-related adverse events 10, 12, 11, 11; Parkinsonism 5, 6, 6, 4; Hyperkinesia 2, 2, 2, 4; Tremor 3, 2, 2, 3; Dyskinesia 1, 2, 3, 1; Dystonia 0, 1, 1, 2.

Parkinsonism group includes: Extrapyramidal disorder, hypertonia, musculoskeletal stiffness, parkinsonism, drooling, masked facies, muscle tightness, hypokinesia

Hyperkinesia group includes: Akathisia, restless legs syndrome, restlessness

Dyskinesia group includes: Dyskinesia, choreoathetosis, muscle twitching, myoclonus, tardive dyskinesia

Dystonia group includes: Dystonia, muscle spasms

The results across all phases of the maintenance trial exhibited comparable findings. In the 9-week, fixed-dose, double-blind, placebo-controlled trial, the proportions of Parkinsonism and akathisia assessed by incidence of rating scales were higher in the INVEGA® SUSTENNA™ 156 mg group (18% and 11%, respectively) than in the INVEGA® SUSTENNA™ 78 mg group (9% and 5%, respectively) and placebo group (7% and 4%, respectively).

In the 13-week study involving 234 mg initiation dosing, the incidence of any treatment-emergent EPS-related adverse events was similar to that of the placebo group (8%), but exhibited a dose-related pattern with 6%, 10%, and 11% in the INVEGA® SUSTENNA™ 234/39 mg, 234/156 mg, and 234/234 mg groups, respectively. Hyperkinesia was the most frequent category of EPS-related adverse events in this study, and was reported at a similar rate between the placebo (4.9%) and INVEGA® SUSTENNA™ 234/156 mg (4.8%) and 234/234 mg (5.5%) groups, but at a lower rate in the 234/39 mg group (1.3%).

Dystonia: *Class Effect:* Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Laboratory Test Abnormalities: In the pooled data from the two double-blind, placebo-controlled, 13-week, fixed-dose trials, a between-group comparison revealed no medically important differences between INVEGA® SUSTENNA™ and placebo in the proportions of subjects experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no differences between INVEGA® SUSTENNA™ and placebo in the incidence of discontinuations due to changes in hematology, urinalysis, or serum chemistry, including mean changes from baseline in fasting glucose, insulin, c-peptide, triglyceride, HDL, LDL, and total cholesterol measurements. However, INVEGA® SUSTENNA™ was associated with increases in serum prolactin [see Warnings and Precautions]. The results from the 13-week study involving 234 mg initiation dosing, the 9-week, fixed-dose, double-blind, placebo-controlled trial, and the double-blind phase of the maintenance trial exhibited comparable findings.

Pain Assessment and Local Injection Site Reactions: In the pooled data from the two 13-week, fixed-dose, double-blind, placebo-controlled trials, the mean intensity of injection pain reported by subjects using a visual analog scale (0 = no pain to 100 = unbearably painful) decreased in all treatment groups from the first to the last injection (placebo: 10.9 to 9.8; 39 mg: 10.3 to 7.7; 78 mg: 10.0 to 9.2; 156 mg: 11.1 to 8.8). The results from both the 9-week, fixed-dose, double-blind, placebo-controlled trial and the double-blind phase of the maintenance trial exhibited comparable findings.

In the 13-week study involving 234 mg initiation dosing, occurrences of induration, redness, or swelling, as assessed by blinded study personnel, were infrequent, generally mild, decreased over time, and similar in incidence between the INVEGA® SUSTENNA™ and placebo groups. Investigator ratings of injection pain were similar for the placebo and INVEGA® SUSTENNA™ groups. Investigator evaluations of the injection site after the first injection for redness, swelling, induration, and pain were rated as absent for 69-100% of subjects in both the INVEGA® SUSTENNA™ and placebo groups. At Day 92, investigators rated absence of redness, swelling, induration, and pain in 95-100% of subjects in both the INVEGA® SUSTENNA™ and placebo groups.

Adverse Reactions Reported With Oral Paliperidone: The following is a list of additional adverse reactions that have been reported with oral paliperidone in subjects with schizophrenia:

Cardiac disorders: atrioventricular block first degree, palpitations, sinus arrhythmia
Gastrointestinal disorders: abdominal pain, swollen tongue
General disorders and administration site conditions: edema
Immune system disorders: anaphylactic reaction
Musculoskeletal and connective tissue disorders: muscle rigidity
Nervous system disorders: tremor
Reproductive system and breast disorders: priapism, breast discharge
Vascular disorders: ischemia

Adverse Reactions Reported With Risperidone: Paliperidone is the major active metabolite of risperidone. Adverse reactions reported with oral risperidone and risperidone long-acting injection can be found in the ADVERSE REACTIONS sections of the package inserts for those products.

DRUG INTERACTIONS

Since paliperidone palmitate is hydrolyzed to paliperidone *[see Clinical Pharmacology (12.3) in full PI]*, results from studies with oral paliperidone should be taken into consideration when assessing drug-drug interaction potential.

Potential for INVEGA® SUSTENNA™ to Affect Other Drugs: Given the primary CNS effects of paliperidone *[see Adverse Reactions]*, INVEGA® SUSTENNA™ should be used with caution in combination with other centrally acting drugs and alcohol. Paliperidone may antagonize the effect of levodopa and other dopamine agonists.

Because of its potential for inducing orthostatic hypotension, an additive effect may be observed when INVEGA® SUSTENNA™ is administered with other therapeutic agents that have this potential *[see Warnings and Precautions]*.

Paliperidone is not expected to cause clinically important pharmacokinetic interactions with drugs that are metabolized by cytochrome P450 isozymes. *In vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by cytochrome P450 isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4, and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. Paliperidone is also not expected to have enzyme inducing properties.

Paliperidone is a weak inhibitor of P-glycoprotein (P-gp) at high concentrations. No *in vivo* data are available and the clinical relevance is unknown.

Potential for Other Drugs to Affect INVEGA® SUSTENNA™: Paliperidone is not a substrate of CYP1A2, CYP2A6, CYP2C9, and CYP2C19, so that an interaction with inhibitors or inducers of these isozymes is unlikely. While *in vitro* studies indicate that CYP2D6 and CYP3A4 may be minimally involved in paliperidone metabolism, *in vivo* studies do not show decreased elimination by these isozymes and they contribute to only a small fraction of total body clearance. *In vitro* studies have shown that paliperidone is a P-gp substrate.

Co-administration of oral paliperidone extended release once daily with carbamazepine 200 mg twice daily caused a decrease of approximately 37% in the mean steady-state C_{max} and AUC of paliperidone. This decrease is caused, to a substantial degree, by a 35% increase in renal clearance of paliperidone. A minor decrease in the amount of drug excreted unchanged in the urine suggests that there was little effect on the CYP metabolism or bioavailability of paliperidone during carbamazepine co-administration. On initiation of carbamazepine, the dose of INVEGA® SUSTENNA™ should be re-evaluated and increased if necessary. Conversely, on discontinuation of carbamazepine, the dose of INVEGA® SUSTENNA™ should be re-evaluated and decreased if necessary.

Paliperidone is metabolized to a limited extent by CYP2D6 *[see Clinical Pharmacology (12.3) in full PI]*. In an interaction study in healthy subjects in which a single 3 mg dose of oral paliperidone extended release was administered concomitantly with 20 mg per day of paroxetine (a potent CYP2D6 inhibitor), paliperidone exposures were on average 16% (90% CI: 4, 30) higher in CYP2D6 extensive metabolizers. Higher doses of paroxetine have not been studied. The clinical relevance is unknown.

Co-administration of a single dose of an oral paliperidone extended-release 12 mg tablet with divalproex sodium extended-release tablets (two 500 mg tablets once daily at steady-state) resulted in an increase of approximately 50% in the C_{max} and AUC of paliperidone. Although this interaction has not been studied with INVEGA® SUSTENNA™, a clinically significant interaction would not be expected between divalproex sodium and INVEGA® SUSTENNA™ intramuscular injection.

USE IN SPECIFIC POPULATIONS

Pregnancy: Pregnancy Category C.: There were no treatment-related effects on the offspring when pregnant rats were injected intramuscularly with paliperidone palmitate during the period of organogenesis at doses up to 160 mg/kg, which is 10 times the maximum recommended human 234 mg dose of INVEGA® SUSTENNA™ on a mg/m² basis.

In studies in pregnant rats and rabbits in which paliperidone was given orally during the period of organogenesis, there were no increases in fetal abnormalities up to the highest doses tested (10 mg/kg/day in rats and 5 mg/kg/day in rabbits, which are each 8 times the maximum recommended human dose [12 mg/day] of orally administered paliperidone [INVEGA®] on a mg/m² basis).

In rat reproduction studies with risperidone, which is extensively converted to paliperidone in rats and humans, increases in pup deaths were seen at oral doses which are less than the maximum recommended human dose of risperidone on a mg/m² basis (see RISPERDAL® package insert).

There are no adequate and well controlled studies of INVEGA® SUSTENNA™ in pregnant women. INVEGA® SUSTENNA™ should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Use of first generation antipsychotic drugs during the last trimester of pregnancy has been associated with extrapyramidal symptoms in the neonate. These symptoms are usually self-limited. It is not known whether paliperidone, when taken near the end of pregnancy, will lead to similar neonatal signs and symptoms.

Labor and Delivery: The effect of INVEGA® SUSTENNA™ on labor and delivery in humans is unknown.

Nursing Mothers: In animal studies with paliperidone and in human studies with risperidone, paliperidone was excreted in the milk. Therefore, women receiving INVEGA® SUSTENNA™ should not breast feed infants.

Pediatric Use: Safety and effectiveness of INVEGA® SUSTENNA™ in patients < 18 years of age have not been established.

Geriatric Use: Clinical studies of INVEGA® SUSTENNA™ did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients.

This drug is known to be substantially excreted by the kidney and clearance is decreased in patients with renal impairment *[see Clinical Pharmacology (12.3) in full PI]*, who should be given reduced doses. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration (2.5) in full PI]*.

Renal Impairment: INVEGA® SUSTENNA™ has not been systematically studied in patients with renal impairment [see Clinical Pharmacology (12.3) in full PI]. For patients with mild renal impairment (creatinine clearance ≥ 50 mL/min to < 80 mL/min), recommended initiation of INVEGA® SUSTENNA™ is with a dose of 156 mg on treatment day 1 and 117 mg one week later, both administered in the deltoid muscle. Thereafter, follow with monthly injections of 78 mg in either the deltoid or gluteal muscle.

INVEGA® SUSTENNA™ is not recommended in patients with moderate or severe renal impairment (creatinine clearance < 50 mL/min).

Hepatic Impairment: INVEGA® SUSTENNA™ has not been studied in patients with hepatic impairment. Based on a study with oral paliperidone, no dose adjustment is required in patients with mild or moderate hepatic impairment. Paliperidone has not been studied in patients with severe hepatic impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: INVEGA® SUSTENNA™ (paliperidone) is not a controlled substance.

Abuse: Paliperidone has not been systematically studied in animals or humans for its potential for abuse.

Dependence: Paliperidone has not been systematically studied in animals or humans for its potential for tolerance or physical dependence.

OVERDOSAGE

Human Experience: No cases of overdose were reported in premarketing studies with INVEGA® SUSTENNA™. Because INVEGA® SUSTENNA™ is to be administered by health care professionals, the potential for overdosage by patients is low.

While experience with paliperidone overdose is limited, among the few cases of overdose reported in premarketing trials with oral paliperidone, the highest estimated ingestion was 405 mg. Observed signs and symptoms included extrapyramidal symptoms and gait unsteadiness. Other potential signs and symptoms include those resulting from an exaggeration of paliperidone's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension, and QT prolongation.

Paliperidone is the major active metabolite of risperidone. Overdose experience reported with risperidone can be found in the OVERDOSAGE section of the risperidone package insert.

Management of Overdosage: There is no specific antidote to paliperidone, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consideration should be given to the prolonged-release characteristics of INVEGA® SUSTENNA™ and the long apparent half-life of paliperidone when assessing treatment needs and recovery. Multiple drug involvement should also be considered.

In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of paliperidone. Similarly the alpha-blocking properties of bretylium might be additive to those of paliperidone, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures, such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of paliperidone-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Manufactured by:
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More Clues Uncovered in Suicide's Many Mysteries

Most people who think about or attempt suicide don't die by suicide. Why is this—why do so many suicidal people choose life? An Ontario psychiatrist wants to find out.

BY JOAN AREHART-TREICHEL

Slowly but surely, psychiatric scientists are unmasking the factors that heighten people's risk of committing suicide, experts on the subject indicated at the annual meeting of the Canadian Psychiatric Association in St. John's, Newfoundland, in August.

Some of the variables are childhood adversity, medical illnesses, impulsivity, aggression, and certain personality disorders, James Bolton, M.D., an assistant professor of psychiatry at the University of Manitoba, reported.

Studies have shown that physicians are at a somewhat higher risk of suicide than is the general population, Michael Myers, M.D., a professor of clinical psychiatry at the State University of New York Downstate Medical Center and an authority on physicians' psychiatric problems, said. However, physicians who are perfectionists, narcissists, or rugged individualists are at even greater risk of committing suicide, he explained.

Credit: Joan Arehart-Treichel

James Bolton, M.D.: "Comorbidity is very important in suicide attempts."

Bolton and his colleagues used data from the U.S. National Epidemiologic Survey on Alcohol and Related Conditions to identify risk factors for suicide in people with major depression. Out of some 35,000 persons who took part in the survey, some 6,000 had a major depression, and out of this sample, 169 subsequently made a suicide attempt. Bolton and his team then looked to see which characteristics besides depression might have predicted suicide attempts. The answer was posttraumatic stress disorder or borderline personality disorder. "So comorbidity is very important in suicide attempts," Bolton asserted.

Myers concurred. If physicians who are perfectionistic or narcissistic are also depressed, they can be in especially grave danger of suicide, he noted. The same is the case for physicians who are depressed and abuse substances, he added.

Martine Flament, M.D., Ph.D., of the University of Ottawa reported that she and her colleagues had conducted a study of 49 child or adolescent suicide attempters in a pediatric emergency room and compared them with age- and gender-matched control subjects. Their findings showed that both the trait of impulsivity and the presence of depression were highly prevalent in children and youth attempting suicide.

Not getting help, especially the right kind of help, can also predispose people to suicide. Alain Lesage, M.D., of the University of Montreal and colleagues interviewed the families of 102 people who had killed themselves to find out whether the latter had sought professional help or not. More than half had visited a mental health specialist during the year preceding their deaths. But only 5 percent had had any contact with addiction services, even though two-thirds suffered from substance abuse as well as depression. So there is a need for "greater coordination and integration of mental health specialists and addiction services within the health care system," Lesage urged.

And just as psychiatrists are unmasking the many variables that increase people's risk of suicide, they are also starting to identify the ingredients that shield people from it, speakers at the meeting indicated.

For example, most people who think about suicide do not actually attempt it, Bolton noted. The situation is similar for suicide attempts, Jennifer Brasch, M.D., pointed out—most people who attempt suicide actually do not end up killing themselves. Brasch is medical director of the psychiatric emergency service at St. Joseph's Healthcare in Hamilton, Ontario.

So what is it that keeps people from moving beyond suicidal ideation to suicide attempts, or from suicide attempts to completed suicide?

"We don't really understand how the shift takes place," Brasch admitted. So she is trying to find the answers, and in a novel way.

The way is a Web site that she launched a year ago—<www.thereasons.ca>. It invites people who have recovered from being suicidal to post their stories. To date, some 7,300 people from 89 countries have visited the site, and 57 have recorded their suicide recovery stories. The stories are starting to give Brasch insights into some of the ingredients that help people recover from suicidality, she said—for instance, knowing that a therapist was there for them during their anguish. In fact, connection with other people has been a major lifeline in every story she has received so far, she said. ■

Differentiating Schizophrenia From Bipolar Disorder Can Be Difficult

The line between bipolar disorder and schizophrenia seems to be fuzzier than previously thought, sometimes making diagnosis very difficult.

BY JOAN AREHART-TREICHEL

Although schizophrenia and bipolar disorder have long been considered distinct illnesses, the demarcation between the two may be thinner than previously believed.

So reported some psychiatrists at the annual meeting of the Canadian Psychiatric Association in St. John's, Newfoundland, in August.

The psychiatrists were Glenda MacQueen, M.D., Ph.D., chair of psychiatry at the University of Calgary; Roger McIntyre, M.D., an associate professor of psychiatry and pharmacology at the University of Toronto, and Ashok Malla, M.D., a professor of psychiatry at McGill University.

There are a number of reasons why the line between schizophrenia and bipolar disorder seems to be fuzzier than previously thought, the speakers indicated.

Some of the same brain abnormalities that can be found in subjects with schizophrenia can also be found in bipolar subjects, McIntyre reported. Moreover, these same brain abnormalities can be found in some unaffected first-degree relatives of individuals with schizophrenia and in some unaffected first-degree relatives of individuals with bipolar disorder, suggesting that they are inherited and common to people with either schizophrenia or bipolar disorder.

Even though psychiatrists usually assume that cognitive impairment is only experienced by individuals with schizophrenia, not by those with bipolar disorder, individuals with the latter can experience it as well, MacQueen said.

And just as bipolar individuals can have cognitive deficits, they can also experience another hallmark of schizophrenia—psychotic symptoms, MacQueen stated.

Still another link between schizophrenia and bipolar disorder is the risk of the metabolic syndrome—weight gain, metabolic disturbances, even cardiovascular disease. Certainly the reason why patients with either schizophrenia or bipolar disorder develop the syndrome can sometimes be blamed on the use of psychotropic medications or on the pursuit of unhealthy lifestyles, Malla said. But in other instances, he suspects, the metabolic syndrome can be attributed to biological abnormalities common to both schizophrenia and bipolar disorder. One possible candidate is a gene that codes for inflammatory responses in the body, he noted. It was recently identified in both bipolar and schizophrenia subjects.

Another commonality between schizophrenia and bipolar disorder is the difficulty that patients with either disorder have in achieving a functional recovery, the speakers pointed out. True, more bipolar patients than schizophrenia patients do recover, but nonetheless not all bipolar patients do, they said.

Finally, could it be that some patients who start off with bipolar disorder evolve into having schizophrenia? The speakers believed that this is a possibility.

Thus, as the case for an overlap between schizophrenia and bipolar illness grows, it raises questions about diagnosis. When should patients receive a diagnosis of schizophrenia? When should they receive a diagnosis of bipolar disorder? And how does a diagnosis of schizoaffective disorder fit into the picture? There are no simple answers here, the speakers noted.

Some audience members concurred. For instance, one reported that she has had great trouble determining whether mentally ill people in a homeless shelter have schizophrenia, bipolar disorder, or schizoaffective disorder, especially when they also abuse alcohol or use cocaine. ■

Researchers Try to Assess Dimensions of Resilience

Resilience is becoming a major international research topic. For instance, children on various continents are being filmed to explore how they successfully cope with adversity.

BY JOAN AREHART-TREICHEL

"The concept of resilience is becoming a hot topic," Donna Stewart, M.D., university professor and chair of women's health at the University of Toronto, reported at the annual meeting of the Canadian Psychiatric Association in St. John's, Newfoundland, in August.

Oddgeir Friborg, Ph.D., a psychologist at the University of Tromso in Norway, is a leading resilience researcher, said Stewart. He and his colleagues are testing a Resilience Scale for Adults (RSA) to distinguish people who are emotionally hardy and bounce back from adversity from those who are more vulnerable and must struggle to regain their footing. The military is especially interested in this scale, Stewart said, since "posttraumatic stress disorder is an enormous problem for the military everywhere."

Friborg and his colleagues also looked to see whether their RSA could predict subjects who may be more resilient to pain. It could, they reported in the August 2006 *Journal of Psychosomatic Research*. They likewise developed an instrument to measure resilience in adolescents. They found that youth who scored higher on this instrument exhibited significantly lower levels of depressive symptoms, even when controlling for gender, age, the number of stressful life events, and level of social anxiety. Their findings were published in the January 2007 *Clinical Child Psychology and Psychiatry*.

Meanwhile, resilience research is taking place at the Resilience Research Center in Halifax, Nova Scotia, Stewart reported. It is under the direction of Michael Ungar, Ph.D., a professor of social work at Dalhousie University. The center is bringing together leaders in the field of resilience research from different disciplines and cultural backgrounds. They are using diverse approaches to study how children, adolescents, and families cope with various kinds of diversity.

For instance, the purpose of their International Resilience Project is to develop a better, more culturally sensitive understanding of how youth around the world effectively cope with the adversities that they face. During the first three years of the project, data from some 1,500 children on five continents will be collected and analyzed. Part of the data collection will consist of filming the children in their real-life settings to learn how they successfully deal with poverty, war, violence, parental illness, or other misfortunes.

Some programs that are designed to make people hardier also look promising, Stewart reported. The Public Health Agency of Canada has a program called Nobody's Perfect: Building Resiliency in Canadian Children for Over Twenty Years. For 20 years now, through the program, parents of young children can meet together weekly to discuss their parenting concerns and to strengthen their parenting skills. In Australia, there is the Friends program, which aims to prevent childhood anxiety and depression by building emotional resilience in children. This cognitive-behavioral intervention can be applied in either a grade-school or a high-school setting.

Programs such as these need to be rigorously evaluated, Stewart indicated, "and once we have found which are effective, make them more widely available."

And as resilience research gains momentum, hopefully it will benefit psychiatric treatment as well, she added. For instance, it's possible that psychiatrists might eventually be able to use a resilience scale in their practices to help predict patient's responses to treatment. ■

Several Strategies Successful For Treating Anxiety Disorders

CBT can benefit patients with generalized anxiety disorder. For patients who have both anxiety and depression, the best strategy is to place them on medications first, and then add CBT later.

BY JOAN AREHART-TREICHEL

Generalized anxiety disorder (GAD) can be seen in all clinical settings, and in primary care, practitioners are usually good at identifying GAD patients, Richard Swinson, M.D., said at the annual meeting of the Canadian Psychiatric Association in St. John's, Newfoundland, in August.

"By the time [patients with GAD] see me, or other psychiatrists, they are longstanding worriers, that is, the more difficult cases," said Swinson, a professor emeritus of psychiatry at McMaster University and medical director of the Anxiety Treatment Research Center at St. Joseph's Healthcare in Hamilton, Ontario.

No matter the severity of GAD, there are effective treatments for it that can lead patients "to full recovery," he said.

Three SSRI antidepressants and two SNRI antidepressants have been approved for treating GAD in Canada, he noted, and there is some evidence that anticonvulsants or antipsychotics can help GAD patients. At first antipsychotics were used as SSRI augmenters for GAD, but a recent approach is to use them as monotherapy, and that has been found useful in clinical studies, he said.

Cognitive-behavioral therapy (CBT) can also benefit GAD patients, Swinson noted. He said a good resource in this area is Michel Dugas, Ph.D., director of the anxiety disorders laboratory at Concordia University in Montreal. Over the past 16 years, Dugas has conducted research on the origins of GAD and has developed a CBT treatment for it, which has been validated in a number of trials. Dugas has also written a book called *Cognitive-Behavioral Treatment for Generalized Anxiety Disorder: From Science to Practice*, which provides a step-by-step treatment of GAD.

For patients who have both GAD and depression, the best strategy is to place them on medications first and then to add CBT later, Swinson advised. The combination strategy should help alleviate both their anxiety and their depression, he indicated.

Other common comorbid conditions for GAD include another anxiety disorder, alcohol abuse, personality disorders, and bipolar disorder, Swinson pointed out. ■

COMPILED BY JUN YAN

Regulatory Briefs

• The Food and Drug Administration (FDA) is requiring manufacturers to add a precaution on the labels of all ***antipsychotics*** about the risks of leukopenia, neutropenia, and agranulocytosis associated with the entire drug class. These adverse events related to white-blood-cell counts have been reported to the agency in clinical trials or postmarketing reports. Patients with an already low white blood-cell count and a history of drug-induced leucopenia/neutropenia may be at a higher risk for developing such problems if they are taking antipsychotics. Clinicians should carefully monitor patients for symptoms of infection if neutropenia develops and discontinue the drug if neutrophil count falls below 1000/mm^3. The labeling change applies to both first- and second-generation antipsychotics.

The FDA labeling changes are posted at <www.fda.gov/safety/medwatch/safetyinformation/ucm172740.htm>.

• The FDA and the European Medicines Agency have launched a collaborative initiative to share standards and information for the regulation of clinical-trial practices, the FDA announced on August 3. The initiative includes sharing the agencies' reports from routine inspection and monitoring of clinical-trial sites, streamlining procedures, and communicating regulatory legislation and guidelines with each other. As more pharmaceutical and medical-device companies conduct global trials and seek marketing approval with clinical data collected abroad, the two agencies hope to share the inspection resources in monitoring compliance and assessing ethical conduct of clinical trials.

• The FDA approved ***paliperidone*** extended-release oral tablets for acute treatment of schizoaffective disorder as either monotherapy or adjunctive therapy to mood stabilizers and/or antidepressants, according to a July 31 announcement by Ortho-McNeil-Janssen Pharmaceuticals, a subsidiary of Johnson and Johnson. Two randomized, double-blind, placebo-controlled trials were conducted in patients with schizoaffective disorder for six weeks to support the approval.

In these trials patients either received paliperidone alone or were given paliperidone along with a mood stabilizer with or without an antidepressant. Patients on a dosage of 12 mg/day (with the option of reducing to 9 mg/day) of paliperidone showed statistically significant improvement over placebo patients on Positive and Negative Syndrome Scale (PANSS) total scores. A lower dosage (6 mg/day with the option of reducing to 3 mg/day) did not achieve significant difference in PANSS total score between the active treatment and placebo groups. Paliperidone had already been approved for acute and maintenance treatment of schizophrenia. It is currently the only medication carrying the approved indication for schizoaffective disorder.

The approved prescribing information for paliperidone tablets is posted at <www.invega.com/invega/shared/pi/invega.pdf>.

• The FDA has approved the once-monthly, long-acting formulation of ***paliperidone palmitate*** injection for acute and maintenance treatment of schizophrenia, Ortho-McNeil-Janssen announced on August 4. The approval was based on four short-term clinical studies and one long-term study in which paliperidone palmitate was compared with placebo. In this formulation, paliperidone comes in prefilled syringes, and the first two intramuscular injections should be administered one week apart, followed by monthly injections thereafter. The company also manufactures risperidone long-acting injection, which is dosed once every two weeks. On August 27 Johnson and Johnson announced its decision to terminate the development of a once-every-four-week formulation of ***risperidone***.

The approved prescribing information for paliperidone palmitate injection is posted at <www.invegasustenna.com/invegasustenna/shared/pi/invegasustenna.pdf>.

• The FDA has approved ***guanfacine*** extended-release tablets for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children and adolescents aged 6 to 17, Shire announced on September 3. Also used to treat hypertension, guanfacine is an alpha$_{2A}$ adrenergic receptor agonist. Shire developed this once-daily formulation specifically for the treatment of ADHD. The product, which is being marketed under the brand name of Intuniv, will not be a controlled medication.

In two randomized, double-blind, placebo-controlled clinical trials, children and adolescents treated with guanfacine improved in ADHD Rating Scale-IV total scores from baseline, and the difference between the active drug and placebo was statistically significant. The most common adverse events seen in the trials included somnolence, headache, fatigue, upper abdominal pain, and sedation. Adverse effects related to alpha agonists, such as hypotension, bradycardia, and syncope, were also observed in some patients. Prescribers are urged to assess patients' heart rate and blood pressure before starting the medication, followed by periodic monitoring.

Industry Briefs

• Labopharm Inc., a Canadian company, said on August 25 that the FDA accepted its response to a previous letter the agency had issued regarding the company's ***trazodone*** extended-release tablets, a once-daily formulation of the first-generation antidepressant developed by the company and currently awaiting FDA marketing approval. According to the company, the agency's letter had initially rejected the new drug application because of deficiencies discovered at a manufacturing plant but cited no safety or efficacy concerns about the medication. A final decision on the application will be made by February 2010.

• Dainippon Sumitomo Pharma, a Japanese pharmaceutical company, announced on August 26 positive results from a phase 3 clinical trial of ***lurasidone***, a second-generation antipsychotic in development. Lurasidone binds to dopamine D$_2$, serotonin 5-HT$_7$, 5-HT$_{2A}$, 5-HT$_{1A}$, and noradrenalin alpha$_{2c}$ receptors. In the randomized, double-blind, controlled trial, 478 patients with schizophrenia were given lurasidone 40 mg/day or 120 mg/day, placebo, or olanzapine 15 mg/day for six weeks. Olanzapine was included as an active comparator to determine whether the trial was conducted with enough sensitivity to be able to detect a difference between active treatment and the placebo effect.

At both dosage levels, lurasidone was more effective in reducing patients' psychotic symptoms as measured by the PANSS total score. Lurasidone did not beat olanzapine in the primary efficacy endpoint. The most common adverse events associated with lurasidone were akathisia, somnolence, sedation, extrapyramidal effects, nausea, and dystonia. The median weight gain after the six-week study was 0.9 kg in the 40 mg/day lurasidone group, 0.5 kg in the 120 mg/day group, 0 kg in the placebo group, and 3.1 kg in the olanzapine group. The company said it plans to file a new drug application for lurasidone with the FDA in early 2010.

• The investigational drug ***pimavanserin***, which is being studied for Parkinson's disease psychosis, failed to meet the primary efficacy endpoint in a phase 3 trial conducted by its maker, Acadia Pharmaceuticals, according to a September 1 company announcement. In a double-blind, placebo-controlled trial, 298 patients diagnosed with psychosis related to Parkinson's disease were randomly assigned to pimavanserin 10 mg/day or 40 mg/day or to placebo. After six weeks of treatment, symptoms improved from baseline in all three groups, as indicated by the Scale for the Assessment of Positive Symptoms (SAPS) score. The SAPS score decreased by 5.8 points and 6.7 points in the pimavanserin 10 mg and 40 mg groups, respectively. Neither change differed significantly from the 5.9-point reduction in the placebo group.

Pimavanserin is a serotonin 5-HT$_{2A}$ receptor inverse agonist being developed for psychosis associated with Parkinson's and Alzheimer's diseases. The company said it plans to continue the phase 3 development. ■

Survey Reveals Psychopathology Of Many Arsonists

Arsonists tend to engage not only in fire setting, but also in a wide swath of other antisocial behaviors, such as assault, robbery, rape, weapon use, and cruelty to animals.

BY JOAN AREHART-TREICHEL

Although adult arsonists can cause a devastating loss in property and lives, very little is known about them.

However, the 2001-2002 National Epidemiologic Survey on Alcohol and Related Conditions, a nationally representative sample of some 43,000 Americans aged 18 or older, gave some scientists an unprecedented opportunity to learn more about adult arsonists because one of the many questions asked of those surveyed was the following: "In your entire life, did you ever start a fire on purpose to destroy someone else's property or just to see it burn?"

Out of the approximately 43,000 survey respondents, some 400 individuals answered yes to this question, the scientists reported online July 10 in *Comprehensive Psychiatry*. Thus, extrapolating from this finding, it looks as if arsonists constitute 1 percent of the U.S. population.

Moreover, by comparing survey responses from the individuals who reported having intentionally started fires with those from the individuals who had not, the scientists were able to glean some valuable insights into adult arsonists.

• They tend to be male, white, 18 to 35 years old, and living in the West of the United States, but not of any particular income, educational level, or marital status.

• "One of the more surprising results demographically was that [U.S.-born] Americans are approximately two and a half times more likely than foreign-born Americans to set fires," the lead investigator, Michael Vaughn, Ph.D., told *Psychiatric News*. Vaughn is an assistant professor in St. Louis University's Department of Public Policy Studies.

• Arsonists are 12 times more likely to have antisocial personality disorder than are people who do not set fires. They tend to engage not only in fire setting but in a wide swath of other antisocial behaviors, such as assault, robbery, rape, weapon use, and cruelty to animals. They often come from antisocial families. They often have obsessive-compulsive personality disorder, alcohol use disorder, and/or marijuana use disorder.

"I expect the study findings will be of interest not only to the psychiatric community, but also to insurance-company personnel, municipal firefighters, and other entities affected by the serious costs associated with arson," Vaughn noted. For instance, their findings might help the police better profile arsonists.

*please see **Arsonists** on page 44*

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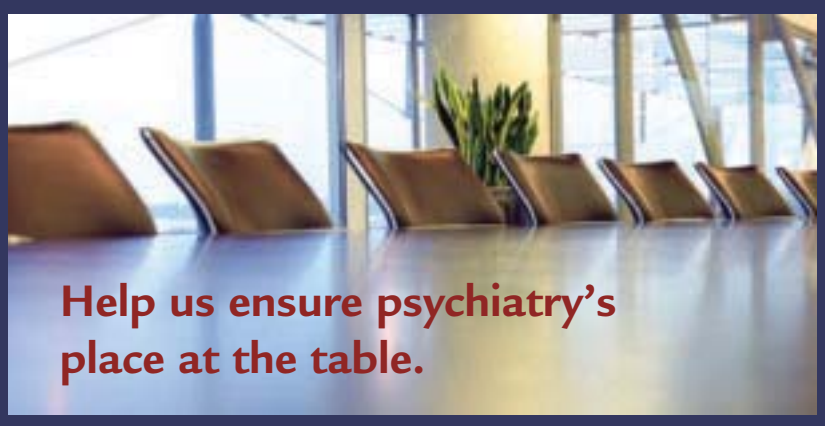

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Home Visitation

continued from page 9

quently touted as a way to prevent parental child abuse and neglect.

That laudable goal has led more than 40 state governments to fund various types of voluntary home-visitation programs that serve up to 500,000 children and their parents every year, according to research estimates. McDermott said, however, that those served are only 15 percent of the population that needs such assistance.

McDermott sponsored a bill (HR 2667) to fund home visitation earlier this year, but it never advanced. Similar legislation sponsored by Sen. Robert Menendez (D-N.J.) also stalled. However, much of the language from the McDermott legislation was rolled into the massive health care reform bill (HR 3200) approved in July by three House of Representatives committees.

The push for the federal funding through the health reform bill—$750 million in the first five years—stems from the contention by visitation advocates that a massive boost is needed to reach millions of children at risk for abuse.

President Obama's proposed budget also requests $8.6 billion for such programs, but congressional Democrats dropped the program from their budget bills.

Unintended Consequences Feared

Critics of the home-visitation program said they support the goal of reduced child abuse but worry that the "voluntary" provisions are poorly defined and thus could easily morph into a mandatory program for many parents, including those who home-school their children.

"Once the federal government gives the money to the states, there is no oversight or even mandate that states make sure the programs are voluntary," maintained Will Estrada, director of federal relations for the Home School Legal Defense Association. He and other critics note that although the current legislation describes the programs as voluntary, the language does not specify whether they remain voluntary if a parent changes his or her mind after agreeing to participate.

"If families want to choose these programs, that's great. But if you have to let a government official in to teach you how to raise your children and to monitor that your children are developing, then you could easily lose control of your children and have them taken away," Estrada said.

The nonspecific language leaves ample room for "mission creep" of home-visitation programs to require participation of large swaths of the public eventually, said Stephen Krason, Ph.D., president of the Society of Catholic Social Scientists.

"It's valid to be concerned that something that appears to be voluntary can evolve to be mandatory," Krason said.

McDermott's office did not respond to requests for comment from *Psychiatric News* about the potential for abuse in the program.

Solving a Problem?

Supporters of home visitation maintain the programs effectively address a growing problem.

"The increase of child abuse and neglect cases . . . is a sobering sign that our efforts to date are insufficient," said Joan Sharp, executive director of the Council for Children and Families, at a congressional hearing in June on federal support for home-visitation programs.

However, research on home-visitation programs generally has found that the programs do not achieve the highly touted goal of preventing child abuse or neglect, according to researchers who have reviewed the studies on home visitation.

"Of those programs that look at child abuse and neglect directly (i.e., substantiated cases), only a few have reduced child abuse and neglect," said Jeanne Brooks-Gunn, Ph.D., at the congressional hearing. She is a professor of child development at the Teachers College and College of Physicians and Surgeons at Columbia University who supports home visitation.

Others are supportive of the goals of the program, even as they question the premise that efforts are needed to prevent a nationwide wave of parental child abuse.

Richard Wexler, executive director of National Coalition for Child Protection Reform, highlighted the findings of home-visitation researchers that child maltreatment is relatively rare in the general population, which runs counter to suggestions of an abuse epidemic.

"That's worth remembering amid the hype about an 'epidemic of child abuse' and all the damage that hype can do to children, as well as helping to explain why any reduction in maltreatment caused by home visiting will be hard to detect," Wexler said.

Information on the visitation bills can be accessed at <http://Thomas.loc.gov> by searching on the bill numbers, HR 2667 and S 1267>. ■

Access

continued from page 9

had experienced one of the medication-access problems.

They also found that the mean predicted probability of visiting an emergency department was .41 for patients with an access issue and .27 for those with no access issue.

Does the study, which looked at the first 12 months after the initiation of the Part D program in 2006, suggest anything about the program today?

"One might expect access problems to be lower after the first year and the initial transitions," Huskamp told *Psychiatric News*. "However, each year since then, a large number of dual eligibles (for example, over 1 million for 2007 and over 2 million for 2008) were re-randomized to plans when the new year's premium for the plan they were enrolled in exceeded the benchmark for dual-eligible plans. Because of the re-randomization, one would expect a higher rate of medication-access problems for these individuals.

"Thus, medication-access issues due to plan switching or changes in plan coverage rules are likely to still be an issue for a large number of dual eligibles," she said.

"Part D and Dually Eligible Patients With Mental Illness: Medication-Access Problems and Use of Intensive Services" is posted at <http://psychservices.psychiatryonline.org/cgi/content/full/60/9/1169#T1>. ■

Health Reform

continued from page 10

quickly expand the use of those approaches throughout Medicare.

Mental health advocates also remained very optimistic about enactment of a health care overhaul before Congress adjourns for the year.

Rep. Patrick Kennedy (D-R.I.) told congressional staffers and advocates that the public would become more supportive of reform if it was framed as a way to expand Americans' freedom to obtain needed care and independence from the burden of untreated illness. Advocates should stress that the lives of all Americans would be improved by having access to high-quality medical care, he suggested.

"We're going to define health care in the broadest sense so that [Americans] are able to live long lives that are not impeded in any way," Kennedy said.

Information on the Alliance for Health Reform forum is posted at <www.kff.org/abr090409video.cfm>. ■

Brain MRI

continued from page 27

also found in the groups when you looked at them separately—in both [the prodromal and schizophrenia] groups, worsening delusions were associated with greater hyperactivity.

"Moreover, in the prodromal group, hyperactivity also tracked positively with avolition and social withdrawal," Schobel said. The latter are negative symptoms associated with worsening outcome.

The findings are an important first step in the effort to prevent schizophrenia or to more rapidly treat those who do experience a first-episode of psychosis.

In a statement released by Columbia University announcing the study, Jeffrey Lieberman, M.D., who is leading a new effort at the National Institute of Mental Health to develop optimal treatments for first-episode psychosis, cited the benefits of early intervention.

"Research has shown that early intervention and treatment can prevent the debilitating effects of schizophrenia by dramatically slowing progression, reducing mortality and disability, and increasing recovery of one of mankind's most costly mental disorders," said Lieberman, who is Lawrence E. Kolb Professor and chair of the Department of Psychiatry at Columbia University and director of the New York State Psychiatric Institute.

An abstract of "Differential Targeting of the CA1 Subfield of the Hippocampal Formation by Schizophrenia and Related Disorders" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/66/9/938>. ■

letters to the editor

New Blood Needed?

I was delighted to see so many of my old friends nominated to lead APA (see article on page 1). But if that is a pleasure for me, it is a problem for our Association. I hope that some of our younger members will seize the opportunity to be petition candidates in our next election. Back in the Cro-Magnon era, I myself ran as a petition candidate for both Area trustee and vice president. Back then I thought APA needed new leadership, and I think we need it now.

ALAN A. STONE, M.D.
Cambridge, Mass.

Editor's note: The deadline for petition candidates is October 15. More information is available by contacting Ricardo Juarez at rjuarez@psych.org or (703) 907- 8527.

We Need to Go Back

Thank you for the thoughtful and comprehensive review of the presidential symposium in the article "Experts Call for New Ways to Collaborate With Pharma" in the July 3 issue. For one who wasn't at APA's 2009 annual meeting, what was conveyed was informative and encouraging. I have found it interesting that in my new part-time work as a prison psychiatrist, I have found the use of older antidepressants and antipsychotics to be generally quite satisfactory in many cases.

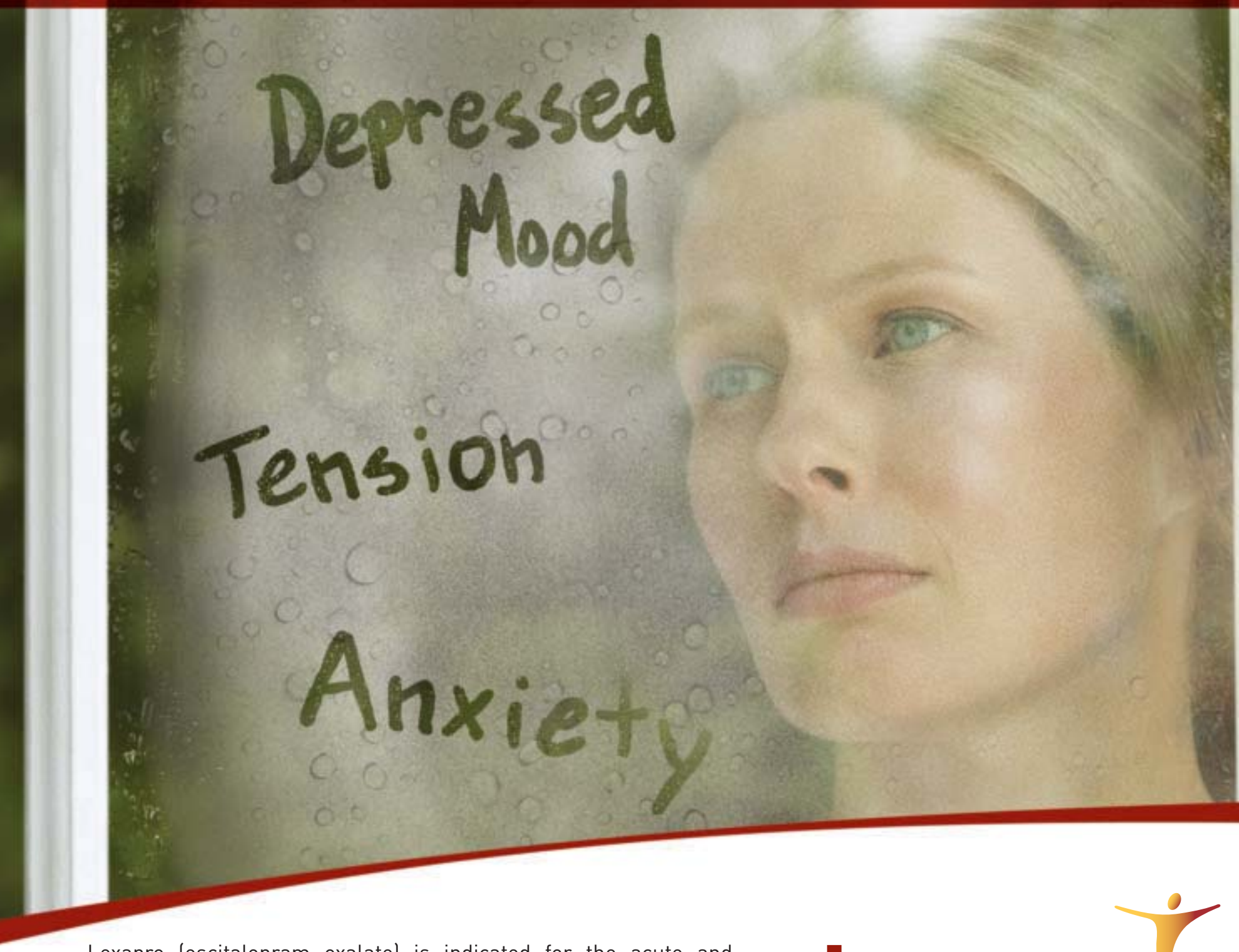
I would like to make an additional point. It is clear that our field has become more biological, and more and more psychiatrists tend to do 15-minute med checks. As Dr. Steven Sharfstein once said during his presidency, the biopsychosocial model has become the bio-bio-bio model. My sense is that the strong influence of pharma was one of the major factors, in addition to managed care and reimbursement issues, that led to this change. I doubt that just changing our relationship to pharma will head us back in the other direction. What can we now do to reestablish us as biopsychosocial psychiatrists?

H. STEVEN MOFFIC, M.D.
Milwaukee, Wis.

Readers are invited to submit letters not more than 500 words long for possible publication. *Psychiatric News* reserves the right to edit letters and to publish them in all editions, print, electronic, or other media. Receipt of letters is not acknowledged. Letters should be sent by mail to *Psychiatric News*, APA, Suite 1825, 1000 Wilson Boulevard, Arlington, Va. 22209 or by e-mail to pnews@psych.org. Clinical opinions are not peer reviewed and thus should be independently verified.

Treat core symptoms[1,2]

of Major Depressive Disorder (MDD) & Generalized Anxiety Disorder (GAD)



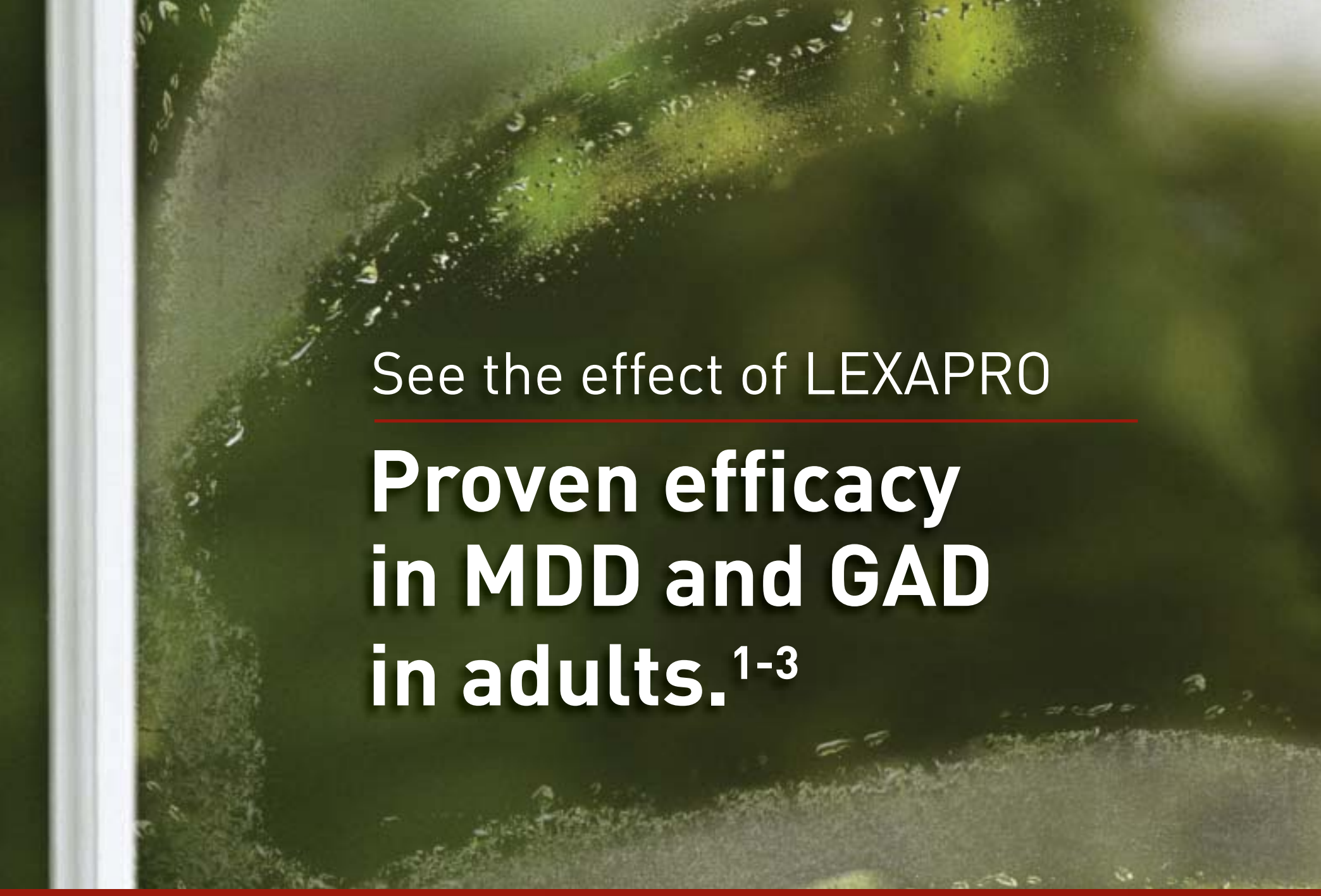
Lexapro (escitalopram oxalate) is indicated for the acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12-17 years. Lexapro is also indicated for the acute treatment of generalized anxiety disorder (GAD) in adults.

Lexapro® escitalopram oxalate

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age.

Please see additional Important Safety Information on following pages.



- Significantly higher rates of response and remission vs placebo in adults[2,4]
- Significantly improved quality-of-life (QOL) scores vs placebo in adults[1,2]

Lexapro (escitalopram oxalate) is indicated for the acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12-17 years. Lexapro is also indicated for the acute treatment of generalized anxiety disorder (GAD) in adults.

IMPORTANT SAFETY INFORMATION (continued)

Contraindications

- Lexapro is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). There have been reports of serious, sometimes fatal, reactions with some cases resembling neuroleptic malignant syndrome (NMS) and serotonin syndrome. Features may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Serotonin syndrome was reported for two patients who were concomitantly receiving linezolid, an antibiotic which has MAOI activity. Lexapro should not be used in combination with an MAOI or within 14 days of discontinuing an MAOI. MAOIs should not be initiated within 14 days of discontinuing Lexapro.
- Lexapro is contraindicated in patients taking pimozide or with hypersensitivity to escitalopram or citalopram.

Warnings and Precautions

- All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality and unusual changes in behavior, especially within the first few months of treatment or when changing the dose. Consideration should be given to changing the therapeutic regimen, including discontinuing medication, in patients whose depression is persistently worse, who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Families and caregivers of patients treated with antidepressants should be alerted about the need to monitor patients daily for the emergence of agitation, irritability, unusual changes in behavior, or the emergence of suicidality, and report such symptoms immediately. Prescriptions for Lexapro should be written for the smallest quantity of tablets, consistent with good patient management, in order to reduce the risk of overdose.

- Prescribed to over 18 million US patients[5]
- Widely available on health plan formularies without restrictions[6]

- A major depressive episode may be the initial presentation of bipolar disorder. In patients at risk for bipolar disorder, treating such an episode with an antidepressant alone may increase the likelihood of precipitating a mixed/manic episode. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine if they are at risk for bipolar disorder. Lexapro should be used cautiously in patients with a history of mania or seizure disorder. Lexapro is not approved for use in treating bipolar depression.
- The concomitant use of Lexapro with other SSRIs, SNRIs, triptans, tryptophan, antipsychotics or other dopamine antagonists is not recommended due to potential development of life-threatening serotonin syndrome or neuroleptic malignant syndrome (NMS)-like reactions. Reactions have been reported with SNRIs and SSRIs alone, including Lexapro, but particularly with drugs that impair metabolism of serotonin (including MAOIs). Management of these events should include immediate discontinuation of Lexapro and the concomitant agent and continued monitoring.
- Patients should be monitored for adverse reactions when discontinuing treatment with Lexapro. During marketing of Lexapro and other SSRIs and SNRIs, there have been spontaneous reports of adverse events occurring upon discontinuation, including dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias), anxiety, confusion, headache, lethargy, emotional lability, insomnia and hypomania. A gradual dose reduction rather than abrupt cessation is recommended whenever possible.

Please see additional Important Safety Information on next page.

Lexapro®
escitalopram oxalate

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO: Proven efficacy in MDD and GAD in adults[1-3]

Warnings and Precautions (continued)

- SSRIs and SNRIs have been associated with clinically significant hyponatremia. Elderly patients and patients taking diuretics or who are otherwise volume-depleted appear to be at a greater risk. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.
- SSRIs (including Lexapro) and SNRIs may increase the risk of bleeding. Patients should be cautioned that concomitant use of aspirin, NSAIDs, warfarin or other anticoagulants may add to the risk.
- Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro does not affect their ability to engage in such activities.
- Lexapro should be used with caution in patients with severe renal impairment or with diseases or conditions that alter metabolism or hemodynamic responses. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day.
- For pregnant or nursing mothers, Lexapro should be used only if the potential benefit justifies the potential risk to the fetus or child.

Adverse Reactions

- In clinical trials of MDD, the most common adverse reactions in adults treated with Lexapro (approximately 5% or greater and at least twice the incidence of placebo) were nausea (15% vs 7%), insomnia (9% vs 4%), ejaculation disorder (9% vs <1%), fatigue (5% vs 2%), somnolence (6% vs 2%), and increased sweating (5% vs 2%). In pediatric patients, the overall profile of adverse reactions was similar to that seen in adults; however, the following additional adverse reactions were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.
- In clinical trials of GAD, the most common adverse reactions in adults treated with Lexapro (approximately 5% or greater and at least twice the incidence of placebo) were nausea (18% vs 8%), ejaculation disorder (14% vs 2%), insomnia (12% vs 6%), fatigue (8% vs 2%), decreased libido (7% vs 2%) and anorgasmia (6% vs <1%).

Please see accompanying brief summary of prescribing information for LEXAPRO, including Boxed Warning.

References: 1. Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry.* 2002;63:331-336. **2.** Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible-dose study. *Depress Anxiety.* 2004;19:234-240. **3.** LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2009. **4.** Wade A, Lemming OM, Hedegaard KB. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol.* 2002;17:95-102. **5.** SDI, April 2008. Depression and Anxiety Treatment Market Overview. Based on longitudinal analysis of US electronic retail pharmacy claims submitted for third-party reimbursement. **6.** Data on file, Forest Laboratories, Inc.

Forest Pharmaceuticals, Inc.
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Visit the LEXAPRO website at www.lexapro.com

Lexapro® escitalopram oxalate

LEXAPRO® (escitalopram oxalate) TABLETS/ORAL SOLUTION **Rx Only**

Brief Summary: For complete details, please see full Prescribing Information for Lexapro.

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Lexapro or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Lexapro is not approved for use in pediatric patients less than 12 years of age. *[See Warnings and Precautions: Clinical Worsening and Suicide Risk, Patient Counseling Information: Information for Patients, and Used in Specific Populations: Pediatric Use].*

INDICATIONS AND USAGE: Major Depressive Disorder-Lexapro (escitalopram) is indicated for the acute and maintenance treatment of major depressive disorder in adults and in adolescents 12 to 17 years of age [*see Clinical tudies*]. A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least five of the following nine symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, a suicide attempt or suicidal ideation. **Generalized Anxiety Disorder**-Lexapro is indicated for the acute treatment of Generalized Anxiety Disorder (GAD) in adults [*see Clinical Studies*]. Generalized Anxiety Disorder (DSM-IV) is characterized by excessive anxiety and worry (apprehensive expectation) that is persistent for at least 6 months and which the person finds difficult to control. It must be associated with at least 3 of the following symptoms: restlessness or feeling keyed up or on edge, being easily fatigued, difficulty concentrating or mind going blank, irritability, muscle tension, and sleep disturbance.

CONTRAINDICATIONS: Monoamine oxidase inhibitors (MAOIs)-Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated [*see Warnings and Precautions*]. **Pimozide**-Concomitant use in patients taking pimozide is contraindicated [*see Drug Interactions*]. **Hypersensitivity to escitalopram or citalopram**-Lexapro is contraindicated in patients with a hypersensitivity to escitalopram or citalopram or any of the inactive ingredients in Lexapro.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk-Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1.

TABLE 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated
	Increases Compared to Placebo
<18	14 additional cases
18-24	5 additional cases
	Decreases Compared to Placebo
25-64	1 fewer case
≥65	6 fewer cases

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases. The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Dosage and Administration*]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers [*see also Patient Counseling Information*]. Prescriptions for Lexapro should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder**-A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with 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. It should be noted that Lexapro is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions**-The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Lexapro treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Lexapro with MAOIs intended to treat depression is contraindicated. If concomitant treatment of Lexapro with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Lexapro with serotonin precursors (such as tryptophan) is not recommended. Treatment with Lexapro and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated. **Discontinuation of Treatment with Lexapro**-During marketing of Lexapro and other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, and hypomania. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Lexapro. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate [*see Dosage and Administration*]. **Seizures**-Although anticonvulsant effects of racemic citalopram have been observed in animal studies, Lexapro has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the product's premarketing testing. In clinical trials of Lexapro, cases of convulsion have been reported in association with Lexapro treatment. Like other drugs effective in the treatment of major depressive disorder, Lexapro should be introduced with care in patients with a history of seizure disorder. **Activation of Mania/Hypomania**-In placebo-controlled trials of Lexapro in major depressive disorder, activation of mania/hypomania was reported in one (0.1%) of 715 patients treated with Lexapro and in none of the 592 patients treated with placebo. One additional case of hypomania has been reported in association with Lexapro treatment. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorders treated with racemic citalopram and other marketed drugs effective in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, Lexapro should be used cautiously in patients with a history of mania. **Hyponatremia**-Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Lexapro. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH), and was reversible when Lexapro was discontinued. Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk [*see Geriatric Use*]. Discontinuation of Lexapro should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death. **Abnormal Bleeding**-SSRIs and SNRIs, including Lexapro, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to the risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs and SNRIs use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Lexapro and NSAIDs, aspirin, or other drugs that affect coagulation. **Interference with Cognitive and Motor Performance**-In a study in normal volunteers, Lexapro 10 mg/day did not produce impairment of intellectual function or psychomotor performance. Because any psychoactive drug may impair judgment, thinking, or motor skills, however, patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro therapy does not affect their ability to engage in such activities. **Use in Patients with Concomitant Illness**-Clinical experience with Lexapro in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using Lexapro in patients with diseases or conditions that produce altered metabolism or hemodynamic responses. Lexapro has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day [*see Dosage and Administration*]. Because escitalopram is extensively metabolized, excretion of unchanged drug in urine is a minor route of elimination. Until adequate numbers of patients with severe renal impairment have been evaluated during chronic treatment with Lexapro, however, it should be used with caution in such patients [*see Dosage and Administration*]. **Potential for Interaction with Monoamine Oxidase Inhibitors**-In patients receiving serotonin reuptake inhibitor drugs in combination with a monoamine oxidase inhibitor (MAOI), there have been reports of serious, sometimes

fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

ADVERSE REACTIONS: Clinical Trials Experience-Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Clinical Trial Data Sources; Pediatrics (6 -17 years)**-Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established. **Adults**-Adverse events information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. 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 tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment; Major Depressive Disorder; Pediatrics (6 -17 years)**-Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Lexapro and greater than placebo) associated with discontinuation was insomnia (1% Lexapro, 0% placebo). **Adults**-Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder; Adults**-Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials; Major Depressive Disorder; Pediatrics (6 -17 years)**-The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions (excluding those which appear in Table 2 and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion. **Adults**-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 2
Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Major Depressive Disorder

Adverse Reaction	Lexapro (N=715)	Placebo (N=592)
Autonomic Nervous System Disorders		
Dry Mouth	6%	5%
Sweating Increased	5%	2%
Central & Peripheral Nervous System Disorders		
Dizziness	5%	3%
Gastrointestinal Disorders		
Nausea	15%	7%
Diarrhea	8%	5%
Constipation	3%	1%
Indigestion	3%	1%
Abdominal Pain	2%	1%
General		
Influenza-like Symptoms	5%	4%
Fatigue	5%	2%
Psychiatric Disorders		
Insomnia	9%	4%
Somnolence	6%	2%
Appetite Decreased	3%	1%
Libido Decreased	3%	1%
Respiratory System Disorders		
Rhinitis	5%	4%
Sinusitis	3%	2%
Urogenital		
Ejaculation Disorder[1,2]	9%	<1%
Impotence[2]	3%	<1%
Anorgasmia[3]	2%	<1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=225 Lexapro; N=188 placebo).
[3]Denominator used was for females only (N=490 Lexapro; N=404 placebo).

Generalized Anxiety Disorder; Adults-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were nausea, ejaculation disorder (primarily ejaculatory delay), insomnia, fatigue, decreased libido, and anorgasmia. Table 3 enumerates the incidence, rounded to the nearest percent of treatment-emergent adverse events that occurred among 429 GAD patients who received Lexapro 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

TABLE 3
Treatment-Emergent Adverse Reactions Observed with a Frequency of ≥ 2% and Greater Than Placebo for Generalized Anxiety Disorder

Adverse Reactions	Lexapro (N=429)	Placebo (N=427)
Autonomic Nervous System Disorders		
Dry Mouth	9%	5%
Sweating Increased	4%	1%
Central & Peripheral Nervous System Disorders		
Headache	24%	17%
Paresthesia	2%	1%
Gastrointestinal Disorders		
Nausea	18%	8%
Diarrhea	8%	6%
Constipation	5%	4%
Indigestion	3%	2%
Vomiting	3%	1%
Abdominal Pain	2%	1%
Flatulence	2%	1%
Toothache	2%	0%
General		
Fatigue	8%	2%
Influenza-like Symptoms	5%	4%
Musculoskeletal System Disorder		
Neck/Shoulder Pain	3%	1%
Psychiatric Disorders		
Somnolence	13%	7%
Insomnia	12%	6%
Libido Decreased	7%	2%
Dreaming Abnormal	3%	2%
Appetite Decreased	3%	1%
Lethargy	3%	1%
Respiratory System Disorders		
Yawning	2%	1%
Urogenital		
Ejaculation Disorder[1,2]	14%	2%
Anorgasmia[3]	6%	<1%
Menstrual Disorder	2%	1%

[1]Primarily ejaculatory delay.
[2]Denominator used was for males only (N=182 Lexapro; N=195 placebo).
[3]Denominator used was for females only (N=247 Lexapro; N=232 placebo).

Dose Dependency of Adverse Reactions-The potential dose dependency of common adverse reactions (defined as an incidence rate of ≥5% in either the 10 mg or 20 mg Lexapro groups) was examined on the basis of the combined incidence of adverse events in two fixed-dose trials. The overall incidence rates of adverse events in 10 mg Lexapro-treated patients (66%) was similar to that of the placebo-treated patients (61%), while the incidence rate in 20 mg/day Lexapro-treated patients was greater (86%). Table 4 shows common adverse reactions that occurred in the 20 mg/day Lexapro group with an incidence that was approximately twice that of the 10 mg/day Lexapro group and approximately twice that of the placebo group.

TABLE 4
Incidence of Common Adverse Reactions in Patients with Major Depressive Disorder

Adverse Reaction	Placebo (N=311)	10 mg/day Lexapro (N=310)	20 mg/day Lexapro (N=125)
Insomnia	4%	7%	14%
Diarrhea	5%	6%	14%
Dry Mouth	3%	4%	9%
Somnolence	1%	4%	9%
Dizziness	2%	4%	7%
Sweating Increased	<1%	3%	8%
Constipation	1%	3%	6%
Fatigue	2%	2%	6%
Indigestion	1%	2%	6%

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, 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 physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

TABLE 5
Incidence of Sexual Side Effects in Placebo-Controlled Clinical Trials

Adverse Event	Lexapro	Placebo
	In Males Only	
	(N=407)	(N=383)
Ejaculation Disorder (primarily ejaculatory delay)	12%	1%
Libido Decreased	6%	2%
Impotence	2%	<1%
	In Females Only	
	(N=737)	(N=636)
Libido Decreased	3%	1%
Anorgasmia	3%	<1%

There are no adequately designed studies examining sexual dysfunction with escitalopram treatment. Priapism has been reported with all SSRIs. While it is difficult to know the precise risk of sexual dysfunction associated with the use of SSRIs, physicians should routinely inquire about such possible side effects. **Vital Sign Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with Lexapro treatment. In addition, a comparison of supine and standing vital sign measures in subjects receiving Lexapro indicated that Lexapro treatment is not associated with orthostatic changes. **Weight Changes**-Patients treated with Lexapro in controlled trials did not differ from placebo-treated patients with regard to clinically important change in body weight. **Laboratory Changes**-Lexapro and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables, and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with Lexapro treatment. **ECG Changes**-Electrocardiograms from Lexapro (N=625), racemic citalopram (N=351), and placebo (N=527) groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed (1) a decrease in heart rate of 2.2 bpm for Lexapro and 2.7 bpm for racemic citalopram, compared to an increase of 0.3 bpm for placebo and (2) an increase in QTc interval of 3.9 msec for Lexapro and 3.7 msec for racemic citalopram, compared to 0.5 msec for placebo. Neither Lexapro nor racemic citalopram were associated with the development of clinically significant ECG abnormalities. **Other Reactions Observed During the Premarketing Evaluation of Lexapro**-Following is a list of treatment-emergent adverse events, as defined in the introduction to the ADVERSE REACTIONS section, reported by the 1428 patients treated with Lexapro for periods of up to one year in double-blind or open-label clinical trials during its premarketing evaluation. The listing does not include those events already listed in Tables 2 & 3, those events for which a drug cause was remote and at a rate less than 1% or lower than placebo, those events which were so general as to be uninformative, and those events reported only once which did not have a substantial probability of being acutely life threatening. Events are categorized by body system. Events of major clinical importance are described in the Warnings and Precautions section. Cardiovascular - hypertension, palpitation. Central and Peripheral Nervous System Disorders - light-headed feeling, migraine. Gastrointestinal Disorders - abdominal cramp, heartburn, gastroenteritis. General - allergy, chest pain, fever, hot flushes, pain in limb. Metabolic and Nutritional Disorders - increased weight. Musculoskeletal System Disorders - arthralgia, myalgia jaw stiffness. Psychiatric Disorders - appetite increased, concentration impaired, irritability. Reproductive Disorders/Female - menstrual cramps, menstrual disorder. Respiratory System Disorders - bronchitis, coughing, nasal congestion, sinus congestion, sinus headache. Skin and Appendages Disorders - rash. Special Senses - vision blurred, tinnitus. Urinary System Disorders - urinary frequency, urinary tract infection. **Post-Marketing Experience; Adverse Reactions Reported Subsequent to the Marketing of Escitalopram**-The following additional adverse reactions have been identified from spontaneous reports of escitalopram received worldwide. These adverse reactions have been chosen for inclusion because of a combination of seriousness, frequency of reporting, or potential causal connection to escitalopram and have not been listed elsewhere in labeling. However, because these adverse reactions were reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These events include: Blood and Lymphatic System Disorders: anemia, agranulocytis, aplastic anemia, hemolytic anemia, idiopathic thrombocytopenia purpura, leukopenia, thrombocytopenia. Cardiac Disorders: atrial fibrillation, bradycardia, cardiac failure, myocardial infarction, tachycardia, torsade de pointes, ventricular arrhythmia, ventricular tachycardia. Ear and Labyrinth Disorders: vertigo Endocrine Disorders: diabetes mellitus, hyperprolactinemia, SIADH. Eye Disorders: diplopia, glaucoma, mydriasis, visual disturbance. Gastrointestinal Disorders: dysphagia, gastrointestinal hemorrhage, gastroesophageal reflux, pancreatitis, rectal hemorrhage. General Disorders and Administration Site Conditions: abnormal gait, asthenia, edema, fall, feeling abnormal, malaise. Hepatobiliary Disorders: fulminant hepatitis, hepatic failure, hepatic necrosis, hepatitis. Immune System Disorders: allergic reaction, anaphylaxis. Investigations: bilirubin increased, decreased weight, electrocardiogram QT prolongation, hepatic enzymes increased, hypercholesterolemia, INR increased, prothrombin decreased. Metabolism and Nutrition Disorders: hyperglycemia, hypoglycemia, hypokalemia, hyponatremia. Musculoskeletal and Connective Tissue Disorders: muscle cramp, muscle stiffness, muscle weakness, rhabdomyolysis. Nervous System Disorders: akathisia, amnesia, ataxia, choreoathetosis, cerebrovascular accident, dysarthria, dyskinesia, dystonia, extrapyramidal disorders, grand mal seizures (or convulsions), hypoaesthesia, myoclonus, nystagmus, Parkinsonism, restless legs, seizures, syncope, tardive dyskinesia, tremor. Pregnancy, Puerperium and Perinatal Conditions: spontaneous abortion. Psychiatric Disorders: acute psychosis, aggression, agitation, anger, anxiety, apathy, completed suicide, confusion, depersonalization, depression aggravated, delirium, delusion, disorientation, feeling unreal, hallucinations (visual and auditory), mood swings, nervousness, nightmare, panic reaction, paranoia, restlessness, self-harm or thoughts of self-harm, suicide attempt, suicidal ideation, suicidal tendency. Renal and Urinary Disorders: acute renal failure, dysuria, urinary retention. Reproductive System and Breast Disorders: menorrhagia, priapism. Respiratory, Thoracic and Mediastinal Disorders: dyspnea, epistaxis, pulmonary embolism, pulmonary hypertension of the newborn. Skin and Subcutaneous Tissue Disorders: alopecia, angioedema, dermatitis, ecchymosis, erythema multiforme, photosensitivity reaction, Stevens Johnson Syndrome, toxic epidermal necrolysis, urticaria. Vascular Disorders: deep vein thrombosis, flushing, hypertensive crisis, hypotension, orthostatic hypotension, phlebitis, thrombosis.

DRUG INTERACTIONS: Serotonergic Drugs-Based on the mechanism of action of SNRIs and SSRIs including Lexapro, and the potential for serotonin syndrome, caution is advised when Lexapro is coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort [*see Warnings and Precautions*]. The concomitant use of Lexapro with other SSRIs, SNRIs or tryptophan is not recommended. **Triptans**-There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Lexapro with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases [*see Warnings and Precautions*]. **CNS Drugs**- Given the primary CNS effects of escitalopram, caution should be used when it is taken in combination with other centrally acting drugs. **Alcohol**-Although Lexapro did not potentiate the cognitive and motor effects of alcohol in a clinical trial, as with other psychotropic medications, the use of alcohol by patients taking Lexapro is not recommended. **Monoamine Oxidase Inhibitors (MAOIs)**-[*see Contraindications and Warnings and Precautions*]. **Drugs That Interfere With Hemostasis (NSAIDs, Aspirin, Warfarin, etc.)**-Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate the risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Lexapro is initiated or discontinued. **Cimetidine**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of 400 mg/day cimetidine for 8 days resulted in an increase in citalopram AUC and C_{max} of 43% and 39%, respectively. The clinical significance of these findings is unknown. **Digoxin**-In subjects who had received 21 days of 40 mg/day racemic citalopram, combined administration of citalopram and digoxin (single dose of 1 mg) did not significantly affect the pharmacokinetics of either citalopram or digoxin. **Lithium**-Coadministration of racemic citalopram (40 mg/day for 10 days) and lithium (30 mmol/day for 5 days) had no significant effect on the pharmacokinetics of citalopram or lithium. Nevertheless, plasma lithium levels should be monitored with appropriate adjustment to the lithium dose in accordance with standard clinical practice. Because lithium may enhance the serotonergic effects of escitalopram, caution should be exercised when Lexapro and lithium are coadministered. **Pimozide and Celexa**-In a controlled study, a single dose of pimozide 2 mg co-administered with racemic citalopram 40 mg given once daily for 11 days was associated with a mean increase in QTc values of approximately 10 msec compared to pimozide given alone. Racemic citalopram did not alter the mean AUC or C_{max} of pimozide. The mechanism of this pharmacodynamic interaction is not known. **Sumatriptan**-There have been rare postmarketing reports describing patients with weakness, hyperreflexia, and incoordination following the use of an SSRI and sumatriptan. If concomitant treatment with sumatriptan and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline, citalopram, escitalopram) is clinically warranted, appropriate observation of the patient is advised. **Theophylline**-Combined administration of racemic citalopram (40 mg/day for 21 days) and the CYP1A2 substrate theophylline (single dose of 300 mg) did not affect the pharmacokinetics of theophylline. The effect of theophylline on the pharmacokinetics of citalopram was not evaluated. **Warfarin**-Administration of 40 mg/day racemic citalopram for 21 days did not affect the pharmacokinetics of warfarin, a CYP3A4 substrate. Prothrombin time was increased by 5%, the clinical significance of which is unknown. **Carbamazepine**-Combined administration of racemic citalopram (40 mg/day for 14 days) and carbamazepine (titrated to 400 mg/day for 35 days) did not significantly affect the pharmacokinetics of carbamazepine, a CYP3A4 substrate. Although trough citalopram plasma levels were unaffected, given the enzyme-inducing properties of carbamazepine, the possibility that carbamazepine might increase the clearance of escitalopram should be considered if the two drugs are coadministered. **Triazolam**-Combined administration of racemic citalopram (titrated to 40 mg/day for 28 days) and the CYP3A4 substrate triazolam (single dose of 0.25 mg) did not significantly affect the pharmacokinetics of either citalopram or triazolam. **Ketoconazole**-Combined administration of racemic citalopram (40 mg) and ketoconazole (200 mg), a potent CYP3A4 inhibitor, decreased the C_{max} and AUC of ketoconazole by 21% and 10%, respectively, and did not significantly affect the pharmacokinetics of citalopram. **Ritonavir**-Combined administration of a single dose of ritonavir (600 mg), both a CYP3A4 substrate and a potent inhibitor of CYP3A4, and escitalopram (20 mg) did not affect the pharmacokinetics of either ritonavir or escitalopram. **CYP3A4 and -2C19 Inhibitors**-*In vitro* studies indicated that CYP3A4 and -2C19 are the primary enzymes involved in the metabolism of escitalopram. However, coadministration of escitalopram (20 mg) and ritonavir (600 mg), a potent inhibitor of CYP3A4, did not significantly affect the pharmacokinetics of escitalopram. Because escitalopram is metabolized by multiple enzyme systems, inhibition of a single enzyme may not appreciably decrease escitalopram clearance. **Drugs Metabolized by Cytochrome P4502D6**-*In vitro* studies did not reveal an inhibitory effect of escitalopram on CYP2D6. In addition, steady state levels of racemic citalopram were not significantly different in poor metabolizers and extensive CYP2D6 metabolizers after multiple-dose administration of citalopram, suggesting that coadministration, with escitalopram, of a drug that inhibits CYP2D6, is unlikely to have clinically significant effects on escitalopram metabolism. However, there are limited *in vivo* data suggesting a modest CYP2D6 inhibitory effect for escitalopram, i.e., coadministration of escitalopram (20 mg/day for 21 days) with the tricyclic antidepressant desipramine (single dose of 50 mg), a substrate for CYP2D6, resulted in a 40% increase in C_{max} and a 100% increase in AUC of desipramine. The clinical significance of this finding is unknown. Nevertheless, caution is indicated in the coadministration of escitalopram and drugs metabolized by CYP2D6. **Metoprolol**-Administration of 20 mg/day Lexapro for 21 days in healthy volunteers resulted in a 50% increase in C_{max} and 82% increase in AUC of the beta-adrenergic blocker metoprolol (given in a single dose of 100 mg). Increased metoprolol plasma levels have been associated with decreased cardioselectivity. Coadministration of Lexapro and metoprolol had no clinically significant effects on blood pressure or heart rate. **Electroconvulsive Therapy (ECT)**-There are no clinical studies of the combined use of ECT and escitalopram.

USE IN SPECIFIC POPULATIONS: Pregnancy; Pregnancy Category C-In a rat embryo/fetal development study, oral administration of escitalopram (56, 112, or 150 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased fetal body weight and associated delays in ossification at the two higher doses (approximately ≥ 56 times the maximum recommended human dose [MRHD] of 20 mg/day on a body surface area [mg/m^2] basis). Maternal toxicity (clinical signs and decreased body weight gain and food consumption), mild at 56 mg/kg/day, was present at all dose levels. The developmental no-effect dose of 56 mg/kg/day is approximately 28 times the MRHD on a mg/m^2 basis. No teratogenicity was observed at any of the doses tested (as high as 75 times the MRHD on a mg/m^2 basis). When female rats were treated with escitalopram (6, 12, 24, or 48 mg/kg/day) during pregnancy and through weaning, slightly increased offspring mortality and growth retardation were noted at 48 mg/kg/day which is approximately 24 times the MRHD on a mg/m^2 basis. Slight maternal toxicity (clinical signs and decreased body weight gain and food consumption) was seen at this dose. Slightly increased offspring mortality was also seen at 24 mg/kg/day. The no-effect dose was 12 mg/kg/day which is approximately 6 times the MRHD on a mg/m^2 basis. In animal reproduction studies, racemic citalopram has been shown to have adverse effects on embryo/fetal and postnatal development, including teratogenic effects, when administered at doses greater than human therapeutic doses. In two rat embryo/fetal development studies, oral administration of racemic citalopram (32, 56, or 112 mg/kg/day) to pregnant animals during the period of organogenesis resulted in decreased embryo/fetal growth and survival and an increased incidence of fetal abnormalities (including cardiovascular and skeletal defects) at the high dose. This dose was also associated with maternal toxicity (clinical signs, decreased body weight gain). The developmental no-effect dose was 56 mg/kg/day. In a rabbit study, no adverse effects on embryo/fetal development were observed at doses of racemic citalopram of up to 16 mg/kg/day. Thus, teratogenic effects of racemic citalopram were observed at a maternally toxic dose in the rat and were not observed in the rabbit. When female rats were treated with racemic citalopram (4.8, 12.8, or 32 mg/kg/day) from late gestation through weaning, increased offspring mortality during the first 4 days after birth and persistent offspring growth retardation were observed at the highest dose. The no-effect dose was 12.8 mg/kg/day. Similar effects on offspring mortality and growth were seen when dams were treated throughout gestation and early lactation at doses ≥ 24 mg/kg/day. A no-effect dose was not determined in that study. There are no adequate and well-controlled studies in pregnant women; therefore, escitalopram should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Pregnancy-Nonteratogenic Effects-Neonates exposed to Lexapro and other SSRIs or SNRIs, late in the third trimester, have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions*]. Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1-2 per 1000 live births in the general population and is associated with substantial neonatal morbidity and mortality. In a retrospective, case-control study of 377 women whose infants were born with PPHN and 836 women whose infants were born healthy, the risk for developing PPHN was approximately six-fold higher for infants exposed to SSRIs after the 20th week of gestation compared to infants who had not been exposed to antidepressants during pregnancy. There is currently no corroborative evidence regarding the risk for PPHN following exposure to SSRIs in pregnancy; this is the first study that has investigated the potential risk. The study did not include enough cases with exposure to individual SSRIs to determine if all SSRIs posed similar levels of PPHN risk. When treating a pregnant woman with Lexapro during the third trimester, the physician should carefully consider both the potential risks and benefits of treatment [*see Dosage and Administration*]. Physicians should note that in a prospective longitudinal study of 201 women with a history of major depression who were euthymic at the beginning of pregnancy, women who discontinued antidepressant medication during pregnancy were more likely to experience a relapse of major depression than women who continued antidepressant medication. **Labor and Delivery**-The effect of Lexapro on labor and delivery in humans is unknown. **Nursing Mothers**-Escitalopram is excreted in human breast milk. Limited data from women taking 10-20 mg escitalopram showed that exclusively breast-fed infants receive approximately 3.9% of the maternal weight-adjusted dose of escitalopram and 1.7% of the maternal weight-adjusted dose of desmethylcitalopram. There were two reports of infants experiencing excessive somnolence, decreased feeding, and weight loss in association with breastfeeding from a racemic citalopram-treated mother; in one case, the infant was reported to recover completely upon discontinuation of racemic citalopram by its mother and, in the second case, no follow-up information was available. Caution should be exercised and breastfeeding infants should be observed for adverse reactions when Lexapro is administered to a nursing woman. **Pediatric Use**-Safety and effectiveness of Lexapro has not been established in pediatric patients (less than 12 years of age) with Major Depressive Disorder. Safety and effectiveness of Lexapro has been established in adolescents (12 to 17 years of age) for the treatment of major depressive disorder [*see Clinical Studies*]. Although maintenance efficacy in adolescent patients with Major Depressive Disorder has not been systematically evaluated, maintenance efficacy can be extrapolated from adult data along with comparisons of escitalopram pharmacokinetic parameters in adults and adolescent patients. Safety and effectiveness of Lexapro has not been established in pediatric patients less than 18 years of age with Generalized Anxiety Disorder. **Geriatric Use**-Approximately 6% of the 1144 patients receiving escitalopram in controlled trials of Lexapro in major depressive disorder and GAD were 60 years of age or older; elderly patients in these trials received daily doses of Lexapro between 10 and 20 mg. The number of elderly patients in these trials was insufficient to adequately assess for possible differential efficacy and safety measures on the basis of age. Nevertheless, greater sensitivity of some elderly individuals to effects of Lexapro cannot be ruled out. SSRIs and SNRIs, including Lexapro, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Hyponatremia*]. In two pharmacokinetic studies, escitalopram half-life was increased by approximately 50% in elderly subjects as compared to young subjects and C_{max} was unchanged [*see Clinical Pharmacology*]. 10 mg/day is the recommended dose for elderly patients [*see Dosage and Administration*]. Of 4422 patients in clinical studies of racemic citalopram, 1357 were 60 and over, 1034 were 65 and over, and 457 were 75 and over. No overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but again, greater sensitivity of some elderly individuals cannot be ruled out.

DRUG ABUSE AND DEPENDENCE: Abuse and Dependence; Physical and Psychological Dependence-Animal studies suggest that the abuse liability of racemic citalopram is low. Lexapro has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. The premarketing clinical experience with Lexapro did not reveal any drug-seeking behavior. However, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate Lexapro patients for history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse (e.g., development of tolerance, incrementations of dose, drug-seeking behavior).

OVERDOSAGE: Human Experience-In clinical trials of escitalopram, there were reports of escitalopram overdose, including overdoses of up to 600 mg, with no associated fatalities. During the postmarketing evaluation of escitalopram, Lexapro overdoses involving overdoses of over 1000 mg have been reported. As with other SSRIs, a fatal outcome in a patient who has taken an overdose of escitalopram has been rarely reported. Symptoms most often accompanying escitalopram overdose, alone or in combination with other drugs and/or alcohol, included convulsions, coma, dizziness, hypotension, insomnia, nausea, vomiting, sinus tachycardia, somnolence, and ECG changes (including QT prolongation and very rare cases of torsade de pointes). Acute renal failure has been very rarely reported accompanying overdose. **Management of Overdose**-Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric evacuation by lavage and use of activated charcoal should be considered. Careful observation and cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive care. Due to the large volume of distribution of escitalopram, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. There are no specific antidotes for Lexapro. In managing overdosage, consider the possibility of multiple-drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose.

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 Rev. 05/09

Donna Norris, M.D.

John Oldham, M.D.

Election

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Assembly speaker, is an at-large trustee on the Board of Trustees.

Burlington, Vt., psychiatrist David Fassler, M.D., currently secretary-treasurer of APA, is running for the treasurer post, and will compete against Paul Summergrad, M.D., of Boston, a member of the Steering Committee on Practice Guidelines.

In addition, two of APA's seven Areas will hold elections for their trustee in 2010. In Area 3, which consists of New Jersey, Pennsylvania, Delaware, Maryland, and the District of Columbia, Brian Crowley, M.D., of Washington, D.C., will run against the incumbent, John Urbaitis, M.D., of Baltimore.

In Area 6, which is made up of the five district branches in California, Barton Blinder, M.D., of Newport Beach will compete against Marc Graff, M.D., of Reseda.

(The nominees for the Board's Area trustee positions are selected by their Area councils rather than by the APA Nominating Committee.)

Also to be elected is the member-in-training trustee-elect (MITTE). The candidates for this post are Sarah Johnson, M.D., a PGY-3 resident at the University of Louisville, and Samir Sabbag, M.D., a PGY-3 resident at Jackson Memorial Hospital/University of Miami. The MITTE position has been a nonvoting one since its inception, but beginning next May it will be converted to a voting position. That means that when the next Board is seated, at the close of the 2010 APA annual meeting, members-in-training will have two voting members on the Board of Trustees.

At its March meeting the Board voted to make several changes to its composition (*Psychiatric News*, April 17) that are reflected in the positions that are up for election next year. The Trustees eliminated the vice-president post and two of the three at-large positions. The remaining at-large position is the one for an early career psychiatrist and will be up for election in 2012 when incumbent Joyce Spurgeon, M.D., completes her three-year term. The Trustees holding the other two at-large positions will complete their terms, one ending in 2010 and the other in 2011. The current vice president, Jeffrey Geller, M.D., will complete his term, which ends in 2011.

Paper and electronic ballots will be sent to APA members on December 22 along with candidate information and voting instructions. Members who would like to receive only an electronic ballot should make the appropriate selection at <www.psych.org/options>. The deadline for receipt of all ballots is 5 p.m. Eastern time on February 5, 2010.

More information on the election and nominations process is posted at <www.psych.org/resources/governance/elections.aspx>. ■

Settlement

continued from page 1

ity involving Warner-Lambert, another pharmaceutical company it had acquired.

U.S. Attorney for the District of Massachusetts Mike Loucks said Pfizer was illegally marketing the drugs named in this lawsuit during the same time it was negotiating a settlement for the same charges in the gabapentin case.

The DOJ has resolved a string of similar cases with other pharmaceutical companies in recent years. In January, Eli Lilly and Co. reached a $1.41 billion settlement for off-label marketing of olanzapine, the largest such settlement before the current Pfizer case.

Pfizer had already released some information about the settlement figure eight months ago as it reported a huge markdown on its 2008 fourth-quarter profit. It came at the same time that Pfizer announced plans to acquire Wyeth, another major pharmaceutical company, for $68 billion.

The settlement includes a criminal fine of over $1.1 billion for the felony charge, which is the largest criminal fine in DOJ history, said Associate Attorney General Thomas Perelli at a press conference. About $1 billion will go to Medicare, Medicaid, and other government-funded health care programs because these programs had paid for the drugs under false claims.

The DOJ said it began investigating Pfizer's marketing practice after whistleblower lawsuits were filed against the company in Pennsylvania, Massachusetts, and Kentucky in 2003. The six whistleblowers will receive a total of $102 million from the settlement. ■

Applications Invited For APA/Shire Fellowship

Applications are invited for the 2010-2011 APA/Shire Child and Adolescent Psychiatry Fellowship Program. Fellowships will be awarded to five residents to travel to APA's 2010 and 2011 annual meetings and to work with mentors on issues in child and adolescent psychiatry.

The fellowship was established in 2002 to interest general psychiatry residents in considering careers in child and adolescent psychiatry through specific educational opportunities unavailable to them otherwise.

The fellowship is open to PGY-1 through PGY-3 residents. Applicants must be APA members and have approval from their training director or department chair.

The deadline for applications is November 20. They must include a completed application form; a 500-word letter of interest detailing the applicant's experience, knowledge, and career path; curriculum vitae; and a letter of support from a residency training director or department chair including the applicant's potential contribution to child and adolescent psychiatry.

The fellowship is supported by an unrestricted educational grant from Shire Pharmaceuticals.

Application materials are posted at <www.psych.org/share/OMNA/APAShireChildAdolescentPsychiatryFellowship.aspx>. More information is available from Alison Bondurant at abondurant@psych.org or (703) 907-8639. ■

Depression

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modifications for reducing risk in some populations, and we now have hypotheses about the mechanisms at work," said Taylor in an interview.

Other studies highlight progress but also illustrate its inconclusive nature. Writing in the July *Circulation*, longtime researchers Nancy Frasure-Smith, Ph.D., of McGill University and the Université de Montréal; François Lespérance, M.D., of the Université de Montréal; and colleagues studied depression in 974 patients with atrial fibrillation and congestive heart failure. Antidepressant medication use was not recorded. They reported that "elevated depression scores significantly predicted cardiovascular mortality (primary outcome), arrhythmic death, and all-cause mortality." Adjusted outcomes were similar whether treatment was focused on control of cardiac rate or control of cardiac rhythm. Marital status was a second independent risk factor in this cohort, "with the greatest risk observed in those who were both depressed and unmarried."

A second study in the same issue of *Circulation* by Suzanne Arnold, M.D., M.H.A., of Saint Luke's Heart Institute in Kansas City, Mo., and colleagues, looked at the discrepancy between angina severity and ischemia as measured by single-photon emission computed tomography (SPECT). The 735 patients also underwent extensive psychosocial assessment for anxiety, depression, neuroticism, alexithymia, and somatosensory amplification.

Among the 191 patients with verified ischemia, those with prior coronary revascularization, anxiety, and depressive symptoms experienced more frequent angina than those without those characteristics, despite having the same degree of heart vessel blockage. Thus, wrote Arnold and colleagues, "The present results suggest that psychosocial factors may significantly modulate patients' anginal response to myocardial ischemia."

Since this was a cross-sectional study, the authors could not infer causality, but they noted the prevalence of psychosocial symptoms among their patients and suggested that treatment plans include provision for their treatment.

Taylor, a coauthor on the AHA science advisory with Frasure-Smith, Lespérance, and others, also recently published the results of a small trial that further illustrates the good news–bad news aspect about the relationship of depression and cardiac disease. He and his colleagues randomized 48 depressed patients to treatment with cognitive-behavioral therapy (CBT) or to a waiting list as controls. To avoid confounding caused by drug side effects, they did not use antidepressant drugs.

An average of 15 CBT sessions resulted in a significant decline in Hamilton Depression Inventory and Beck Depression Inventory scores. About 57 percent (13 of 23) of CBT participants achieved remission, compared with 4 percent (1 of 25) of wait-listed patients. Treated patients showed a decline in triglycerides and heart rate, both signs of improvement.

However, there were no changes in respiratory sinus arrhythmia or cortisol levels during stress testing, the primary cardiovascular outcomes.

"The overall lack of change in the primary biological and physiological variables, and the sustained difference between [wait-listed] and CBT and normal controls at post [intervention] suggests that these variables are quite stable and not amenable to change through psychological intervention or affected by change in mood, at least in the short run," wrote the authors. The study was published online July 3 in the *Journal of Psychiatric Research*.

"I was frustrated that intervention had such little impact," said Taylor.

Despite the inconclusive outcomes of these and other trials, the AHA advisory says that "effective depression treatment may improve health outcomes."

Both heart disease and depression should be treated according to clinical guidelines, even if the details of how they are connected are not fully known, cardiologists and psychiatrists agree. Treating depression may improve adherence to cardiovascular treatment, while even nonpharmaceutical treatment for heart disease—like diet and exercise—may also lighten the burden of depression.

Eventually, however, after more is known about the interrelation of the two conditions, physicians will be able to tailor treatment for one in the context of the other to improve the chances of successful treatment, said Davison.

"Psychiatrists may not see [heart disease] as in their realm, but I see it as very much what psychiatrists should be doing," said Taylor.

An abstract of "Psychiatric Characteristics Associated With Long-term Mortality Among 361 Patients Having an Acute Coronary Syndrome and Major Depression" is posted at: <http://archpsyc.ama-assn.org/cgi/content/abstract/66/9/1022>. An excerpt from the editorial "Is It Time to Treat Depression in Patients With Cardiovascular Disease?" is posted at <http://circ.ahajournals.org/cgi/content/extract/120/2/99>. An abstract of "Does Improving Mood in Depressed Patients Alter Factors That May Affect Cardiovascular Disease Risk?" can be accessed at <www.sciencedirect.com> by searching on the title and clicking on "Preview." ■

Biomarker

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or schizophrenia registered significantly higher levels than in controls or PTSD patients (see chart on page 25).

Clinically, p11 mRNA expression in patients with PTSD also correlated positively with scores on the Hamilton Rating Scale for Depression and on measures of trauma severity and frequency, although not with the Hamilton Rating Scale for Anxiety or the Impact of Event Scale–Revised. However, p11 mRNA levels did not correlate with depression or anxiety scores among patients with bipolar disorder, depression, or schizophrenia.

"[T]his study provides preliminary findings that [peripheral blood mononuclear cell] p11 mRNA expression levels could be used as a potential biomarker for differentiating PTSD from other major psychiatric disorders," wrote Zhang and colleagues.

The study did not report the effects of any medications on p11 or glucocorticoid receptor expression, and there were too few men in the PTSD cohort to compare gender effects reliably.

However, Zhang will have the chance to make up the latter shortcoming and replicate his findings using a much larger sample shortly. He and his colleagues will travel to Fort Bragg, N.C., to collect blood samples and several psychometric measures from 1,200 U.S. troops returning from war for a double-blind study of p11 and glucocorticoid expression levels. He is also participating in the U.S. Army/NIMH study of suicide risk and protective factors that began this summer (*Psychiatric News*, August 21.)

Although much more work on p11 remains to be done before it can be considered a true biomarker for PTSD, Zhang believes that eventually its full mechanism will be understood, leading to quick, in-office tests. Continuing measurements might then also help monitor treatment.

An abstract of "Levels of the Potential Biomarker p11 in Peripheral Blood Cells Distinguish Patients With PTSD From Those With Other Major Psychiatric Disorders" can be accessed at <www.sciencedirect.com/science/journal/00223956> by clicking on Volume 43, Issue 13, and then "Preview" under the study title. ■

Arsonists

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Also, "Given the substantial personal and social costs related to arson, prevention and treatment interventions targeting fire setters potentially could save lives and property," Vaughn and his colleagues wrote.

The study was funded by the National Institutes of Health.

An abstract of "Prevalence and Correlates of Fire Setting in the United States: Results From the National Epidemiological Survey on Alcohol and Related Conditions" can be accessed at <www.sciencedirect.com> under "Browse by Title," "C," and then "Comprehensive Psychiatry Articles in Press." ■

BRIEF SUMMARY

CLOZAPINE TABLETS USP

℞ only

Before prescribing clozapine, the physician should be thoroughly familiar with the details of this prescribing information.

BOXED WARNING

1. AGRANULOCYTOSIS

BECAUSE OF A SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT, CLOZAPINE SHOULD BE RESERVED FOR USE IN (1) THE TREATMENT OF SEVERELY ILL PATIENTS WITH SCHIZOPHRENIA WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD ANTIPSYCHOTIC DRUG TREATMENT, OR (2) FOR REDUCING THE RISK OF RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR.

PATIENTS BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WHITE BLOOD CELL (WBC) COUNT AND ABSOLUTE NEUTROPHIL COUNT (ANC) BEFORE INITIATION OF TREATMENT AS WELL AS REGULAR WBC COUNTS AND ANCs DURING TREATMENT AND FOR AT LEAST 4 WEEKS AFTER DISCONTINUATION OF TREATMENT (SEE WARNINGS).

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WBC COUNT AND ANC ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION (SEE WARNINGS).

2. SEIZURES

SEIZURES HAVE BEEN ASSOCIATED WITH THE USE OF CLOZAPINE. DOSE APPEARS TO BE AN IMPORTANT PREDICTOR OF SEIZURE, WITH A GREATER LIKELIHOOD AT HIGHER CLOZAPINE DOSES. CAUTION SHOULD BE USED WHEN ADMINISTERING CLOZAPINE TO PATIENTS HAVING A HISTORY OF SEIZURES OR OTHER PREDISPOSING FACTORS. PATIENTS SHOULD BE ADVISED NOT TO ENGAGE IN ANY ACTIVITY WHERE SUDDEN LOSS OF CONSCIOUSNESS COULD CAUSE SERIOUS RISK TO THEMSELVES OR OTHERS (SEE WARNINGS).

3. MYOCARDITIS

ANALYSES OF POSTMARKETING SAFETY DATABASES SUGGEST THAT CLOZAPINE IS ASSOCIATED WITH AN INCREASED RISK OF FATAL MYOCARDITIS, ESPECIALLY DURING, BUT NOT LIMITED TO, THE FIRST MONTH OF THERAPY. IN PATIENTS IN WHOM MYOCARDITIS IS SUSPECTED, CLOZAPINE TREATMENT SHOULD BE PROMPTLY DISCONTINUED (SEE WARNINGS).

4. OTHER ADVERSE CARDIOVASCULAR AND RESPIRATORY EFFECTS

ORTHOSTATIC HYPOTENSION, WITH OR WITHOUT SYNCOPE, CAN OCCUR WITH CLOZAPINE TREATMENT. RARELY, COLLAPSE CAN BE PROFOUND AND BE ACCOMPANIED BY RESPIRATORY AND/OR CARDIAC ARREST. ORTHOSTATIC HYPOTENSION IS MORE LIKELY TO OCCUR DURING INITIAL TITRATION IN ASSOCIATION WITH RAPID DOSE ESCALATION. IN PATIENTS WHO HAVE HAD EVEN A BRIEF INTERVAL OFF CLOZAPINE, i.e., 2 OR MORE DAYS SINCE THE LAST DOSE, TREATMENT SHOULD BE STARTED WITH 12.5 mg ONCE OR TWICE DAILY (SEE WARNINGS and DOSAGE AND ADMINISTRATION).

SINCE COLLAPSE, RESPIRATORY ARREST AND CARDIAC ARREST DURING INITIAL TREATMENT HAS OCCURRED IN PATIENTS WHO WERE BEING ADMINISTERED BENZODIAZEPINES OR OTHER PSYCHOTROPIC DRUGS, CAUTION IS ADVISED WHEN CLOZAPINE IS INITIATED IN PATIENTS TAKING A BENZODIAZEPINE OR ANY OTHER PSYCHOTROPIC DRUG (SEE WARNINGS).

5. INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. ANALYSES OF SEVENTEEN PLACEBO-CONTROLLED TRIALS (MODAL DURATION OF 10 WEEKS), LARGELY IN PATIENTS TAKING ATYPICAL ANTIPSYCHOTIC DRUGS, 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 (e.g., HEART FAILURE, SUDDEN DEATH) OR INFECTIOUS (e.g., PNEUMONIA) IN NATURE. OBSERVATIONAL STUDIES SUGGEST THAT, SIMILAR TO ATYPICAL ANTIPSYCHOTIC DRUGS, TREATMENT WITH CONVENTIONAL ANTIPSYCHOTIC DRUGS MAY INCREASE MORTALITY. THE EXTENT TO WHICH THE FINDINGS OF INCREASED MORTALITY IN OBSERVATIONAL STUDIES MAY BE ATTRIBUTED TO THE ANTIPSYCHOTIC DRUG AS OPPOSED TO SOME CHARACTERISTIC(S) OF THE PATIENTS IS NOT CLEAR. CLOZAPINE IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS.

CONTRAINDICATIONS

Clozapine is contraindicated in patients with a previous hypersensitivity to clozapine or any other component of this drug, in patients with myeloproliferative disorders, uncontrolled epilepsy, paralytic ileus, or a history of clozapine-induced agranulocytosis or severe granulocytopenia. As with more typical antipsychotic drugs, clozapine is contraindicated in severe central nervous system depression or comatose states from any cause.

Clozapine should not be used simultaneously with other agents having a well-known potential to cause agranulocytosis or otherwise suppress bone marrow function. The mechanism of clozapine-induced agranulocytosis is unknown; nonetheless, it is possible that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression.

WARNINGS

General

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS TREATED WITH ANTIPSYCHOTIC DRUGS ARE AT AN INCREASED RISK OF DEATH COMPARED TO PLACEBO. CLOZAPINE IS NOT APPROVED FOR THE TREATMENT OF PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS (SEE BOXED WARNING).

AGRANULOCYTOSIS

BECAUSE OF THE SIGNIFICANT RISK OF AGRANULOCYTOSIS, A POTENTIALLY LIFE-THREATENING ADVERSE EVENT (SEE FOLLOWING), CLOZAPINE SHOULD BE RESERVED FOR USE IN THE FOLLOWING INDICATIONS: 1) FOR TREATMENT OF SEVERELY ILL SCHIZOPHRENIC PATIENTS WHO FAIL TO SHOW AN ACCEPTABLE RESPONSE TO ADEQUATE COURSES OF STANDARD DRUG TREATMENT FOR SCHIZOPHRENIA, EITHER BECAUSE OF INSUFFICIENT EFFECTIVENESS OR THE INABILITY TO ACHIEVE AN EFFECTIVE DOSE DUE TO INTOLERABLE ADVERSE EFFECTS FROM THOSE DRUGS. CONSEQUENTLY, BEFORE INITIATING TREATMENT WITH CLOZAPINE, IT IS STRONGLY RECOMMENDED THAT A PATIENT BE GIVEN AT LEAST 2 TRIALS, EACH WITH A DIFFERENT STANDARD DRUG PRODUCT FOR SCHIZOPHRENIA, AT AN ADEQUATE DOSE, AND FOR AN ADEQUATE DURATION. 2) FOR REDUCING THE RISK FOR RECURRENT SUICIDAL BEHAVIOR IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER WHO ARE JUDGED TO BE AT RISK OF RE-EXPERIENCING SUICIDAL BEHAVIOR.

CLOZAPINE IS AVAILABLE ONLY THROUGH A DISTRIBUTION SYSTEM THAT ENSURES MONITORING OF WHITE BLOOD CELL (WBC) COUNT AND ABSOLUTE NEUTROPHIL COUNT (ANC) ACCORDING TO THE SCHEDULE DESCRIBED BELOW PRIOR TO DELIVERY OF THE NEXT SUPPLY OF MEDICATION.

AS DESCRIBED IN TABLE 1, PATIENTS WHO ARE BEING TREATED WITH CLOZAPINE MUST HAVE A BASELINE WBC COUNT AND ANC BEFORE INITIATION OF TREATMENT, AND A WBC COUNT AND ANC EVERY WEEK FOR THE FIRST 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) HAVE BEEN MAINTAINED DURING THE FIRST 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNTS AND ANC CAN BE MONITORED EVERY 2 WEEKS FOR THE NEXT 6 MONTHS. THEREAFTER, IF ACCEPTABLE WBC COUNTS AND ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) HAVE BEEN MAINTAINED DURING THE SECOND 6 MONTHS OF CONTINUOUS THERAPY, WBC COUNT AND ANC CAN BE MONITORED EVERY 4 WEEKS.

WHEN TREATMENT WITH CLOZAPINE IS DISCONTINUED (REGARDLESS OF THE REASON), WBC COUNT AND ANC MUST BE MONITORED WEEKLY FOR AT LEAST 4 WEEKS FROM THE DAY OF DISCONTINUATION OR UNTIL WBC ≥3500/mm³ AND ANC ≥2000/mm³.

Agranulocytosis

Background

Agranulocytosis, defined as an ANC of less than 500/mm³, has been estimated to occur in association with clozapine use at a cumulative incidence at 1 year of approximately 1.3%, based on the occurrence of 15 U.S. cases out of 1,743 patients exposed to clozapine during its clinical testing prior to domestic marketing. All of these cases occurred at a time when the need for close monitoring of WBC counts was already recognized. Agranulocytosis could prove fatal if not detected early and therapy interrupted. Of the 149 cases of agranulocytosis reported worldwide in association with clozapine use as of December 31, 1989, 32% were fatal. However, few of these deaths occurred since 1977, at which time the knowledge of clozapine-induced agranulocytosis became more widespread, and close monitoring of WBC counts more widely practiced. In the U.S., under a weekly WBC count monitoring system with clozapine, there have been 585 cases of agranulocytosis as of August 21, 1997; 19 were fatal (3%). During this period 150,409 patients received clozapine. A hematologic risk analysis was conducted based upon the available information in the Clozaril® National Registry (CNR) for U.S. patients. Based upon a cut-off date of April 30, 1995, the incidence rates of agranulocytosis based upon a weekly monitoring schedule, rose steeply during the first two months of therapy, peaking in the third month. Among clozapine patients who continued the drug beyond the third month, the weekly incidence of agranulocytosis fell to a substantial degree. After six months, the weekly incidence of agranulocytosis declines still further, however, it never reaches zero. It should be noted that any type of reduction in the frequency of monitoring WBC counts may result in an increased incidence of agranulocytosis.

Risk Factors

Experience from clinical development, as well as from examples in the medical literature, suggest that patients who have developed agranulocytosis during clozapine therapy are at increased risk of subsequent episodes of agranulocytosis. Analysis of WBC count data from the Clozaril® National Registry also suggests that patients who have an initial episode of moderate leukopenia (3000/mm³ >WBC ≥2000/mm³) are at an increased risk of subsequent episodes of agranulocytosis. Except for bone marrow suppression during initial clozapine therapy, there are no other established risk factors, based on world-wide experience, for the development of agranulocytosis in association with clozapine use. However, a disproportionate number of the U.S. cases of agranulocytosis occurred in patients of Jewish background compared to the overall proportion of such patients exposed during domestic development of clozapine. Most of the U.S. cases of agranulocytosis occurred within 4 to 10 weeks of exposure but neither dose nor duration is a reliable predictor of this problem. Agranulocytosis associated with other antipsychotic drugs has been reported to occur with a greater frequency in women, the elderly, and in patients who are cachectic or have a serious underlying medical illness; such patients may also be at particular risk with clozapine, although this has not been definitely demonstrated.

WBC Count and ANC Monitoring Schedule

Table 1 provides a summary of the frequency of monitoring that should occur based on various stages of therapy (e.g., initiation of therapy) or results from WBC count and ANC monitoring tests (e.g., moderate leukopenia). The text that follows should be consulted for additional details regarding the treatment of patients under the various conditions (e.g., severe leukopenia).

Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat or any other signs of infection occurring at any time during clozapine therapy. Such patients should have a WBC count and ANC performed promptly.

Table 1. Frequency of Monitoring based on Stage of Therapy or Results from WBC Count and ANC Monitoring Tests

Situation	Hematological Values for Monitoring	Frequency of WBC and ANC Monitoring
Initiation of therapy	WBC ≥3500/mm³ ANC ≥2000/mm³ Note: Do not initiate in patients with 1) history of myeloproliferative disorder or 2) clozapine-induced agranulocytosis or granulocytopenia	Weekly for 6 months
6 months to 12 months of therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 2 weeks for 6 months
12 months of therapy	All results for WBC ≥3500/mm³ and ANC ≥2000/mm³	Every 4 weeks ad infinitum
Immature forms present	N/A	Repeat WBC and ANC
Discontinuation of Therapy	N/A	Weekly for at least 4 weeks from day of discontinuation or until WBC ≥3500/mm³ and ANC >2000/mm³
Substantial drop in WBC or ANC	Single Drop or cumulative drop within 3 weeks of WBC ≥3000/mm³ or ANC ≥1500/mm³	1. Repeat WBC and ANC 2. If repeat values are 3000/mm³ ≤WBC ≤3500/mm³ and ANC <2000/mm³, then monitor twice weekly
Mild Leukopenia ---------- Mild Granulocytopenia	3500/mm³ >WBC ≥3000/mm³ and/or 2000/mm³ >ANC ≥1500/mm³	Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ then return to previous monitoring frequency
Moderate Leukopenia ---------- Moderate Granulocytopenia	3000/mm³ >WBC ≥2000/mm³ and/or 1500/mm³ >ANC ≥1000/mm³	1. Interrupt therapy 2. Daily until WBC >3000/mm³ and ANC >1500/mm³ 3. Twice-weekly until WBC >3500/mm³ and ANC >2000/mm³ 4. May rechallenge when WBC >3500/mm³ and ANC >2000/mm³ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks ad infinitum
Severe Leukopenia ---------- Severe Granulocytopenia	WBC <2000/mm³ and/or ANC <1000/mm³	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3000/mm³ and ANC >1500/mm³ • Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ • Weekly after WBC >3500/mm³
Agranulocytosis	ANC ≤500/mm³	1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: • Daily until WBC >3000/mm³ and ANC >1500/mm³ • Twice weekly until WBC >3500/mm³ and ANC >2000/mm³ • Weekly after WBC >3500/mm³

***WBC = white blood cell count; ANC = absolute neutrophil count**

Decrements in WBC Count and/or ANC

Consult Table 1 above to determine how to monitor patients who experience decrements in WBC count and ANC at any point during treatment. Additionally, patients should be carefully monitored for flu-like symptoms or other symptoms suggestive of infection.

Non-Rechallengeable Patients

If the total WBC count falls below 2000/mm³ or the ANC falls below 1000/mm³, bone marrow aspiration should be considered to ascertain granulopoietic status and patients should not be rechallenged with clozapine. Protective isolation with close observation may be indicated if granulopoiesis is determined to be deficient. Should evidence of infection develop, the patient should have appropriate cultures performed and an appropriate antibiotic regimen instituted.

Patients discontinued from clozapine therapy due to significant granulopoietic suppression have been found to develop agranulocytosis upon rechallenge, often with a shorter latency on re-exposure. To reduce the chances of rechallenge occurring in patients who have experienced significant bone marrow suppression during clozapine therapy, a single, national master file (i.e., Non-rechallengeable Database) is maintained confidentially.

Treatment of Rechallengeable Patients

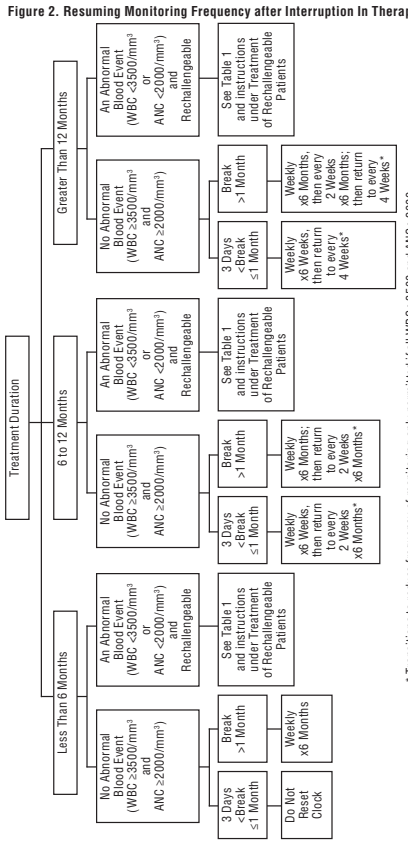
Patients may be rechallenged with clozapine if their WBC count does not fall below 2000/mm³ and the ANC does not fall below 1000/mm³. However, analysis of data from the Clozaril® National Registry suggests that patients who have an initial episode of moderate leukopenia (3000/mm³ >WBC ≥2000/mm³) have up to a 12 fold increased risk of having a subsequent episode of agranulocytosis when rechallenged compared to the full cohort of patients treated with clozapine. Although clozapine therapy may be resumed if no symptoms of infection develop, and when the WBC count rises above 3500/mm³ and the ANC rises above 2000/mm³, prescribers are strongly advised to consider whether the benefit of continuing clozapine treatment outweighs the increased risk of agranulocytosis.

Analyses of the Clozaril® National Registry have shown an increased risk of having a subsequent episode of granulopoietic suppression up to a year after recovery from the initial episode. Therefore, as noted in Table 1 above, patients must undergo weekly WBC count and ANC monitoring for one year following recovery from an episode of moderate leukopenia and/or moderate granulocytopenia regardless of when the episode develops. If acceptable WBC counts and ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) have been maintained during the year of weekly monitoring, WBC counts can be monitored every 2 weeks for the next 6 months. If acceptable WBC counts and ANC (WBC ≥3500/mm³ and ANC ≥2000/mm³) continue to be maintained during the 6 months of every 2 week monitoring, WBC counts can be monitored every 4 weeks thereafter, ad infinitum.

Interruptions in Therapy

Figure 2 provides instructions regarding reinitiating therapy and subsequently the frequency of WBC count and ANC monitoring after a period of interruption.

Figure 2. Resuming Monitoring Frequency after Interruption In Therapy.



* Transitions to reduce frequency of monitoring only permitted if all WBC ≥3500 and ANC ≥2000.

Eosinophilia

In clinical trials, 1% of patients developed eosinophilia, which, in rare cases, can be substantial. If a differential count reveals a total eosinophil count above 4,000/mm³, clozapine therapy should be interrupted until the eosinophil count falls below 3,000/mm³.

Seizures

Seizure has been estimated to occur in association with clozapine use at a cumulative incidence at one year of approximately 5%, based on the occurrence of one or more seizures in 61 of 1,743 patients exposed to clozapine during its clinical testing prior to domestic marketing (i.e., a crude rate of 3.5%). Dose appears to be an important predictor of seizure, with a greater likelihood of seizure at the higher clozapine doses used.

Caution should be used in administering clozapine to patients having a history of seizures or other predisposing factors. Because of the substantial risk of seizure associated with clozapine use, patients should be advised not to engage in any activity where sudden loss of consciousness could cause serious risk to themselves or others, e.g., the operation of complex machinery, driving an automobile, swimming, climbing, etc.

Myocarditis

Post-marketing surveillance data from four countries that employ hematological monitoring of clozapine-treated patients revealed: 30 reports of myocarditis with 17 fatalities in 205,493 U.S. patients (August 2001); 7 reports of myocarditis with 1 fatality in 15,600 Canadian patients (April 2001); 30 reports of myocarditis with 8 fatalities in 24,108 U.K. patients (August 2001); 15 reports of myocarditis with 5 fatalities in 8,000 Australian patients (March 1999). These reports represent an incidence of 5.0, 16.3, 43.2, and 96.6 cases/100,000 patient-years, respectively. The number of fatalities represent an incidence of 2.8, 2.3, 11.5, and 32.2 cases/100,000 patient-years, respectively.

The overall incidence rate of myocarditis in patients with schizophrenia treated with antipsychotic agents is unknown. However, for the established market economies (WHO), the incidence of myocarditis is 0.3 cases/100,000 patient-years and the fatality rate is 0.2 cases/100,000 patient-years. Therefore, the rate of myocarditis in clozapine-treated patients appears to be 17 to 322 times greater than the general population and is associated with an increased risk of fatal myocarditis that is 14 to 161 times greater than the general population.

The total reports of myocarditis for these four countries was 82 of which 51 (62%) occurred within the first month of clozapine treatment, 25 (31%) occurred after the first month of therapy and 6 (7%) were unknown. The median duration of treatment was 3 weeks. Of 5 patients rechallenged with clozapine, 3 had a recurrence of myocarditis. Of the 82 reports, 31 (38%) were fatal and 25 patients who died had evidence of myocarditis at autopsy. These data also suggest that the incidence of fatal myocarditis may be highest during the first month of therapy.

Therefore, the possibility of myocarditis should be considered in patients receiving clozapine who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or electrocardiographic findings such as ST-T wave abnormalities or arrhythmias. It is not known whether eosinophilia is a reliable predictor of myocarditis. Tachycardia, which has been associated with clozapine treatment, has also been noted as a presenting sign in patients with myocarditis. Therefore, tachycardia during the first month of therapy warrants close monitoring for other signs of myocarditis.

Prompt discontinuation of clozapine treatment is warranted upon suspicion of myocarditis. Patients with clozapine-related myocarditis should not be rechallenged with clozapine.

Other Adverse Cardiovascular and Respiratory Effects

Orthostatic hypotension with or without syncope can occur with clozapine treatment and may represent a continuing risk in some patients. Rarely (approximately 1 case per 3,000 patients), collapse can be profound and be accompanied by respiratory and/or cardiac arrest. Orthostatic hypotension is more likely to occur during initial titration in association with rapid dose escalation and may even occur on first dose. In one report, initial doses as low as 12.5 mg were associated with collapse and respiratory arrest. When restarting patients who have had even a brief interval off clozapine, i.e., 2 days or more since the last dose, it is recommended that treatment be reinitiated with one-half of a 25 mg tablet (12.5 mg) once or twice daily (see DOSAGE AND ADMINISTRATION).

Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.

Tachycardia, which may be sustained, has also been observed in approximately 25% of patients taking clozapine, with patients having an average increase in pulse rate of 10 to 15 bpm. The sustained tachycardia is not simply a reflex response to hypotension, and is present in all positions monitored. Either tachycardia or hypotension may pose a serious risk for an individual with compromised cardiovascular function.

A minority of clozapine-treated patients experience ECG repolarization changes similar to those seen with other antipsychotic drugs, including S-T segment depression and flattening or inversion of T waves, which all normalize after discontinuation of clozapine. The clinical significance of these changes is unclear. However, in clinical trials with clozapine, several patients experienced significant cardiac events, including ischemic changes, myocardial infarction, arrhythmias, and sudden death. In addition there have been postmarketing reports of congestive heart failure, pericarditis, and pericardial effusions. Causality assessment was difficult in many of these cases because of serious preexisting cardiac disease and plausible alternative causes. Rare instances of sudden death have been reported in psychiatric patients, with or without associated antipsychotic drug treatment, and the relationship of these events to antipsychotic drug use is unknown.

Clozapine should be used with caution in patients with known cardiovascular and/or pulmonary disease, and the recommendation for gradual titration of dose should be carefully observed.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics including clozapine. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with antipsychotic drugs. 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 dysrhythmias).

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to identify cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system (CNS) pathology.

The management of NMS should include 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, 2) intensive symptomatic treatment and medical monitoring, and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

There have been several reported cases of NMS in patients receiving clozapine alone or in combination with lithium or other CNS-active agents.

Tardive Dyskinesia

A syndrome consisting of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of treatment, which patients are likely to develop the syndrome.

There are several reasons for predicting that clozapine may be different from other antipsychotic drugs in its potential for inducing tardive dyskinesia, including the preclinical finding that it has a relatively weak dopamine-blocking effect and the clinical finding of a low incidence of certain acute extrapyramidal symptoms, e.g., dystonia. A few cases of tardive dyskinesia have been reported in patients on clozapine who had been previously treated with other antipsychotic agents, so that a causal relationship cannot be established. There have been no reports of tardive dyskinesia directly attributable to clozapine alone. Nevertheless, it cannot be concluded, without more extended experience, that clozapine is incapable of inducing this syndrome.

Both the risk of developing the syndrome and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic drug treatment is withdrawn. Antipsychotic drug treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptom suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, clozapine should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. As with any antipsychotic drug, chronic clozapine use should be reserved for patients who appear to be obtaining substantial benefit from the drug. In such patients, the smallest dose and the shortest duration of treatment should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on clozapine, drug discontinuation should be considered. However, some patients may require treatment with clozapine despite the presence of the syndrome.

PRECAUTIONS

General

Because of the significant risk of agranulocytosis and seizure, both of which present a continuing risk over time, the extended treatment of patients failing to show an acceptable level of clinical response should ordinarily be avoided. In addition, the need for continuing treatment in patients exhibiting beneficial clinical responses should be periodically re-evaluated. Although it is not known whether the risk would be increased, it is prudent either to avoid clozapine or use it cautiously in patients with a previous history of agranulocytosis induced by other drugs.

Cardiomyopathy

Cases of cardiomyopathy have been reported in patients treated with clozapine. The reporting rate for cardiomyopathy in clozapine-treated patients in the U.S. (8.9 per 100,000 person-years) was similar to an estimate of the cardiomyopathy incidence in the U.S. general population derived from the 1999 National Hospital Discharge Survey data (9.7 per 100,000 person-years). Approximately 80% of clozapine-treated patients in whom cardiomyopathy was reported were less than 50 years of age; the duration of treatment with clozapine prior to cardiomyopathy diagnosis varied, but was >6 months in 65% of the reports. Dilated cardiomyopathy was most frequently reported, although a large percentage of reports did not specify the type of cardiomyopathy. Signs and symptoms suggestive of cardiomyopathy, particularly exertional dyspnea, fatigue, orthopnea, paroxysmal nocturnal dyspnea, and peripheral edema should alert the clinician to perform further investigations. If the diagnosis of cardiomyopathy is confirmed, the prescriber should discontinue clozapine unless the benefit to the patient clearly outweighs the risk.

Fever

During clozapine therapy, patients may experience transient temperature elevations above 100.4°F (38°C), with the peak incidence within the first 3 weeks of treatment. While this fever is generally benign and self-limiting, it may necessitate discontinuing patients from treatment. On occasion, there may be an associated increase or decrease in WBC count. Patients with fever should be carefully evaluated to rule out the possibility of an underlying infectious process or the development of agranulocytosis. In the presence of high fever, the possibility of Neuroleptic Malignant Syndrome (NMS) must be considered. There have been several reports of NMS in patients receiving clozapine, usually in combination with lithium or other CNS-active drugs. (see **Neuroleptic Malignant Syndrome [NMS]**, under **WARNINGS**).

Pulmonary Embolism

The possibility of pulmonary embolism should be considered in patients receiving clozapine who present with deep vein thrombosis, acute dyspnea, chest pain or with other respiratory signs and symptoms. As of December 31, 1993, there were 18 cases of fatal pulmonary embolism in association with clozapine therapy in users 10 to 54 years of age. Based upon the extent of use observed in the Clozaril® National Registry, the mortality rate associated with pulmonary embolus was 1 death per 3,450 person-years of use. This rate was about 27.5 times higher than that in the general population of a similar age and gender (95% Confidence Interval; 17.1, 42.2). Deep vein thrombosis has also been observed in association with clozapine therapy. Whether pulmonary embolus can be attributed to clozapine or some characteristic(s) of its users is not clear, but the occurrence of deep vein thrombosis or respiratory symptomatology should suggest its presence.

Hepatitis

Caution is advised in patients using clozapine who have concurrent hepatic disease. Hepatitis has been reported in both patients with normal and preexisting liver function abnormalities. In patients who develop nausea, vomiting, and/or anorexia during clozapine treatment, liver function tests should be performed immediately. If the elevation of these values is clinically relevant or if symptoms of jaundice occur, treatment with clozapine should be discontinued.

Anticholinergic Toxicity

Eye

Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of narrow angle glaucoma.

Gastrointestinal

Clozapine use has been associated with varying degrees of impairment of intestinal peristalsis, ranging from constipation to intestinal obstruction, fecal impaction and paralytic ileus (see **ADVERSE REACTIONS**). On rare occasions, these cases have been fatal. Constipation should be initially treated by ensuring adequate hydration, and use of ancillary therapy such as bulk laxatives. Consultation with a gastroenterologist is advisable in more serious cases.

Prostate

Clozapine has potent anticholinergic effects and care should be exercised in using this drug in the presence of prostatic enlargement.

Interference with Cognitive and Motor Performance

Because of initial sedation, clozapine may impair mental and/or physical abilities, especially during the first few days of therapy. The recommendations for gradual dose escalation should be carefully adhered to, and patients cautioned about activities requiring alertness.

Use in Patients with Concomitant Illness

Clinical experience with clozapine in patients with concomitant systemic diseases is limited. Nevertheless, caution is advisable in using clozapine in patients with renal or cardiac disease.

Use in Patients Undergoing General Anesthesia
Caution is advised in patients being administered general anesthesia because of the CNS effects of clozapine. Check with the anesthesiologist regarding continuation of clozapine therapy in a patient scheduled for surgery.
Information for Patients
Physicians are advised to discuss the following issues with patients for whom they prescribe clozapine:
- Patients who are to receive clozapine should be warned about the significant risk of developing agranulocytosis. Patients should be advised to report immediately the appearance of lethargy, weakness, fever, sore throat, malaise, mucous membrane ulceration or other possible signs of infection. Particular attention should be paid to any flu-like complaints or other symptoms that might suggest infection.
  - Patients should be informed that clozapine tablets will be made available only through a special program designed to ensure the required blood monitoring in order to reduce the risk of developing agranulocytosis. Patients should be informed that their WBC count and ANC will be monitored as follows:
    - Weekly blood tests are required for the first 6 months.
    - If acceptable WBC counts and ANCs (WBC ≥3500/mm^3 and ANC ≥2000/mm^3) have been maintained during the first 6 months of continuous therapy, then WBC counts and ANCs can be monitored every 2 weeks for the next 6 months.
    - Thereafter, if acceptable WBC counts and ANCs have been maintained during the second 6 months of continuous therapy, WBC counts and ANCs can be monitored every 4 weeks.
- Patients should be informed of the significant risk of seizure during clozapine treatment, and they should be advised to avoid driving and any other potentially hazardous activity while taking clozapine.
- Patients should be advised of the risk of orthostatic hypotension, especially during the period of initial dose titration.
- Patients should be informed that if they miss taking clozapine for more than 2 days, they should not restart their medication at the same dosage, but should contact their physician for dosing instructions.
- Patients should notify their physician if they are taking, or plan to take, any prescription or over-the-counter drugs or alcohol.
- Patients should notify their physician if they become pregnant or intend to become pregnant during therapy.
- Patients should not breast-feed an infant if they are taking clozapine.

Drug Interactions
The risks of using clozapine in combination with other drugs have not been systematically evaluated.
Pharmacodynamic-Related Interactions
The mechanism of clozapine-induced agranulocytosis is unknown; nonetheless, the possibility that causative factors may interact synergistically to increase the risk and/or severity of bone marrow suppression warrants consideration. Therefore, clozapine should not be used with other agents having a well-known potential to suppress bone marrow function.
Given the primary CNS effects of clozapine, caution is advised in using it concomitantly with other CNS-active drugs or alcohol.
Orthostatic hypotension in patients taking clozapine can, in rare cases (approximately 1 case per 3,000 patients), be accompanied by profound collapse and respiratory and/or cardiac arrest. Some of the cases of collapse/respiratory arrest/cardiac arrest during initial treatment occurred in patients who were being administered benzodiazepines; similar events have been reported in patients taking other psychotropic drugs or even clozapine by itself. Although it has not been established that there is an interaction between clozapine and benzodiazepines or other psychotropics, caution is advised when clozapine is initiated in patients taking a benzodiazepine or any other psychotropic drug.
Clozapine may potentiate the hypotensive effects of antihypertensive drugs and the anticholinergic effects of atropine-type drugs. The administration of epinephrine should be avoided in the treatment of drug-induced hypotension because of a possible reverse epinephrine effect.
Pharmacokinetic-Related Interactions
Clozapine is a substrate for many CYP 450 isozymes, in particular 1A2, 2D6, and 3A4. The risk of metabolic interactions caused by an effect on an individual isoform is therefore minimized. Nevertheless, caution should be used in patients receiving concomitant treatment with other drugs that are either inhibitors or inducers of these enzymes.
Concomitant administration of drugs known to induce cytochrome P450 enzymes may decrease the plasma levels of clozapine. Phenytoin, nicotine, and rifampin may decrease clozapine plasma levels, resulting in a decrease in effectiveness of a previously effective clozapine dose.
Concomitant administration of drugs known to inhibit the activity of cytochrome P450 isozymes may increase the plasma levels of clozapine. Cimetidine, caffeine, citalopram, ciprofloxacin, and erythromycin may increase plasma levels of clozapine, potentially resulting in adverse effects. Although concomitant use of clozapine and carbamazepine is not recommended, it should be noted that discontinuation of concomitant carbamazepine administration may result in an increase in clozapine plasma levels.
In a study of schizophrenic patients who received clozapine under steady state conditions, fluvoxamine or paroxetine was added in 16 and 14 patients, respectively. After 14 days of co-administration, mean trough concentration of clozapine and its metabolites, N-desmethylclozapine and clozapine N-oxide, were elevated with fluvoxamine by about three-fold compared to baseline concentrations. Paroxetine produced only minor changes in the levels of clozapine and its metabolites. However, other published reports describe modest elevations (less than two-fold) of clozapine and metabolite concentrations when clozapine was taken with paroxetine, fluoxetine, and sertraline. Therefore, such combined treatment should be approached with caution and patients should be monitored closely when clozapine is combined with these drugs, particularly with fluvoxamine. A reduced clozapine dose should be considered.
A subset (3% to 10%) of the population has reduced activity of certain drug metabolizing enzymes such as the cytochrome P450 isozyme P450 2D6. Such individuals are referred to as "poor metabolizers" of drugs such as debrisoquin, dextromethorphan, the tricyclic antidepressants, and clozapine. These individuals may develop higher than expected plasma concentrations of clozapine when given usual doses. In addition, certain drugs that are metabolized by this isozyme, including many antidepressants (clozapine, selective serotonin reuptake inhibitors, and others), may inhibit the activity of this isozyme, and thus may make normal metabolizers resemble poor metabolizers with regard to concomitant therapy with other drugs metabolized by this enzyme system, leading to drug interaction.
Concomitant use of clozapine with other drugs metabolized by cytochrome P450 2D6 may require lower doses than usually prescribed for either clozapine or the other drug. Therefore, coadministration of clozapine with other drugs that are metabolized by this isozyme, including antidepressants, phenothiazines, carbamazepine, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.
Carcinogenesis, Mutagenesis, Impairment of Fertility
No carcinogenic potential was demonstrated in long-term studies in mice and rats at doses approximately 7 times the typical human dose on a mg/kg basis. Fertility in male and female rats was not adversely affected by clozapine. Clozapine did not produce genotoxic or mutagenic effects when assayed in appropriate bacterial and mammalian tests.
Pregnancy
Teratogenic Effects
Pregnancy category B
Reproduction studies have been performed in rats and rabbits at doses of approximately 2 to 4 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to clozapine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, and in view of the desirability of keeping the administration of all drugs to a minimum during pregnancy, this drug should be used only if clearly needed.
Nursing Mothers
Animal studies suggest that clozapine may be excreted in breast milk and have an effect on the nursing infant. Therefore, women receiving clozapine should not breast-feed.
Pediatric Use
Safety and effectiveness in pediatric patients have not been established.
Geriatric Use
Clinical studies of clozapine did not include sufficient numbers of subjects age 65 and over to determine whether they respond differently from younger subjects.
Orthostatic hypotension can occur with clozapine treatment and tachycardia, which may be sustained, has been observed in about 25% of patients taking clozapine (see **BOXED WARNING**, **Other Adverse Cardiovascular and Respiratory Effects**). Elderly patients, particularly those with compromised cardiovascular functioning, may be more susceptible to these effects.
Also, elderly patients may be particularly susceptible to the anticholinergic effects of clozapine, such as urinary retention and constipation (see **PRECAUTIONS, Anticholinergic Toxicity**).
Dose selection for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy. Other reported clinical experience does suggest that the prevalence of tardive dyskinesia appears to be highest among the elderly, especially elderly women (see **WARNINGS, Tardive Dyskinesia**).

ADVERSE REACTIONS
Associated with Discontinuation of Treatment
Sixteen percent of 1,080 patients who received clozapine in premarketing clinical trials discontinued treatment due to an adverse event, including both those that could be reasonably attributed to clozapine treatment and those that might more appropriately be considered intercurrent illness. The more common events considered to be causes of discontinuation included: CNS, primarily drowsiness/sedation, seizures, dizziness/syncope; cardiovascular, primarily tachycardia, hypotension and ECG changes; gastrointestinal, primarily nausea/vomiting; hematologic, primarily leukopenia/granulocytopenia/agranulocytosis; and fever. None of the events enumerated accounts for more than 1.7% of all discontinuations attributed to adverse clinical events.
Extrapyramidal Symptoms
Dystonia
Class effect
Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups. Clozapine, an atypical antipsychotic, is associated with a low incidence of dystonia (see **WARNINGS, Tardive Dyskinesia**).
Commonly Observed
Adverse events observed in association with the use of clozapine in clinical trials at an incidence of greater than 5% were: central nervous system complaints, including drowsiness/sedation, dizziness/vertigo, headache and tremor; autonomic nervous system complaints, including salivation, sweating, dry mouth and visual disturbances; cardiovascular findings, including tachycardia, hypotension and syncope; and gastrointestinal complaints, including constipation and nausea; and fever. Complaints of drowsiness/sedation tend to subside with continued therapy or dose reduction. Salivation may be profuse, especially during sleep, but may be diminished with dose reduction.
Incidence in Clinical Trials
The following table enumerates adverse events that occurred at a frequency of 1% or greater among clozapine patients who participated in clinical trials. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence Among Patients Taking Clozapine in Clinical Trials (Excluding the InterSePT™ Study) (N = 842) (Percentage of Patients Reporting)

Body System	
Adverse Event[a]	**Percent**
Central Nervous System	
Drowsiness/Sedation	39
Dizziness/Vertigo	19
Headache	7
Tremor	6
Syncope	6
Disturbed sleep/Nightmares	4
Restlessness	4
Hypokinesia/Akinesia	4
Agitation	4
Seizures (convulsions)	3[b]
Rigidity	3
Akathisia	3
Confusion	3
Fatigue	2
Insomnia	2
Hyperkinesia	1
Weakness	1
Lethargy	1
Ataxia	1
Slurred speech	1
Depression	1
Epileptiform movements/Myoclonic jerks	1
Anxiety	1
Cardiovascular	
Tachycardia	25[b]
Hypotension	9
Hypertension	4
Chest pain/Angina	1
ECG change/Cardiac abnormality	1
Gastrointestinal	
Constipation	14
Nausea	5
Abdominal discomfort/Heartburn	4
Nausea/Vomiting	3
Vomiting	3
Diarrhea	2
Liver test abnormality	1
Anorexia	1
Urogenital	
Urinary abnormalities	2
Incontinence	1
Abnormal ejaculation	1
Urinary urgency/frequency	1
Urinary retention	1
Autonomic Nervous System	
Salivation	31
Sweating	6
Dry mouth	6
Visual disturbances	5
Integumentary (Skin)	
Rash	2
Musculoskeletal	
Muscle weakness	1
Pain (back, neck, legs)	1
Muscle spasm	1
Muscle pain, ache	1
Respiratory	
Throat discomfort	1
Dyspnea, shortness of breath	1
Nasal congestion	1
Hemic/Lymphatic	
Leukopenia/Decreased WBC/Neutropenia	3
Agranulocytosis	1[b]
Eosinophilia	1
Miscellaneous	
Fever	5
Weight gain	4
Tongue numb/sore	1

[a] Events reported by at least 1% of clozapine patients are included.
[b] Rate based on population of approximately 1,700 exposed during premarket clinical evaluation of clozapine.

The following table enumerates adverse events that occurred at a frequency of 10% for either treatment group in patients who took at least 1 dose of study medication during their participation in InterSePT, which was an adequate and well-controlled 2 year study evaluating the efficacy of clozapine relative to olanzapine in reducing the risk of emergent suicidal behavior in patients with schizophrenia or schizoaffective disorder. These rates are not adjusted for duration of exposure.

Treatment-Emergent Adverse Experience Incidence[1] Among Patients Taking Clozapine or Olanzapine in the InterSePT™ Study (Percentage of Patients Reporting)

	Clozapine N = 479 % Reporting	**Olanzapine N = 477 % Reporting**
Adverse Events		
Salivary hypersecretion	48%	6%
Somnolence	46%	25%
Weight increased	31%	56%
Dizziness (excluding vertigo)	27%	12%
Constipation	25%	10%
Insomnia NEC	20%	33%
Nausea	17%	10%
Vomiting NOS	17%	9%
Dyspepsia	14%	8%

[1] AEs are listed by frequency in clozapine group, and included in the table are those for which the risk ratio of clozapine over olanzapine or of olanzapine over clozapine was greater than 1.5.
NEC - not elsewhere classified
NOS - not otherwise specified

Other Events Observed During the Premarketing Evaluation of Clozapine
This section reports additional, less frequent adverse events which occurred among the patients taking clozapine in clinical trials. Various adverse events were reported as part of the total experience in these clinical studies; a causal relationship to clozapine treatment cannot be determined in the absence of appropriate controls in some of the studies. The table above enumerates adverse events that occurred at a frequency of at least 1% of patients treated with clozapine. The list below includes all additional adverse experiences reported as being temporally associated with the use of the drug which occurred at a frequency less than 1%, enumerated by organ system.
Central Nervous System: loss of speech, amentia, tics, poor coordination, delusions/hallucinations, involuntary movement, stuttering, dysarthria, amnesia/memory loss, histrionic movements, libido increase or decrease, paranoia, shakiness, Parkinsonism, and irritability.
Cardiovascular System: edema, palpitations, phlebitis/thrombophlebitis, cyanosis, premature ventricular contraction, bradycardia, and nosebleed.
Gastrointestinal System: abdominal distention, gastroenteritis, rectal bleeding, nervous stomach, abnormal stools, hematemesis, gastric ulcer, bitter taste, and eructation.
Urogenital System: dysmenorrhea, impotence, breast pain/discomfort, and vaginal itch/infection.
Autonomic Nervous System: numbness, polydipsia, hot flashes, dry throat, and mydriasis.
Integumentary (Skin): pruritus, pallor, eczema, erythema, bruise, dermatitis, petechiae, and urticaria.
Musculoskeletal System: twitching and joint pain.
Respiratory System: coughing, pneumonia/pneumonia-like symptoms, rhinorrhea, hyperventilation, wheezing, bronchitis, laryngitis, and sneezing.
Hemic and Lymphatic System: anemia and leukocytosis.
Miscellaneous: chills/chills with fever, malaise, appetite increase, ear disorder, hypothermia, eyelid disorder, bloodshot eyes, and nystagmus.
Postmarketing Clinical Experience
Postmarketing experience has shown an adverse experience profile similar to that presented above. Voluntary reports of adverse events temporally associated with clozapine not mentioned above that have been received since market introduction and that may have no causal relationship with the drug include the following:
Central Nervous System: delirium; EEG abnormal; exacerbation of psychosis; myoclonus; overdose; paresthesia; possible mild cataplexy; and status epilepticus.
Cardiovascular System: atrial or ventricular fibrillation and periorbital edema.
Gastrointestinal System: acute pancreatitis; dysphagia; fecal impaction; intestinal obstruction/paralytic ileus; and salivary gland swelling.
Hepatobiliary System: cholestasis; hepatitis; jaundice.
Hepatic System: cholestasis.
Urogenital System: acute interstitial nephritis and priapism.
Integumentary (Skin): hypersensitivity reactions: photosensitivity, vasculitis, erythema multiforme, and Stevens-Johnson Syndrome.
Metabolic and Nutritional Disorders: hypercholesterolimia (very rare); and hypertriglyceridemia (very rare).
Musculoskeletal System: myasthenic syndrome and rhabdomyolysis.
Respiratory System: aspiration and pleural effusion.
Hemic and Lymphatic System: deep vein thrombosis; elevated hemoglobin/hematocrit; ESR increased; pulmonary embolism; sepsis; thrombocytosis; and thrombocytopenia.
Vision Disorders: narrow angle glaucoma.
Miscellaneous: CPK elevation; hyperglycemia; hyperuricemia; hyponatremia; and weight loss.
DRUG ABUSE AND DEPENDENCE
Physical and psychological dependence have not been reported or observed in patients taking clozapine.
DOSAGE AND ADMINISTRATION
Treatment-Resistant Schizophrenia
Initial Treatment
It is recommended that treatment with clozapine begin with one-half of a 25 mg tablet (12.5 mg) once or twice daily and then be continued with daily dosage increments of 25 to 50 mg/day, if well-tolerated, to achieve a target dose of 300 to 450 mg/day by the end of 2 weeks. Subsequent dosage increments should be made no more than once or twice weekly, in increments not to exceed 100 mg. Cautious titration and a divided dosage schedule are necessary to minimize the risks of hypotension, seizure, and sedation.
In the multicenter study that provides primary support for the effectiveness of clozapine in patients resistant to standard drug treatment for schizophrenia, patients were titrated during the first 2 weeks up to a maximum dose of 500 mg/day, on a t.i.d. basis, and were then dosed in a total daily dose range of 100 to 900 mg/day, on a t.i.d. basis thereafter, with clinical response and adverse effects as guides to correct dosing.

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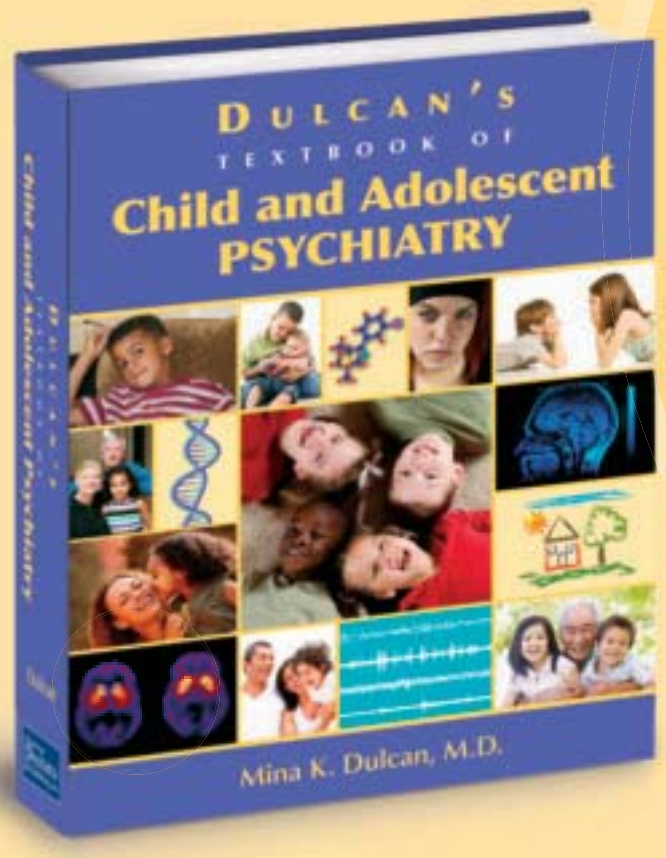

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- Additional chapters address special clinical considerations such as children of ill parents AND legal/ethical issues
- Wide-ranging emphasis on treatment—expanded from seven to eighteen chapters—includes psychopharmacology, brain-based innovative treatments, and a spectrum of psychosocial approaches that focus on individual, family, therapeutic milieu, and systemic models of care.
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Use the many resources of the APA Job Bank at psych.org/jobbank to meet qualified candidates and make a smart recruitment decision. Advertise in the *Psychiatric Services* and/or *Psychiatric News* classifieds and the APA Job Bank and receive a 10% discount on each. For more information, contact Alice Kim at (703) 907-7330 or classads@psych.org

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Candidates and Employers

During the meeting, stop by the APA Job Bank booth in the APA Member Center to search the database and ask a representative to demonstrate Job Bank features. The Institute on Psychiatric Services is the APA's leading educational conference on clinical issues and community mental health—for information, visit psych.org/ips

APA Member Center and Job Bank

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for Neuroscience & Human Behavior

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UCLA's Department of Psychiatry and Biobehavioral Sciences, in conjunction with the Semel Institute for Neuroscience & Human Behavior, seeks a full-time junior level academic Psychiatrist or Clinical Psychologist to provide treatment for children with OCD and their families. The candidate would be expected to collaborate closely with UCLA's Child OCD, Anxiety, and Tic Disorders Program faculty and clinical staff.

The successful candidate will be expected to develop a program of independent research related to developing techniques in working with both children and families of children with OCD. Candidates should have demonstrated ability to acquire extramural research funding. Candidates must be licensed to practice in the state of California. Excellent teaching and mentoring skills are required.

Send curriculum vitae, a statement of research accomplishments and future plans, and the names and complete addresses of three references (do not send letters) via email to: **Child Psychiatry Search Committee Chair, c/o Elizabeth Hiramoto, Psychiatry Academic Personnel Office at ehiramoto@mednet.ucla.edu**

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November 6	October 23
Novemeber 20	November 6

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ARIZONA

University of Arizona

The University of Arizona's **Psychiatry Department** is recruiting adult and child psychiatrists to join a progressive and growing academic department located in the beautiful Southwest. Candidates must have current credentials to practice medicine in the United States and be Board-certified or -eligible in Psychiatry.

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Child Psychiatrist / Assistant or Associate Professor or Professor, Clinical Psychiatry Job # 39689 - Responsibilities include child and adolescent services for outpatient care and in a correction/residential treatment setting. Other duties include providing a significant contribution to the didactic and supervisory component for training programs. Individuals must be Board-certified or -eligible in Child and Adolescent Psychiatry. Salary: DOE

For additional information and/or to apply visit www.uacareertrack.com and reference specific job # from above. If you have questions, please contact: Ashley Lott, Human Resources, Dept. of Psychiatry, 1501 N. Campbell Avenue, P.O. Box 245002, Tucson, AZ 85724-5002; (520) 626-3819; or aelott@email.arizona.edu. Review of applications is ongoing until positions are filled. The University of Arizona is an EEO/AA Employer-M/W/D/V

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CALIFORNIA

Directorship of the UCSD Academic Outpatient Psychiatry Program

The UCSD Department of Psychiatry (http://psychiatry.ucsd.edu) is seeking experienced psychiatric candidates at the Associate or Full Professor level for the Directorship of the Department's primary Outpatient Psychiatry Program. This is a busy clinical program and it is the major site for the training of our PGY3 residents in the diagnosis and treatment of psychiatric outpatients. The clinic is the largest ambulatory psychiatry program in the region, admitting approximately 2,000 patients annually, and has a much deserved reputation for clinical excellence. Candidates must be Board Certified or Eligible, and already have or can qualify for a medical license in the State of California. A strong scientific track record of peer-reviewed grants and publications is necessary. Experience and demonstrated leadership and administrative skills for overseeing psychiatric clinical programs is preferred. Professorial series and rank will be determined by experience. Candidates should submit letters of interest and their CVs to the Search Committee "A", University of California, San Diego, Department of Psychiatry, 9500 Gilman Drive, 0603, La Jolla, CA 92093-0603. Review of applications will begin on October 23, 2009 and will continue until the position is filled. UCSD is an Equal Opportunity/Affirmative Action Employer with a strong institutional commitment to excellence through diversity.

UC DAVIS SCHOOL OF MEDICINE DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

Chief, Addiction Psychiatry Division. The Department of Psychiatry and Behavioral Sciences at the UC Davis School of Medicine is recruiting a ladder rank/in residence Associate Professor or Professor of Psychiatry to develop a new Division of Addiction Psychiatry. The successful candidate will be proposed for an appointment to an endowed professorship in addiction psychiatry which is currently in the process of being established. The candidate will also be proposed for appointment to the Northern California VA Health System to coordinate substance abuse clinical services, research and education at their Sacramento site. The successful candidate should have a record of federally supported research in addiction psychiatry and experience in establishing and growing new research-oriented clinical enterprises. A start-up package will be provided so the candidate may recruit several additional faculty members with experience in addiction psychiatry research. The search committee is chaired by Professor Cameron Carter, Chief of the department's schizophrenia research program and Director of the medical center's Imaging Research Center. The successful candidate should be board certified in general psychiatry, and be in possession of, or eligible for, a California Medical license.

For full consideration, applications must be received by December 31, 2009. Position is open until filled, but no later than December 31, 2009. Interested candidates should email a curriculum vitae and letter of interest in response to Position #PY-05R-09 to Juli Koeberlein at juli.koeberlein@ucdmc.ucdavis.edu and contact Professor Carter at cameron.carter@ucdmc.ucdavis.edu for more information. In conformance with applicable law and University policy, the University of California, Davis, is an equal opportunity/affirmative action employer.

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CHILD PSYCHIATRIST TEACHING ATTENDING. The University of California, Davis, Department of Psychiatry and Behavioral Sciences is recruiting a Health Sciences Assistant/Associate Clinical Professor for the Child Psychiatry Division. The position is in the clinician/teaching academic series. The individual will provide outpatient psychiatry services and teaching at the Child and Adolescent Psychiatry Clinic operated by the County of Sacramento. The clinic serves as a teaching site for general psychiatry residents, child psychiatry residents, postdoctoral psychology fellows and medical students. The successful candidate should be licensed or license eligible in the State of California and board eligible or certified in general psychiatry and child and adolescent psychiatry, and have an interest in psychiatric education and training. The successful candidate will lecture in seminars and case conferences, and provide group and individual supervision of clinical cases. The candidate will also provide clinical teaching for child and general psychiatry residents, psychology fellows, medical students and other mental health professionals including timely and appropriate evaluation of trainee performance.

For full consideration, applications must be received by December 31, 2009. Position is open until filled but not later than March 31, 2010. Interested candidates should email a curriculum vitae and letter of interest in response to Position #PY-01R-10 to Juli Koeberlein at juli.koeberlein@ucdmc.ucdavis.edu. In conformance with applicable law and University policy, the University of California, Davis, is an equal opportunity/affirmative action employer.

http://www.ucdmc.ucdavis.edu/psychiatry/

UC DAVIS SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

Health Sciences Assistant/Associate Clinical Professor. The University of California, Davis, Department of Psychiatry and Behavioral Sciences is recruiting for a Health Sciences Assistant/Associate Clinical Professor in the clinician/teaching series to serve as a teaching attending on the Psychosomatic Medicine Service located at the UC Davis Medical Center in Sacramento. The Unit is staffed with three UC Davis faculty, general psychiatry residents, and UC Davis medical students. Experience in teaching and supervision of medical students, residents, and other mental health professionals is highly desirable. The successful candidate should be board eligible or certified in general psychiatry, be in possession of, or eligible for, a California Medical license, and have an interest in psychiatric education and training. Completion of a fellowship in Psychosomatic Medicine is highly desirable but not required. The successful candidate will lecture in seminars and case conferences, and provide group and individual supervision of clinical cases. The candidate will also provide clinical teaching for general psychiatry residents, psychology fellows, medical students and other mental health professionals including timely and appropriate evaluation of trainee performance.

For full consideration, applications must be received by November 30, 2009. Position is open until filled, but no later than February 28, 2010. Interested candidates should email a curriculum vitae and letter of interest in response to Position #PY-07R-09 to Juli Koeberlein at juli.koeberlein@ucdmc.ucdavis.edu. In conformance with applicable law and University policy, the University of California, Davis, is an equal opportunity/affirmative action employer.

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CALIFORNIA
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Patton State Hospital is recruiting board certified/eligible psychiatrists. Patton is a Joint Commission accredited, 1500 bed, adult forensic psychiatric hospital, with an extremely interesting and challenging patient population. The hospital is nestled below Arrowhead and the San Bernardino Mountains, 65 miles east of Los Angeles; an hour's drive to beaches, Palm Springs, or mountain lakes and skiing. Salary with Board Certification starts at **$18,622 and goes to $21,311 monthly.** Salary for Board Eligible starts at **$18,146 and goes to $20,711 monthly.** In addition, Patton offers excellent benefits (health, dental, and vision; license renewal; malpractice insurance; tax-deferred compensation; paid annual leave and 12 holidays (plus one personal holiday), as well as seven days per fiscal year of Continuing Medical Education leave). Voluntary on call duty is compensated on an hourly basis over and above base salary. We provide civil service security and retirement plans (including safety retirement). For confidential consideration, send CV to George Christison, M.D., (A) Medical Director, 3102 East Highland Avenue, Patton, California 92369, (909) 425-7326 or Fax (909) 425-6635.

UC DAVIS SCHOOL OF MEDICINE
DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES

Health Sciences Assistant/Associate Clinical Professor - APSS Clinic. The University of California, Davis, Department of Psychiatry and Behavioral Sciences is recruiting for a Health Sciences Assistant/Associate Clinical Professor in the clinician/teaching series to serve as teaching attending at the Adult Psychiatry Support Services Clinic located next to the UC Davis Medical Center in Sacramento. The Clinic is staffed with four UC Davis faculty, two general psychiatry residents, and two medical students. Experience in teaching and supervision of medical students, residents, and other mental health professional is highly desirable. The successful candidate should be board eligible or certified in general psychiatry, be in possession of or eligible for a California Medical license, and have an interest in psychiatric education and training. The successful candidate will lecture in seminars and case conferences, and provide group and individual supervision of clinical cases. The incumbent will provide clinical teaching for general psychiatry residents, psychology fellows, medical students and other mental health professionals including timely and appropriate evaluation of trainee performance.

For full consideration, applications must be received by November 30, 2009. Position is open until filled, but no later than February 28, 2010. Interested candidates should email a curriculum vitae and letter of interest in response to Position #PY-06R-09 to juli.koeberlein@ucdmc.ucdavis.edu. In conformance with applicable law and University policy, the University of California, Davis, is an equal opportunity/affirmative action employer.

http://www.ucdmc.ucdavis.edu/psychiatry/

Karl E. Douyon, M.D., Inc.
Psychiatrists are needed as independent contractors for Locum Tenens positions in California. Pay is $175 per hour depending on location. On call pay is extra. Hours are flexible for weekdays and some weekends. Call 805-644-4093. Fax resumes to 805-830-6300. karledouyonmd.com

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CAREERS AS WIDE OPEN AS THE HORIZON
In Riverside County, the future is bright.

New Salaries Announced
"The Best Psychiatrist Opportunities in California"

The County of Riverside in beautiful Southern California is seeking general adult and sub-specialty trained psychiatrists to serve the growing needs of clients in our County-operated public mental health system.

We offer **excellent compensation** for psychiatrists through regular employment (up to: $225,630, non-Bd.C.; $238,364 Bd.C.; $250,722, Mult.Bd.C.) with a **great benefit package, including County payment of employee retirement contributions** to the Public Employee Retirement System (PERS) equal to 8% of salary with retirement formula 3%@ age 60, with **generous annual leave and CME leave.** We provide additional compensation for inpatient and jail services.

Psychiatrists are especially needed for Riverside County Regional Medical Center (RCRMC) - Emergency Treatment Services (ETS) and Inpatient Treatment Facility (ITF). Additional outpatient psychiatrist hours are needed for Mid-County clinics and clinics in the Palm Springs/Indio area. A current California license required.

Join our team of competent, committed, and caring medical staff. **Come to Southern California** to live and work in our ideal climate within close proximity to our beaches, mountains, forests and the greater L.A. metropolitan area's vast array of cultural, educational, sporting and recreation opportunities, plus some of the most affordable housing in California.

If you are interested in discussing any of our psychiatric positions, please contact Jerry L. Dennis, MD, Medical Director (Ph: 951-358-4621), and send your CV to Tiffany Mott by E-mail to tmott@rc-hr.com

Riverside County....Beyond Your Expectations

COLORADO

BOULDER: General or Child Psychiatrist. Staff and Admin/Clinical positions. Inpatient & Partial programs. Fulltime positions offering salary, benefits and incentive plan. Newly acquired UHS hospital. Contact: Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

CONNECTICUT

Full time psychiatrist, inpatient or outpatient service. Dept of Psychiatry at outstanding community hospital in central CT. Experienced, collegial, professional, multidisciplinary team. Reasonable call, competitive salary & benefits. Respond in confidence to Robert Grillo MD, Chairman Dept Psychiatry Middlesex Hospital robert_grillo_md@midhosp.org

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INPATIENT ADULT PSYCHIATRIST-CENTRAL CT
FT/PT opportunity for BC/BE adult psychiatrist in 16-bed inpatient service with a community hospital offering a comprehensive mental health continuum. Enjoy working with an established team bringing a multidisciplinary approach to patient care. Crisis Center located in emergency department. This position offers a competitive salary and benefits and adaptable hours for the right individual. Call 1:5.

The practice is located in a family-oriented city located approximately two hours from NYC and Boston and 20 minutes to the capitol city of Hartford. Enjoy the charm of four seasons with a choice of attractive communities with Connecticut's best rated schools, shopping, award-winning restaurants, and regional theatre and easy access to skiing and the coast.

For more information about this opportunity, please contact Carolyn Doughtie of Physician Recruitment at 800.892.3846 or fax/email your CV to 860.585.3133. EOE

Email address: cdoughti@bristolhospital.org

CONSULTATION-LIAISON PSYCHIATRIST

The Yale University School of Medicine, Department of Psychiatry, is seeking a full time consultation liaison psychiatrist. Candidates must be licensed (or license eligible) to practice in the state of Connecticut, eligible for medical staff privileges at Yale-New Haven Hospital, and board eligible in psychiatry. Added qualifications in psychosomatic medicine highly desirable. This is an exciting academic opportunity in a behavioral medicine program involving both outpatient and inpatient work, with opportunities for teaching and research. The position carries academic appointment commensurate with experience.

Available fall, 2009. To apply please contact Paul Desan, MD, PhD, 20 York St CB2039, New Haven, CT 06504, paul.desan@yale.edu. Yale University is an affirmative action, equal opportunity employer. Applications from women and minority group members are encouraged.

DELAWARE

WILMINGTON / NEWARK & DOVER: Child Psychiatrist. Inpatient/partial programs. Very competitive salary, benefits & incentive plans. Will sponsor visa candidates. Contact Joy Lankswert @ 866-227-5415; OR email joy.lankswert@uhsinc.com

DISTRICT OF COLUMBIA

Washington, DC
George Washington University Medical Center

Founded in 1977, this ACGME-accredited fellowship in Psychosomatic Medicine is currently accepting applications for three PGY-V positions starting July 1, 2010. Under the guidance of **Thomas N. Wise, M.D.** and **Catherine C. Crone, M.D.,** the fellowship offers training in both inpatient and outpatient settings at a large tertiary care teaching facility that provides care to a diverse socioeconomic and cross-cultural patient population. This includes extensive experience in oncology, Ob-Gyn, HIV, pulmonary, cardiology, and organ transplantation. Emphasis is placed on a balance of clinical experience and didactic teaching addressing the biopsychosocial approach to understanding the medically ill patient. The experience is enhanced further by constant mentoring throughout the academic year along with efforts to tailor the training experience according to the individual fellow's interests and career goals. Opportunities in teaching, research, and outpatient psychotherapy are readily available and strongly encouraged. The program is based at Inova Fairfax Hospital, an 833-bed hospital located near Washington, D.C.

Interested individuals should contact
Catherine C. Crone MD, Fellowship Director
George Washington University Medical Center
c/o Inova Fairfax Hospital
3300 Gallows Rd, Falls Church, VA 22042
(703) 776-3380 Fax: (703) 776-3029
cathy.crone@inova.org

FLORIDA

DAYTONA - MELBOURNE - ORLANDO - MIAMI - FORT LAUDERDALE - PALM BEACH - OCALA - GAINESVILLE - FORT MYERS - SARASOTA - PENSECOLA - JACKSONVILLE - Psychiatrists needed for rapidly expanding Nursing Home Service. Great support. No call. Average Salary 210K + benefits. Part-time available. Some travel required. Must have FL Medicare & FL Medicaid individual provider #s. No Restrictions (H1B Candidates Considered). Call our administrator, Christy, at 866-936-5250.

PSYCHIATRISTS - Full-Time, Tampa Bay area in Florida. For over three decades BayCare Behavioral Health has continually developed, improved and adapted treatment, rehabilitation and support services to best suit the changing behavioral health needs in the communities we serve. Qualified candidates must have State of Florida Medical License, DEA and 3 years psych experience. Board certified preferred. Apply at www.BayCareJobs.com or call 727-816-9853 x229. EOE, DFWP

GEORGIA

ATLANTA: General, Geriatric & Child Psychiatrists - Inpatient & partial programs. Medical Director and Staff positions. Fulltime offering salary, benefits & bonus plans. Weekend moonlighting also available for day shifts only at several UHS hospitals - no overnight call. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

FLOYD Behavioral Health Center

Hospitalist Psychiatrist position and an Office-Based position with a dynamic and expanding 53-bed, adult behavioral health enter. Programs include adult psychiatry, chemical dependency and geriatrics, and all patients are admitted on a voluntary basis.

Nestled in the foothills of northwestern Georgia, Rome is surrounded by seven hills and the Coosa, Etowah and Oostanaula Rivers. Rome is a unique small city that has been recognized as the "Number One Small City in the Southeast" and is an hour from Atlanta as well as Chattanooga. Rome boasts a flourishing health care community with more than 350 practicing physicians. Our area enjoys a mild climate and offers quality educational and cultural opportunities.

Floyd offers a competitive salary with great benefits and bonus opportunities. This position is available for J-1 Visa candidates and the qualified candidate will be joining a successful, experienced psychiatric physician already practicing in this role. Outstanding compensation includes full benefits and relocation for the right executive. For confidential consideration, please apply online at www.floyd.org. For more information email Cami Legacy (clegacy@floyd.org) or call 706.509.3964.

KENTUCKY

Radcliff - easy commute from LOUISVILLE: Child or General Psychiatrist for inpatient & outpatient services. Highly competitive salary, benefits, & bonus. Will sponsor visa candidates. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

LOUISIANA

The Department of Psychiatry and Neurology at Tulane University School of Medicine is recruiting a geriatric psychiatrist for a full-time faculty position. The candidate will spend part of their time at the Southeast Louisiana Veterans Health Care System (SLVHCS) and will also be involved in the new initiatives in both clinical geriatric care and special geriatric education programs at Tulane. Responsibilities include patient care as well as contributing to the various teaching and training programs of Tulane University's Department of Psychiatry and Neurology at the SLVHCS. He/she will be provided the opportunity to pursue their research interests. The person selected for this position must be professionally competent and be board eligible/certified in general psychiatry and in geriatric psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Salary will be competitive and commensurate with the level of the candidate's academic appointment. Applications will be accepted until a suitable qualified candidate is found. Applicants should send letter of interest, updated CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1440 Canal Street TB48, New Orleans, LA 70112. Interested and eligible candidates may obtain further information by contacting Daniel K. Winstead, MD at 504-988-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admissions and in employment.

BC/BE Psychiatrist

OCHSNER ST. ANNE GENERAL HOSPITAL is seeking:

- A BC/BE Psychiatrist for an employed position in Raceland, Louisiana
- Located 40 miles from New Orleans with a population of approximately 40,000
- Not-for-profit critical access hospital providing inpatient & outpatient services with high quality, cost-effective emergency, medical & surgical care
- Part of nationally renowned health system of 7 hospitals, 700+ member physician group, and 35 health centers
- Very competitive salary and benefits
- Family-oriented community with year-round outdoor activities
- Favorable malpractice environment in Louisiana
- Ochsner Health System is an equal opportunity employer.

Please email CVs to: profrecruiting@ochsner.org or call (800) 488-2240. Ref# APSTA09. EOE.

CHILD PSYCHIATRISTS - DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for BE/BC child psychiatrists at the instructor or assistant professor level, salary commensurate with experience. Clinical responsibilities available in the areas of inpatient psychiatry, community based child and adolescent psychiatry, and early childhood mental health. Teaching responsibilities include the supervision of residents, clinical psychology fellows and interns, and medical students rotating through the clinical facilities serviced by this position as well as the presentation of grand rounds and participation in the didactic series in child psychiatry. Clinical research is strongly encouraged. The persons selected must be professionally competent and be board eligible/certified in general psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until a suitable qualified candidate is found. Send CV and list of professional/academic references to Charley Zeanah, Jr, MD, Professor and Vice Chair, Child and Adolescent Psychiatry, Tulane University School of Medicine, Department of Psychiatry and Neurology, 1440 Canal Street TB52, New Orleans, LA 70112 (czeanah@tulane.edu). Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for several general and forensic psychiatrists (clinical track) for our growing department, at the Assistant/Associate Professor level. Candidates must have completed an approved general psychiatry residency and be board certified/eligible in general psychiatry and forensic psychiatry, respectively. Responsibilities will include direct patient care, teaching of medical students and house officers, and research (clinical and basic science) at various state hospitals, state correctional institutions, and at Tulane University Health Sciences Center. Time allocations will be based upon individual situations. Applicants must be eligible to obtain a Louisiana medical license. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until suitable qualified candidates are found. Send CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1440 Canal Street TB48, New Orleans, LA 70112. For further information, you may contact Dr. Winstead, at 504-988-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

The Southeast Louisiana Veterans Health Care System (SLVHCS), formerly the New Orleans Veterans Affairs Medical Center and the Department of Psychiatry and Neurology at Tulane University School of Medicine seek a candidate to fill the position of Chief, Mental Health Service at SLVHCS. All candidates will have clinical, administrative, teaching and research responsibilities and must be board eligible/certified and have academic credentials to be qualified for a faculty appointment at Tulane University School of Medicine

Applicants should have both clinical and administrative experience, and may be psychiatrists, psychologists, nurses, or social workers. A doctoral degree is required. Applicants must possess a knowledge and understanding of health care policies, missions, and operating programs, and be knowledgeable about mental health care delivery and about mental health information management. He/she will be involved in the design of the Mental Health areas of the new VA hospital planned for Southeast Louisiana. United States citizenship or permanent residency is required. Salary and academic rank will be commensurate with qualifications and experience of the applicant.

We will continue to accept applications until a suitable qualified candidate is found. Interested applicants should mail a curriculum vitae with a list of 7 references to Daniel K. Winstead MD, Tulane Dept. of Psychiatry and Neurology, 1440 Canal Street TB48, New Orleans, LA 70112 or e-mail CV and references to winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admissions and in employment.

MAINE

Adult and Child/Adolescent Psychiatrists
Nation's 1st Psychiatric Magnet Hospital seeking BC/BE psychiatrists for both our adult and child/adolescent inpatient and outpatient programs. We are a thriving, non-profit, private community-based hospital offering acute psychiatric care for adults and children, as well as chemical dependency programs. One of only two private psychiatric hospitals in Maine. We offer physicians clinical practice in a highly collaborative, multi-disciplinary setting. Competitive salary/benefit package. Send CV to: VP of Medical Affairs, The Acadia Hospital, P.O. Box 422, Bangor, ME 04402-0422.
www.acadiahospital.org

Adult IP Psychiatrist - Scenic Central Maine
MaineGeneral Medical Center in Augusta/Waterville, Maine is seeking a BC/BE adult psychiatrist with interests in inpatient psychiatry or outpatient psychiatry/substance abuse. You will be joining a staff of six employed physicians who provide multidisciplinary inpatient, outpatient, and consultative services. We have a 30-bed inpatient program at our Thayer Campus in Waterville, five Intensive Outpatient Programs in Waterville and Augusta, an ACT Team, and an outpatient program providing psychiatric and substance abuse treatment. We also provide consultative support for our inpatient medical and surgical services. We offer excellent benefits including relocation assistance and competitive salary. MaineGeneral is located in scenic central Maine and is a short drive away from ski resorts, lakes and rivers, award-winning golf courses, abundant hiking trails, and the beautiful Maine coast. We are just an hour north of Portland, Maine's largest city, and three hours from Boston. Send your CV to Lisa Nutter, Physician Recruiter at lisa.nutter@mainegeneral.org or call 1-800-344-6662. For more information, visit www.mainegeneral.org.

MARYLAND

Springfield Hospital Center is seeking Board-certified or Board-eligible **general psychiatrists** for our 350-bed MHA adult inpatient facility. Salary is negotiable, within MHA guidelines. Our rural, tobacco-free campus is 22 miles west of Baltimore, convenient to the Chesapeake Bay, Washington, and a variety of cultural, historic, sports, and recreational venues. Benefits include 27 paid days off in the first year, subsidized health insurance, free parking, a generous retirement program, and a truly pleasant workplace. A Medical Services physician is always on campus to attend to patients' somatic needs. Staff psychiatrists are not expected to work after hours, but some choose to supplement their salary by providing evening and weekend/holiday coverage under contract. In addition, we offer after-hours coverage contracts to psychiatrists who are not full-time staff members. Please send CV to **Jonathan Book, M.D., Clinical Director, SHC, 6655 Sykesville Road, Sykesville, MD 21784. For questions, call (410)970-7006 or e-mail JBook@dhmh.state.md.us.** EOE

MASSACHUSETTS

Faculty Position, Department of Psychiatry
Beth Israel Deaconess Medical Center
Harvard Medical School

The Department of Psychiatry at Beth Israel Deaconess Medical Center (BIDMC), a major teaching hospital of Harvard Medical School, is seeking an exceptionally qualified candidate for the position of DIRECTOR OF PSYCHOPHARMACOLOGY. This full-time faculty position involves half-time commitment to the Department's Clinical Psychopharmacology Service. Responsibilities include clinical consultation, supervision of psychiatric residents, and service delivery in the Psychiatry Ambulatory Service, as well as clinical consultation in the Inpatient Unit. The appointee will be expected to play a leadership role in the Department's clinical, academic and educational programs, including the Harvard Longwood Psychiatry Residency Training Program. The position also provides 50% time for clinically oriented research in psychopharmacology. Departmental start?up funds commensurate with experience and scope will be available to assist with development of an externally funded research program in psychopharmacology. Applicants should have at least two years of specialized clinical and research experience in psychopharmacology. Additional requirements include Board Certification in Psychiatry and eligibility for licensure in Massachusetts. Applicants should send a statement of interest and experience, curriculum vitae, and the names, addresses, phone numbers, and e-mail addresses of three references to: David C. Jimerson, M.D., Chair, Psychopharmacology Search Committee, Dept. of Psychiatry, BIDMC, 330 Brookline Ave., Boston, MA 02215. E-mail: psychopharm.search@bidmc. harvard.edu Correspondence by e-mail is preferred. Women and underrepresented minorities are strongly encouraged to apply. A Harvard Medical School appointment at an appropriate rank is available.

MARLBOROUGH, MASSACHUSETTS - UMass Department of Psychiatry is seeking candidates for a full time psychiatrist at its affiliated general hospital in Marlborough, Massachusetts. The position primarily involves providing treatment and clinical care supervision on the unit's superb partial hospital program and some amount of inpatient coverage. Our Department of Psychiatry has a large clinical faculty with clinical, teaching and academic opportunities at a wide variety of inpatient and outpatient programs. We have faculty development programs, commitment to our care, training and research missions, and a great living and learning environment in Central Massachusetts. If you want to know more about job opportunities or the department in general, please email psychiatryrecruitment@umassmemorial.org or fax to 508-856-5990. AA/EOE

Starr Psychiatric Center seeks a 20-30 hr psychiatrist for dynamic established psychiatric practice On Boston's South Shore. Medical model, multi-disciplinary staff. Stimulating environment, good pay. Clinic has a reputation for successful care, where others have failed. Email davidzstarr@juno.com or call 508.580.2211.

High Point Treatment Center is seeking a 40 hr week psychiatrist to allocate 20 hrs managing 8-beds Inpatient Psychiatric Unit and 20 hrs allocated to outpatient services located in Plymouth, MA. Salary ranging from $170,000 - $190,000. No weekends, paid holidays and leave time. Health benefits available. If willing to work an additional 1 hr per day salary range would be $200,000 - $215,000. If interested, please contact Jim Horvath at 508-503-2455 or email to jim.horvath@hptc.org.

BOSTON areas - Brookline, Jamaica Plain, Pembroke, Lowell and Westwood: Child & General Psychiatrists. Inpatient/partial programs. Staff & Medical Director Positions depending on location. Very competitive salaries, benefits & incentive plans. **NO CALL.** Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com

MICHIGAN

Medical Director - An Easy Income of $220k to $240k (Or More) - No long workdays necessary to make a great income. Seeking Psychiatrist for clinical and part-time administrative responsibilities on Psychiatric Services in a hospital in Saginaw, MI. Adult and C/A psychiatric services. Salary w/benefits is also an option. Very close to Bay City on Lake Huron and Flint. Only an hour and a half to Detroit and Ann Arbor. Please call **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

GRAND RAPIDS - Staff Psychiatrist. Inpatient and Outpatient practice position. Collegial clinical care & work environment. Very competitive salary & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

MISSISSIPPI

North Central Mississippi, just one hour south of **Memphis, TN.** Medical Director/Associate Medical Director opportunities available for 15-bed Adult and 22-bed Geriatric inpatient units, in addition to a 23-bed Chemical Dependency Program. Excellent income potential and practice opportunity. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

MISSOURI

Seeking Adult, Child and Adolescent Psychiatrist for Community Mental Health Center in Southeast Missouri.

Family Counseling Center (FCC) is an innovative behavioral health center providing comprehensive psychiatric and addiction treatment services in Southeast Missouri. FCC is a leader in rural mental health services providing a continuum of services and social supports for clients with psychiatric needs. FCC is widely recognized for its innovative approach resulting in numerous grants and recognition at local, state and federal levels.

A professional, technologically advancing environment of collegiality with other trained psychiatrists along with a superb team of therapists, social workers and case managers awaits potential applicants. Family Counseling Center meets the requirements of underserved populations and J1 applications are welcome.

Qualifications/Responsibilities: Board eligible/certified with license in Missouri required with commitment to community-based psychiatry. Job responsibilities involve primarily outpatient psychiatry with limited and scheduled inpatient and telepsychiatry duties. The psychiatrist may work a 4 day, 10 hour schedule if desired. The compensation package allows for potential income of up to $220,000 annually with additional fringe benefits. Employer paid malpractice insurance, health insurance, retirement plan, and three weeks annual vacation and one week annual CME will be provided in addition to income potential.

The location is Kennett, Missouri, a small town located near interstate 55 to access Memphis and Jackson Tennessee; Jonesboro, Arkansas and Arkansas State University; and Cape Girardeau and Southeast Missouri State University in approximately 1.5 hours or less. Kennett is the hometown of internationally acclaimed entertainer Sheryl Crow and provides a safe, friendly place for families to live.

We will be attending APA conference. Please call Dr. Ravdeep Khanuja, Medical Director at 573-776-4465 if interested to setup a time to meet.

KANSAS CITY - Staff and potential Admin/Clinical positions. General and specialty inpatient and partial programs. Fulltime position s offering salary, benefits and incentive plan. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

MONTANA

Rocky Mountain Paradise! Consider an exciting new practice opportunity for two NEW distinct **Adult** and **Geriatric** Inpatient Psychiatric Units, comprised of **26** total beds in **Helena, MT.** Nestled beneath the foothills of the Montana Rockies, **Helena,** the Capital of Montana, is alive with history and culture. This charming and beautiful Victorian city of 70,000 people provides a diverse attraction with many street festivals, theater, museums, symphonies, fairs and rodeos. There is truly something for everyone here! Excellent practice opportunity with great income ($200K+) and unparalleled quality of life! For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

NEVADA

The University of Nevada School of Medicine Department of Psychiatry is seeking qualified candidates for Associate/Full Professor, Chairperson, Department of Psychiatry, Statewide. The successful candidate will have a strong academic and administrative background in medical education, excellence in teaching medical students and residents in an ACGME accredited residency or medical school. M.D. or equivalent and board certified in Psychiatry are required. For more information, please contact Search Coordinator, Michelle Hogan at 702-671-2384 or mhogan@medicine.nevada.edu. To apply, please visit https://consensus.medicine.nevada.edu. EEO/AA. Women and underrepresented groups are encouraged to apply.

NEW HAMPSHIRE

Staff Psychiatrist in New England - Package of 180K-210K - Rich Benefits and 15K in Tax Savings. Inpatient focused responsibilities based at Concord Hospital in Concord, NH. Require ECT training/experience. Interest in TMS is desired. Option to participate in clinical teaching. EMR. One hour to Boston, the White Mountains, or the Atlantic Coast. No state income tax or sales tax. **Germaine Lorbert at 800-678-7858, x63704 or glorbert@cejkasearch.com; www.cejkasearch.com.** ID#133805PY.

NEW JERSEY

Psychiatrist - Adult/Child - Immediate Opening Full/Part Time. Work independently in Brand New Facility, all support services included.
Beautiful location and office. Fax CV to Denise Hunt @732701-8418 or email: dhunt@bridgementalhealth.com

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CHILD & ADOLESCENT PSYCHIATRIST/GENERAL ADULT PSYCHIATRIST

Child psychiatrist and General Adult Psychiatrist to join unique, private, fee for service, child, adolescent & adult therapy Center in New Jersey. Center provides wide array of services, provides high quality care, is successful and continues to grow. Locations in Cedar Knolls, Westfield, Ridgewood and Princeton. Openings currently available in each location. Compensation is generous. Hours are flexible. Collegial atmosphere is quite pleasant. E-mail CV to abbazn@aol.com.

Westampton Township - Just East of Philadelphia. Addiction Psychiatrist or General Psychiatrist with interest in dual diagnoses. Very competitive compensation and benefits. No on site weekend call required. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

NEW YORK CITY & AREA

BC/BE Psychiatrists to provide Consultation-Liaison services in Long Term Care settings (NH, SNF).
Facilities Located in NYC Metro area, Long Island and Westchester, Putnam, Dutchess, Rockland, Orange and Ulster Counties.
Priority positions for: Staten Island, Duchess and Orange Counties.
PT/FT Well above average salaries/benefits, flexible hours.
Recent graduates encouraged to apply.

Please contact: Carlos Rueda, M.D. at Tel: 718-239-0030 or via fax: 718-239-0032 E-mail: crueda@neuropsychllp.com

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Premier HealthCare

BC/BE Psychiatrists
Child/Adolescent

Throggs Neck, Bronx or
Sheepshead Bay, Brooklyn
1-2 Days (Mon-Fri)

Astoria, Queens
Saturdays

YAI/Premier HealthCare is a nationally recognized, well-established NYC diagnostic & treatment center for people with developmental disabilities and their families.

This is an opportunity to work with a professional staff of doctors and nurses in a multi-cultural, team environment. Growing field for learning. Send CV to: Karen Meyers, Clinical Recruiter, Premier HealthCare, 460 West 34 Street, N.Y., N.Y. 10001 Fax 212-563-4836. Email: kmeyers@yai.org . EOE.

On Call Psychiatrists: Psychiatrists, Fellows and Senior Residents to cover days, nights, weekends and Holidays in the Psychiatric Emergency Department at the Long Island College Hospital. Please fax resume to: THE LONG ISLAND COLLEGE HOSPITAL, DEPARTMENT OF PSYCHIATRY, 339 Hicks Street, FAX: (718) 780-1827 Attn: Judith Velez or call 718-780-1065.

PSYCHIATRISTS

Lutheran Medical Center and Lutheran Family Health Center in Southwest Brooklyn, offering a continuum of community-oriented behavioral health services within the Department of Psychiatry, have openings available for the following:

AMBULATORY CLINIC - F/T - ADDICTION & ADULT PSYCHIATRISTS - Tailored for psychiatrists with expertise in psychopharmacology, but also multidisciplinary team participation, where therapists prepare treatment plans. We welcome interests in teaching, geriatrics, HIV populations, and/or Clozaril, among others. Our Ambulatory team offers treatment in facilities that have a federal HPSA (Health Profession Shortage Area) designation for loan repayment purposes, a financial plus. Bilingual English/Spanish, Chinese or Arabic is considered a premium.

INPATIENT/ED MOONLIGHTING PSYCHIATRISTS - Rare blocks of weekly Moonlighting shifts available (Weeknights, Weekends and Holidays) for NYS-licensed Psychiatrists to cover ED/CL/Detox Services and/or Adult Psych Unit. Includes payment of Part-Time malpractice insurance premiums if contracting for blocks of shifts. Ideal setting for Fellows, part-time & pvt practice Psychiatrists to stabilize income in a physician-friendly setting!

Please fax 718-630-8594, email: tirvin@lmcmc.com or send resume/CV to: Tracey Irvin, Dept. of Psychiatry, Lutheran HealthCare, Suite 2-45, 150 55th Street, Brooklyn, NY 11220. EOE/AA M/F/D/V

LUTHERAN HEALTHCARE
www.LutheranHealthCare.com

Outpatient Psychiatrists

The Department of Psychiatry at The Mount Sinai Medical Center in Manhattan has an opening for a General Adult Psychiatrist. The FT/PT position includes outpatient work at the World Trade Center Mental Health Program with opportunities for teaching and clinical research. The position will include an academic appointment commensurate with experience. Qualified candidates will possess an MD or DO degree, be board eligible or certified in General Adult Psychiatry and preferably have additional experience in treating mood and anxiety disorders. Spanish and/or Polish speaking physicians are strongly encouraged to apply. The Mount Sinai Medical Center is a premier 1,171 bed tertiary-care facility internationally acclaimed for excellence in clinical care, education and scientific research in nearly every aspect of medicine.

Interested applicants should contact Fatih Ozbay, MD, Associate Medical Director of the WTC Mental Health Program at (212) 241 8462 or email fatih.ozbay@mssm.edu

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Child and Adolescent Psychiatrist
P/T - 10-15 hours per week (evenings and/or weekends) in a Child and Family Mental Health Center in Brooklyn. Excellent compensation. No call. Fax resume to (718) 553-6769, or email to clinicaldirector@nypcc.org

NEW YORK STATE

St. Lawrence Psychiatric Center, a fully accredited NYS Office of Mental Health facility, seeks licensed psychiatrists to work in an outpatient clinic setting. Applicants (licensed or license-eligible in NY) interested in adult, children/youth, and sex offender inpatient opportunities are also encouraged to apply. In addition to salary ($161,750 to $174,198) and guaranteed additional compensation for voluntary participation in an on-call program, benefits package includes medical/dental/vision insurance, paid vacation, holiday and sick time, an excellent retirement plan, and educational and professional leaves. SLPC is an EO/AAE, federally designated as MHPSA.

Located on the scenic St. Lawrence Seaway in northern New York, St. Lawrence Psychiatric Center is located within reasonable driving distance of many cultural, educational and economic opportunities, including metropolitan Ottawa and Montreal, Canada, and Syracuse, NY. Close proximity to the Adirondack Mountains and Canada offers easy access to a wide variety of unspoiled natural areas and provides abundant recreational opportunities throughout the year.

Submit letter of interest to: Rosella Turnbull, St. Lawrence Psychiatric Center, One Chimney Point Drive, Ogdensburg, NY 13669 or at slmrrmt@omh.state.ny.us. If you have questions, please call (315) 541-2189.

ELMIRA PSYCHIATRIC CENTER
Adult and Adolescent Psychiatrists

Board Certified - $172,269 - $176,903
Licensed Physician - $141,751
Limited Permit - $107, 318 - $115,905

- All positions **M-F 8-4:30** with **no managed care insurance demands**
- **Optional** participation in a low stress on-call program with **potential** to earn up to an **extra $74,000/year**
- Student loan repayment available
- Excellent NYS benefits package
- Inpatient, Outpatient and Day Treatment services
- Our location offers: quality housing prices; little traffic; regional airport; Cornell University; 4hr drive to NYC, Toronto & Philadelphia; 5 ½ hr drive to Boston & DC; less than 1hr to Finger Lakes

For further info contact: Patricia Santulli, Director of Human Resources at: Elmira Psychiatric Center, 100 Washington Street, Elmira, NY 14901 or
e-mail: elpopms@omh.state.ny.us or
call: (607) 737-4726 or fax: (607) 737-4722
An AA//EOE Employer

Ulster County Mental Health, an outpatient clinic with a wide range of services, has a potential opening for Staff Psychiatrist. Position requires a recovery-oriented board certified or board-eligible community psychiatrist to treat adult patients. AOT interest is a bonus. UCMH is located in the beautiful Hudson Valley, two hours north of NYC. Competitive salary, on-site psychopharmacology supervision and collegial atmosphere. No on-call or weekends. Hours and benefits to be determined. FAX CV to JuLita Adamczak, MD, Medical Director, FAX #845-340-4094.

Western New York-Chautauqua Region: Jamestown Psychiatric PC is seeking a Psychiatrist to join our rapidly growing Adult and Child Psychiatric team. Competitive salary and flexible growth opportunities are offered. We will offer a starting bonus to eligible candidates. Loan repayment, J1 or H1 assistance available. Please contact Mrs. Linda Jones, office manager @ lj@psychwebmd.com or Phone 716-483-2603. Fax CV and qualifications to 716-483-2828.

PENNSYLVANIA

Psychiatrists:

Currently we have exciting full- and part-time positions in a rapidly expanding department. Opportunities include responsibilities in and outside our five-hospital health system. There are immediate openings for child/adolescent, adult and addictions psychiatrists.

There are also practice options in a traditional psychotherapy model. Evening and weekend positions also available. Excellent salaries, no on-call nor rounding responsibilities ever and exceptional benefits package offered. Send CV to Kevin Caputo, M.D., Vice President and Chairman, Department of Psychiatry, Crozer-Keystone Health System, One Medical Center Blvd., Upland, PA 19013 or contact the department manager, Kathy Waring at 610-619-7413

Horizon Health, in partnership with **St. Vincent Health Center (Voted 5th Best Place to work in Pennsylvania!),** a 436-bed tertiary care hospital in **Erie, PA,** has an exciting opportunity for a **Medical Director** for a **32-bed** Adult and Geriatric Inpatient Psychiatric Program. Opportunities for input and growth, tertiary care, teaching opportunities in FP residency program and LECOM medical school. Excellent compensation package with full benefits. Located on the shores of **Lake Erie** with 7 miles of beaches, Erie is the **fourth largest city** in Pennsylvania with a metropolitan population of 280,000. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

School of Medicine
TEMPLE UNIVERSITY®

Psychiatrists

Temple University School of Medicine, Department of Psychiatry and Behavioral Science, has faculty and non-faculty openings in Inpatient, Consultation and Liaison, Emergency Psychiatry, and Childhood and Adolescent Psychiatry. Responsibilities include providing clinical care. Faculty members are also responsible for teaching residents and medical students. Candidate must be board-eligible or board-certified (preferred). Rank and salary commensurate with experience.

To apply, submit curriculum vitae to Dr. William Dubin, Acting Chair, Department of Psychiatry and Behavioral Science, C/O Scott Caldie, Director of Physician Recruitment, Temple University School of Medicine, 3420 N. Broad Street, MRB, Suite 101, Philadelphia, PA 19140. E-mail: scott.caldie@tuhs.temple.edu

Temple University is an affirmative action/equal opportunity employer and strongly encourages applications from women and minorities. Further information about Temple University School of Medicine is available at http://www.temple.edu/medicine/

CLARION (Western PA) and SHIPPENSBURG (near Harrisburg). General or Child Psychiatrists for inpatient & partial program services. Very competitive salary, benefits and incentive plans. Student loan assistance negotiable in Clarion. Contact Joy Lankswert @ 866-227-5415; OR email joy.lankswert@uhsinc.com

RHODE ISLAND

Psychiatry

Psychiatrist Adult, Inpatient and Outpatient (Mood Disorders)

The Department of Psychiatry, Rhode Island Hospital, a Lifespan partner and Brown University affiliated program, is seeking a psychiatrist to join an established adult partial hospital program. The program involves treating patients with a wide range of acute conditions, and includes psychiatric management and group therapy components. The partial hospital is one division within a comprehensive department of psychiatry with a full range of clinical and academic programs. The candidate must be Board Certified or eligible, and may be eligible for a clinical appointment at The Warren Alpert Medical School of Brown University. Salary and benefits commensurate with level of training. To learn more about us and our offerings, visit www.lifespan.org. Please send CV along with a letter of interest to Richard J. Goldberg, M.D., Psychiatrist- in-Chief, APC-9, Rhode Island Hospital, 593 Eddy St, Providence, RI 02903 and/or e-mail to rjgoldberg@lifespan.org.

Lifespan is an EOE.

SOUTH CAROLINA

CHIEF
of
MENTAL HEALTH SERVICE

The WJB Dorn Veterans Affairs Medical Center (VAMC) is seeking an individual with clinical leadership and managerial skills to direct our Mental Health Service. Dorn VA Medical Center, part of the VA Southeast Network (VISN 7), is a 216-bed facility, encompassing medical, surgical, psychiatric, and geriatric care. The medical center provides care to approximately 67,000 veterans in the midlands and upstate South Carolina. Community Based Outpatient Clinics (CBOCs) are located in Anderson, Greenville, Spartanburg, Florence, Orangeburg, Sumter, and Rock Hill, SC, and provide primary care, mental health, and telemedicine services. Dorn VAMC is affiliated with the University of South Carolina (USC) School of Medicine and provides teaching services for students and residents. USC is the state's flagship research university, with Schools of Public Health, Nursing, Pharmacy, and an active Graduate School.

The Chief of Mental Health will assist in planning and development of our long-term strategic initiative to create a "Mental Health Center of Excellence." Applicants should be from one of the four core mental health professional disciplines: Nursing, Psychiatry, Psychology, and Social Work and should have experience and expertise in research, administering programs, clinics, staff, and trainees. This individual will be responsible for oversight, direction, and development of outpatient, inpatient, and tele-mental health services at the Medical Center and its CBOCs and joint program development with the USC School of Medicine. The successful candidate will qualify for a faculty appointment at University of South Carolina commensurate with training and experience.

Columbia's variety in cultural and recreational activities, its location (2 hours from the ocean and 2 hours from the mountains), and weather (mild winters), make it a pleasant place to live. Columbia has an excellent airport, a thriving arts and cultural community, fine restaurants, an abundance of golf courses and mountain-biking trails, and whitewater and trout fishing within the city limits. Large lakes which offer world-class fishing, sailing, water-skiing, and waterfront camping are a short drive away.

Interested individuals should send their CV and 3 professional references to:

Human Resources (05M)
WJB Dorn VA Medical Center
6439 Garners Ferry Road
Columbia, SC 29209-1639
Fax: 803-695-6702
Phone: 803-776-4000, extension 6264
Also refer to: http://www.usajobs.opm.gov #09-188-COS for more information
For specific information concerning the position, contact:
Dr. Stephen Hawes
Chair, Search Committee
Director of Mental Health Service
803-776-4000, extension 7143

THE DIVISION OF CHILD AND ADOLESCENT PSYCHIATRY in the Department of Neuropsychiatry and Behavioral Science, University of South Carolina School of Medicine, is recruiting a board-eligible/board-certified Child and Adolescent Psychiatrist. This is a full-time, non-tenure-track position.

The University of South Carolina Child and Adolescent Psychiatry Faculty are committed to pursuing excellence in clinical training, formal instruction and research. The Department of Neuropsychiatry has established a reputation characterized by commitment to community and the underserved, encouraging individual faculty growth in an environment that is collegial. This position includes opportunities to teach psychiatry residents and medical students, through outpatient assessments and consultation services for the Department of Juvenile Justice and the Palmetto Children's Hospital. Additional responsibilities include providing clinical services through the School of Medicine Specialty Clinics, as well as participating in research activities.

Please submit a letter of application with a curriculum vitae to:
Richard K. Harding, MD, Chair, 3555 Harden Street Extension, Suite 300, Columbia, SC 29203 or fax to 803-434-1043. *The University of South Carolina is an equal opportunity institution.*

TENNESSEE

Board-certified/eligible psychiatrists needed for a large Psychiatry Service at Mountain Home VAMC in Johnson City, Tennessee. Inpatient/outpatient psychiatrist on a 24 bed teaching unit staffed by two psychiatrists, 1 NP, 1 PA, and residents rotating from ETSU College of Medicine. Must be board certified in psychiatry or board eligible if within 2 years of residency completion. Join staff of 30 prescribers, including 18 psychiatrists at ETSU-affiliated residency training program with medical students, adult and med-psych residencies. Clinical appointment potential and some teaching expected. Research a plus. On-call (full time positions only) is backup to residents and shared amongst staff psychiatrists.

NO STATE INCOME TAX, LOW COST OF LIVING, BEAUTIFUL MOUNTAINOUS REGION, LOTS OF PARKS, GOLF COURSES, LAKES, NATIONAL FOREST.

Inquiries: Tana Johnson, (423) 926-1171, ext. 7184, or Tana.Johnson@va.gov and George.Brown@va.gov. Applications and/or CVs to: James H. Quillen VA Medical Center P.O. Box 4000 (05), Mountain Home, TN 37684 or Fax: (423) 979-3443 or Email: mtnhomehrmservice@va.gov

Equal Opportunity Employer

One hour south of Memphis, TN, in North Central Mississippi. Medical Director/Associate Medical Director opportunities available for 15-bed Adult and 22-bed Geriatric inpatient units, in addition to a 23-bed Chemical Dependency Program. Excellent income potential and practice opportunity. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

TEXAS

Texas Gulf Coast Medical Group

Psychiatrist to join a respected and well established large family and multi-specialty practice in Webster, Texas, a Houston suburb. The patients are waiting for you! Brand new officebuilding with EMR and state of the art equipment. Lakes, the ocean, fishing, golfing, excellent schools, and warm temperatures year round. See our website at www.txgulfcoastmed.com or fax your CV to (281) 724-0210

DALLAS area - SHERMAN. General Psychiatrist - Private practice of inpatient and outpatient.
WEST TEXAS San Angelo: Child Psychiatrist. Great private practice opportunity. Busy practice from start. **Offering student loan assistance.**
Contact: Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

The Department of Psychiatry and Behavioral Sciences of the University of Texas Medical School at Houston has an extraordinary opportunity for psychiatrists seeking to develop and implement new inpatient and outpatient clinical and research initiatives. Under new leadership, the Department is looking to expand clinical and research areas and is seeking general psychiatrists, child and adolescent psychiatrists and geriatric psychiatrists to join a growing academic department dedicated to excellence in clinical care, research and education. The Medical School is part of the University of Texas Health Science Center Houston, located in the Texas Medical Center - the largest medical center in the world. The Department of Psychiatry will shortly be moving into a brand-new building that will house the new Institute of Psychiatry. Individuals applying for these positions must be Board Certified in general psychiatry, child & adolescent psychiatry and geriatric psychiatry or have completed an accredited training in these specialty and subspecialty areas in the United States. Additionally, they must be licensed or be eligible for licensing in the State of Texas. Depending upon the applicant's qualification and credentials, faculty appointments at the level of Assistant Professor, Associate Professor or Professor will be offered. Salary levels are very competitive and also carry excellent fringe benefit packages. To find out more information about these unique academically-driven positions or to apply for them, please write to Jair C. Soares, M.D., Professor and Chair, and include a copy of your curriculum vitae and a letter of interest to 1300 Moursund Street, Houston, Texas 77030, e-mail: Jair.C.Soares@uth.tmc.edu phone 713-500-2507; fax 713-500-2553. The University of Texas Health Science Center at Houston is an EO/AA employer. M/F/D/V

Associate Professor

The Department of Psychiatry at the University of Texas Medical Branch in Galveston is seeking an Associate Professor for our Adult division.

Responsibilities include direct patient care, resident supervision and teaching. Research opportunities are available. The position can be required to work in any of our three locations one of which is located in Webster; the other two are on Galveston Island. The position reports directly to the Chair of the Department. Minimum qualifications are medical doctor with a Texas medical license and must have graduated from an accredited Psychiatry Residency Program. Board certified in Psychiatry and Neurology with experience in clinical psychiatry is preferred.

Candidates with interest and skills in this area should send a curriculum vitae and cover letter to: Robert M.A. Hirschfeld, M.D., The University of Texas Medical Branch, Department of Psychiatry, 301 University, Galveston, TX 77555-0188.

The University of Texas Medical Branch at Galveston is an equal opportunity, affirmative action institution which proudly values diversity. Candidates of all backgrounds are encouraged to apply.

Interested in loving where you live and work? Then consider- Lufkin

Lufkin State Supported Living Center is looking for a psychiatrist. We are located in beautiful deep east Texas near two national forests, boasting of great lakes, parks and one of the best golf courses in Texas. According to the Chamber of Commerce- Lufkin is the #1 Micropolitan community in Texas and has many dining and shopping opportunities. Lufkin State Supported Living Center is a developmental facility for people with mental retardation and physical disabilities as well as persons with dual diagnosis which includes mental illness. A typical work schedule is Monday - Friday 8 a.m. to 5 p.m. The work environment is casual and the medical problems are challenging. We have a strong support system and offer excellent benefits (competitive salary, retirement, health/dental insurance, paid vacation and sick days, life insurance, longevity pay, up to 15 paid holidays per year, and more). A three bedroom, home with a formal dining/living room and den is available on campus with all bills paid and a modest rent.

For more information, call 936-853-8350, or e-mail: gale.wasson@dads.state.tx.us

VIRGINIA

FACILITY MEDICAL DIRECTOR

Eastern State Hospital (ESH), a Joint Commission Accredited Hospital, seeks a BC/BE psychiatrist licensed by the Virginia Board of Medicine. Our new Geriatric Center (150 beds) opened April 2008; the Adult Mental Health Center (150) beds), under construction, opens June 2010.

Candidate will provide direction, oversight and supervision of all Clinical Departments; Psychology, Social Work, Psychosocial Rehabilitation; and supervision and coordination of activities of the Medical Staff. Demonstrated knowledge and experience in administrative and clinical activities in the field of mental health required. Must be experienced and knowledgeable of joint Commission Standards and CMS Regulations. Candidate will also facilitate a broader clinical interface with other facility and community service entities. Educational affiliations include the College of William & Mary, and Eastern Virginia Medical School.

Salary range $175,000-220,000 accompanied by comprehensive state benefits package (paid malpractice, disability, and life and health insurance). ESH has been in continuous operation for 235 years!

Send CV's to:
Human Resources Department
Eastern State Hospital
4601 Ironbound Road
Williamsburg, VA 23188-2652
Tour: www.esh.dmhmrsas.virginia.gov
To apply on line:
https//jobs.agencies.virginia.gov
(757) 253-5411
(757) 253-4996 fax

EOE

VIRGINIA COMMONWEALTH UNIVERSITY, Department of Psychiatry, School of Medicine, is recruiting a BE/BC Psychiatrist to serve as **Chair, Division of Ambulatory Psychiatry, position available as of July 1, 2008.** Duties include development of new programs, ambulatory care research, ambulatory resident and student education, and direction of general and specialty clinics and staff supervision. Significant experience in academic ambulatory care, teaching, administration and clinical research required. Faculty with funded research preferred. Ambulatory Care Clinics are located at the VCU Medical Campus, and have an estimated 16,000 patient visits/year. Department of Psychiatry employs over 80 fulltime faculty and is nationally ranked in federally funded research. Richmond, the State Capital, has moderate climate and rich mix of history, a diverse multicultural community, excellent housing and public/private schools. Internet provides comparative cost of living. Send CV to Search Committee, c/o Marie Roach, VCU, Box 980710, Richmond VA 23298. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, persons with disabilities, and minorities are encouraged to apply.

VIRGINIA COMMONWEALTH UNIVERSITY: The Department of Psychiatry, School of Medicine, is recruiting a BE/BC Psychiatrist to serve as Outpatient Director of the Virginia Treatment Center for Children (VTCC), Ambulatory Care Psychiatry, at the VCU Medical Center. Duties include development of new programs, outpatient clinical care, ambulatory resident and student education, and direction of medical clinics and staff supervision. The VTCC is a leader in clinical education and is growing in research capabilities. Academic experience, including clinical education, research and scholarly endeavors, preferred. VCU Department of Psychiatry employs over 80-fulltime faculty and is nationally ranked in federally funded research. Richmond, the State Capitol, has moderate climate and rich mix of history, a diverse multicultural community, excellent housing, and public/private schools. Internet provides comparative cost of living. Send CV to Marie Roach, Human Resources, Department of Psychiatry, VCU, Box 980710, Richmond, VA 23298 (Fax 804-828-1472). VCU is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

ADDICTIONS PSYCHIATRY, FACULTY CHAIR

The Department of Psychiatry, Medical College of Virginia at Virginia Commonwealth University, in collaboration with the Hunter Holmes McGuire Veterans Administration Medical Center, and VCU Institute for Drug and Alcohol Studies, is recruiting an academic physician Chair for the Division of Addiction Psychiatry. Chair is responsible for developing research, teaching and clinical programs. Funded ACGME accredited Addictions Fellowship. Strong programs in psychiatric genetics, epidemiology, pharmacology, toxicology, and women's health. Emerging School of Public Health. State funded health practitioner impairment program, laboratory and community based research are active areas for collaboration. Department of Psychiatry has over 75 full-time faculty, 39 residents, multiple fellowships and research centers including an addiction genetics research center. The Veterans Administration Medical Center has robust residential and outpatient addictions programming, and an outstanding program in Psychiatry and Primary Care. VCU is Virginia's largest university with robust health science campus and 750-bed university hospital. Richmond, the State Capital, has moderate climate, a rich history, cultural activities, excellent choices for urban, suburban, or country living, outstanding public/private schools. See comparative cost of living via Internet at www.coli.org/. Virginia Commonwealth University is an Equal Opportunity/Affirmative Action employer. Women, persons with disabilities, and minorities are encouraged to apply. Send applications to Joel J. Silverman, M.D., Chairman, c/o Marie Baker-Roach, Department of Psychiatry, MCV/VCU Box 980710, Richmond, VA 23298. Please contact Dr. Joel Silverman at 804/828-9156 or email jsilverman@mcvh-vcu.edu

VIRGINIA BEACH

Outstanding private practice opportunity for board certified psychiatrist to join 1 psychiatrist and 3 therapists in well-established (25 year) out-patient practice caring for children, adolescents and adults. Partnership plan with opportunity to own. Guarantee $120,000 plus monthly bonus. Contact Dan Darby, MD at Tel: (757) 425-5050 Fax: (757) 425-1389.

WASHINGTON

CHIEF, BEHAVIORAL HEALTH SERVICE STAFF PSYCHIATRIST

The Veterans Affairs Medical Center in Spokane, WA, is seeking a Board Certified Psychiatrist to fill the position of **Chief, Behavioral Health Service.** This physician administrator manages the mental health service line. 10% of the time is performing clinical duties, which may include covering the 8-bed inpatient psychiatric ward, or working in one of the outpatient clinics.

We are also seeking a **Staff Psychiatrist** to provide assessment and management of psychiatric care for veterans, including traumatic brain injury, and Operation Enduring Freedom/Operation Iraqi Freedom evaluations and treatment.

Located in the heart of the Pacific Northwest, Spokane is a vibrant community with a population of approximately 300,000. Spokane offers exceptional recreational, educational and cultural opportunities in a four-season climate.

Our physicians enjoy a unique quality mix of career and leisure time. Benefits include:
- Salaried position
- Malpractice coverage
- Excellent retirement program
- Generous paid vacation/sick/CME days
- 10 paid holidays

Call or send resume in confidence to:
Donna Dehart-Ray, RN, MS,
MD/Nurse Recruiter
4815 N. Assembly
Spokane, WA 99205-6197
Telephone: (509) 434-7657
Fax: (509) 434-7134

An Equal Opportunity Employer

WEST VIRGINIA

PSYCHIATRIST-West Virginia University School of Medicine, The Department of Behavioral Medicine and Psychiatry, has ongoing opportunities and faculty positions for full-time, part-time or per diem BE/BC psychiatrists in various locations throughout the state of West Virginia, including its primary clinical, educational and research location in Morgantown, WV, as well as William R. Sharpe Jr. Hospital, a 150-bed, JCAHO-accredited, state psychiatric hospital in Weston, WV. Responsibilities include patient care and teaching, with opportunities for research. Positions will remain open until filled. Contact Susan Clayton at sclayton@hsc.wvu.edu. WVU is an AA/EO employer.

West Virginia School of Osteopathic Medicine, Lewisburg, WV is seeking a fulltime, tenure, faculty in Psychiatry. Duties include teaching medical students, interns, residents; developing psychiatric curriculum for students years 1-2; developing curriculum, rotational components and evaluation instruments for students years 3-4; maintaining a clinical practice. Research supported but not required. D.O. or M.D. degree, completed residency, board certification or eligibility in Psychiatry and clinical experience in general psychiatry. Must be able to be licensed in WV, which requires a rotating osteopathic internship for osteopathic physicians.

Excellent benefit package including the availability of fully paid malpractice insurance, educational loan repayment. Salary and faculty rank based on experience and training. Information at WWW.WVSOM.EDU . Apply by contacting Leslie Bicksler, Director HR at lbicksler@wvsom.edu , 304/647-6279. AA/EOE.

PSYCHIATRIST-Valley HealthCare System has a full-time position available within a four county catchment area in WV, incl. the primary clinical location in Morgantown. Duties include providing psychiatric intakes, pharmacological management, treatment direction and treatment plan supervision. Apply online at www.valleyhealthcare.org EOE

WISCONSIN

Eau Claire, Wisconsin: Luther Midelfort - Mayo Health System, is seeking a **BC/BE Adult Psychiatrist** who is collaborative in his/her approach and engages the non-physician team and patient in a collegial manner. Position is primarily outpatient, but call involves inpatient coverage. Call of 1:6. Outpatient and inpatient unit are on the same floor of the hospital. This position involves travel one day/week for outreach. Luther Midelfort - Mayo Health System is a vertically integrated, physician directed hospital and multi-specialty clinic of 237 physicians owned by Mayo Clinic. Our physicians practice evidence-based, protocol-driven medicine. Eau Claire is a university community with a metro area of 95,000, located 90 minutes east of Minneapolis. Business Week ranked Eau Claire as the best place to raise your kids in the State of Wisconsin (11/10/08). Outstanding schools, a family oriented community, a state with a favorable malpractice climate, and a strong compensation and benefits package may be expected. For more information, contact Cyndi Edwards 800-573-2580, fax 715-838-6192, or e-mail edwards.cyndi@mayo.edu . You may also visit our website at www.luthermidelfort.org EOE

WYOMING

CASPER - Psychiatrist for inpatient & outpatient services. Highly competitive salary, benefits, & bonus plan. Student loan assistance negotiable. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

International

AUSTRALIA & NEW ZEALAND
PSYCHIATRY JOBS
Gen. Adult - Child & Adoles. - Forensics
Locum Tenens or Permanent Jobs
Salaries of up to 350,000 per annum
www.IMRpsychiatry.com

Fellowships

Psychosomatic Medicine Fellowship, Portland, Oregon. Recruiting for 07/01/10 ACGME-accredited PGY5 level, at Oregon Health & Science Univ and Portland VA Med Center. Flexible program with clinical and research opportunities. Training sites include ambulatory care, specialty services, and consultation to inpatient med/surg. Research and clinical strengths in health services, mental disorders in primary care, pain, end-of-life/palliative care, ethics, mood disorders, Parkinson's disease, and substance abuse. Contact Dr. Steven Dobscha, Portland VA Med. Ctr., PO Box 1034 (P3MHADM), Portland, OR 97207; at steven.dobscha@va.gov. EOE.

Geropsychiatry Fellowship, Portland Oregon, Recruiting for July 1, 2010 ACGME-accr PGY5 level, at Ore Hlth Sci Univ and Portland VA Med Center. Flexible program with either research or clinical emphasis. Training sites include inpatient, outpatient, nursing home and community. Research and clinical strengths in end-of-life/palliative care, ethics, mood disorders, dementias, Parkinson's disease, and substance abuse. Opportunity, support and mentoring will be provided to fellow for research training. Contact Linda Ganzini, MD, MPH, Director of Geriatric Psychiatry Training, Mental Health Div, R & D 66 , PO box 1034, Portland, OR 97207 or at Linda.ganzini@va.gov EOE.

PSYCHOSOMATIC MEDICINE FELLOWSHIPS AND CHIEF RESIDENCY POSITIONS AT YALE UNIVERSITY

This ACGME-accredited one-year fellowship has five Psychosomatic Medicine Fellowship positions available at the PGY-V level or above, starting July 1, 2010. Applications for Chief Resident positions are also welcome (PGY IV year training does not provide eligibility for subspecialty board certification). The program offers training in inpatient and outpatient consultation-liaison psychiatry at Yale New Haven Hospital and at the VA Connecticut Healthcare System, with multiple specialty electives. An Equal Opportunity employer. Please contact Paul Desan, MD, PhD, Yale New Haven Hospital, 20 York St CB2039, New Haven, CT 06504, paul.desan@yale.edu, (203) 785-2618.

PSYCHOSOMATIC MEDICINE FELLOWSHIP

One year exciting, well-established, fellowship program, one of the first accredited by the ACGME, in a 750-bed university hospital, accepting applications for July 1, 2010. Advanced training offered to psychiatrists who have completed residency. Please write or call: James L. Levenson, M.D., Chairman, C-L Division, VCU Health System, Department of Psychiatry, Box 980268, Richmond, VA. 23298-0268, jlevenson@mcvh-vcu.edu (804) 828-0762 or Sherif Meguid, M.D. aabdel-meguid@mcvh-vcu.edu

Practice for Sale

Busy psychiatric practice for sale in South Orange County, California. Very good revenue. Will stay to help the transition. Call 949-278-5584 or Fax to 949-348-0231.

Psychopharmacology practice for sale in picturesque New England seacoast town north of Boston serving adults, adolescents and children. Established 10 years with high net and excellent growth potential. Ideal for a single practitioner or couple. Short/long term lease available in established location. Some owner financing negotiable. $139,000. Reply to: Box P-514, Psychiatric News, Attention: Alice Kim, American Psychiatric Association, 1000 Wilson Blvd, Suite 1825 Arlington, VA 22209

PRACTICE FOR SALE: Busy and profitable 25 year old clinical practice, Seattle, WA. Two Eastside sites with excellent growth potential. $841,000 revenue in 2008. Well over 9,000 clinical hours were billed in 2008. Owned and operated by a couple (Ph.D. and MSW). 10 contract therapists plus support staff. Interested? Call (425) 241-4113.

Courses & Workshops

Psychiatry Board Review for ABPN II
Cost-effective strategies for busy clinicians. Over 90 vignettes!
Visit www.psychedu.com

Pristiq® desvenlafaxine Extended-Release Tablets

BRIEF SUMMARY. See package insert for full Prescribing Information. For further product information and current package insert, please visit www.wyeth.com or call our medical communications department toll-free at 1-800-934-5556.

WARNING: Suicidality and Antidepressant Drugs

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of Pristiq or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. Pristiq is not approved for use in pediatric patients [see Warnings and Precautions (5.1), Use in Specific Populations (8.4), and Patient Counseling Information (17.1 in the full prescribing information)].

INDICATIONS AND USAGE: Pristiq, a selective serotonin and norepinephrine reuptake inhibitor (SNRI), is indicated for the treatment of major depressive disorder (MDD).

CONTRAINDICATIONS: Hypersensitivity-Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the Pristiq formulation. **Monoamine Oxidase Inhibitors-**Pristiq must not be used concomitantly in patients taking monoamine oxidase inhibitors (MAOIs) or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with SNRI or SSRI treatment or with other serotonergic drugs. Based on the half-life of desvenlafaxine, at least 7 days should be allowed after stopping Pristiq before starting an MAOI [see Dosage and Administration (2.5) in the full prescribing information].

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk-Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive-compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1 of the full prescribing information. No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, ie, beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [see Warnings and Precautions (5.9) and Dosage and Administration (2.3) in the full prescribing information for a description of the risks of discontinuation of Pristiq]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. Screening patients for bipolar disorder-A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with 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. It should be noted that Pristiq is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions-** The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Pristiq treatment, but particularly with concomitant use of serotonergic drugs (including triptans), with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Serotonin syndrome in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of Pristiq with MAOIs intended to treat depression is contraindicated [see Contraindications (4.2)]. If concomitant treatment of Pristiq with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. The concomitant use of Pristiq with serotonin precursors (such as tryptophan) is not recommended. Treatment with Pristiq and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur, and supportive symptomatic treatment should be initiated. **Elevated Blood Pressure-** Patients receiving Pristiq should have regular monitoring of blood pressure since dose-dependent increases were observed in clinical studies. Pre-existing hypertension should be controlled before initiating treatment with Pristiq. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported with Pristiq. Sustained hypertension- Sustained blood pressure increases could have adverse consequences. For patients who experience a sustained increase in blood pressure while receiving Pristiq, either dose reduction or discontinuation should be considered [see Adverse Reactions (6.1)]. Treatment with Pristiq in controlled studies was associated with sustained hypertension, defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥90 mm Hg and ≥10 mm Hg above baseline for 3 consecutive on-therapy visits. In clinical studies, regarding the proportion of patients with sustained hypertension, the following rates were observed: placebo (0.5%), Pristiq 50 mg (1.3%), Pristiq 100 mg (0.7%), Pristiq 200 mg (1.1%), and Pristiq 400 mg (2.3%). Analyses of patients in Pristiq controlled studies who met criteria for sustained hypertension revealed a dose-dependent increase in the proportion of patients who developed sustained hypertension. **Abnormal Bleeding-**SSRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma-**Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania-**During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease-**Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [see Adverse Reactions (6.1)]. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation-**Dose-related elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [see Adverse Reactions (6.1)]. **Discontinuation of Treatment with Pristiq-** Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in major depressive disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [see Dosage and Administration (2.4) and Adverse Reactions (6.1) in full prescribing information]. **Renal Impairment-**In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [see Clinical Pharmacology (12.6) in full prescribing information]. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [see Dosage and Administration (2.2) in full prescribing information]. **Seizure-**Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hyponatremia-** Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6) in full prescribing information]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine-** Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia-** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

ADVERSE REACTIONS: Clinical Studies Experience: The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥5% and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Adverse reactions reported as reasons for discontinuation of treatment- The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). Common adverse reactions in placebo-controlled MDD studies- Table 3 in full PI shows the incidence of common adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. Cardiac disorders: Palpitations, Tachycardia, Blood pressure increased; Gastrointestinal disorders: Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; General disorders and administration site conditions: Fatigue, Chills, Feeling jittery, Asthenia; Metabolism and nutrition disorders: Decreased appetite, weight decreased; Nervous system disorders: Dizziness, Somnolence, Headache, Tremor, Paraesthesia, Disturbance in attention; Psychiatric Disorders: Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; Renal and urinary disorders: Urinary hesitation; Respiratory, thoracic, and mediastinal disorders: Yawning; Skin and subcutaneous tissue disorders: Hyperhidrosis, Rash; Special Senses: Vision blurred; Mydriasis, Tinnitus, Dysgeusia; Vascular Disorders: Hot flush. Sexual function adverse reactions-Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). Men Only: Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; Women Only: Anorgasmia; Other adverse reactions observed in premarketing clinical studies: Other infrequent adverse reactions occurring at an incidence of <2% in MDD patients treated with Pristiq were: Immune system disorders – Hypersensitivity. Investigations – Liver function test abnormal, blood prolactin increased. Nervous system disorders – Convulsion, syncope, extrapyramidal disorder. Psychiatric disorders – Depersonalization, hypomania. Respiratory, thoracic and mediastinal disorders – Epistaxis. Vascular disorders – Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [see Warnings and Precautions (5.7)]. Discontinuation events-Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥5% include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information]. Laboratory, ECG and vital sign changes observed in MDD clinical studies-The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. Lipids-Elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [see Warnings and Precautions (5.8)]. Proteinuria-Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. ECG changes-Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. Vital sign changes-Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. Orthostatic hypotension- In the short-term, placebo-controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease ≥30 mm Hg from supine to standing position) occurred more frequently in patients ≥65 years of age receiving Pristiq (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients <65 years of age receiving Pristiq (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218). **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [see Warnings and Precautions (5.13)]. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [see Contraindications (4.2)]. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [see Warnings and Precautions (5.2)]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)-** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on in vitro data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- In vitro studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- In vitro, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- In vitro, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** In vitro, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-** There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects– Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [see Warnings and Precautions (5.2)]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [see Dosage and Administration (2.2)]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [see Box Warning and Warnings and Precautions (5.1)]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-** Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [see Adverse Reactions (6)]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [see Warnings and Precautions (5.12)]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information]. **Hepatic Impairment-** The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. No adjustment in starting dosage is necessary for patients with hepatic impairment.

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose >600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the Overdosage section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also 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. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician 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 (PDR®).

This brief summary is based on Pristiq Prescribing Information W10529C004, revised February 2009.

Wyeth®

254124-01

For the treatment of adults with major depressive disorder

The start is just the beginning

It's not just about starting your adult patients with MDD on therapy; it's about helping them toward their treatment goals. Patients should be periodically reassessed to determine the need for continued treatment.[1]

PRISTIQ 50 mg:

- **SNRI therapy with efficacy proven in 8-week clinical studies**
- **One recommended therapeutic dose from the start**
- **Discontinuation rate due to adverse events comparable to placebo in 8-week clinical studies[1]**

Pristiq® desvenlafaxine 50 mg

think beyond start™

IMPORTANT TREATMENT CONSIDERATIONS

PRISTIQ 50-mg Extended-Release Tablets are indicated for the treatment of major depressive disorder in adults.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of PRISTIQ or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older. Depression and certain other psychiatric disorders are themselves associated with increases in the risk of suicide. Patients of all ages who are started on antidepressant therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber. PRISTIQ is not approved for use in pediatric patients.

Contraindications

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

Warnings and Precautions

- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.**
- Development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions have been reported with SNRIs and SSRIs alone, including PRISTIQ treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs that impair the metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. If concomitant use with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since sustained increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.
- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose (by giving 50 mg of PRISTIQ less frequently) rather than abrupt cessation is recommended whenever possible.
- Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or end-stage renal disease (ESRD). The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.
- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence ≥5% and twice the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

Reference: 1. Pristiq® (desvenlafaxine) Prescribing Information, Wyeth Pharmaceuticals Inc.

Please see brief summary of Prescribing Information on adjacent page.

For more information on PRISTIQ, please visit **www.PristiqHCP.com**.

Pristiq® desvenlafaxine EXTENDED-RELEASE TABLETS

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