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:* myodonus, 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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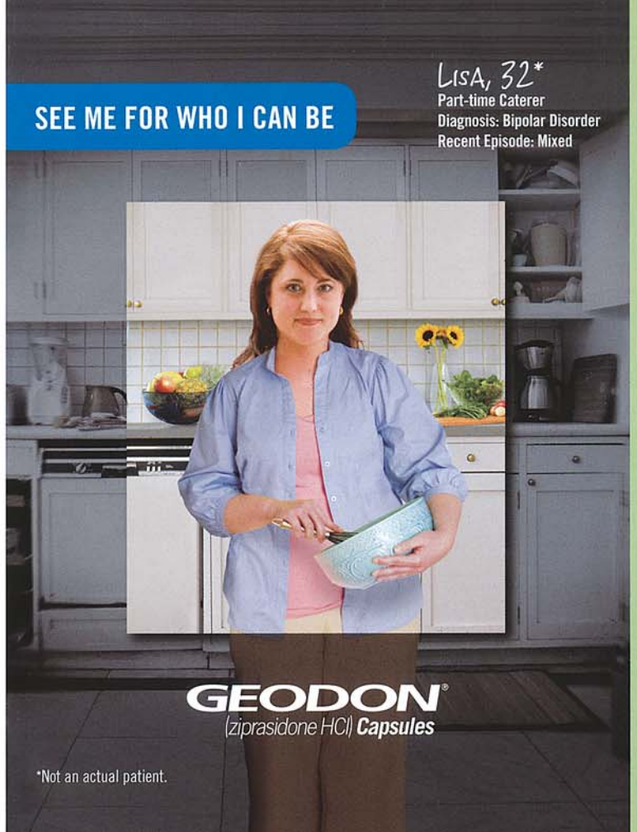

GEODON is indicated for the treatment of acute manic or mixed episodes associated with bipolar disorder, with or without psychotic symptoms.

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.

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

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 2/2968 (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. 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/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 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 higher doses 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: Aaron Levin

Rep. Michael Michaud (D-Maine) tells attendees at a Capitol Hill symposium cosponsored by APA and the National Alliance on Mental Illness that U.S. service members returning from Iraq or Afghanistan need help overcoming stigma and barriers to mental health care. See story below.

Health Reform Advances With MH Amendments On Board

The health reform measure includes several provisions whose aim is to improve access to mental health care, including an expanded mandate for the insurance parity provisions enacted last year.

BY RICH DALY

An expansion of insurance coverage for mental health care is a major component of a compromise health care overhaul bill approved by a key congressional committee in October after months of often contentious negotiation.

The measure, sponsored by Sen. Max Baucus (D-Mont.), chair of the Senate Finance Committee, was approved by that panel on October 13. It was the last of five health care reform bills to advance beyond the committee level. The Baucus legislation was the only health care bill to receive any Republican support—Maine's Olympia Snowe cast the only GOP vote for it. It would provide an $829 billion 10-year expansion to provide insurance to about half of the more than 40 million Americans who lack coverage.

The legislation has drawn cautious support from a variety of health care advocacy groups; however, many physician organizations have reservations about its extensive use of clinician reimbursement cuts to provide some of the $404 billion in Medicare and Medicaid savings that would fund coverage expansions in the rest of the health care system.

please see ***Health Reform*** *on page 33*

Congress, MH Experts Address Stressors Facing Soldiers

APA marshals its forces to educate members of Congress about the complex mental health needs of U.S. troops and their families.

BY AARON LEVIN

APA reiterated its support for expanded mental health services and research for members of the U.S. Armed Forces and their families at a Capitol Hill symposium cosponsored with the National Alliance on Mental Illness in late September as part of Mental Illness Awareness Week.

APA is on record urging Congress to improve access to mental health services—including those for substance use disorders—for returning soldiers and their families, reduce mental illness stigma, and boost funding for the Veterans Health Administration workforce. APA has also testified in favor of increased funding for research on posttraumatic stress disorder (PTSD), traumatic brain injuries (TBI), substance abuse, and suicide.

"Many young service members are just a few months away from childhood and seeing things they hope never to see again," said Rep. John Fleming, M.D. (R-La.), at the symposium. Fleming formerly served as a physician in the U.S. Navy and has experience treating substance abuse disorders.

Fleming also serves on the House Armed Services Military Personnel Subcommittee, which has held hearings on legislation to increase the number of scholarships for training mental health professionals, especially those qualified to work with military populations, and to require the secretary of defense to create a demonstration project to provide postdeployment mental health debriefings for all returning troops.

Substance abuse among troops represents another area of heightened concern, added neuroscientist Timothy Condon, Ph.D., deputy director of the National Institute on Drug Abuse. "We know that social stressors increase the risk of initiation and use of drugs, addiction, and risk of relapse from recovery."

One of the current wars' most common injuries can be tied, at least hypothetically, to substance abuse, Condon said.

"Not much data links substance use disorders with TBI, but the orbital frontal cortex is affected by TBI and is also involved in substance use disorders due to its role in inhibitory control, executive function, and decision making," he said.

Smoking is one coping mechanism for those under stress, Condon noted, and smoking rates are higher in the military than in the general population—32

please see ***Stressors*** *on page 33*

Let APA Know

If insurers have recently notified you about changes to their policies regarding mental health coverage, please let APA know by contacting the Managed Care HelpLine at (800) 343-4671 or hsf@psych.org.

Despite the fact that no regulations have yet been issued, some insurers have responded to the new federal parity law with policy changes that may have a negative impact on your patients and your practice. APA is doing everything it can to mitigate these changes, but can only do so to the extent that it knows about them.

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Narcotic Pain Medication May Get Harder-to-Abuse Formulation

A proposed OxyContin reformulation is designed to make the medication more difficult to crush or dissolve in water, thus reducing its potential for abuse and overdose.

BY JUN YAN

A new formulation of oxycodone designed to curtail widespread abuse of OxyContin, a long-acting tablet containing oxycodone, recently received support for marketing approval from a panel of advisors to the Food and Drug Administration (FDA).

Purdue Pharma manufactures the current OxyContin tablet formulation, which is designed to release oxycodone hydrochloride slowly through a controlled-release coating. However, a large amount of oxycodone can be released if the tablet is crushed into a powder, which allows the active drug to be absorbed quickly when it is smoked, snorted, or injected after being dissolved in water.

The new formulation adds a resin coating to the tablet formulation, which is then more resistant to chewing or crushing than is the current formulation, Purdue maintains. The resin additive also makes it harder to dissolve oxycodone from the tablet into a solution. FDA reviewers of the new drug application concluded that "the tamper-resistant properties of the reformulated OxyContin are limited, but . . . may provide an advantage over the currently available OxyContin."

At a September 24 joint meeting, the Anesthetic Life Support Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee voted 14 to 4, with one abstention, in favor of approving the new formulation. The FDA is not required to follow advisory committee recommendations but usually does so.

This reformulation of OxyContin was previously reviewed by an advisory committee in May 2008. At that time, Purdue proposed to market only the lower dosages (10 mg to 40 mg) in the new formulation. The committee turned down the application, citing insufficient data to prove the reduced abuse potential and concerns about the continued availability of the current formulation in higher dosages (60 mg and 80 mg).

Abuse of and addiction to prescription narcotics have been growing problems in the United States in recent years. The latest survey conducted by the federal Substance Abuse and Mental Health Services Administration showed that misuse of prescription pain relievers had steadily increased among young adults aged 18 to 25 from 4.1 percent in 2002 to 4.6 percent 2008.

If the new formulation is approved, Purdue plans to stop distributing the current OxyContin product and replace all dosages with the new formulation. The company also stated in an announcement that it is discussing with the FDA development of a postmarketing surveillance plan and a risk evaluation and mitigation strategy, as required for certain opioid analgesics, for the new OxyContin formulation as a way to minimize the risk of abuse and overdose. ■

Important Annual Meeting Announcements

- **For APA Members Only: Register Early!**
  APA members will have an exclusive opportunity to register and make their hotel reservations for APA's 2010 annual meeting in New Orleans beginning **November 17.** Nonmembers will not be able to do so until December 17. Meeting and hotel information, including hotel rates and descriptions and course information, will go live on APA's Web site at <www.psych.org> on November 17. APA members may access this information by logging into Members Corner.

- **Look for Annual Meeting Information Online**
  APA has gone *green!* The Association is trying to do its part in helping save the environment, while also saving money on printing and mailing costs. Thus, APA is no longer mailing the Annual Meeting Advance Registration Packet, but is instead posting information about annual meeting registration, housing, the preliminary program, courses, and other topics on its Web site. As noted above, the information can be accessed at <www.psych.org> beginning November 17.

More information is available by contacting Vernetta Copeland at (703) 907-7382 or vcopeland@psych.org.

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- ***Psychiatric News* Web Site:** pn.psychiatryonline.org/
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Some Thoughts on Recent Events

BY ALAN F. SCHATZBERG, M.D.

This has been a busy fall for APA on multiple fronts. I'd like to tell you about some of our important activities in this column.

As I have reported, health care reform continues to hold the limelight, as Congress addresses the needs of the uninsured, possible systems of care, and financial issues in light of the increased national deficit. Consequently, reform has been the main priority area of our Government Relations staff, as they have worked tirelessly to review and respond to the various initiatives before Congress. APA continues to work with our medical colleagues whenever possible, and we have joined with the AMA in supporting a public option, as long as physicians can opt out without penalty. We have, however, focused specifically on issues that affect *our* patients and their access to care. We continue to work on ensuring that the progress we have made on parity is not lost or harmed through unintended consequences and that we build on it by eliminating exclusions based on prior illness and by mandating that mental health including substance abuse coverage is a basic benefit in any new plans created or covered by proposed legislation.

Our Institute on Psychiatric Services was held in early October in New York City. While the institute historically has focused on community and hospital psychiatrists, in recent years we have added a focus on sessions directed at psychiatry residents, and this year we expanded the program to address issues devoted more to general clinical practice. Sessions on psychotherapies, psychopharmacology, neurostimulatory devices, and medical comorbidity were presented by leading experts in the field and were very well received by attendees. In fact, we drew the highest number of professional registrants ever. I appreciate the leadership and creativity of Dr. Steve Goldfinger and the program committee, as well as the contributions of Dr. Debbie Hales, Jill Gruber, and other staff, to make this such an exciting and satisfying meeting. (Coverage of the institute will begin in the next issue of *Psychiatric News.)* Next year's meeting will be in Boston, and we plan to build on this year's successful innovations.

APA's journal *Psychiatric Services* provides a similar level of information for clinicians. Under the superb leadership of Dr. Howard Goldman and the editorial board, the articles and special sections have been expanded, providing excellent science and practical translation to clinical systems of care. The journal became a free member benefit a few years ago, and, regrettably, because of the decline of advertising that has impacted not only this journal but many other journals throughout the field of medicine, we had to make the difficult decision to reinstitute charging a subscription fee. Nonetheless, I encourage you to subscribe to this gem of a journal if you have not already done so. The information it provides addresses a range of issues affecting psychiatric care that will help you improve your clinical practice. Members are eligible for a special discount. (See <http://store.appi.org/main.aspx?pageid=journal/journal&id=PSY>.)

While our major focus is in advocacy, science, and education, none of our work happens without the input of members and the infrastructure of staff. Just as Congress has to address the financial implications of changes in health care, so do we need to address the implications of external changes affecting our finances. APA's revenue derives from three sources: member dues, meetings revenue (a combination of registration, advertising, and exhibit fees), and publications (primarily advertising). This year, as I mentioned above, there has been a major drop in advertising revenue from our periodicals, as well as exhibits revenue in our meetings. For 2009, we had anticipated a shortfall in revenue of approximately $600,000, but with the continued erosion of advertising and other revenues, we are facing a shortfall of about double that amount. Thankfully, we have reasonably healthy reserves that can cover this year's shortfall; however, the Budget and Finance Committee as well as the Board of Trustees are determined to ensure that APA and its subsidiaries have aggregate positive and realistic budgets as well as careful longer-range financial planning.

Since we cannot anticipate that advertising and other revenues will return to their old levels, we need to reassess our planning for 2010 and beyond. The Budget and Finance Committee, led by Dr. Frank Brown from Emory, met in mid-October to revise next year's budget. Not surprisingly, this was a difficult meeting, as the committee reviewed the revenue and expenses and recommended $1.6 million in budget cuts that will be sent to the Board in December for final action.

The proposed cuts come on the heels of reductions instituted this past year for the Board of Trustees, Joint Reference Committee, and components. There is no question that these cuts will cause some pain to APA and its subsidiaries, to district branches, to the Assembly, and to APA staff. But while these changes may be difficult to accept, fiscal discipline is vital if APA is to remain strong and effective and focused on our mission and priorities.

As we deal with these difficult decisions, I welcome your comments and suggestions. I also welcome your comments and suggestions regarding other areas in which your Association is active. Please write me at aschatzberg@psych.org. ■

Parity to Become Federal Law Despite Rule-Making Delay

Some advocates are concerned about the delay because the law's parity requirements for insurers will become effective on January 1, 2010, regardless of whether federal regulations are finalized by then.

BY RICH DALY

Federal officials failed to meet an October deadline to issue regulations guiding the implementation of a landmark law that requires insurance parity coverage for mental illnesses. However, the law will become effective at the start of 2010 irrespective of the status of the final federal rules.

Kathleen Sebelius, secretary of Health and Human Services (HHS), wrote to congressional leaders on October 2 to inform them that regulations for the 2008 mental health parity law would be delayed until January 2010. The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (PL 110-343) required federal officials to issue regulations guiding its implementation by October 3, 2009.

Federal officials said the delay in the rules followed extensive comments from the public about the parity law. Sebelius said that HHS, the Labor Department, and the Treasury Department, which are jointly responsible for implementing the parity law, received more than 400 written comments from mental health stakeholders and the public on various aspects of the law so far this year.

The delay came as little surprise to some mental health care experts, who said that the time between the October 2008 enactment of the law and the deadline for issuance of its complex regulations—a mere 12 months—was just too short to do the job right.

"It would have been better to have regulations out earlier, but that wasn't going to happen," said Andrew Sperling, J.D., director of legislative affairs for the National Alliance on Mental Illness.

In the meantime, federal health officials have directed insurers to make reasonable efforts to adhere to the law's intent in the absence of regulations, according to mental health advocates.

Toward that end, America's Health Insurance Plans, a trade association representing health insurers, told advocates that insurance firms already have changed policies to come into compliance with the law, although insurers are seeking further guidance from regulators on some technical questions.

Federally regulated insurers are not expected to overtly ignore requirements that they cover mental illness treatments at parity with other health conditions in plans that offer psychiatric coverage. Still, there are concerns that flawed implementation of the law by insurers—intentional or unintentional—could occur during this unregulated period to the detriment of patients.

In a May 2009 letter to the HHS, Labor, and Treasury secretaries, James H. Scully Jr., M.D., medical director of APA, wrote, "APA has concerns that, after the implementation of parity, insurers will employ less visible means of restricting access to treatment for mental illness and/or substance use disorders that will perpetuate the discriminatory coverage schemes that the [parity law] sought to eliminate."

More recently, Sen. Al Franken (D-Minn.) and Rep. Patrick Kennedy (D-R.I.) led other members of Congress in writing Sebelius about their concerns that the lack of regulations could lead to "misinterpretations" of the law.

Even though the parity law included sufficient detail for insurers to begin to change their rules to comply with it, advocates said regulations are crucial. Clear and precise regulations could help avoid potential problems in insurance coverage decisions regarding scope of services, medical management, treatment limitations, and the use of separate deductibles for mental health care.

For instance, among the changes required by the law are equalization of cost-sharing policies, day and visit limitations, maximum out-of-pocket limits, and other deductibles.

In his letter to the HHS, Labor, and Treasury secretaries, Scully urged regulators to encourage insurance plans to offer a "combined deductible" for both mental health and medical/surgical benefits. Although the 2008 parity law allows plans to offer so-called separate but equal deductibles, federal regulators helped spur parity compliance when they asked insurers of federal employees to integrate deductibles after parity coverage was required for those workers several years ago.

please see ***Delay*** *on page 34*

Federal Rule Limits Use Of Genetic Test Results

An interim final rule to prevent genetic discrimination could have a big impact on people with mental illness, as research increasingly points to genetics as a factor in the etiology of psychiatric disorders.

BY RICH DALY

Federal regulators recently issued an interim final rule to implement a 2008 law barring insurers and employers from using Americans' genetic information to deny them insurance coverage, change their rates, or discriminate against them in the workplace. But more protections may be needed.

The departments of Health and Human Services (HHS), Treasury, and Labor issued the rule on October 1 to implement provisions of the Genetic Information and Nondiscrimination Act of 2008 (GINA, PL 110-233), which states that health insurers cannot cancel, deny, refuse to renew, or change the terms or premiums of coverage based solely on an individual's genetic risk of a specific disease. It also forbids employers from using a person's genetic information when making hiring, firing, promotion, and other employment-related decisions.

A 90-day public-comment period has been set for the interim final rule, closing on January 5, 2010.

"Echoing the late Sen. Ted Kennedy, our efforts to protect Americans undergoing genetic testing from having the results of that testing used against them by their insurance companies is one of the first major new civil rights of the new century," said HHS Secretary Kathleen Sebelius in a written statement about the rule.

Under the rule, insurers cannot request, require, or buy genetic information, and they are generally prohibited from asking individuals or family members to undergo a genetic test. The rule, however, allows three potential exceptions to the overall ban on requests for someone to undergo genetic testing—when a "health care professional" requests one, for payment-determination questions, and for research purposes. The rule also defines genetic information, genetic services, genetic testing, and related terms and phrases.

Aim Is to Encourage Testing

The law and the interim final rule aim to encourage more Americans to undergo potentially lifesaving genetic testing without fear that the information will be used against them. Genetic testing can help in the early diagnosis and treatment of several disorders, help assess risk, and provide scientists with valuable data as they try to develop new medicines, treatments, and therapies, said Sebelius.

APA is reviewing the regulations and working on preparing a response. APA has long supported such a genetic-privacy measure as part of its advocacy for greater patient confidentiality protections. APA's concerns about privacy in this area stem, in part, from the increasing number of links researchers have identified between genetics and some mental illnesses. The misuse of such information could have a devastating impact on people with mental illness, supporters of the legislation had warned when Congress was considering it.

> **"How on earth are you going to know if [insurers and employers] use the information against you if they already have access to it?"**

Loopholes Could Undermine Intent

Some privacy rights advocates have warned, however, that loopholes in the GINA law will allow future discrimination by employers and insurers.

Psychiatrist Deborah Peel, M.D., founder of Patient Privacy Rights, an advocacy group, said that GINA and the new rule do nothing to keep employers and insurers from accessing patients' genetic information.

"How on earth are you going to know if [insurers and employers] use the information against you if they already have access to it?" Peel told *Psychiatric News*. "Genetics are not destiny, but [insurers and employers] don't care."

The Coalition for Patient Privacy, which Peel founded and includes the American Civil Liberties Union and the Bazelon Center for Mental Health Law, plans to push for legislation requiring that informed consent be obtained from individuals before their genetic information can be released.

Further information on GINA and the new rule is posted at <www.hhs.gov/ocr/privacy/hipaa/understanding/special/genetic/index.html>. ■

Mentally Ill People May Gain Benefits of Coordinated Care

The widespread use of coordinated care could have a major impact on people with serious mental illness, who die 25 years prematurely on average due to untreated nonpsychiatric illnesses.

BY RICH DALY

Mental health advocates are cautiously optimistic that a final health care reform bill will retain an initiative to provide the first widespread use of coordinated medical care for people with mental illness.

A version of health care reform that was approved by the Senate Finance Committee in October (see page 1) includes an option for every state Medicaid plan to use so-called medical homes that reimburse physicians to coordinate the care of a patient with multiple health conditions. The legislation explicitly includes mental illnesses among the conditions for which the medical home would coordinate care.

The addition of people with mental illness as a Medicaid "target population" eligible to participate in the first nationwide medical-home program is seen as a victory by mental health advocates, because even people who do receive treatment for psychiatric disorders may not get treatment for other medical conditions.

"Mental health is essential to overall health, and we're very pleased with how mental health has been integrated into health care reform," said William Emmet, director of the Campaign for Mental Health Reform, during a Capitol Hill briefing in September on mental health and medical homes in health care reform.

The proposed program would be a significant change to Medicaid. Although that state and federal partnership is the single largest payer for mental health care in the nation, like other major health care payers, Medicaid does not fund coordinated care for people with psychiatric illness. The consequences of uncoordinated care include sicker patients who die earlier than they would have if they had not had mental illness, according to researchers.

"That's where we have seen a massive yawning gap and tragic consequences from the lack of access to effective primary care for people with serious mental illness," said Andrew Sperling, J.D., director of legislative affairs for the National Alliance on Mental Illness, in an interview with *Psychiatric News*.

Younger Age of Death Common

One high-profile study found, for example, that people with mental illness treated in the public health system die 25 years younger than the national average, mainly due to a lack of appropriate primary care. The 2006 study by Colton and Mandersheid was published in the April 2006 *Preventing Chronic Disease*.

Research also has found that mental illness rates are significantly higher among patients with certain chronic conditions—such as diabetes, heart disease, and asthma—than they are in the general population.

"We don't have a lack of evidence [on effective treatments]. We have a lack of demand to implement that evidence."

The potential for coordinated care to improve overall patient health is particularly great when mental health treatment is provided in primary care, the setting in which patients often first report psychiatric symptoms to a clinician.

"There is no way there is enough system capacity to see all of the people with mental illness within the behavioral health care sector," said Joseph Parks, M.D., director of the Division of Comprehensive Psychiatric Services in the Missouri Department of Mental Health. "It's a good thing that they are seen in primary care settings, because many of these people have other chronic health care problems."

Parks called the coordination of primary care and mental health treatment "a marriage made in heaven" because many primary care physicians want help with patients who have substance abuse disorders, for example, while many substance abuse clinicians lack primary care medical support.

"It's a common problem," said Ted Epperly, M.D., an Idaho family physician, about the inability to find mental health treatment for his primary care patients. "I can't tell you how often we see it."

Funding Is Critical

Despite the research supporting a coordinated approach to care, such programs for people with psychiatric illness have been largely limited to pilot programs and local efforts of small groups of clinicians because major health care payers have balked at paying for it.

Currently, only 10 percent of U.S. patients are treated using evidence-based, integrated-care models, said John Bartlett, M.D., M.P.H., a senior project advisor at the Carter Center Mental Health Program in Atlanta.

Parks said such care coordination will become widespread only when the major private insurers, as well as public ones such as Medicare and Medicaid, pay clinicians to provide such care.

"We need to demand better performance from our payer system, both public and private," he said.

One incentive for congressional leaders to add care coordination to Medicaid is the potential for significant cost savings. Patients with nonpsychiatric chronic health conditions and mental illness incur significantly higher health care costs, on average, than chronically ill patients who do not have a mental illness, according to 2003 data from the federal Agency for Healthcare Research and Quality (AHRQ). The AHRQ study found that, on average, $1,913 is spent annually on care for adults with a chronic health condition and no mental illness, while $3,545 is spent on chronically ill adults with mental illness.

Coordinated care could help control such costs if it increases the use of evidence-based approaches in the treatment of psychiatric illnesses, said Bartlett. A growing body of evidence shows that the use of "effective approaches" to mental health care in primary care settings through care coordination can double the effectiveness of that care. Current widespread deviation from evidence-based mental health treatments leaves 70 percent of people treated for depression, for instance, without clinically significant improvement after two months, he noted.

"We don't have a lack of evidence [on effective treatments]," Bartlett said. "We have a lack of demand to implement that evidence."

Information on efforts to include coordinated care for mental illness in health reform legislation is posted at <www.mbreform.org>. ■

APA Honors Member Of Congress

The efforts of a member of Congress to expand patients' access to psychiatric medications led APA to recognize his work with its annual accolade for a public official.

Rep. Lloyd Doggett (D-Texas) was awarded the Jacob K. Javits Award for Public Service on September 30 to honor his work on behalf of people with mental illness. That included his efforts as a member of the powerful House Ways and Means Committee to amend the Medicare Part D prescription-drug program. The Medicare Improvements for Patients and Providers Act of 2008 (PL 110-275)—enacted in July 2008—included provisions championed by Doggett to expand Part D coverage to benzodiazepines. Those medications were left out of the original law creating the Medicare drug program because of concerns about their abuse potential.

Credit: Office of Rep. Lloyd Doggett

Former APA President Carolyn Robinowitz, M.D., presents APA's Jacob K. Javits Award for Public Service to Rep. Lloyd Doggett (D-Texas) in his district office.

Doggett also amended the measure to require that Part D cover "all or substantially all" medications in both the antipsychotic and antidepressant classes. The prescription-drug program generally allows insurers to offer coverage for only a few drugs within each class, but mental health advocates maintained that when it comes to antidepressants and antipsychotics, patients may have to try several before they find one that works for them.

"Medicare patients need these critical protections in coverage to avoid interruption in care and to remain functional," said Carolyn Robinowitz, M.D., a past APA president who presented the award to Doggett. "Disruptions in psychiatric medication coverage may lead to job loss or reduced productivity, hospitalization, and other costly and avoidable consequences."

Doggett also was recognized as a strong supporter of mental health parity legislation, which was enacted last year.

The Javits award honors the legacy of the late U.S. senator from New York by annually recognizing the work of state or federal officials on behalf of patients with mental illness and the field of psychiatry. Past recipients include former senators Gordon Smith (R-Ore.), Paul Wellstone (D-Minn.), and Pete Domenici (R-N.M.).

Federal Stimulus Plan Allows Major Medicaid Enrollment Expansion

Despite some unexpected Medicaid expansion, the recession has led nearly all states to implement cost-cutting policies, with the most popular being cuts or freezes in reimbursement for physicians and other health professionals.

BY RICH DALY

Recession-fighting federal stimulus money allowed one-third of the states to expand their Medicaid programs in the last fiscal year, which produced the biggest nationwide boost in Medicaid enrollment in six years.

The growth in Medicaid spending—despite the biggest drop in state tax revenue in many years—was identified through an annual state survey released in September by the Kaiser Family Foundation's Commission on Medicaid and the Uninsured.

The survey reported state estimates that Medicaid enrollment grew by an average of 5.4 percent in Fiscal 2009, which surpassed the anticipated 3.6 percent increase the Kaiser researchers projected at the start of the fiscal year. Similarly, total Medicaid spending grew by an average 7.9 percent in Fiscal 2009, the highest

please see ***Medicaid*** *on page 34*

Child Psychiatrist Wins Prestigious Honor

Alvin Poussaint, M.D., is the fifth physician and third psychiatrist to be given the Smithsonian Institution's John P. McGovern Award in behavioral science.

BY STEPHANIE WHYCHE

"Alvin Poussaint, M.D."

Say the name and some TV viewers of the 1980s and 1990s may recall that he served as script consultant to the sitcom "The Cosby Show."

Radio and TV talk show audiences today may see him as the man who appears with comedian and actor Bill Cosby when he speaks out on the chronic health and social problems found in some African-American communities.

Still others might first think of Poussaint as author of *Come on People*, the 2007 book he cowrote with Cosby.

But family, friends, and colleagues know that while Poussaint's work with Cosby over the years may garner him the most mainstream-media visibility, he is renowned in his own right. The Harlem-born, Ivy League–educated psychiatrist has contributed for decades to the public's understanding of child development, family life, race, and multicultural relations. He has peeled back for public view the psychosocial dynamics of bigotry and prejudice and how both play out in the media.

In recognition of his work, the professor of psychiatry at Harvard Medical School and APA distinguished life fellow has received many awards and accolades. His latest came in late September when he was presented the John P. McGovern Award for behavioral sciences by the Smithsonian Institution in Washington, D.C.

Poussaint is the 11th recipient of the award—the fifth physician and third psychiatrist. The other psychiatrists were Robert Butler, M.D., and James Comer, M.D., M.P.H.

Poussaint "is a very important figure," said Wilton Dillon Sr., Ph.D., an anthropologist and scholar emeritus of the Smithsonian's National Museum of Natural History, in an interview with *Psychiatric News*.

Credit: Liza Green, Harvard College

Alvin Poussaint, M.D.: The Smithsonian's John P. McGovern Award in behavioral science "was a special award . . . even more than an honorary degree from a college."

"All of us who helped to choose him were very much impressed that he went way beyond the Freudian couch to be an active educator for the public at large."

The McGovern award is named after and made possible through an endowment by the late John McGovern, M.D., an allergist, educator, author, and medical historian.

"It was a special award, I think, for me—even more than an honorary degree from a college," Poussaint told *Psychiatric News*. "I have a great deal of respect and regard for the Smithsonian representing the cultural aspects of America."

Poussaint has lectured on college campuses and written books and numerous articles for mainstream magazines and newspapers on major health and social issues. His views, he said, are informed by his psychiatric knowledge and activism in social justice and in the civil-rights movement.

Anthropology is another of his interests, he said. During the award program, Poussaint was interviewed by Johnnetta Betsch Cole, Ph.D., director of the Smithsonian's National Museum of African Art, herself a past recipient of the McGovern award and an anthropologist. "I was delighted that Cole was the interviewer," he said.

Their wide-ranging discussion examined the societal forces at play that negatively impact the development of physically, emotionally, and psychologically healthy children—from poor parenting to the impact of negative media images

please see ***Poussaint*** *on page 8*

Psychiatrist's Frequent Flying Brings Rewards, Not Points

Peter Uhlmann, M.D., lives in a town of 18,000 in British Columbia and travels many miles to provide care in even smaller outposts.

BY AARON LEVIN

Peter Uhlmann, M.D.'s, psychiatric practice covers an area of about 1.2 million square miles, pretty much everything east of the Yukon and west of Greenland, give or take an island or two.

For a total of three months every year, scattered over four trips in different seasons, Uhlmann flies from his home in Powell River, British Columbia, to half a dozen communities in the Canadian regions of the Northwest Territories and Nunavut.

Lighting out for the territories comes naturally for Uhlmann. His travels before and after settling in Powell River have taken him around the globe. A native of Chicago, he graduated from the University of Illinois at Chicago Medical School in 1965 and spent two years in the U.S. Public Health Service, first as a Peace Corps physician in Somalia and then on the Colville Indian Reservation in Washington state.

He and his wife discovered Powell River in 1969 and began building a house there. He split his psychiatry residency between the University of British Columbia and the University of Auckland in New Zealand.

He returned to Powell River, dividing his time between private practice and serving as director of psychiatry at Powell River General Hospital. While there, he helped develop a short-term assessment program—staffed by specially trained nurses backed up by the hospital psychiatrist and local family doctors—to serve as a single entry point for adults into the mental health services offered in the coastal town of 18,000 people.

Uhlmann's practice came to a temporary halt in 1994 when he was diagnosed with lymphoma. It took a few years for him to get back to work.

Beginning in 1996, he worked as a consulting psychiatrist at several mental health centers in British Columbia and then spent two years on a Navajo reservation in New Mexico. His time at the Crown Point, N.M., hospital of the U.S. Indian Health Service (IHS) reminded him of the differences between the U.S. and Canadian ways of practicing medicine.

Conditions Isolated and Cold

"In Canada I can practice as I see fit," he said. "Working for the IHS was closer to the Canadian system, but I have avoided locums in the U.S. in nongovernment settings. It is medical practice suited to doctors and the health system, rather than patients."

Since 2005, the provincial governments of the Northwest Territories and Nunavut have employed him to serve those half dozen isolated communities, which are accessible only by air.

Nunavut is the province carved out of the older and formerly larger Northwest Territories 10 years ago. The region is home to fewer than 30,000 people, mostly Inuit (the people formerly known as Eskimos). The region comprises 772,000 square miles of "rocky tundra with stunted vegetation located above the tree line [and] snow covered most of the year," according to its government's Web site. Winter lasts nine months, and the average January temperature is 22 degrees below zero Fahrenheit. There is one 21-kilometer road between two towns. Ships or planes move people and goods in and out.

The Northwest Territories is nearly as isolated. Its 42,637 citizens live in its one city (Yellowknife, the capital, population 19,155) or are scattered across 425,000 square miles in 31 smaller settlements.

Uhlmann may take more than a dozen flights during a two-week stint in the Arctic because there are no direct flights between the small villages he serves. Air service depends on the weather. Once, an expected 45-minute flight cascaded into a 26-hour ordeal when the plane scheduled to pick him up arrived nine hours late. Uhlmann had to return to Yellowknife and take another series of flights. Accommodations are the local "hotel," usually a mobile home.

Credit: R. Peter Uhlmann, M.D.

With only one human per 23 square miles in the Canadian Arctic, a visitor has to find friends wherever possible. Peter Uhlmann, M.D., stands beside an inunnguaq, an Inuit stone marker in the form of a stylized human being.

"The people are wonderful, but there is never a simple case," he said. "There is a lot of trauma, dysfunction, substance abuse, and violence."

Forced Cultural Change Has Impact

He attributes these conditions to forced cultural change in the 1950s when the Canadian government pushed nomadic aboriginal people into permanent villages, destroying their traditional way of life.

Once in a clinic, Uhlmann can diagnose patients and recommend treatment to local personnel, but can't stay long enough to provide therapy. "Sometimes there are counseling services, sometimes not," he said. The government flies in doctors and nurses to some clinics for a few weeks at a time on short-term contracts, so there's little continuity of care once Uhlmann returns home. One community saw 50 family doctors come and go in a single year, he said.

Uhlmann has an affinity for what he calls transcultural psychiatry. Besides the Canadian Arctic, he has consulted and worked at distant psychiatric outposts around the world, from China to Ukraine.

"In Powell River, I was part of the community, which gave me a good understanding of people and their lives," he said. "Elsewhere, I have to accept the fact that I'm an outsider."

That means adjusting to life on the tundra. Concepts of time are different, for instance. Patients frequently miss appointments, but Uhlmann has learned to team up with a nurse and just walk through the small community to the patient's house.

Low educational levels and poor English-language skills raise other barriers. If he needs a translator, he has to be careful, and not just with words. In these compact settlements, a local health department employee who knows English may also be related to the patient, who then might be less than forthcoming with someone he or she knows.

Sorting out these relationships to create a useful family history isn't simple either. The Inuit practice a form of cultural adoption, in which a person may claim many siblings, only one of whom is biologically related.

Part of Uhlmann's time in the north is spent teaching the local nurses and members of the Royal Canadian Mounted Police more about mental illness. Progress trying to link up with local governments or school systems has, however, gone slowly. He occasionally provided telepsychiatry services to his communities, but funding cuts have stopped that for the time being.

His travels and his illness have provided insights that continue to inform his remote practice, but he is also aware of its limitations.

"I know I'm doing something useful, but it's a stop-gap answer," he concludes.

An article by Uhlmann, "Rural Psychiatric Practice," is posted at <www.peterublmann.com/Pages/article_rural.html>. ■

Colenda Named Chancellor of W.Va. School

Christopher Colenda, M.D., M.P.H., became chancellor for health sciences at the West Virginia University Robert C. Byrd Health Sciences Center on November 1 after serving for seven years as dean of the Texas A&M Health Science Center College of Medicine.

A geriatric psychiatrist by training, Colenda is a member of the Liaison Committee for Medical Education, National Board of Medical Examiners, Accreditation Council for Graduate Medical Education, and American Board of Psychiatry and Neurology. He also serves on the Psychological Health External Advisory Subcommittee for the Defense Health Board at the U.S. Department of Defense, and the Administrative Board of the Council of Deans for the Association of American Medical Colleges.

Colenda was selected as a delegate to the White House Conference on Aging in Washington, D.C., in 2005. He is a recipient of APA's Jack Weinberg Award in Geriatric Psychiatry and a Special Commendation from APA's Council of Aging. ■

Poussaint

continued from page 7

on families, to how America's consumer-driven culture can play havoc with the efforts of parents who try to pass positive moral values on to their children.

"He wrote frequently in his early years for *Ebony* magazine," recalled Dillon, formerly a member of the board of the Institute for Psychiatry and Foreign Affairs. "Long before Obama came along, he was talking about responsibility—for parents to take responsibility for their children's education."

Poussaint received his medical degree in 1960 from Cornell University. He completed his residency in psychiatry at the University of California at Los Angeles while earning a master's degree in psychiatry with an emphasis on psychopharmacology. Later he moved to Mississippi to provide medical care to civil-rights workers.

He is a fellow of the American Association for the Advancement of Science and a member of the American Academy of Child and Adolescent Psychiatry. He is the faculty associate dean of student affairs at Harvard and director of the Media Center of the Judge Baker Children's Center in Boston, and he continues to serve as a media consultant, advocating for "more responsible programming." ■

SEE ME FOR WHO I CAN BE

Greg, 35*
Diner Worker
Diagnosis: Schizophrenia

*Not an actual patient.

Do you see your patients' full potential?

GEODON is indicated for the treatment of schizophrenia.

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

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 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/mm^3) 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. 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, hypercalcemia, 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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Novel Strategies Try to Avert Wars' Psychological Damage

Military training that addresses both the physical and emotional realities of combat may better prepare soldiers for what they could face during and after their time in a war zone.

BY AARON LEVIN

Credit: Ben Wilking/iStockphoto

Some American troops preparing for deployment to Iraq or Afghanistan have taken part in combat training using movie special effects that create a heightened sense of realism not only for the combat experience but for the emotions it generates as well.

Soldiers and marines sweep through villages constructed to look like dusty Middle Eastern towns and populated by Iraqi or Afghan actors while trying to sort friend from foe and dodging blank gunfire and noisy, but harmless, Hollywood explosions. Other actors, some of them veterans who have lost arms or legs, convincingly mimic traumatic amputations gushing fake blood.

That kind of realistic combat training might make soldiers more resilient when facing the shock of real battle, said Col. Jacques Ricard, a physician who is the chief land staff medical advisor for Canadian Forces. Ricard spoke at a program on the fighting in Afghanistan held at the Canadian Embassy in Washington, D.C., in September.

"Training gets the combat soldier or medic to do his job right in extremely stressful settings, even if later he decides he never wants to do it again," said Ricard.

Much of the Canadian experience with military stress in recent decades came from participation in peacekeeping operations, especially in the former Yugoslavia, he said. "There, our troops saw mass graves left from ethnic cleansing, local poverty, and motor-vehicle accidents and faced the perception of threats but not battle injuries or deaths."

With Canada's participation in NATO action in Afghanistan, however, it has suffered about 100 troops killed in action, 500 battle injuries, and 150 psychological injuries so far.

"There is a lag between the mission and the manifestation of psychological injuries," he said. "A tsunami of mentally disabled veterans is coming."

Realistic training may help, but so will having peers share prior combat experience with new troops, deploying mental health support personnel farther forward, continuing the use of "decompression" stops in Cyprus on the way home, and educating soldiers and their supervisors about mental health problems and care for those problems.

Canadian Forces' medical staff try to keep psychologically injured soldiers close to their units in the hope that they will recover and return to duty, but if that doesn't work, they can be repatriated, said Ricard.

Among U.S. troops, mental illness is the leading cause of hospital bed days and the second-ranking reason for medical encounters, said Lt. Col. Michael Bell, a physician with the U.S. Army Center for Health Promotion and Preventive Medicine. These mental health problems arise from more than the familiar stressors such as lengthy and multiple deployments, combat, sleep deprivation, battle wounds, and the sight of civilian casualties, he noted. "Stress also comes from soldiers doing unfamiliar jobs—like armored troops going on foot patrol—or from a changing sense of mission as we move to counterinsurgency," said Bell.

The United States has sought to counteract this stress by placing clinicians as close as possible to where its troops patrol or fight and by educating soldiers about how and when to seek mental health care.

However, Bell pointed out, "Stigma remains a pervasive problem and crops up in four different ways."

On a personal level, a soldier's sense of worthlessness may block him or her from seeking help, he said. Soldiers may fear that disclosure of mental health problems could harm their careers. Ridicule and gossip from peers may be the worst manifestation of stigma. Senior leaders in the military have come to appreciate the harm that entrenched stigma directed at mental health problems and treatment causes, but mid-level management remains a problem, despite antistigma education efforts.

"If soldiers have high combat exposure and poor leadership, they end up with more mental health problems," he said. "But many also say they have grown as a result of deployment and combat, and the outcome may depend on their unit leadership and peer support."

> **"A tsunami of mentally disabled veterans is coming."**

"If given good training, there is less chance that one event will push them over the edge," said psychologist Sonya Norman, Ph.D., an assistant professor in residence at the University of California at San Diego's Department of Psychiatry.

Learning in a heightened emotional state produced by realistic training exercises improves recall in a way similar to that produced by the emotional reactions that arise in combat, she explained. "Feelings of incompetence increase stress, while inaccurate appraisal by the soldier of threats, leads to errors and more stress."

Furthermore, combat often shatters the sense, ingrained since childhood, of a just, orderly world, said Norman. "For some, that leads to feelings of self-blame and that the world is completely meaningless, full of danger, and that they can't control it."

She cited the case of a soldier who, acting legally under the rules of engagement, shot and killed a civilian in Iraq. The man came to see himself as a "monster" afterward. Norman used realistic training videos to spark discussions with the soldier and ultimately get him to use self-Socratic methods to address memories of the event.

"You can't prevent psychological or moral injuries; you can only reduce them," said Norman. "The patient will always have the image and the knowledge of the event, but he can learn to live with it." ■

SAMHSA Helps Abuse Programs Improve Outcomes, Efficiency

A new SAMHSA publication offers guidance on how to integrate evidence-based practices for substance abuse treatment into clinical practice.

BY MARK MORAN

The Substance Abuse and Mental Health Services Administration has released a technical-assistance publication for substance abuse programs wishing to implement "best practices."

Written for substance abuse treatment administrators, managers, and supervisors, the 72-page manual, titled "Implementing Change in Substance Abuse Treatment Programs," suggests practical and efficient approaches for introducing and implementing evidence-based practices (EBPs). It includes steps for assessing an organization's readiness to adopt new practices, identifying priorities in adopting EBPs, evaluating progress, and sustaining change over time.

The manual covers principles of implementing change, preplanning and planning for change, implementation of EBPs, evaluation, and sustainability.

According to the manual, implementing EBPs can offer the following benefits to treatment programs:

• **Improve client outcomes:** EBPs are interventions shown to be effective with specific client populations.

• **Increase access to effective treatment:** Implementing interventions and programs with proven effectiveness gives an organization the greatest chance of helping the most people.

• **Engage staff:** Implementing change involves the entire organization. Involving staff and key stakeholders in the process can improve buy-in, enhance motivation, and ultimately reduce turnover.

• **Improve operating margins:** EBPs can reduce treatment costs while improving outcomes. More effective interventions and processes can reduce relapse and recidivism, requiring fewer treatment cycles. Proven, targeted treatments also may enable programs to eliminate less-effective program elements and increase volume, thereby improving the bottom line.

• **Save time:** EBPs can streamline treatment, reduce duplication of services and strategies, and increase staff productivity. If planned well, implementation efforts can foster efficient tracking of clients and outcomes, setting the groundwork for future change and adjustments.

• **Transform organizations from reactive to responsive:** Through the process of planning and implementing change, organizations can develop the infrastructure to readily identify and address problems and implement solutions.

• **Provide justification for funding:** Systematic data collection and the evaluation of outcomes are parts of the change process. Evaluation provides valuable information for grant and accreditation applications and documents outcomes to sell the program. Evaluation data also can be used to justify a shift in funding to practices that have proven outcomes.

"Implementing Change in Substance Abuse Treatment Programs" is posted at <http://download.ncadi.samhsa.gov/prevline/pdfs/SMA09-4377.pdf>. ■

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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®
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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.

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People With Schizophrenia Another of Hitler's Targets

Incidence patterns showing a dramatic increase in new cases of schizophrenia in Germany in the years after World War II underscore the erroneous nature of exclusively genetic theories of the disease that informed the killing program.

BY MARK MORAN

"I've always been fascinated with the Holocaust," said psychiatrist E. Fuller Torrey, M.D. "It's always seemed to me the most important thing that has happened in my lifetime. And I'm especially intrigued that it happened in the country that had at the time the highest level of education in the world. That's always said something important to me—we think we are civilized, but the truth is that we are only a few years out of the trees. Our veneer of civilization is remarkably thin."

That interest in the Nazi Holocaust recently led Torrey to examine one of the less-publicized aspects of the Nazi Party's murderous quest for racial and genetic "purity"—namely, the systematic murder and sterilization of people with mental illness, especially schizophrenia.

In an article in the September 16 online Advance Access section of *Schizophrenia Bulletin*, Torrey noted that the project had the participation of individual German psychiatrists and encountered little or no organized resistance from the German psychiatric profession. Culling data from published sources in English and German, Torrey and fellow researcher Robert Yolken, Ph.D., summarized the grim facts: in the years 1933 to 1945, between 220,000 and 269,500 individuals with schizophrenia were either sterilized or killed, representing all of those persons with schizophrenia living in Germany at the time.

Moreover, the systematic killing of patients with schizophrenia appears to have served as a kind of trial for the methods that would later be adopted in the colossal destruction of European Jewry. Torrey and Yolken wrote that in July 1939, two months before Germany's invasion of Poland, Adolf Hitler asked his personal physician to draft a law permitting the killing of mental patients; Hitler signed it into law on September 1 of that year, the day of the invasion.

"The planning and logistics for such mass murder elicited much discussion," they wrote. "The method finally chosen was the release of carbon monoxide gas into a closed room outfitted to look like a shower room and the subsequent burning of the bodies in crematoria. Gold fillings were removed from the teeth of the deceased and used to partially pay for the program. In early January 1940, the first 20 patients were led into a 'shower room' at the Brandenburg asylum and killed. This method was judged to be highly successful and was later adapted for the killing of Jews."

Several Ideas Collide to Justify Killings

In their article, Torrey and Yolken recount the growing popularity in the early 20th century of the ideas of eugenics and racial hygiene; the dramatic increase in the number of institutionalized psychiatric patients following World War I, when Germany underwent extensive economic hardship, and the subsequent search for ways to decrease their numbers and associated costs; the growing support for "euthanasia" among Nazi leaders and some within German psychiatry; and finally the development of a policy and program for killing mental patients—known as Aktion T-4—and the spread of methods used in the program to the larger project of killing Jews and others in the Holocaust.

The authors acknowledged that the quantity and quality of data on the subject have limitations and that the number of individuals killed in the project is an informed guess based on reasonableness and consistency with related data. They urged more research in this area of the history of psychiatry.

Torrey and Yolken cited 26 sources on the history of the Holocaust, medicine, and racial policies under the Nazis, and epidemiology of schizophrenia before and after the era of Nazi rule. Among these are *Death and Deliverance: "Euthanasia" in Germany c. 1900–1945* by Michael Burleigh (Cambridge University Press, 1994); *Cleansing the Fatherland: Nazi Medicine and Racial Hygiene* by Aly, Chroust, and Pross (Johns Hopkins University Press, 1994); and *Racial Hygiene: Medicine Under the Nazis* by Robert Proctor (Harvard University Press, 1988).

A Story Seldom Told

Torrey told *Psychiatric News* that the story of the killing of schizophrenia patients is relatively unknown. "I have talked to friends and colleagues about it, and one of the most surprising things is the number of colleagues who have never heard about it," Torrey said in an interview. "This includes people my own age. It's something we don't talk about, but it's very important to realize this happened. Psychiatrists played a leading role in it, and it is part of our history.

"If we forget it, it's at our own risk," Torrey said.

Was there no protest against the policy? "There were individuals who protested certainly," Torrey said. "I'm not aware of any protest from organized German psychiatry. If you wanted a bright future in Nazi Germany, you would not be enhancing your prospects by saying 'We shouldn't be doing this.'

"German colleagues have said to me, 'You forget that there were people who were trying to save patients,' " Torrey said. "I'm sure that happened. Of the degree to which it happened, I've never seen a good estimate."

Torrey and Yolken pointed out that the Nazis' reasoning for killing patients with schizophrenia was also founded on an erroneous notion that the disease was entirely genetic. The number of existing cases—or the prevalence—of the disease after the war was low, as expected, because of the killings.

More surprising was the fact that the incidence, or the number of new cases, was high suggesting that factors other than genes played an important role in schizophrenia.

For instance, the first postwar study of the incidence of schizophrenia in Germany was done in Mannheim in 1965, 20 years after the last patients had been sterilized or killed. That study found an incidence rate of 53.6 per 100,000—which was two to three times as high as the rates in the United States and England; other postwar studies found similar results.

Torrey and Yolken discussed several possibilities for this, but suggested that the most likely explanation is that social conditions after the war produced environmental factors—famine, disease, and poverty—that led to an increase in new cases of schizophrenia.

"An example was the increase in schizophrenia in Holland that followed the Dutch Hunger Winter in 1944–1945," they noted. "The cause of the high schizophrenia incidence rates in postwar Germany is thus not apparent and is an appropriate subject for additional research."

An abstract of "Psychiatric Genocide: Nazi Attempts to Eradicate Schizophrenia" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/abstract/sbp097>. ■

Communities Can Be 'Trained' To Prevent Substance Abuse

Evidence-based, custom-tailored interventions designed to prevent risky behavior in young adolescents reduce alcohol use and delinquent behavior, finds a new government study.

BY EVE BENDER

Communities That Care (CTC), a system of individualized, evidence-based substance-use-prevention programs, reduces risky behaviors such as alcohol use, smoking, and fighting in adolescents, according to the results of the Community Youth Development Study, published in the September 7 *Archives of Pediatric and Adolescent Medicine*.

Eighth-grade students living in communities that employed CTC strategies were about 33 percent less likely to begin smoking and drinking than peers living in control communities that had no such prevention programs, and were 25 percent less likely to engage in delinquent behavior—which can be a predictor of future substance use—than eighth graders living in control communities.

The CTC program is designed to take into account individual communities' needs in terms of behaviors that place adolescents at risk. Under the program, community leaders such as clergy, teachers, health workers, social workers, and other volunteers receive training that enables them to implement the prevention strategies based on community needs. These strategies can focus on a range of issues, such as preventing drug and alcohol use, ameliorating family conflict, reducing violence, and preventing HIV/AIDS, for instance.

Intervention communities received six training sessions delivered over the course of a year by certified CTC trainers. In addition, community leaders received training on how to implement a CTC system based on the needs of their community. In this study "communities" were freestanding incorporated towns that were not suburbs of larger cities. These towns were matched with regard to population, crime, and poverty rates before random assignment to control or Communities That Care conditions. This allowed researchers to assess the effects of CTC itself without risk of results from other initiatives that could have spilled over if they had selected large cities or suburbs of large cities for the trial.

"What makes Communities That Care unique is that it enables communities to identify their own special issues so that they can handpick the right prevention programs," National Institute on Drug Abuse (NIDA) Director Nora Volkow, M.D., stated in a press release issued by the agency in September.

To evaluate the CTC program, researchers analyzed results from the Youth Development survey, which was administered in the classrooms of 4,407 fifth graders from 24 communities in Colorado, Illinois, Kansas, Maine, Oregon, Utah, and Washington beginning in 2003. The survey included questions about drug and alcohol use and delinquent behaviors such as shoplifting, property damage, and fighting. Students were surveyed annually for four years or through eighth grade.

Community leaders in 12 of the communities were randomly assigned to undergo CTC training and implementation. The 12 other communities did not implement the CTC prevention programs.

The researchers from the University of Washington and the University of South Carolina analyzed the results of the study and found that students from control communities were 41 percent more likely to engage in delinquent behavior between the fifth and eighth grades than were children in the same grade range who lived in CTC communities.

In addition, they found that students in the control communities were 60 percent more likely to start drinking between

please see ***Communities*** *on page 32*

Should Med Students Be Protected From Their Own Internet Use?

Medical students may be jeopardizing their future careers when they post photos of themselves getting drunk or make callous comments online, because nothing is completely private in cyberspace.

BY JUN YAN

Credit: Alashi/iStockphoto

Teaching professionalism to medical students may be lagging when it comes to the issue of how to behave appropriately on the Internet, according to a recent survey of U.S. medical schools.

Online behaviors by medical students that are deemed unprofessional and result in school interventions appear to be common, the anonymous survey found. Among the responses from 78 medical-school administrators in charge of student affairs, 47 (60 percent) said they were aware of at least one incident in the prior year related to students' online postings.

Among the examples cited were posting too much confidentiality-threatening information about patients on blogs and Facebook, which many respondents said were the most serious violations. Other types of incidents included posting sexually suggestive photos; posting text, photos, and videos depicting intoxication or use of illicit drugs; requesting inappropriate friendships with patients on Facebook; and using profanity or making discriminatory or disparaging comments about faculty, classmates, or their schools.

The survey was conducted by researchers from George Washington University School of Medicine and Johns Hopkins University School of Medicine. More than half (78 out of 130) of the medical schools that received the survey responded. The results were published in the September 23/30 *Journal of the American Medical Association*.

Trainees, faculty, and other staff were the ones who most frequently reported the incidents to administrators. Thirty of the responding schools issued informal warnings to the students involved in the incidents. Formal disciplinary actions, including temporary suspensions, were handed out at 12 of the schools. Three schools dismissed students for serious or repeated online violations.

Social-networking sites such as blogs, Facebook, Twitter, and YouTube have evolved rapidly in recent years, especially among young people. Users post and share a variety of materials, including photos and videos, in a public or semi-public manner. Data collected by the Pew Research Center showed that at least 75 percent of American young adults aged 18 to 24 use social-networking sites, and this percentage continues to grow rapidly.

Not only are medical schools struggling with setting policies for students' online behaviors, but also experienced physicians, including psychiatrists, face plenty of ethical ambiguities and dilemmas in this realm (*Psychiatric News*, July 17). Currently, there are no consistent, widely accepted guidelines for either physicians or medical students that clearly define the boundaries of unprofessional and unethical online behavior.

In the survey of medical schools, 28 administrators said that their school policies "broadly cover student-posted online content." However, only five of those 28 schools explicitly address Internet use in their policies. Of the 46 schools reporting that they have no such policies, five said they were developing policies to address students' online postings.

The survey authors acknowledged that the line between unprofessional online behaviors and free speech is often unclear, and "medical students may not be aware of how online posting can. . . jeopardize their careers."

Although the line regarding patient privacy is clearly drawn, other types of online expression may be out of schools' jurisdiction, said Damir Huremovic, M.D., director of psychosomatic medicine services at Nassau County University Medical Center in New York, in an interview with *Psychiatric News*. Huremovic gave a presentation on this subject at the APA annual meeting in May in San Francisco.

Huremovic questioned whether medical schools have a role in regulating students' postings on Facebook or on personal Web spaces. "I don't think we should be policing private behaviors," he commented. "Doctors use profanities outside of their work, and they should be allowed to do so." Students should be afforded similar freedom of expression in their private lives, he believes, and schools need to spell out official policies and expectations about students' Internet postings clearly and in advance.

The president of the American Medical Student Association (AMSA), Lauren Hughes, M.D., told *Psychiatric News* that she has heard similar issues from AMSA members and other students. AMSA cur-

please see ***Internet*** *on page 34*

APA Gains New 100% Club Member

The Dartmouth-Hitchcock Medical Center Psychiatry Residency Program is inducted into APA's 100% Club.

The 2008-2009 residency program at Dartmouth-Hitchcock Medical Center in Lebanon, N.H., is now a member of APA's 100% Club. This means that all the program's residents are members of APA. The program, run by Dartmouth Medical School, is directed by Ronald Green, M.D.

The 100% Club was created to encourage the psychiatry department chairs and residency program directors to promote APA membership to their residents. As 100% Club members, the program receives a group picture of its residents and faculty mounted on a wooden plaque and a major psychiatry textbook, and each resident receives an online subscription to *Focus: The Journal of Lifelong Learning*. Both the textbook and journal are published by American Psychiatric Publishing Inc.

Psychiatry residents and directors of residency programs seeking more information about APA's 100% Club should contact Nancy Delanoche of APA's Division of Education at (703) 907-8635 or e-mail Delanoche at ndelanoche@psych.org. ■

Credit: The Dartmouth-Hitchcock Medical Center Psychiatry Residency Program

From left: Vince Watts, M.D. (associate training director), Ronald Green, M.D. (training director), Daniel Bateman, M.D., Robert Cotes, M.D., Steven Powell, M.D., Micah Krempasky, M.D., Geoffrey Sinner, M.D., Sarah Akerman, M.D., Michael Przydzielski, M.D., Joseph Dwaihy, M.D., Benjamin Wood, D.O., Jodi Marshall, M.D., Julia Frew, M.D., Evan McCord, M.D., Sarah Walsh, M.D., Lynn McCormick, M.D., Linda Call, M.D., Aleem Khan, M.D., Alan Green, M.D. (department chair). Not pictured: Stacey Carloni, M.D., Karin Reed, M.D., Diane Stevens, M.D., Marcy Traum, M.D., Ekaterina Hurst, M.D., Cassie Karlsson, M.D., Ryosuke Kawatsuji, M.D., Joel Peterson, M.D., Abby Reineck, M.D., Candace Thompson, M.D., Donald Ammerman, M.D.

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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.

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

62-1014307R R2 03/09

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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

APA's Election Guidelines Emphasize Dignity, Courtesy, and Fairness

The Nominating Committee selected the candidates for the 2010 election (*Psychiatric News*, October 2), marking the start of the campaign season, and members may want to familiarize themselves with the campaign guidelines.

Guidelines prescribing members' election-related activities were established by the Board of Trustees in the early 1970s, when APA began having contested elections, and have been updated to address major concerns. These concerns are: (1) to guard against massive campaign efforts "buying" an election win, particularly if those efforts are financed by resources from outside the membership, (2) the revulsion against campaign committees and unwelcome bids for public support, (3) the growing distress of the membership at being deluged with campaign materials, and (4) a belief among some members that large-scale campaigning is inconsistent with their conception of APA's professional image.

Thus the guidelines aim "to encourage fair and open campaigning by APA members on a level playing field by (1) specifying permitted and prohibited election-related activities, (2) fostering opportunities for candidates to educate their colleagues about the issues, (3) informing voters about candidate experiences and views, (4) keeping costs down, and (5) maintaining dignified and courteous conduct appropriate to the image of a profession." Personal attacks against opponents are not permitted.

Candidates and their supporters must use their own resources for election activities (Section A.3). Use of APA, Area Council, and state association/district branch resources or personnel is prohibited. There are limits on the number of letters that each person may write (400 letters for national candidates or 100 for Area or member-in-training trustee-elect office; Section C.1).

The guidelines for use of electronic media should be noted carefully. While there is no limit on the number of campaign messages that may be sent by e-mail (Section B.1, first paragraph), the most common infraction of the guidelines is campaign messages sent without the required "APA Campaigning" at the start of the subject line. The only APA-supported list serve that may be used for campaigning is Member-to-Member (Section B.1, last paragraph).

APA's Web site will once again contain information about candidates, with links to the homepages of candidates who have Web sites.

The Elections Committee recognizes that there always will be problems in implementing the guidelines and in creating guidelines that are entirely equitable, but members have indicated their general satisfaction with the current guidelines. The committee investigates any possible violation of which it becomes aware and reports violations to the Board (Section D.3). The committee is open to suggestions from members on how to improve or change the guidelines.

The Elections Committee encourages members to get involved in the election process, to become informed about the candidates, and to support the candidates of their choice through personal letters, e-mails, or personal contact, and, mainly, to vote in the election. Further, members are urged to vote electronically and to make electronic voting (without receiving a paper ballot) their choice by visiting the following Web page on the APA Web site at <www.psych.org/optinoptout/>.

On December 22 voting members with e-mail addresses on file with APA will receive an e-mail with instructions for voting online, and paper ballots will be mailed on the same date to those not voting electronically. Further election information and information about the candidates will be included in the December 4 issue of *Psychiatric News*. ■

This article was prepared by APA's Elections Committee.

APA ELECTION GUIDELINES FOR CANDIDATES AND SUPPORTERS

These election guidelines are based on those approved as amended by the Board of Trustees in September 2009.

A General Guidelines

The intent of the guidelines is to encourage fair and open campaigning by APA members on a level playing field by (1) specifying permitted and prohibited election related activities, (2) fostering opportunities for candidates to educate their colleagues about the issues, (3) informing voters about candidate experiences and views, (4) keeping costs down, and (5) maintaining dignified and courteous conduct appropriate to the image of a profession. Candidates are to state their own positions on issues and their own plans for the Association directly and positively, but may not make personal attacks against their opponents. Third-party endorsements in campaign communications are not allowed.

Candidates are to inform members they ask for support about the guidelines by sending a copy or calling attention to the guidelines on the APA Web site.

Campaigning (written or e-mail solicitation of votes or support) is not permitted until after Nominating Committee nominations are reported to the Board of Trustees. Members should withhold commitments of their final support or votes until after all candidates are known. Members circulating petitions to be nominated may not use the petition process for campaign/electioneering purposes beyond asking for signatures on petitions.

1. **Compliance:** Each candidate receives a copy of these guidelines and a statement to sign, certifying that he/she has read the guidelines; promises to abide by them; will immediately report any deviations of which he/she becomes aware to the Elections Committee; and will notify and try to correct any supporter upon learning of an actual or potential deviation. The Elections Committee investigates any potential violation by a candidate or supporter of which it becomes aware, and reports violations to the Board of Trustees. The procedures used by the Elections Committee to investigate and report campaign violations are in Chapter 2 of the *Operations Manual* and will be sent to candidates with these Election Guidelines.

   When candidates or their supporters are unclear about whether an intended campaign action is permitted, they should seek the opinion of the Elections Committee before taking action. The Elections Committee will respond with a ruling concerning the proper interpretation of the guidelines and inform all candidates in order to maintain a "level playing field."

2. **APA members in other organizations:** All APA members are expected to abide by the APA Election Guidelines in APA elections, including in their capacity as officers and members of other organizations. APA requests that other organizations adhere to the intent of the campaign guidelines and provide fair and equitable coverage of opposing candidates.

3. **Money/resources:** Candidates/supporters must use their own resources for election activities. Fundraising is not permitted, nor is sharing of materials, such as letters, postcards, and stamps (with the exception of mailing addresses purchased from APA). Candidates/supporters may not organize campaign committees, and candidates may not enter into agreements to campaign together. Use of APA, Area Council/state association, or district branch resources or personnel is prohibited.

B Guidelines for Electronic Media

Candidates and their supporters using electronic media for campaign purposes are expected to comply with the guidelines set forth in Section A.

1. **E-mail and List Servers:** There are no limits on the number of campaign messages sent by e-mail. E-mail used for campaign purposes must comply with the intent of the guidelines with regard to content and must start with the words "APA Campaigning" in the subject line. Obtaining e-mail addresses is the responsibility of the candidates and their supporters using resources only as specified in Section A.3. E-mail addresses are not to be provided by APA, Area Councils/state associations, or district branches. See also Section C.

   Candidates may create their own list servers to facilitate communication with and among their supporters.

   APA list servers are created for conducting the business of an APA component. Thus, no list server using APA technology (except for Member-to-Member) may be used for campaigning. This includes district branch and Area Council/state association list servers. List servers of other psychiatric organizations may be used for campaigning if permitted by those organizations.

2. **APA's Web site:** APA will include information on all candidates (the photos, biographies, and statements printed in *Psychiatric News)* and on the election itself (campaign guidelines, ballot mailing and return dates, etc.) on its Web site. This election information can be accessed through the election logo and linked to other information as appropriate.

3. **Candidates' homepages:** APA will provide links from its Web site to the individual homepages of the candidates. Each candidate is responsible for setting up and financing his/her own homepage, as well as any campaign communication on Member-to-Member. Posting of third-party letters of support on candidate Web sites is prohibited. There will be a disclaimer on APA's Web site stating that candidates' homepages are their own creation and responsibility, and that APA takes no responsibility for information posted on them. APA reserves the right to cut the link between its Web site and a candidate's homepage if a candidate violates the campaign guidelines. No other individual, institutional, or organizational homepages will be used for campaigning.

C Guidelines for Use of Campaign Letters

1. **Letters:** Election "letters" include letters, postcards, and faxes asking for a member's election support. Single copies of a CV, fact sheet, and biography may be included with the election letters or mailed separately and are not included in the letter limits. Handouts may be made available at any meetings attended by the candidate.
   - Each candidate/supporter must generate his/her own "letters" with his/her own personal resources; no APA, Area Council/state association, or district branch resources may be used.
   - Each candidate/supporter may write up to 400 letters for candidates for national office or 100 for candidates for Area trustee or for MITTE.
   - Mailing addresses may be purchased from APA, Area Councils/state associations, or district branches and may be shared.
   - Candidates may not provide multiple copies of documents for distribution to supporters.

D Guidelines for Candidate Presentations

1. **Presentations:** Candidates may attend no more than four mutual presentations with their opponent(s). All candidates must attend to present. Presentations made via proxy statements or modes other than physical attendance are prohibited. If all candidates have been given equal opportunity to attend and one cannot attend, the other candidate(s) may present, but must count the presentation as one of eight made in his/her professional capacity (see below). The annual presentation at the Assembly and its attendant Area Council and committee meetings counts as one of the four mutual presentations. In addition, grand rounds, lectures, presentations at APA meetings, and other kinds of presentations made in one's professional capacity should be limited to no more than eight during the campaign period. "Presentations" are those made to an audience with a significant number of psychiatrists, academic/psychiatric gatherings such as grand rounds, hospital lectures, etc. Running for office should not inhibit or prohibit candidates from conducting their usual professional business; every effort should be made to define "usual professional business" in the narrowest sense.

E Guidelines for Area Councils/State Associations, District Branches, and Those Holding Appointed or Electioned Positions in Those Organizations for APA

1. **Money/resources:** APA, Area Council/state association, or district branch funds, services, or staff may not be used to endorse, support, or promote any candidate; however, Area Council/state association, or district branch funds—not APA funds—may be used to support the expenses of candidates invited to the branch/Area meeting for election purposes (see #3 below). APA, Area Council/state association, or district branch organizational stationery may not be used. Candidates/supporters who hold appointed or elected APA, Area Council/state association, or district branch positions may refer to their titles in the body of the letter, but if they choose to sign the letter, they may not do so over their APA organizational title. Likewise, e-mails may not be "signed" using an APA organizational title.

2. **Newsletters:** Area Council/state association or district branch newsletters may announce as news items of up to 150 words per candidate the candidacy for national office or Area trustee of member(s) of that Area Council/state association or district branch, with pictures. Editorial endorsement of candidates is prohibited, as are letters to the editor in support of (or opposition to) candidates. Newsletters may print statements or other materials by or about a candidate only if they give equal opportunity to opposing candidates. Newsletters may not be distributed beyond the usual newsletter distribution.

3. **Meetings:** Candidates invited to attend Area Council/state association or district branch meetings to campaign may do so only if their opponent is also invited to the same meeting. Candidates making scientific presentations at Area Council/state association or district branch meetings must count them as one of their eight meetings and may not discuss election issues unless their opponents have been given an equal opportunity to do so.

Investing in Early Intervention Cuts Psychosis Treatment Costs

Patients in the early-intervention program were more likely to be in remission, have fewer negative symptoms, and to have paid employment than were patients receiving usual care.

BY MARK MORAN

A comprehensive early intervention program for first-episode psychosis—designed to provide evidence-based treatments as soon as possible after a first psychotic break—appears to be cost-effective compared with usual treatment over the long term.

Nearly eight years after initial treatment for first psychosis, annual treatment costs for each patient in an early-treatment program were on average more than $6,000 less than per-patient treatment costs for individuals receiving usual care. The report appeared in the September *Schizophrenia Bulletin*.

"Investment in early intervention in psychosis services is an efficient use of health care resources and is worthy of widespread implementation," study author Cathy Mihalopoulos, a health economist at Deakin University in Victoria, Australia, told *Psychiatric News*.

Coauthor Patrick McGorry, M.D., Ph.D., a professor of psychiatry at Australia's University of Melbourne, added that he believes "not investing in early intervention and treatment for at least two years [following first psychosis] is economically irresponsible."

Mihalopoulos and McGorrry studied costs associated with the Early Psychosis Prevention and Intervention Centre (EPPIC) in Melbourne. EPPIC, begun in 1992, is designed to identify patients at the earliest stage from onset of psychosis and to provide intensive phase-specific treatment for up to two years thereafter. As part of the program, a mobile team called the Early Psychosis Assessment Team (EPAT) was established to serve as the sole entry point to EPPIC. Through networking and carefully targeted community education activities, EPAT has sought to raise community awareness of psychosis in young people and promote recognition and early referral.

In the new study, direct mental health service costs incurred subsequent to the first year of treatment and symptomatic and functional outcomes of 32 participants initially treated for up to two years at EPPIC were compared with those of a matched cohort of 33 participants initially treated with usual care. Costs associated with treatment were measured using published Australian prices.

Almost eight years after initial treatment, EPPIC subjects displayed lower levels of positive psychotic symptoms, were more likely to be in remission, and had a more favorable course of illness compared with the controls. Fifty-six percent of the EPPIC cohort was in paid employment over the last two years compared with 33 percent of controls.

Moreover, each EPPIC patient cost on average $3,445 per year to treat compared with $9,503 for controls.

Mihalopoulos said the study confirms and extends the results of an initial economic evaluation of first-year costs and outcomes of treatment for patients in EPPIC. That study, published in the July 1999 *Acta Psychiatrica Scandinavica*, found that the first-year costs incurred by the EPPIC sample were less than those of patients treated in a model of care that prevailed in the community prior to EPPIC, with improved quality of life and fewer negative symptoms. (The earlier standard of care included enhanced inpatient care for a first episode, as in EPPIC, but with standard aftercare in the community.)

"The key reason for this difference was due to less hospital use by the EPPIC cohort," Mihalopoulos told *Psychiatric News*. "Interestingly, the first EPPIC study found that the EPPIC cohort used more community-based mental health services compared to the historical controls. But our new [long-term] study found that the EPPIC cohort used less community-based outpatient services over the longer term. So the current study confirms the initial findings with the observation that community service use also seems to reduce over the longer term."

There are some 200 early-intervention programs for first psychosis in Europe, the United Kingdom, and North America, according to the authors, but Mihalopoulos and McGorry said they know of no studies of cost-effectiveness of programs in North America. Mihalopoulos cautioned that cost-effectiveness across programs is difficult or impossible to determine, since costs for similar services can differ dramatically across different countries and health care systems.

Nevertheless, the several studies of cost-effectiveness that exist for European and United Kingdom programs all show significant reductions in cost for the early-intervention programs.

Mihalopoulos added that one study by Knapp and colleagues comparing costs of schizophrenia care in five European countries found that inpatient costs seem to vary less than other costs. That study, "Comparing Patterns and Costs of Schizophrenia Care in Five European Countries: the EPSILON Study," appeared in the January 2002 *Acta Psychiatrica Scandinavica*.

"This suggests that early psychosis interventions are likely to be of benefit in Western countries that have a mix of inpatient, outpatient, and community services available," she said. "So while the degree of cost savings may vary from system to system, there are compelling reasons to believe that such savings are possible anywhere."

"Is Early Intervention in First Psychosis Cost-Effective Over the Long-Term?" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/full/35/5/909>. An abstract of "EPPIC: An Evolving System of Early Detection and Optimal Management" is posted at <http://schizophreniabulletin.oxfordjournals.org/cgi/content/abstract/22/2/305>. ■

Inability to Fund Basic Needs Linked to Cognitive Decline

Hispanic Americans who cannot meet their basic needs are especially susceptible to cognitive decline. Whether helping them meet those needs would counter such decline remains to be seen.

BY JOAN AREHART-TREICHEL

Older Hispanic Americans who do not have enough money to cover their basic needs appear to be more vulnerable to cognitive decline than are older Hispanic Americans who have sufficient money for such needs.

So reported Natalie Sachs-Ericsson, Ph.D., a clinical psychologist at Florida State University, and coworkers in the September *Journal of Aging and Health*.

The study was based on data collected from 1993 to 1996 from a representative sample of about 3,000 community-dwelling Mexican Americans aged 65 or older living in five southwestern states.

Subjects' demographic and health information was collected. For example, subjects were asked questions about gender, age, education, and place of birth. To assess income, subjects were asked to select the income category that best represented their family income during the previous year.

Subjects also completed the Center for Epidemiological Studies–Depression Scale, which is a commonly used self-report instrument to evaluate depressive symptoms. In addition, they were asked whether they had ever been told by a doctor that they had had a heart attack, stroke, high blood pressure, diabetes, or cancer. Self-reported health problems have been found to have good agreement with both medical records and physician reports.

Information was also collected about whether subjects had trouble paying for basic living expenses such as food, clothing, housing, transportation, and health care. Subjects were given the Mini-Mental Status Examination to evaluate cognitive function, both at the start of data collection (1993-1994) and at the end of data collection (1995-1996).

The researchers then attempted to determine whether those subjects who had reported not having enough money to pay for their basic needs—59 percent of the sample—were more likely to experience cognitive decline over the two-year follow-up period than were the rest of the subjects. The researchers also considered possibly confounding factors such as educational level, depressive symptoms, and history of heart attack, stroke, high blood pressure, diabetes, or cancer.

Even when these potentially confounding factors were considered, those who had reported not having enough money to cover basic needs were significantly more likely to experience cognitive decline in the two-year follow-up period than were those who had reported having enough money.

The question, of course, is why?

The researchers suspect that there was a cause-and-effect association at work.

For example, if older Hispanic Americans did not have enough money to buy food, then inadequate nutrition might lead to a deficiency in B vitamins, the antioxidant vitamins C and E, and the anti-inflammatory omega-3 polyunsaturated fatty acids, which might effect cognitive decline.

Or if older Hispanic Americans did not have enough money to pay for health care or for medications, a lack of health care might increase progression of stroke, heart disease, or diabetes, which might lead to cognitive decline.

Or if older Hispanic Americans were chronically stressed by not having enough money to pay for the basics, the stress might make them vulnerable to cognitive decline. Indeed, there is evidence that chronic stress can damage neurons, especially in the hippocampus, which is vital to memory, the researchers pointed out. Also, there is evidence that stress can decrease brain-derived neurotropic factor (BDNF) in the hippocampus, and a paucity of BDNF has been linked to Alzheimer's disease. In brief, "having a problem with basic needs is a huge chronic stressor, which can affect the brain in bad ways," Sachs-Ericsson noted during an interview with *Psychiatric News*.

If correct, the researchers' hypothesis—that inadequate money for basic necessities led to cognitive decline in many of their subjects—might have important public health implications, they believe. For example, if poor, older Hispanic Americans were given help in obtaining food, health care, and medications, they might be shielded to some extent from cognitive decline.

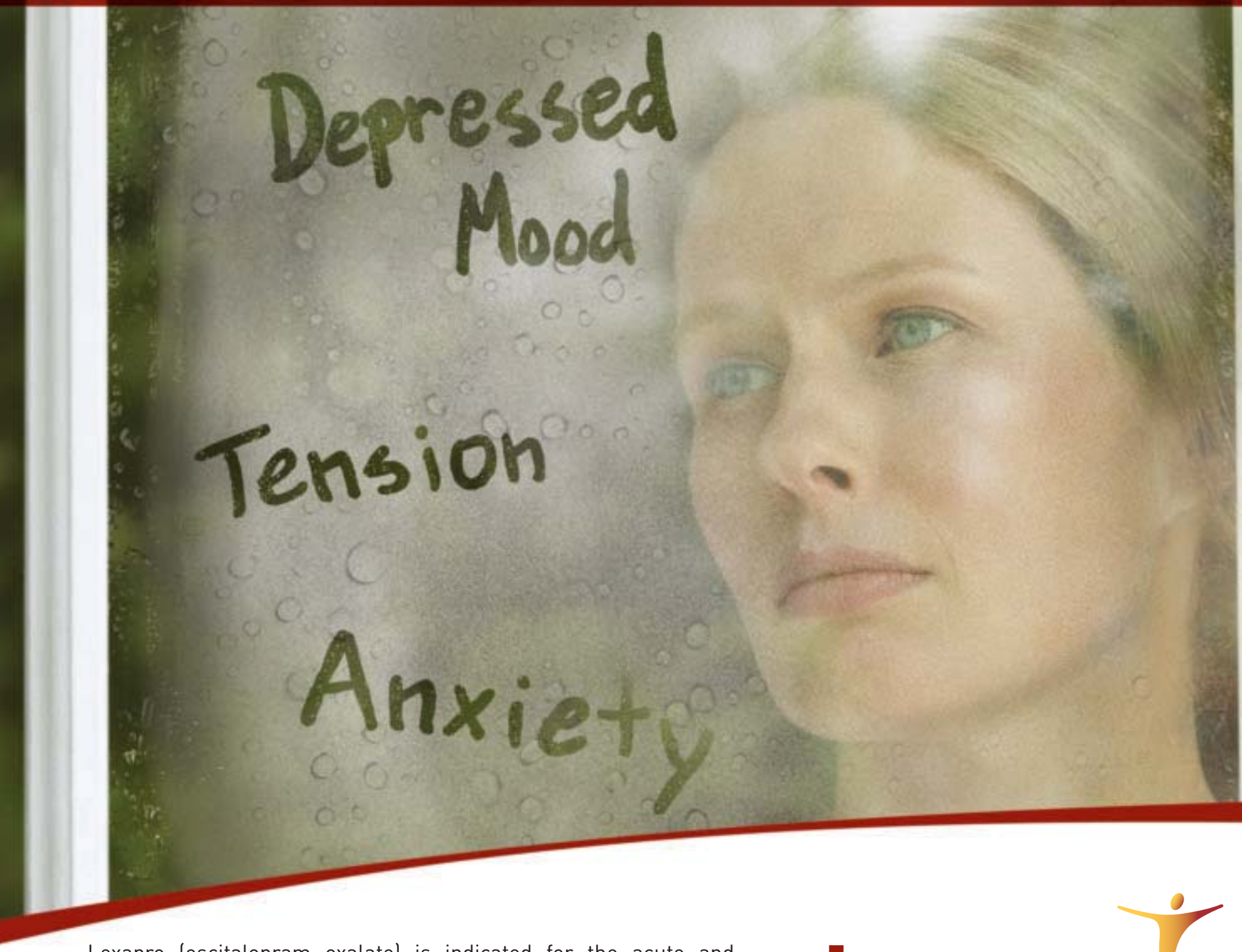
In any event, there is a pressing need to find ways to reduce the incidence of cognitive decline in the Hispanic-American population, Sachs-Ericsson and her coworkers concluded. Hispanic Americans are one of the fastest-growing segments of the U.S. population, Hispanic Americans appear to be more susceptible to Alzheimer's disease or dementia than are non-Hispanic white Americans, and Hispanic Americans seem to show symptoms of Alzheimer's seven years earlier than non-Hispanic white Americans (*Psychiatric News*, October 1, 2004).

The study was funded by the National Institute on Aging.

An abstract of "Problems Meeting Basic Needs Predict Cognitive Decline in Community-Dwelling Hispanic Older Adults" is posted at <http://jab.sagepub.com/cgi/content/abstract/21/6/848>. ■

Treat core symptoms[1,2]

of Major Depressive Disorder (MDD) & Generalized Anxiety Disorder (GAD)



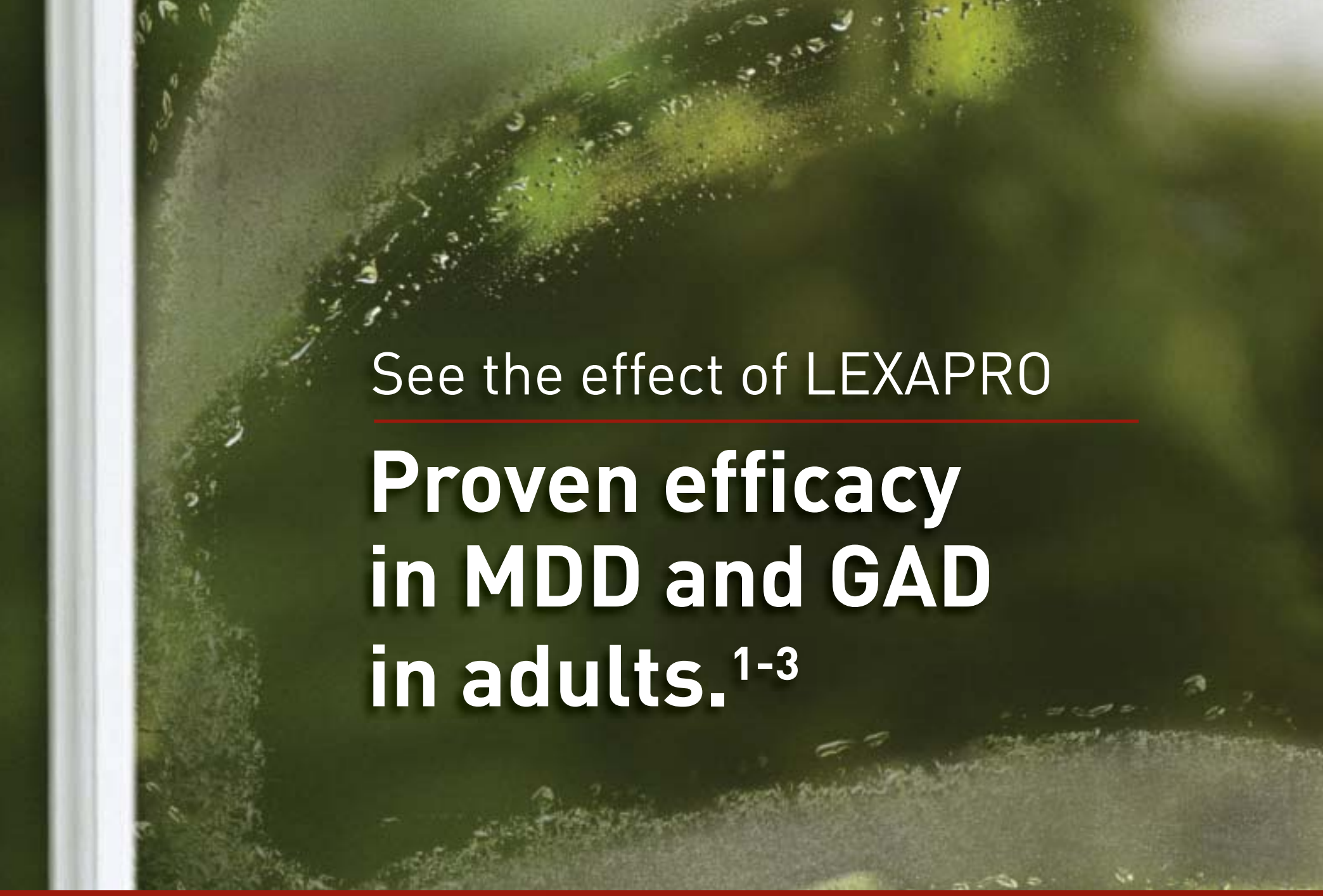
Lexapro (escitalopram oxalate) is indicated for the acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12-17 years. Lexapro is also indicated for the acute treatment of generalized anxiety disorder (GAD) in adults.

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.

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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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EEG Biomarker May Reveal If Antidepressant Is Working

Measuring the faint electrical signals from the brain may give a hint about whether depression-affected neurons are being reshaped by an antidepressant the patient is taking.

BY JUN YAN

As psychiatrists know all too well, treating depression can be a slow process. Patients often have to take an antidepressant for four to eight weeks before finding out whether they are responding to the medication. A biomarker derived from electroencephalography (EEG) provides some hope for hastening the process, however, by measuring the brain's response to an antidepressant after only a week of treatment, sometimes weeks before symptom relief is clinically observed.

This EEG-based biomarker, known as the Antidepressant Treatment Response (ATR) Index, is a composite index being developed by Aspect Medical Systems, a medical-device company based in Norwood, Mass. The ATR biomarker is calculated from specific quantitative EEG measurements taken before and one week after the patient starts an antidepressant.

Four electrodes are placed on the patient's forehead and two on the earlobes as the patient sits in a reclining chair. The EEG measurements are recorded for two closed-eye periods, each lasting six minutes, with an open-eye period of two minutes in between (see photo). The quantitative EEG readings are fed into computer software, which calculates the ATR score, adjusted to a scale of 0 to 100, after the two EEG sessions.

Two articles published in the September 30 *Psychiatry Research* reported results from the Biomarkers for Rapid Identification of Treatment Effectiveness in Major Depression (BRITE-MD) study. Funded by Aspect and conducted at nine research sites, the study showed that the ATR biomarker was able to predict to a reasonable degree depressive patients' eventual response and remission after seven weeks of antidepressant treatment.

In the BRITE-MD study, 375 patients were started on escitalopram 10 mg daily for one week and then randomly assigned to one of three treatment arms for the next six weeks: continuing with escitalopram 10 mg, switching to bupropion extended-release 300 mg, or taking both escitalopram and bupropion.

Majority Met Response Criteria

Of the 73 patients who were randomized to escitalopram for a total of seven weeks of treatment, 52 percent met the response criterion, defined as at least a 50 percent reduction from baseline in the 17-item Hamilton Rating Scale for Depression (HAM-D) total score. In addition, 38 percent reached remission, defined as a HAM-D score of no more than 7 at the end of week 7.

Based on statistical analyses, a best-fit ATR threshold (58.6) predicted response and remission in the escitalopram-treated patients significantly better than chance. Patients with a score higher than the threshold were deemed to have a positive biomarker (more likely to respond), and those with a score lower than the threshold were deemed to have a negative biomarker (less likely to respond).

For predicting response, the ATR biomarker had an accuracy of 74 percent, sensitivity of 58 percent, specificity of 91 percent, positive predictive value (PPV) of 88 percent, and negative predictive value (NPV) of 67 percent. For predicting remission, the accuracy, sensitivity, specificity, PPV, and NPV were 74 percent, 61 percent, 82 percent, 68 percent, and 77 percent, respectively.

In comparison, neither serum concentrations of escitalopram and its active metabolite nor genetic tests of 5HTTLPR and 5HT2a polymorphisms predicted treatment response or remission. Early reduction of HAM-D score from baseline on day 7 did predict eventual response but did not predict remission. Clinicians' impression of symptom improvement and prediction of response and remission on day 7 also fared no better than chance.

The study findings need to be replicated, but so far the ATR biomarker looks promising for future clinical application, said Andrew Leuchter, M.D., the lead study author, in an interview with *Psychiatric News*.

Leuchter is a professor of psychiatry and biobehavioral sciences at the David Geffen School of Medicine at the University of California at Los Angeles, one of the sites that conducted the BRITE-MD study. "The EEG is easy to do, the electrodes are easy to put on, and the whole test takes less than 15 minutes," he noted.

Credit: Aspect Medical System

The Antidepressant Treatment Response biomarker is calculated based on quantitative electroencephalography measurements taken at two sessions: before the start of antidepressant treatment and one week into the treatment.

How It May Work

Researchers do not yet know the exact mechanism of the ATR biomarker, but they think it involves quantitative EEG picking up changes in brain activities long before clinical improvement of mood symptoms appears.

"Most of the brain's energy use goes to create electrical activities [among neurons], which have some relationship to how the brain works and how it responds

please see ***Biomarker*** *on page 34*

Why Does Life Expectancy Grow When Economy Contracts?

Today's Great Recession, as some have dubbed America's economic problems, may not be good for mental health, but it might offer some a silver lining in terms of physical health.

BY JOAN AREHART-TREICHEL

The Great Depression is generally considered a dark period in American history, when millions of Americans lost their jobs, homes, and all of their worldly possessions and when a few despairing Wall Street investors leapt from buildings to their deaths.

Indeed, a new analysis of economic and mortality data from that period has shown that suicides did increase during the Great Depression. But otherwise, the analysis has demonstrated, mortality rates dropped during those years.

These findings were reported online September 28 in the *Proceedings of the National Academy of Sciences* by José Tapia Granados, Ph.D., and Ana Diez-Roux, Ph.D. Tapia is an economist and assistant research scientist at the University of Michigan's Institute for Social Research. Diez-Roux is a professor of epidemiology at the University of Michigan's School of Public Health.

Tapia and Diez-Roux analyzed mortality and economic data from 1920 to 1940 to see whether they could find any correlations between mortality rates and economic downturns and upswings during these years. They could, they found.

From 1930 to 1933, mortality rates decreased for almost all age groups compared with those from 1920 to 1929, and there was an overall gain of six years in life expectancy for the general American population. Nonwhite Americans profited the most, with a gain of eight years in life expectancy.

The only exception to this general pattern was suicide mortality rates, which increased from 1930 to 1933, compared with suicide mortality rates from 1920 to 1929. However, suicides accounted for less than 2 percent of all deaths during 1930 to 1933.

Moreover, for most age groups overall mortality tended to peak—over and above its long-term trend—during years of strong economic expansion (such as 1923, 1926, 1929, and 1936-1937). In contrast, the deep recession of 1921, the Great Depression of 1930 to 1933, and the deep recession of 1938 coincided with generalized declines in mortality rates and peaks in life expectancy.

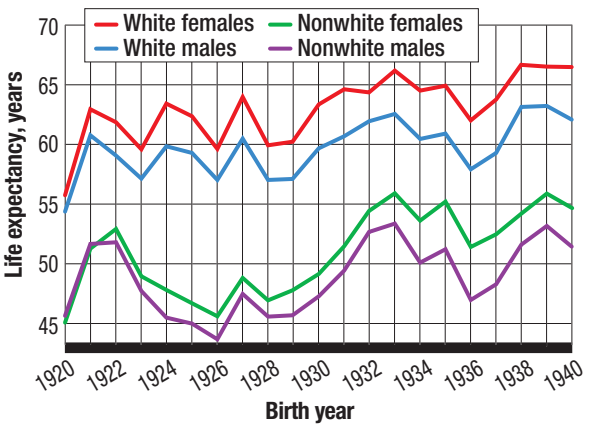
But how to explain these counterintuitive results?

Since this is a study of association, not of cause, it's possible that economic conditions influenced mortality, or that mortality influenced economic conditions, or that the link between economic conditions and mortality could be explained by other factors. Tapia and Diez-Roux suspect that economic conditions influenced mortality. And if that is the case, they reasoned, then the Great Depression, as well as recessions between 1920

please see ***Economy*** *on page 34*

Economy Down, Life Expectancy Up

Life expectancy for white males and females and for nonwhite males and females followed a similar pattern from 1920 to 1940. There was an increase during economic downturns and a decrease during economic upturns. For example, there was an increase during the deep recession of 1921; a decrease in 1926, a year of strong economic expansion; an increase in 1933; and a decrease again in 1936, a year of strong economic expansion.



Source: Jose Tapia Granados, Ph.D., and Ana Diez-Roux, Ph.D., *Proceedings of the National Academy of Sciences,* September 28, 2009

Vaccine Shows Promise In Fighting Cocaine Addiction

Response is proportional to the level of antibody that can be induced by the vaccine, which varies greatly among study participants. Further manipulation of the vaccine may improve efficacy.

BY JUN YAN

A vaccine that keeps cocaine out of the brain shows promise as a viable treatment for cocaine addiction, but researchers must overcome several technical hurdles to increase the vaccine's effectiveness, a 24-week, randomized, placebo-controlled study shows.

The vaccine was made from succinylnorcocaine attached to a manmade fragment of a cholera toxin. Once injected, the vaccine provokes an immune response that causes the body to produce a circulating antibody that binds to cocaine in the bloodstream. Thus, the cocaine molecules absorbed after snorting or injecting are "picked up" and "held" by the antibody, so that they are prevented from entering the brain to produce a high.

The study, conducted between October 2003 and April 2005, enrolled 115 patients at an outpatient methadone clinic who met the criteria for cocaine dependence. About half (58) were randomized to receive the vaccine injections at weeks 0, 2, 4, 8, and 12 (the first injection marked week 0). Fifty-five of the 58 subjects randomized to the vaccine treatment completed all five injections. Maximum anticocaine antibody concentration was reached between week 12 and week 16. The rest of the subjects received placebo in a double-blind manner.

Twenty-one (38 percent) of the 55 vaccinated patients were able to generate a sufficient level of the endogenous anticocaine antibody at or above the target concentration of 43 µg/mL after five injections. These patients had a significantly higher rate of cocaine-free urine samples between week 9 and week 16 than patients who received placebo (see chart). Urine samples were collected and tested three times a week.

More than half (53 percent) of the patients with high antibody levels achieved a 50 percent reduction in cocaine use, significantly higher than the rate (23 percent) among the subjects whose antibody levels remained below 43 µg/mL. One of these patients produced no anticocaine antibody at all.

Once the patient achieves the targeted level, "[the antibody] really blocks cocaine's euphoric effect," said Thomas Kosten, M.D., a professor of psychiatry and neuroscience at Baylor College of Medicine and the senior author of the study, at a press conference. "The participants with highest antibody levels had the greatest reduction of cocaine use, so there was a dose-response relationship."

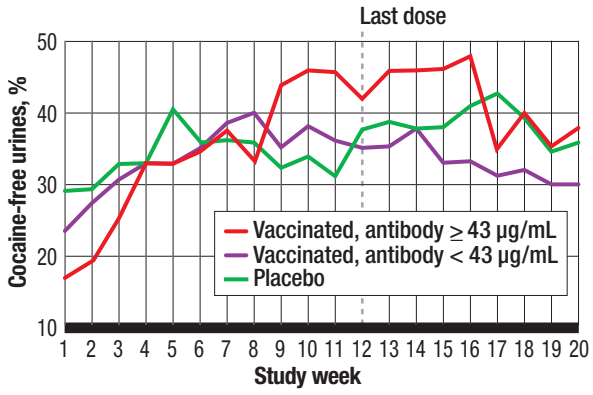
Currently there is no pharmacotherapy to treat cocaine addiction.

"Cocaine abuse is a serious public-health problem, as 1 out of 3 drug-related emergency room visits is associated with abuse of cocaine," said Nora Volkow, M.D., director of the National Institute on Drug Abuse, at the press conference. The institute funded the study.

The anticocaine antibodies began to decline after week 16 in every vaccinated patient. A booster shot is sufficient to bring the antibody level back to the previous peak level, according to Kosten. Thus, he noted, clinical treatment with the vaccine will probably require a booster vaccination every two months to maintain a therapeutic antibody level.

Cocaine Vaccine Efficacy Depends on Antibody Level

In a study of 115 subjects, those who reached the target antibody level (≥ 43 µg/mL) after five cocaine vaccine injections had significantly more cocaine-free urine samples than those who received placebo between week 9 and week 16, when the antibody level peaked. Antibody level began to decline after week 16.



Source: Bridget Martell, M.D., M.A., et al., *Archives of General Psychiatry,* October 2009

The research goal now is to modify the vaccine to induce the cocaine-blocking level of antibody in more patients and to prolong the maintenance of the antibody, Kosten said. He and his colleagues have already developed some second-generation vaccines using different protein carriers and additive ingredients, he reported at the press conference. One of these vaccines is able to produce four to five times higher levels of antibody in animals and stay at the effective level for a longer period.

The researchers had chosen to study patients who were concurrently receiving methadone treatment to maximize study retention and prevent dropout. They also used contingency management strategies, such as paying a small sum for each completed visit, to encourage patients to stay in the study. Impressively, 55 of the 58 patients randomized to vaccination received 12 weeks of treatment, and 94 of all 115 participants completed the entire 24 weeks of the study.

Both Volkow and Kosten suggested that this vaccination strategy may be used to develop treatments for other substance abuse disorders. In fact, three nicotine vaccines are currently being developed by pharmaceutical companies. No company has yet shown an interest, however, in taking over the development of the cocaine vaccine, according to Kosten.

An abstract of "Cocaine Vaccine for the Treatment of Cocaine Dependence in Methadone-Maintained Patients" is posted at <archpsyc.ama-assn.org/cgi/content/abstract/66/10/1116>. ■

Risks of Alzheimer's Drugs May Be Overlooked by Clinicians

Clinicians are urged to consider carefully the benefits of cholinesterase inhibitors, which are marginal in many patients, and the potentially serious safety risks.

BY JUN YAN

Starting cholinesterase inhibitors, a class of medications commonly prescribed for Alzheimer's disease, is associated with a doubled risk for hospitalization due to bradycardia in older patients, but many clinicians appear not to recognize this safety concern, according to a large population study by Canadian researchers.

Cholinesterase inhibitors, including donepezil, rivastigmine, and galantamine, are prescribed for patients with Alzheimer's disease to slow symptom deterioration, but they do not halt or reverse the disease progression. In addition to increasing the availability of acetylcholine in the brain, these drugs have been associated with systemic cholinergic side effects such as upset stomach, diarrhea, hypersalivation, and muscle cramps. This retrospective, case-control study is the first large analysis of the serious cardiac side effect associated with this drug class.

The researchers, led by Laura Park-Wyllie, Pharm.D., at St. Michael's Hospital in Ontario, Canada, scanned the medical and prescription drug data from 1.4 million residents of Ontario province aged at least 67 years between January 2003 and March 2008. They used a mixture of different controls to analyze the likelihood of recent exposure, defined as starting a cholinesterase inhibitor within the past three months, in patients who were hospitalized for bradycardia. First, patients served as their own controls, and their rate of exposure to a cholinesterase inhibitor within three months before hospitalization (risk interval) was compared with their rate of exposure within six to nine months before the hospitalization (reference interval). In addition, these patients were compared with control subjects who were matched in age, sex, clinical characteristics, and exposure to cholinesterase inhibitors, but were not hospitalized for bradycardia.

More than 27,000 older patients who were hospitalized for bradycardia and had any exposure to cholinesterase inhibitor at some point were identified. Only 161 of these patients met the inclusion criteria to allow for the case-control analyses, as they had cholinesterase inhibitor exposure in either the risk or reference interval, but not both. Three-fourths of these patients were prescribed donepezil.

The authors found a statistically significant association between hospitalization due to bradycardia and initiating a cholinesterase inhibitor within the immediately preceding three months. The odds ratio of hospitalization was calculated to be 2.13, with the 95 percent confidence interval between 1.29 and 3.51, for recent cholinesterase inhibitor exposure after controlling for various potential confounding factors.

Since the study focused on the temporal association between drug exposure and hospitalization and did not investigate cases of bradycardia not serious enough for hospitalization or that had resulted in death, it could not assess the absolute risk of bradycardia associated with the drugs, the authors acknowledged.

Seventeen of the 161 hospitalized patients received a pacemaker, and six died before discharge. Of the other 138 patients who were discharged without a pacemaker, 78 (57 percent) were restarted on cholinesterase inhibitors within three months, "presumably because the potential causative role of these drugs in the hospitalization was not appreciated [by their physicians]," the authors wrote. Because these drugs have marginal effectiveness on cognition and functioning in many patients with dementia, the authors pointed out, the risk-benefit balance must be weighed carefully.

The study was published in the September open-source journal *PLoS Medicine*. The authors received grant support from the Canadian Institutes for Health Research and Ontario Ministry of Health and Long-Term Care.

"Cholinesterase Inhibitors and Hospitalization for Bradycardia: A Population-Based Study" is posted at <www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000157>. ■

COMPILED BY JUN YAN

Legal Brief

• In a recent settlement, Eli Lilly and Co. agreed to pay the state of Connecticut $25 million for claims that it illegally marketed its antipsychotic drug Zyprexa (olanzapine) for off-label use, according to a state attorney general's announcement on September 29. The company was accused of promoting the drug for treating dementia, depression, and attention-deficit/hyperactivity disorder (ADHD) in children and other unapproved indications as well as concealing serious side effects of the drug from the public.

Regulatory Briefs

• The American College of Physicians (ACP) issued a policy paper on September 24 calling for broader authority for the Food and Drug Administration (FDA) to tighten medication-related regulations. In particular, the ACP wants the FDA to be given the authority to restrict direct-to-consumer advertising of new drugs during their first two years on the market. Additional ACP recommendations included increasing FDA regulation of drugs manufactured abroad and improving the current system for adverse-event reporting. The organization also called for more funding for the agency.

The ACP paper is posted at <www.acponline.org/advocacy/where_we_stand/policy/fda.pdf>.

• Sanofi-Aventis said on September 16 that it received a Complete Response Letter from the FDA regarding its new drug application for ***eplivanserin***, a serotonin $5HT_{2A}$ receptor antagonist being developed for sleep maintenance in patients with chronic insomnia. The agency requested additional risk-benefit information about the medication, but the company did not indicate whether it would conduct more clinical trials.

Industry Briefs

• GlaxoSmithKline announced on September 21 that it would stop making political contributions and stop funding for-profit medical education and communication companies to produce continuing medical education (CME) programs. It becomes the second large pharmaceutical company, after Pfizer, to cease distributing CME grants to commercial providers as industry-funded CME has come under increasing scrutiny and criticism for serving as a promotional activity for the drug companies' products. However, the company said it would continue to fund CME activities produced by academic medical centers and "national-level professional medical associations."

• Following the approval of guanfacine for the treatment of ADHD, another alpha-2 adrenergic agonist, ***clonidine,*** is now awaiting FDA review for the same indication. A supplemental new drug application was recently submitted by Addrenex seeking the indication for an extended-release formulation of this long-prescribed antihypertensive drug, according to an October 1 company announcement. The medication has been shown to be more effective than placebo in treating ADHD in a randomized, placebo-controlled, phase 3 clinical trial.

Research Briefs

• The National Institute on Drug Abuse announced on September 30 that it awarded a $10 million grant to Nabi Biopharmaceuticals to continue its development of a ***nicotine vaccine*** for use in smoking cessation. The funding has been designated to support the first phase 3 clinical trial of the vaccine.

The vaccine, given by multiple injections, is designed to induce the body to produce an antinicotine antibody, which binds to absorbed nicotine in the bloodstream and prevents it from entering the brain and producing its neurological effect. Thus, smokers do not derive the expected sensation from smoking, making it easier for them to reduce or stop smoking and prevent relapse.

• An investigational drug with a novel mechanism of action showed promise in improving the cognitive function of schizophrenia patients, according to the results from a phase 2b clinical trial released on September 23 by BioLineRx, an Israel-based company currently developing the drug known as ***BL-1020.*** It is an antipsychotic with activities affecting gamma-aminobutyric acid (GABA) and dopaminergic receptors. In the six-week, phase 2b trial, patients randomized to receive BL-1020 had a statistically significantly larger improvement of cognitive function from baseline, measured by the Brief Assessment of Cognition in Schizophrenia score, than did patients in either a group receiving placebo or one receiving risperidone.

• On September 30, Catalyst Pharmaceutical Partners Inc. announced plans to continue development of its investigational drug ***CPP-109*** for the treatment of cocaine and methamphetamine addiction. The decision was based on post-hoc analyses of results from two clinical trials in cocaine and methamphetamine addiction treatment. The trials failed to meet statistical significance in efficacy endpoints in comparisons between the drug and placebo, which the company said was largely due to the low rate of patient compliance. CPP-109 is a proprietary formulation of ***vigabatrin***, an antiseizure medication.

• Data presented at the 2009 European College of Neuropsychopharmacology (ECNP) Congress on September 14 showed that ***asenapine*** surpassed placebo in preventing relapse over six months in stabilized schizophrenia patients. A total of 700 patients were first given asenapine for 26 weeks of open-label treatment. At the end of the open-label phase, 386 of the patients were randomly assigned to an additional 26 weeks of a double-blind, placebo-controlled phase. Efficacy was determined by comparing the time to relapse between the asenapine and placebo groups, and relapse was defined by changes from baseline in the Positive and Negative Syndrome Scale total score and the Clinical Global Impression–Severity of Illness score. The asenapine group had a statistically significantly lower rate of relapse during the double-blind phase and longer time to relapse than did the placebo group.

The study was funded and conducted by Schering-Plough, which is seeking FDA approval of asenapine for long-term maintenance treatment of schizophrenia.

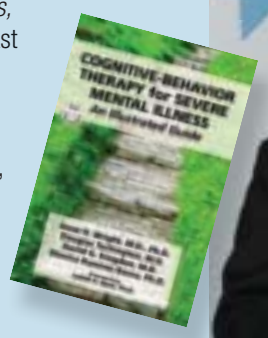
An abstract of the study is posted at <ex2.excerptamedica.com/09ecnp/abstracts/index.cfm?fuseaction=abs.prn&abstractID=P.3.c.057>.

• ***Agomelatine***, an antidepressant recently approved in Europe and currently under phase 3 development in the United States, was compared with fluoxetine in a randomized, double-blind, placebo-controlled study sponsored by its maker, Servier. More than 500 patients with a current episode of major depressive disorder and a 17-item Hamilton Rating Scale for Depression (HAM-D) total score of at least 25 were assigned to receive either agomelatine 25 mg to 50 mg (n=252) or fluoxetine 20 mg to 40 mg (n=263) for eight weeks. The agomelatine group had a statistically significantly greater decrease in HAM-D score from baseline than did the fluoxetine group, with a mean difference of 1.49 points between the groups. The percentage of patients achieving at least a 50 percent reduction in HAM-D score was 71.7 percent in the agomelatine and 63.8 percent in the fluoxetine group; this difference did not reach statistical significance.

Agomelatine is a melatonin MT1/MT2 receptor agonist and serotonin $5HT_{2c}$ receptor agonist. The study results were presented at the September ECNP Congress.

An abstract of the study is posted at <ex2.excerptamedica.com/09ecnp/abstracts/index.cfm?fuseaction=abs.prn&abstractID=P%2E2%2Ec%2E026>. ■

APPI Book Wins BMA Competition



Cognitive-Behavior Therapy for Severe Mental Illness, published by American Psychiatric Publishing Inc. last November, has won first prize in the mental health category of the 2009 British Medical Association Medical Book Competition.

The authors of the book are Jesse H. Wright, M.D., Ph.D., Douglas Turkington, M.D., David G. Kingdon, M.D., and Monica Ramirez Basco, Ph.D.

The main objective of the competition is to encourage the production of high-quality medical books. Prizes are awarded in 26 categories, with an overall winner selected from among them. All entries are individually reviewed and appraised by physicians and educators interested in medical publishing. Reviewers are asked to consider accuracy, currency, originality, book production quality, and whether the title meets the needs of its audience.

Cognitive-Behavior Therapy for Severe Mental Illness is a "how to" guide for using cognitive-behavioral therapy (CBT) for some of the most common and difficult-to-treat psychiatric conditions. It is based on the work the authors have carried out together presenting courses and workshops, previous writings on cognitive-behavioral therapy, and the steady outpouring of research that has documented favorable results when CBT is used to treat severe mental illness. By showing CBT in action in the accompanying DVD, the authors give readers a picture of how CBT methods can be used to tackle challenging clinical problems.

Kingdon, a professor of mental health care delivery at Royal South Hants Hospital and the University of Southampton, one of the book's two authors based in the United Kingdom, welcomed the award as an endorsement of the successful research in this area.

Prof. Sheila McLean, a professor of law and ethics in medicine at the University of Glasgow, presents the British Medical Association's first prize for mental health books to David Kingdon, M.D. He is one of the authors of *Cognitive-Behavior Therapy for Severe Mental Illness,* published by American Psychiatric Publishing Inc.

"We're really pleased that the book and DVD have been acknowledged in this way," he said. "We hope that this will mean that even more mental health professionals and, most importantly, the people experiencing severe mental health problems with whom they work will benefit from it."

The book may be ordered at <www.appi.org/book.cfm?id=62321>.

Save Resources–Vote Online!

APA is urging all members to vote online and no longer rely on a paper ballot. Please visit <www.psych.org/options>, log in, and click on "yes" beside "Electronic Ballot." The deadline to take advantage of this opportunity in time for APA's 2010 election is December 1. Voting online is quick, easy, and secure.

Abused Children May Develop Subtle Physiological Changes

If sexual abuse occurs at certain times during a youngster's development, the abuse can chronically alter the structure of his or her brain.

BY AARON LEVIN

Progress may be slow, but research continues to lay down the building blocks that connect the external world to the brain cells of the growing child. Study of the influence of early adversity on childhood development, for example, began with epidemiology and continues with more specific techniques such as genetics and imaging.

"This may be a relatively underfunded and understudied area, but we are as close to understanding the mechanisms of gene/environment interactions with child development as anything else in psychiatry," said Frank Putnam, M.D., a professor of pediatrics and psychiatry and director of the Mayerson Center for Safe and Healthy Children at Children's Hospital Medical Center in Cincinnati.

For instance, a recent study using magnetic resonance imaging has linked childhood sexual abuse with reduced gray-matter volume in the brain.

The researchers compared MRIs of 23 unmedicated young women aged 19 or 20 who reported at least three episodes of being the victim of forced child sexual abuse before age 18 with MRI images from 14 matched control subjects. The scans revealed reduced gray-matter volume in two areas of the brains of the women who had been abused.

On average, there was an 18.1 percent reduction in volume in the left visual cortex and a 12.6 percent reduction in the right visual cortex of the child sexual abuse subjects, wrote Akemi Tomoda, M.D., Ph.D., of the Developmental Biospychiatry Research Program at McLean Hospital in Belmont, Mass., and colleagues in the October 1 *Biological Psychiatry*.

Further analysis found that gray-matter volume correlated with the duration of child sexual abuse that took place before age 12, but there was no similar correlation with duration of abuse after age 12 or with age of onset of abuse.

This suggested, the authors said, "that exposure to abuse affects visual cortex development, but that vulnerability is limited to an early, sensitive period."

The neurobiological changes during development may be adaptive for victims of child sexual abuse, said Tomoda and colleagues. "[T]he child's brain may endeavor to reduce stress by attenuating the development of sensory systems and pathways relaying recurrent aversive or traumatic experiences."

"These changes in the visual cortex are somewhat unexpected findings," said Putnam, who was not involved in the study. "Earlier studies have provided evidence on processing activity in the visual cortex, but this study may be the first to show differences in its structure."

Tomoda and colleagues also analyzed a subset (n=14) of abused subjects who had not been diagnosed with Axis I psychiatric disorders and found a significant reduction in gray-matter volume among these participants as well. Such changes in the visual cortex may also "help explain the tendency of some patients to interpret ambiguous facial expressions as angry," they said.

A different study found that two variants in the corticotropin-releasing hormone receptor (CRHR1) gene linked the effects of childhood maltreatment to cortisol responses on a standard test. In this case, maltreatment was defined as a moderate to severe score on the Childhood Trauma Questionnaire scales for physical abuse, sexual abuse, emotional abuse, physical neglect, or emotional neglect.

The researchers in this study recruited 129 white, non-Hispanic volunteers. They included 91 with little or no maltreatment and 38 with moderate to severe maltreatment. Maltreated subjects were more likely to be older, to have higher body mass indices, and to have had depression or alcohol problems than those who were not maltreated. The subjects were evaluated with the Structured Clinical Interview for *DSM-IV* and the Childhood Trauma Questionnaire. The dexamethasone/corticotrophin-releasing hormone (DEX/CRH) test was used to measure cortisol, and the subjects' DNA was genotyped for two single-nucleotide polymorphisms in the CRHR1 gene.

The presence of one of the three alleles (called GG) of both single-nucleotide polymorphisms was associated with higher cortisol responses to the test, wrote Audrey Tyrka, M.D., Ph.D., of the Butler Hospital in Providence, R.I., and colleagues, in the same issue of *Biological Psychiatry*.

"Given the role of the Type I receptor in the activation of the HPA axis, as well as involvement in extrahypothalamic brain regions and the behavioral response to stress, these findings suggest that this genotype might increase neurosensitivity to stress," wrote Tyrka and colleagues. The other alleles, which did not show the same effect, might offer some resilience against stress or adversity, they said.

"The GG variant does show a real difference in the maltreated group," said Putnam. "We've seen data on the dysregulation of the HPA axis and psychiatric outcomes for a decade, but this study gets more at the mechanism involved. It shows how child sexual abuse interacts in a complex way with genomics and the environment and leads to high rates of comorbidity and outcomes associated with trauma."

However, Putnam suspected that as in all studies comparing abused and supposedly nonabused subjects, the latter cohort may harbor persons who are unwilling to reveal a history of abuse. Such potential covert abuse among the controls may muddy the data, he said.

Similar studies in cohorts with greater

please see ***Abused Children*** *on page 32*

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.

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

 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.

letters to the editor

Patient-Doctor as Team

The article "Reform Proposals Encourage Patients to Participate in Treatment Decisions" in the September 4 issue accurately identifies the promise of shared decision-making approaches in helping improve mental health care. Such tools enable consumers and their clinicians to make informed treatment decisions together. They represent a fundamental transformation and redesign of service delivery toward person-centered approaches that have been successfully implemented in other fields of medical care. The Substance Abuse and Mental Health Services Administration (SAMHSA) is developing and testing such tools. We look forward to working with psychiatrists and consumers to improve decision-support systems that enhance recovery.

KEN THOMPSON, M.D.
Associate Director for Medical Affairs
SAMHSA/CMHS

PAOLO DEL VECCHIO
Associate Director for Consumer Affairs
SAMHSA/CMHS

More on Psychotherapy

In the September 4 issue, Ethan Kass, D.O., M.B.A., accuses psychodynamic psychiatric practitioners of the belief that "only a psychiatrist trained in psychodynamic psychotherapy knows how to talk and empathize with patients" and of insulting many nonpsychiatric physicians who provide "respectful listening to their patients."

Such statements are not only outrageous on their face, but reflect ignorance of what psychodynamic psychotherapy actually entails by implying that it can be reduced to respectful listening and empathizing, which, without doubt, are practiced routinely by many physicians regardless of specialty. However, a psychiatrist capable of providing comprehensive and integrated mental health care by combining specialized knowledge and therapeutic skills in both psychopharmacology and psychotherapy does indeed provide a therapeutic approach to alleviating suffering that is unique to psychiatrists and that many patients value highly when fortunate enough to have access to such care. Although many patients now end up in split treatment through lack of either awareness or access to the alternative, I have yet to encounter a knowledgeable patient who specifically requested it.

The field of psychiatry offers a rich variety of meaningful avenues to improve and enhance the lives of our patients; therefore, it is a source of profound disappointment to see this once-valued facet of psychiatry disparaged, and its loss celebrated by some within our very own ranks.

LAWRENCE GIUSTRA, M.D.
Atlanta, Ga.

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.

clinical & research news

Abused Children

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ethnic and racial diversity, as well as including subjects with psychosis or bipolar disorder, would match clinical populations more closely, he noted.

Overall, child maltreatment is an often unrecognized variable, invisible in many studies, said Putnam. He added that researchers investigating childhood issues other than child abuse could easily add the Childhood Trauma Questionnaire to their studies to permit controlling for such adversity.

An abstract of "Childhood Sexual Abuse Is Associated With Reduced Gray-Matter Volume in Visual Cortex of Young Women" is posted at <www.journals.elsevierhealth.com/periodicals/bps/article/S0006-3223(09)00507-1/abstract>. An abstract of "Interaction of Childhood Maltreatment With the Corticotropin-Releasing Hormone Receptor Gene: Effects on Hypothalamic-Pituitary-Adrenal Axis Reactivity" is posted at <www.journals.elsevierhealth.com/periodicals/bps/article/S0006-3223(09)00634-9/abstract>. ■

professional news

Communities

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seventh and eighth grades than were their peers in CTC communities.

"This shows that a coalition of community stakeholders armed with tools solidly grounded in prevention science can prevent middle schoolers from starting to use tobacco, starting to drink, and starting to engage in delinquent behavior," said lead author J. David Hawkins, Ph.D., in the press release. Hawkins is founding director of the Social Development Research Group at the University of Washington.

NIDA, the National Institute of Mental Health, and other NIH institutes funded the Community Youth Development Study.

An abstract of "Results of a Type 2 Translational Research Trial to Prevent Adolescent Drug Use and Delinquency" is posted at <archpedi.ama-assn.org/cgi/content/short/163/9/789?home>. ■

Stressors

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percent versus 25 percent. Even those who have quit smoking often start again under the stress of deployment.

In addition, alcohol use is also common in military populations. About 42 percent of soldiers in surveys over the last several years say they have had at least one recent binge-drinking episode, compared with just 21 percent among comparable civilians.

Illicit drug use, however, is down in the military, probably because of the intense stigma against it and the current career-ending, no-tolerance policy, Condon noted.

At the same time, better battlefield medicine means more wounded soldiers survive, some of whom will then live with chronic pain. Treating that pain with opiates may lead to increased risk of substance use disorders, he said.

Suicide in the armed forces has risen sharply in recent years to rates equal to those in comparable, demographically adjusted civilian populations, prompting a $60 million study of suicidality in the Army and Marines (*Psychiatric News*, September 21, 2007, and June 20, 2008). Traditionally, suicide rates in the military have been much lower than those in civilian populations.

The study will survey thousands of soldiers and marines at every step in their careers, from enlistment, through training and possible deployments, to and beyond discharge, said J. John Mann, M.D., a lead investigator in the four-university coalition working on the study. Mann is the Paul Janssen Professor of Translational Neuroscience in the Department of Psychiatry at Columbia University and director of research at the New York State Psychiatric Institute (*Psychiatric News*, August 21).

As many as 80,000 new recruits will undergo a clinical evaluation along with biological measures of stress and resilience at baseline, and contribute DNA and RNA. After combat or other serious events, researchers will take another set of biomarkers from the subjects to look for methylation or other changes. Those cases will be matched with controls for comparison.

Researchers and military personnel hope that intensive data gathering will help reveal biological and other patterns of vulnerability and resilience, said Mann.

"Individuals who develop psychiatric illnesses in stressful settings almost always have preexisting stressors that may not be detected in screens," he pointed out. "A suicide is almost always a consequence of diagnosable psychiatric illness."

As part of the study, researchers will conduct full psychological autopsies of all personnel who completed suicide.

"Combined with a review of military investigations into suicides and medical autopsies, [the psychological autopsies] should help us learn the facts rather than leaving us with speculation," said Mann.

Psychological autopsies include interviews with the friends, relatives, and colleagues of the deceased to gain insight into that individual's thoughts and feelings prior to committing suicide. The process can also be helpful for the interviewees because it gives them a chance to talk and ask questions and perhaps get help to deal with feelings of loss, shame, guilt, or isolation, he said.

Service members need support in gaining access to care and overcoming stigma, emphasized Rep. Michael Michaud, (D-Maine), chair of the House Veterans Affairs Health Subcommittee. When he visits U.S. forces in Iraq and Afghanistan, Michaud said he always asks the commanding general at the base about what he is doing to reduce the stigma against seeking mental health help, he said.

"They always tell me they are doing everything possible," said Michaud. "But inevitably, some lower-ranking soldier comes up to me later and says, 'We're not getting enough help.' "

He praised APA's efforts in working with Congress to overcome stigma issues and obstacles to access.

"Your input to legislation is invaluable," Michaud said. "Regardless of how the political winds blow, it is important to stay active on both sides of the aisle."

An APA fact sheet on the mental health needs of returning veterans and their families is posted at <www.psych.org/MainMenu/AdvocacyGovernmentRelations/GovernmentRelations/CurrentLegislativeFactSheets111thCongress/Mental-Health-Needs-of-Veterans-8-09.aspx>. ■

Health Reform

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The AMA, for example, has raised concerns that the Baucus bill—unlike the House-passed health care bills (three committees have approved varying versions of HR 3200)—would not repeal Medicare's controversial physician-payment formula. The AMA has made repeal of the formula a major item on its agenda, contending that it uses flawed and incomplete data that often result in a recommendation to cut Medicare fees. The Baucus bill would replace a pending 21.5 percent cut in physician reimbursement at the beginning of 2010 with a small one-year increase, while putting off any decision on a long-term replacement of the payment-calculation system. The House health care bills call for replacing the Medicare reimbursement structure.

"Without permanent repeal of the current formula, physicians face cuts of 40 percent over the next few years that will erode access and choice for America's seniors," said AMA President J. James Rohack, M.D., in a written statement.

APA Medical Director James H. Scully Jr., M.D., also urged inclusion of a long-term solution for the Medicare payment formula in a September letter to Baucus *(Psychiatric News, October 16)*. In an attempt to provide a long-term fix, on October 14 Sen. Debbie Stabenow (D-Mich.) introduced the Medicare Physician Fairness Act of 2009, S. 1776, which would "rebase" the sustainable growth rate and thus eliminate the 21.5 percent cut physicians and other health care providers face. The bill also provides a 10-year freeze in lieu of additional payment cuts, allowing for a fair Medicare payment update to be considered as part of health reform. Majority Leader Harry Reid (D-Nev.) brought the bill to the floor for a vote, where it was defeated 53-47 with 12 Democrats and one Independent joining with Republicans to vote "no" on the legislation. Opponents criticized the bill for not including an offset to pay for the fix, estimated to cost $247 billion over 10 years. The Senate will now move forward with the small one-year increase.

Another area of concern for many physicians is the inclusion of penalties related to quality-reporting programs. The bill would mandate participation in a Physician Quality Reporting Initiative (PQRI) that aims to shift Medicare payments from volume-based to a value-based payment system. It would provide participating physicians with a 1 percent bonus payment in 2010 and a 0.5 percent bonus payment in 2011. However, it also would penalize nonparticipating physicians by 1.5 percent of their reimbursements in 2012 and by 2 percent in 2014.

Critics maintain that the current PQRI program has been plagued with problems in providing timely feedback to physicians and approving quality measures applicable to specialty care.

Scully noted that the program could impact psychiatrists in solo or small group practices, because the incentive payments are smaller than the increased costs of reporting on the program's quality measures.

"At a minimum, any proposal to extend or expand the current program must include 'hold harmless' language to protect physicians for whom participation in PQRI is neither reasonable nor feasible," he wrote in his letter to Baucus.

Physicians also could face Medicare reimbursement cuts if they incur higher costs than other clinicians. The Senate Finance Committee bill would establish a program to provide information to physicians on their "resource" use and how it compares with such use by other clinicians who treat similar conditions. However, the bill does not define "resource." If its eventual definition includes medications, psychiatrists could face a 5 percent payment reduction for incurring high costs when they prescribe expensive brand-name drugs that may be more effective than generic options for specific patients.

The House bill does not penalize physicians.

In addition, psychiatrists and other clinicians could bear the brunt of future cost-saving measures initiated by the proposed Independent Medicare Advisory Commission (IMAC) that the Baucus bill would create. The new body would submit proposals to Congress to reduce Medicare spending annually by 1.5 percent. Some physician advocates worry such cuts will fall hardest on them since a White House deal exempted hospitals from reductions by the commission.

At presstime, Senate leaders had planned to combine the Baucus bill with a more liberal health reform bill approved in July by the Senate Health, Education, Labor and Pensions (HELP) Committee. The HELP Committee version largely focused on areas of the health system reform other than physician reimbursement.

The Baucus bill was amended before it was approved by the Finance Committee to include some key mental health coverage protections. Principal among these was an amendment by Stabenow to require parity coverage of mental health care by private insurance plans included in proposed health insurance exchanges, or marketplaces.

Some mental health advocates have said that the amendment was needed, because although the Baucus bill required insurers participating in the insurance exchanges to include mental health services as part of a minimum benefits package, it was unclear whether the extent and cost of those benefits would have to be on a par with non-mental-health benefits. The amendment applied the parity requirements of the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 to plans in the proposed state exchanges.

Other Stabenow amendments that the committee adopted would make it easier for foster children to have access to federal funds for health care, including mental health care in particular and ensure individuals with a serious mental illness are included in the medical home.

Information on the Baucus bill is posted at <http://finance.senate.gov/sitepages/legislation.htm>. ■

Health Reform Gets State-Level Boost

State governors may be key to the success of federal health reform efforts, and a coalition of 22 Democratic governors has joined the call for enactment of a health care system overhaul, providing Democratic lawmakers with an important support base for their efforts.

Twenty-two Democratic governors wrote to congressional leaders on October 2 to urge passage of health care reform legislation by the end of this year.

"Many of the provisions [in the health reform bills] will allow states and territories to achieve long-term savings and help cover those who currently go without coverage," the governors wrote. "We recognize that health reform is a shared responsibility and [that] everyone, including state governments, needs to partner to reform our broken health care system."

The letter was hailed as a victory by the Obama administration, which has sought to broaden support for health care reform beyond just Democrats in Congress.

"These governors know that without reform, health care costs will continue to rise, and they will continue to struggle to balance their budgets," said Health and Human Services Secretary Kathleen Sebelius in a written statement. "Reform will help give our states the relief they need and give the American people the security and stability they deserve."

Six Democratic governors and all the Republican governors declined to sign the letter.

Governors of both parties have expressed concerns over some versions of health care reform that would reduce the number of uninsured in part through major Medicaid expansion, since the program is jointly funded by federal and state money. Such expansion would require new state spending at a time of rising budget deficits.

Other recent support from outside the Beltway included letters from 1,057 state legislators from all 50 states sent last month to Obama and congressional leaders urging enactment of health reform, including the controversial public health insurance option. The effort was organized by the Progressive States Network, a liberal advocacy group.

Earlier supporters of health care reform include state Medicaid officials, who told authors of the Kaiser Family Foundation's Commission on Medicaid and the Uninsured annual survey (see page 1), released in September, that they supported the principles underpinning federal reform, including strategies to expand coverage to the uninsured.

A copy of the governors' letter is posted at <www.democraticgovernors.org/news/press_releases?id=0288>.

Medicaid

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rate in five years and well above the 5.8 percent projected growth.

The overall Medicaid enrollment growth could have a large impact on people with mental illness, because Medicaid now pays for over half of all publicly financed mental health services in the United States and more than 25 percent of all mental health services nationally.

Laurence Miller, M.D., chair of the APA Assembly's Committee on Public and Community Psychiatry, was not surprised that the number of enrollees in Medicaid has increased as unemployment rates soared. His comments to *Psychiatric News* echoed the findings of the Kaiser researchers that the growth was possible because of $87 billion in Medicaid matching grants provided by the American Recovery and Reinvestment Act, often referred to as the federal stimulus law.

However, states are facing the likelihood of future Medicaid cuts after federal stimulus funds are depleted in 2010, Miller said.

"Many of our patients with serious mental illness rely on Medicaid for their services," Miller said. "Any cuts in services could come in the arena of the rehab option services, which would impact programs that are in place to ensure the recovery of these patients."

Future cuts could eventually lead to patients' decompensation and hospitalizations, he said, thus eventually increasing costs of treating Medicaid beneficiaries.

The possibility of future cuts was echoed by officials in about three-fourths of states that expressed concern that budgeted revenues will fall short as the recession continues, resulting in more pressures to trim spending, including for Medicaid.

The recession "has shown the challenges for states of maintaining coverage when state revenues drop during times of economic crisis," said Diane Rowland, executive vice president of the Kaiser Family Foundation and executive director of the Kaiser Commission on Medicaid and the Uninsured.

Current funding commitments led the Kaiser researchers to conclude that Medicaid enrollment growth would accelerate in the current fiscal year to 6.6 percent over Fiscal 2009 levels. (The new federal fiscal year begins on October 1 each year.) Likewise, Medicaid spending is expected to grow by an average of at least 6.3 percent in the current 2010 Fiscal Year.

The researchers explained that the stimulus funds allowed many states to avoid cuts to providers, reductions in benefits, and eligibility tightening, even during a recession-driven growth in enrollment. Eligibility for the federal stimulus funds was limited to states that maintained the same Medicaid eligibility standards, methodologies, and procedures that they had in July 2008.

Some states, however, still made cuts to their Medicaid programs. Among the most often-cited actions states took to produce budget savings were freezes or cuts in their provider payment rates. Thirty-three states cut or froze these rates in Fiscal 2009, which was far more than the 22 states that the Kaiser researchers estimated would do so based on their 2008 survey. The trend appears likely to expand, they noted, with 39 states slated to cut or freeze rates during the current fiscal year.

The survey authors were critical of the payment-rate cuts because they can jeopardize provider participation and inhibit Medicaid enrollees' access to care. Other surveys of physicians have repeatedly found that declining numbers accept Medicaid patients, and low reimbursement rates are frequently cited by the physicians as the reason for their decision.

The authors noted that the reimbursement cuts came as some states had yet to fully restore provider rates to levels seen before the previous economic downturn, which took place from 2001 to 2004.

The survey "The Crunch Continues: An Update on Medicaid Spending, Coverage, and Policy in the Midst of a Recession—Results From a 50-State Medicaid Budget Survey for State Fiscal Years 2009 and 2010" is posted at <www.kff.org/medicaid/7985.cfm?utm_source=kff&utm_medium=homepage_nn&utm_campaign=nn_093009_medicaid50stateSurvey>. ■

Delay

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Regulations also are needed to keep insurers from using "aggressive benefit management" to establish de facto treatment limitations prohibited under the law. One such approach would limit psychiatrists' reimbursements to a narrow set of services, while leaving uncovered other needed services such as coordinating care management, talking with patients' families, and discussing treatment options.

Another regulatory action that APA and other mental health advocates are urging is for federal health officials to conduct "real-time monitoring of insurance coverage and management practices," according to Scully. That would allow regulators to identify and quickly address abuses of the parity law.

More information on congressional efforts to encourage parity regulations is posted at <www.nmha.org/download.cfm?DownloadFile=0724A4F1-1372-4D20-C83393206CDB4865>. ■

Internet

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rently has no plan to issue formal advice or guidelines for students' online conduct, but Hughes expects schools to incorporate the discussion about online behaviors into their overall teaching about professionalism and ethics. "It's a tricky balance between having a respectable online presence and freedom of speech," she agreed.

A recent graduate herself, Hughes has her own page on Facebook, but she said she is very careful about what she puts on it and about setting access limits to the page. However, setting restrictions is no guarantee. Huremovic pointed out that many users do not realize that strangers who are associated with their "friends" can also view their messages.

"I tell my students to be very careful, because anything you post may come back to bite you," he said. "Whatever you put on the Web is public." He also pointed out that online postings can exist for a long time on the Web, and past indiscretions may cause problems years later.

Huremovic believes that the confusion surrounding the intersection of online behaviors and professionalism will only grow larger, and medical schools, associations, professionals, and students will have to engage in more open discussions, particularly because students and school administrators may have vastly different opinions about where the boundaries of privacy lie on the Internet.

"Think about potential consequences before you post something online," Hughes advised. "Some students have a feeling of invincibility, and some are just unaware of the potential risks to their careers."

An abstract of "Online Posting of Unprofessional Content by Medical Students" is posted at <jama.ama-assn.org/cgi/content/abstract/302/12/1309>. ■

Biomarker

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to antidepressant medications," Leuchter explained. The midline prefrontal signals picked up by the electrodes are believed to originate from the anterior cingulate region in the brain, he said, which is a primary region affected by mood disorders and changed by antidepressants. "What we are listening to with the EEG is anterior cingulate activities."

In the BRITE-MD study, two-thirds of the participants were randomly switched to either bupropion or the bupropion-escitalopram combination after taking escitalopram for one week. Statistical analysis identified an ATR cutoff score of 52 that significantly predicted patients' likelihood to respond to either the continued escitalopram or the bupropion. Of those who had an ATR score at or above 52 after one week on escitalopram, 68 percent eventually achieved response to escitalopram, significantly higher than was the case with the 28 percent who had an ATR score below 52. However, patients with ATR scores below 52 on escitalopram (suggesting a lower chance of responding to escitalopram) were significantly more likely to respond to bupropion monotherapy than were those with ATR scores at or above 52 after they were switched to bupropion.

The cutoff score was not able to predict patients' response to the combination therapy.

Thus, the authors suggested, the ATR biomarker may be helpful in quickly identifying patients who are unlikely to respond to one antidepressant but may benefit from a medication switch.

"Our goal is to find something to help guide patient care, to provide a tool for clinicians to make decisions sooner, and to shorten the process of choosing a treatment for patients with depression," said Leuchter.

An abstract of "Comparative Effectiveness of Biomarkers and Clinical Indicators for Predicting Outcomes of SSRI Treatment in Major Depressive Disorder: Results of the BRITE-MD Study" is posted at <www.psy-journal.com/article/S0165-1781(09)00212-1/abstract>. An abstract of "Effectiveness of a Quantitative Electroencephalographic Biomarker for Predicting Differential Response or Remission With Escitalopram and Bupropion in Major Depressive Disorder" is posted at <www.psy-journal.com/article/S0165-1781(09)00159-0/abstract>. ■

Economy

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and 1940, benefited people's physical health.

Yet if their hypothesis is correct, why would people's physical health profit from economic depressions or recessions?

Economic expansions have been linked to increases in smoking and alcohol consumption, reductions in sleep, increases in work stress, increases in atmospheric pollution, and increases in traffic accidents—all of which have been linked to adverse health outcomes and death. So economic depressions or recessions might help shield people from such factors and thereby reduce their death rates.

Since suicides rose during the Great Depression, it is also plausible that people's mental health suffers from economic depressions or recessions, the researchers concluded.

And if these hypotheses are correct, they may have implications for the current severe economic downturn. "My expectation is that the physical health of Americans during the current 'Great Recession' is probably improving, with general mortality falling, though mental distress can be worsening and suicides increasing," Tapia told *Psychiatric News*. "This makes suicide prevention particularly important at present."

The study was partially funded by the Robert Wood Johnson Health and Society Scholars Program.

"Life and Death During the Great Depression" is posted at <www.pnas.org/content/early/2009/09/28/0904491106.abstract>. ■

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Harvard Medical School and the VA Boston Healthcare System are recruiting a Training Director for the Harvard South Shore Psychiatry Residency Training Program (HSS). The Harvard Department of Psychiatry at the VA Boston Healthcare System has undergone a major expansion of teaching, research, and academic clinical programming over the past two years. The current Training Director is assuming the duties of Departmental Chair for Academic Development, which will include ongoing support to HSS including teaching, supervision, and consultative support to the incoming Training Director.

HSS is a consortium program affiliated with Harvard Medical School and sponsored by the VA Boston Healthcare System. Residents rotate among three Boston VA campuses, other Harvard-affiliated training hospitals, and Massachusetts Department of Mental Health facilities. HSS receives stable funding for 32 PGY I-IV resident positions plus ample administrative support, not dependent on GME pass-through funding. Major foci of program excellence include biopsychosocial assessment and interviewing skills, academic development in research, teaching and leadership, evidence-based pharmacotherapy, and manual-guided psychotherapies. Comprehensive program description can be found at **www.harvardsouthshorepsychiatry.org.**

The competitive Training Director candidate will have strong academic credentials, residency administration experience at the site or program level, and demonstrated scholarly ability in a relevant field. The applicant must be board-certified in psychiatry with a minimum of 5 years of post-residency experience, and is expected to qualify for a Harvard Medical School appointment at the Assistant or Associate Professor level.

This position offers a highly competitive federal salary and benefits. VA Boston is an Affirmative Action / Equal Opportunity Employer, and women and individuals from health-underserved minority populations are encouraged to apply.

To apply, candidates should send a letter of interest, CV, and the names of three persons to contact for references to:

Drs. Mark Bauer & Gary Kaplan, Search Committee Co-Chairs
940 Belmont Street, Brockton, MA 02301; or email materials to:
Eugene.Francois@va.gov with a copy to vhabhsjobs@med.va.gov

NIMH National Institute of Mental Health

Department of Health and Human Services
National Institutes of Health
National Institute of Mental Health
Division of Intramural Research Programs
Bethesda, Maryland, USA

The National Institute of Mental Health (NIMH), Division of Intramural Research Programs, is searching for a Staff Clinician to serve in the NIH Clinical Center supporting clinical research in adults and children participating in treatment trials and natural history studies of psychiatric illness. Current studies focus on a wide range of populations and programs including adult and pediatric schizophrenia, mood and anxiety disorders in children and adults, autism, menstrually related mood disorders and psychosomatic medicine in a research setting. Program focused responsibilities include serving as an attending physician in both in and out-patient settings, supporting subjects through wash-out/placebo periods, monitoring challenge studies, novel imaging paradigms and/or investigations with healthy volunteers.

Applicants should have an M.D., be board eligible or board certified in general psychiatry. Salary is commensurate with experience and accomplishments, and a full Civil Service package of benefits (including retirement, health, life, and long-term care insurance, as well as a Thrift Savings Plan, etc.) is available.

NIMH is a major research component of the National Institutes of Health and the Department of Health and Human Services, which have nationwide responsibility for improving the health and well being of all Americans. Interested applicants should send a curriculum vitae and bibliography, together with three letters of reference to: Maryland Pao, M.D., Clinical Director, NIMH, Building 10-CRC, Room 6-5340, MSC 1276, Bethesda MD 20892-1276 USA or e-mail to **paom@mail.nih.gov** by **December 31, 2009** or until position is filled.

(This position is subject to a background investigation and a one-year probationary period.)

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Qualified candidates will have at least two (2) years' experience leading and motivating hospital-based Inpatient Behavioral Health care teams, and at least five (5) years recent inpatient practice experience. Board Certification in Psychiatry and active, valid MN medical licensure are required. We offer a competitive compensation and benefits package, paid malpractice coverage, and a rewarding work environment.

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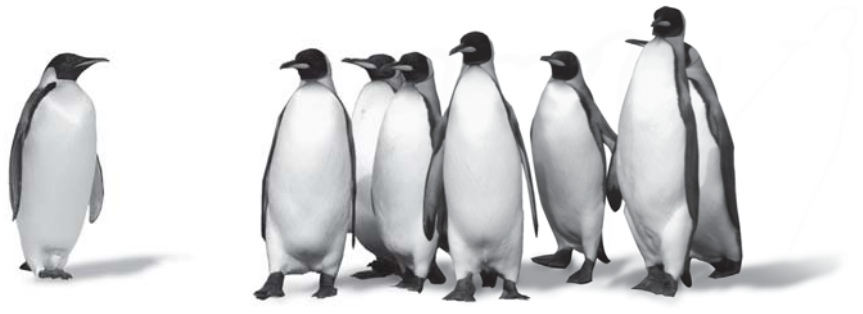

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The University of Illinois College of Medicine at Peoria has recently opened several full time faculty positions in support of a new psychiatry residency training program. The primary responsibilities are education, supervision, and clinical care. Administrative, program development, and scholarship functions are available.

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The department has successfully hired several new faculty, developed community-based affiliations, and has plans for a new state-of-the-art psychiatry training center. With this incredible growth, the remaining positions are perfect opportunities for motivated educators interested in curriculum development, supervision of residents and medical students, and entry into academic medicine.

Competitive salary. Rank commensurate with experience. Applications accepted until positions are filled.

Call, email, or write to: Ryan Finkenbine MD, Department of Psychiatry, University of Illinois College of Medicine at Peoria, 221 NE Glen Oak Ave., 7 West, Peoria, IL 61636; Phone (309) 671-8393; FAX (309) 671-8384; e-mail: ryanf@uic.edu

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Send letter of inquiry and curriculum vitae to
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or call **440.526.3030, extension 7918**.
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Issue	Deadline (Friday, 2 p.m. E.T.)
December 4	November 20
December 18	December 4

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Send resume to Joe K. Long, Director of Human Resources, Taylor Hardin Secure Medical, 1301 Jack Warner Parkway N.E., Tuscaloosa, AL 35404; or email clayton.shealy@hardin.mh.alabama.gov with questions. EOE

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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.

Mental Health — Patton State Hospital — Care and Treatment with Respect and Dignity

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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

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PSYCHIATRIC JOB FAIR!
The Northern California Psychiatric Society's **25th Annual JOB FAIR** for residents and all psychiatrists seeking full or part-time positions to be held **Saturday, January 30, 2010** at 8:30 am in the Millberry Union Conference Center of UCSF in San Francisco. This established event connects more than 20 employers and 100 job seekers throughout the western US. For further information, call (415) 334-2418, ext. 105; FAX (415) 239-2533; or email rgeorgulas@ncps.org.

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CONNECTICUT

Yale - CMHC

The Yale University School of Medicine seeks psychiatrists for full-time faculty positions at the Connecticut Mental Health Center [CMHC] for January and July 2010 that will carry academic appointments at the Assistant or Associate Professor level in the Department of Psychiatry. Outstanding clinical and teaching skills are required for roles in patient care as well as supervision of psychiatry residents and other trainees at CMHC, a core site for training and research within Yale's Department of Psychiatry. The positions include protected time for participation in a variety of Departmental research and educational activities. Applicants must be board certified or eligible in psychiatry, licensed to practice in CT and be legally employable. Experience in the treatment of adolescents or young adults is beneficial for one of the outpatient positions. Please send a CV and 3 references to Jeanne Steiner, D.O., Medical Director CMHC, 34 Park St., New Haven, CT, 06519. Direct inquiries to jeanne.steiner@yale.edu. Review of applications will begin on December 1, 2009 and continue until these positions are filled. Yale University is an affirmative action/equal opportunity employer; applications from women and minority group members are specifically invited.

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.

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

Yale Department of Psychiatry seeks psychiatrists for full-time faculty positions at the Connecticut Mental Health Center (CMHC) for July 2010 that will carry academic appointments at the Assistant or Associate Professor level. Outstanding clinical and teaching skills are required for roles in patient care as well as clinical supervision of psychiatry residents and other trainees at CMHC, a core site for training and research within Dept of Psychiatry. The positions include protected time for participation in a variety of Departmental research and educational activities. Applicants must be board certified or eligible in psychiatry, licensed to practice in CT and be legally employable. Please send a CV and 3 letters of reference no later than December 1, 2009 to Jeanne Steiner, D.O., Medical Director, CMHC, 34 Park St., New Haven, CT 06519. Direct inquiries to Jeanne.steiner@yale.edu. Yale University is an affirmative action/equal opportunity employer; applications from women and minority group members are specifically invited.

DELAWARE

WILMINGTON / NEWARK: Child and General Psychiatrists. Inpatient/partial programs. Very competitive salary, benefits & incentive plans. Contact Joy Lankswert In-house recruiter @ 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.

GEORGIA

ATLANTA: C/A PSYCHIATRIST POSITION

SOUTHERN BEHAVIORAL HEALTHCARE is looking for one full- time competent, stable child and adolescent psychiatrist, who is looking for a long- term relationship in a well- established, dedicated, supportive multidisciplinary group practice. We are located in the Atlanta area, 10 minutes from the airport.
OUTPATIENT PRACTICE ONLY. MON-FRI
Competitive salary with generous benefit package including paid malpractice insurance, paid holidays, vacation and sick leave, medical and dental insurance, and retirement plan.
Please send e-mail to heal650@ bellsouth.net or fax CV to 678 610 7111.

ATLANTA: General, Geriatric & Child Psychiatrists - Inpatient & partial programs. Medical Director and Staff positions. Salaried Fulltime Positions. Weekend moonlighting also available. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

Private Practice seeking FT BC Adult Psychiatrist to take over established Psychiatrists' practice in NE GA. The practice also has a team comprised of 2 Ph.D. Psychologists, an LCSW and an LPC. E-mail CV to mkingphd@gmail.com

FLOYD Behavioral Health Center

Hospitalist Psychiatrist position and an Office-Based position with a dynamic and expanding 53-bed, adult behavioral health center. 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.

Metro Atlanta - Outpatient C&A and Adult psychiatrists sought by progressive comprehensive mental health system. Part time. Flex schedules. Supportive staff. Desirable working conditions. Contract for svcs at competitive pay. Fax vitae to Gretchen Collins @ 770-339-5382.

ILLINOIS

Older Adult Program

Expanding cutting edge state of the art practice in South West suburb of Chicago (Orland Park) is seeking a general psychiatrist with experience working with geriatric population. Geriatric fellowship desirable but not essential. Primary outpatient practice, limited inpatient work at Advocate Christ Medical Center (ACMC). Will help the development of an older adult program in the community providing consultation to a consortium of assisted living and day care facilities. Will join other 5 psychiatrists, and 10 therapists. TMS treatment available. Call every 4 or 5 weekends at ACMC. Group practice will provide malpractice insurance and health benefits, as well as credentialing with insurance carriers. Please email C.V. to moigaviria@usa.net. Candidate must have license to practice in Illinois and be board certified or board eligible. Applications accepted until position is filled.

DuPage County Health Department
Contractual Psychiatrist, Mental Health Service

One of our missions at the DuPage County Health Department, in Wheaton, Illinois, is to provide quality and accessible community mental health services to the seriously and persistently mentally ill of DuPage County.

Responsibilities include diagnostic evaluations, medication management treatment, minimal supportive psychotherapy, and staff consultation, all as part of a comprehensive multidisciplinary clinical team. The current treatment model is for one hour new evaluations and 30 minute follow-up visits for most outpatients. Clinical responsibilities are to outpatients and a small percentage of clientele who are treated in the Health Department's residential treatment programs. No inpatient duties. The psychiatrist participates in emergency response activities as assigned; maintains confidentiality of privileged information; and demonstrates sensitivity and understanding to patients from all ethnic groups, cultures, and sexual orientations.

To qualify you must have a permanent unrestricted Illinois medical license, an Illinois controlled substance certificate, and a Federal DEA certificate. Basic computer skills including adequate keyboard skills are a requirement; we will train you in our e-prescribing and electronic medical record software. Must also have the ability to work with the general public and within a team-oriented environment, and own reliable transportation for availability at any of our various sites within DuPage County.

Professional liability insurance is provided through the Health Department's policy. Contracted employee psychiatrists pay no self-employment tax.

Please fax your resume to Human Resources at 630-221-7811

KANSAS

Bert Nash
Community Mental Health Center, Inc.

The Bert Nash Community Mental Health Center, in Lawrence KS, has an immediate opening for a full time adult psychiatrist for outpatient work. Lawrence is home of the the University of Kansas and Haskell Indian Nations University. Commuting distance from Kansas City and Topeka. Visit our website, www.bertnash.org and click on Employment for more information or contact Karen Baucom, Human Resource Manager at kbaucom@bertnash.org Ph 785-830-1734.

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

NEW ORLEANS - General Psychiatrist - Inpatient/partial programs. Very competitive salary, benefits & incentive plans. Contact: Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

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.

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.

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.

MAINE

SOUTHERN MAINE

How would you like to be valued as part of a professional team for one of Southern Maine's largest mental health and community service based agencies where there is a strong commitment to staff, clients, and their agency mission?

Counseling Services, Inc. is a comprehensive and integrated community mental health center serving adults and children with serious mental health and substance abuse problems. Our programs include Complementary Therapies, Child and Family Primary Care Services, Adult and Family Primary Care Services, Primary Care Support Services, Psychiatric Services, Assessment Referral and Treatment, and Crisis Response Services.

We are currently recruiting for a full or part-time, general psychiatrist to work with adults. The position will involve direct patient care at our community mental health centers. The physician will work with a multi-disciplinary team providing outpatient services to a variety of programs.

We offer a generous time-off program, a comprehensive medical, dental and life insurance benefit, and other attractive incentives.

If you are aware of a qualified individual who would want to explore this exciting opportunity, please contact the Human Resources Department at 207-294-7104. A resume and cover letter may be sent to: Counseling Services, Inc., P.O. Box 1010, Saco, Maine 04072 or human.resources@csimaine.com. We are an equal opportunity employer.

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

Faculty Opportunities
DEPARTMENT OF PSYCHIATRY, UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE, BALTIMORE

The University of Maryland School of Medicine, Department of Psychiatry, is seeking full-time faculty psychiatrists in general adult, geriatric, community psychiatry, consultation-liaison psychiatry, mood disorders and addictions in both inpatient and outpatient settings, including VA. Positions carry full-time faculty appointments at the University of Maryland School of Medicine and offer exciting opportunities for clinical care, teaching and research. Candidates must be ABPN certified or eligible. Academic rank and salary are commensurate with experience. Send letter of introduction and CV to: Anthony F. Lehman, M.D., M.S.P.H., Professor and Chair, Department of Psychiatry, University of Maryland, Baltimore, 110 S. Paca Street, Baltimore, Maryland 21201. The University of Maryland is an AA, EOE, ADA employer. Minorities and women are encouraged to apply.

Psychiatrist: Prince George's County, Md. Health Department. Intensive outpatient treatment program for women with co-occurring disorders. Twenty hours per week. Maryland licensure required. An Equal Opportunity Employer. Background check required. For more information call (301) 324-2832.

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

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.

Full-Time Consult-Liaison Psychiatrist/ Transplant Psychiatrist

This full time consult liaison psychiatrist position is split between transplant psychiatry on a multi-disciplinary medical team and general consult-liaison work at the UMass Memorial Medical Center. General consult liaison sited at Memorial campus and involves work with medically complex cases. The transplant psychiatrist will conduct outpatient pre-screening psychiatric evaluations for potential organ recipient and donor patients. May provide short term medication management. Participates in selection committee. Person should enjoy being part of a multi-disciplinary team and have consult liaison experience.

Our Department of Psychiatry has a large clinical faculty with clinical, teaching, and academic opportunities in a wide variety of inpatient and outpatient settings. We have faculty development programs, and are committed to care, training, and research missions, as well as 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

Attending Psychiatrist-UMass Department of Psychiatry seeks an attending psychiatrist for its adult inpatient unit located at its academic teaching hospital. There is a moderate patient load, with a strong focus on teaching and mentoring students and residents. The unit offers a multidisciplinary approach, a robust group program, excellent care coordination support and serves a wide range of patients. Opportunities for involvement in a full range of academic activities. Faculty appointment at the UMass Medical School.

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. We are an AA/EOE employer. No recruiting agencies please. Thank you.

MASSACHUSETTS
Full-time psychiatry salaried position available January 1, 2010 for growing general hospital Department of Psychiatry. Position includes inpatient responsibility for patients on our 31 bed inpatient unit, Consultation and Liaison Services to the Medical Units, and shared on-call responsibilities as a member of the Department of Psychiatry. Emerson Hospital is a recognized provider of high quality mental health and substance abuse services. We provide a stimulating and collegial atmosphere for the career-minded psychiatrist. Competitive Salary and Benefit package. Additional compensation available for added call responsibilities. The Concord area is an excellent environment to develop a vibrant supplemental private practice. Geriatric expertise and interest in developing ECT Services a plus. Please contact Robert Stern, M.D., Chair, Department of Psychiatry, 978-287-3512 or by e-mail at rstern@emersonhosp.org.

BOSTON areas - Jamaica Plain, Pembroke, Lowell & Westwood: General Psychiatrists. Inpatient/partial programs. Very competitive salaries, benefits & incentive plans. **NO CALL.** Weekend moonlighting also available. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com

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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.

Community Psychiatrist-UMass Department of Psychiatry seeks an outpatient psychiatrist to work with our faculty and staff at Community HealthLink, part of the UMass Memorial Health Care system. CHL is a multi-service, non-profit organization committed to promoting, maintaining and restoring the dignity, well-being and mental health of individuals and families in Central Massachusetts. The psychiatrist works with a dedicated multidisciplinary team and provides evaluation and treatment services to persons with a range of psychiatric and substance abuse disorders. 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. Or, please call Cara Sanford at 508-856-3079. We are an AA/EOE employer. No recruiting agencies please. Thank you.

PACT Psychiatrist - North of Boston, MA

Vinfen Corp, a leading provider of behavioral health services in Eastern MA, seeks two 20 hr/ week part-time psychiatrist or a single full-time psychiatrist as part of its PACT Team (Program for Assertive Community Treatment). One of the positions will be based in Danvers and the other in Lawrence, MA.

PACT is a unique model of care developed in the late 1970s to support severely ill individuals outside of hospitals. Massachusetts began a role out of the model in 2002 and continues to pursue this creative way of delivering care. The Danvers team is new, while the Lawrence team has been in existence since the model began. The PACT teams provide individualized, community based services to about 60 individuals living with serious and persistent mental illness. The psychiatrist works to directly serve these individuals and to serve as a teaching resource to the rest of the team. The doctors are the clinical "captains" but do not have to administer the team; rather the doctor collaborates with the team leader to get the most for the people we serve.

These positions offer an excellent salary, ranging from $70,000 to $100,000 per year for the part-time positions (double for full-time), depending upon experience and salary history. They would be easy to combine with another role such as teaching, private practice or to simply to enjoy time away from work for relaxation and family. Both positions offer an opportunity to learn about an evidence based practice, and to get to know and help your patients in detail in the office and the community.

Qualified candidates will have a Massachusetts Medical License, board certification in Psychiatry and at least five year experience in a related clinical setting. Dual certification in Adult Psychiatry and other related areas such as Substance Abuse is preferred.

Contact Tim de Araujo, VP Human Resources, at (617) 441-1705 for more details or forward your resume to him at dearaujot@vinfen.org. For more information about Vinfen, please visit their website at www.vinfen.org.

Exceptional opportunity
Massachusetts - Boston & Springfield Markets
Adult or Geriatric - Full or Part Time
Very stable and growing network practice.
Flexible scheduling; above market compensation ($240,000 earning); no overhead.
If you have been searching for a practice which enables you to create a perfect work life balance OR you are seeking to supplement finances while building your own private practice, then we should speak in greater detail to see if this is an option for you.
In confidence contact, Dave Pierpont, Stonebridge & Company, 203-256-1185, xt 101 or davep@stonebridgecompany.org

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Adult Community Psychiatrist-UMass Department of Psychiatry seeks a full time outpatient psychiatrist to work with our faculty and staff at the Great Brook Valley Health Center in Worcester, part of the UMass Memorial Health Care system. Great Brook Valley is a mission driven full service comprehensive health care center that offers opportunity for primary care collaboration. Major teaching site for family medicine. Candidate should be mission centered and, preferably, will be bilingual in Spanish. Opportunity for multicultural research in collaboration with UMass Medical School faculty. Faculty appointment at rank commensurate with experience.

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. We are an AA/EOE employer. No recruiting agencies please. Thank you.

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.

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

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Medical Director - Base Salary $220k to $240k - Very Generous Bonus Plan - Close to Springfield - This will be a goldmine to whoever takes this position. Can be inpatient and nursing homes or inpatient and outpatient work. Unit is a 10-bed geropsychiatric program; outpatient primarily adult. Strong hospital support for behavioral health with plans for expansion. Please **call Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

NEW JERSEY

PSYCHIATRIST - FT/PT. OUTPATIENT EVALS & MED MONITORING. NJ license. BC/BE with adults and children. No on call or weekends. Team player. Resumes to: NewPoint Behavioral Health Care, ATTN: Medical Director, 404 Tatum St., Woodbury, NJ 08096, FAX 856.845.0688, EMAIL center@newpointbhc.org

EOE A\A

Child/Adol. Psychiatrist

Child/Adol. Psychiatrist - needed for multidisciplinary group in affluent communities in North/Central N.J. Expertise in pychopharmacology required. NO Managed Care! Please fax CV to (908) 598-2408.

NEW YORK CITY & AREA

Psychiatrists for Clinic - Rego Park Queens Bi-lingual Russian, Part-Time - Immediate Opening

FEGS, a leading provider of behavioral health services in the New York metropolitan area, seeks Board Certified/Eligible Bi-lingual Psychiatrists for psychiatric evaluations and medication management. Must be available to work a minimum of 7 hours a week. Bilingual Russian required. Malpractice insurance covered by agency. Position located in Rego, Park Queens.

Competitive salary, no on-call responsibilities, and comprehensive, generous benefits. EOE.

Apply online to our career page at: www.fegs.org/careers and enter Job Number P01933.
Search by title of Psychiatrist to view all current openings.

MEDICAL DIRECTOR
of Columbia University Medical Center Adult Psychiatry Clinic

Full-time Attending Psychiatrist position available. Main responsibilities are leadership and administration with secondary duties divided among direct clinical care (about one day per week), teaching, and research. The service is a large, busy clinic that provides care to a culturally diverse population. Experience or interest in public psychiatry and fluency in Spanish would be helpful, but are not required. Hours are flexible. Please contact John A. Sahs, M.D. by email sahsjoh@nyp.org.

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

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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.

Prison Health Services Medical P.C. has positions available for F.T., P.T. and Per Diem psychiatrists to join its substantial, comprehensive, multi-disciplined M.H. team at Riker's Island. Salaries and benefits are competitive, the work is rewarding and appreciated. For more info please contact David Rosenberg MD, Supervising Psychiatrist, Tele # 646 717 4061; Address 49-04 19th Ave., Astoria, New York 11105; email rosenbdr@riepf.com

NEW YORK STATE

Psychiatrist-Outpatient

The highly regarded **Pederson-Krag Center** offers positions in the following programs:
Mental Health Clinics - to provide assessments, consultations and treatment services (Smithtown-15hrs; additional 7-10 hours available in Wyandanch.)
Assertive Community Treatment (ACT) - to provide supervision and treatment on and off-site as part of a multidisciplinary team (Smithtown - 14 hrs.)
These positions can be combined for a full-time position. Flexible schedule. Excellent benefits. Competitive salary.
Mail CV to **Roger Kallhovd, M.D., Pederson-Krag Center, 55 Horizon Drive, Huntington, N.Y. 11743 or fax 631-920-8165 EOE/AA www.pedersonkrag.org**

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

Child Psychiatrist- Full time position at one of the country's largest private non-profit residential treatment communities for at risk youth, setting of over 500 males with a continuum s of care including General Residential, Special Needs, Diagnostic, Drug and Alcohol, Intensive Supervision and Community Based Homes. Duties include a nice mix of clinic time for initial evaluations and medication management with campus visits for the more acute settings, milieu consultation and treatment team involvement. Patient load is very manageable in a low stress friendly environment. Join one full and PT Child Psychiatrists. Grove City is a family-oriented small city one hour north of Pittsburgh and an easy commute from their northern suburbs. We offer a 40hour work week, flexible hours with generous salary ($225K+, based on experience), full benefit package includes health and dental insurance, pension plan, vacation and CME time. Information regarding George Junior can be obtained at http://www.georgejuniorrepublic.org/. Interested parties may send CV to Jeff Morris, Vice President at jmorris@georgejuniorrepublic.org, or mail c/o Jeff Morris 233 George Junior Road, Grove City, Pa. 16127 (724) 458-9330, Fax (724) 458-1559.

PITTSBURGH - Opportunities for Adult and Child Outpatient Psychiatrists at Mercy Behavioral Health. We are celebrating our 40th anniversary and continue to experience tremendous growth. Our financially solid organization offers competitive compensation and an excellent benefits package all with a flexible schedule. Contact Jim Jacobson, MD at 412-488-4927 or email JJacobson@mercybh.org.

Psychiatrist
Great Opportunity for Psychiatrist in an established, growing Practice in the beautiful Lehigh Valley, Allentown, Pennsylvania located just one hour north of Philadelphia and two hours west of NYC.
Sacred Heart Healthcare System is seeking a Board Certified or Board Eligible Adult Psychiatrist for a growing Behavioral Health Program including Adult and Geriatric inpatient services. Additionally, there is an opportunity to develop an outpatient practice and client base. We offer a competitive salary and benefits program. Please send your CV to William Mawhinney, Jr. Director Human Resources Sacred Heart Healthcare System 421 Chew St. Allentown, PA, 18102 or by e-mail to wmawhinn@shh.org.

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

CLARION (Western PA) and SHIPPENSBURG (near Harrisburg). General or Child Psychiatrists for inpatient & partial program services. Very competitive salary, benefits & incentive plans. **Student loan assistance negotiable in Clarion.** Contact Joy Lankswert @ 866-227-5415; OR email joy.lankswert@uhsinc.com

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New Geropsychiatric Unit - Eastern PA - Seeking a Psychiatrist to work on new 10-bed inpatient geropsychiatric unit in an impressive med/surg hospital. Adult unit here as well. Offering attractive salary/benefits, relo pkg, and bonus plan. Easy drive to Philadelphia and Baltimore. Please call **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.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

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

TEXAS

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

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.

DALLAS area - Sherman. General sychiatrist - Private practice or Salaried Employment of inpatient & outpatient.
WEST TEXAS San Angelo: Child & General Psychiatrist. Salaried Employment or Private Practice. **Student loan assistance.** Contact: Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

UTAH

PSYCHIATRIST

Ski Park City and Snowbird, attend Sundance film festival, and work in nearby Provo! On-call is optional. Utah State Hospital seeks psychiatrists for adult inpatient unit. JCAHO/MEDICAID/CMS accredited. Electronic chart and pharmacy. New buildings on a 300-acre campus at the base of the mountains. Collegial environment. Salary negotiable, with full benefits. Send CV to: Richard Spencer, MD, Clinical Director, PO BOX 270, Provo, UT 84603, (801) 344-4201, rspencer@utah.gov EOE

PSYCHIATRY, UNIV. OF UTAH SCHOOL OF MEDICINE
Child and adolescent psychiatrists are being sought for three clinical track positions at the Instructor, Assistant, Associate and Professor levels. Applicants will be expected to teach psychiatric residents and medical students and contribute toward their salary through clinical activities. Individuals with diverse clinical and research interests will be considered. Expertise in Child & Adolescent and/or Triple Board psychiatry, with specialty board eligibility/certification in child & adolescent psychiatry and interests in addictions or eating disorders will present the best fits. Send CV and three professional references to William M. McMahon, M.D., Professor and Chair of Psychiatry, Univ. of Utah, Dept. of Psychiatry, 30 N. 1900 E., Suite 5R210, Salt Lake City, UT 84132.

Equal Employment Opportunity
The University of Utah is an Affirmative Action/Equal Opportunity employer and does not discriminate based upon race, national origin, color, religion, sex, age, sexual orientation, gender identity/expression, disability, or status as a Protected Veteran. Upon request, reasonable accommodations in the application process will be provided to individuals with disabilities. To inquire about the University's nondiscrimination policy or to request disability accommodation, please contact: Director, Office of Equal Opportunity and Affirmative Action, 201 S. Presidents Circle, Rm 135, (801)581-8365.

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.

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.

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

WASHINGTON

VA Puget Sound Health Care, American Lake campus, located in Tacoma, Washington, is seeking a board certified/eligible psychiatrist to join our Mental Health Service staff. The incumbent will perform general psychiatric assessment and treatment in a multi-disciplinary setting; work closely with colleagues to provide comprehensive, state-of-the-art outpatient and inpatient mental health care. Experience and competence in treating Post Traumatic Stress and Substance abuse disorders is desirable.

VA Puget Sound is a fully accredited multi-care facility offering Ambulatory Surgical Services, a 65-bed Community Living Center, Primary Care Services, Blind Rehabilitation Services, a Substance Abuse Treatment Program, a Post Traumatic Stress Treatment Program, a 60-bed homeless Domiciliary, and a 27 bed Mental Health Inpatient Unit.

Special programs are offered, such as, Women's Health Clinic, Vocational Rehabilitation, and a Residential Care Program. The city of Tacoma is located at the foot of Mount Rainier, along the shores of Commencement Bay, and is approximately 30 miles from Seattle, Washington. The city is a center for international exports, cultural attractions, historic sites, outdoor activities, stunning natural beauty and offers affordable healthy living. The VA offers a comprehensive benefit package including malpractice coverage, Federal Retirement System, health insurance, life insurance, and Thrift Savings Plan (401k). For more information, please contact, Dr. Andre Tapp, Associate Executive Director, Mental Health Service at 253-589-4176. VA Puget Sound is an equal opportunity employer and values diversity.

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 adult and child 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.

WISCONSIN

Marshfield Clinic has openings for BE/BC Adult Psychiatrists to join our expanding services in Marshfield and Minocqua. At our Marshfield campus, candidates with fellowship training in neuropsychiatry, geriatric or consultative psychiatry are preferred. Our Minocqua practice is primarily outpatient practice with a mix of C/A and adult patients. With highly skilled and dedicated allied providers and support staff, Marshfield Clinic psychiatrists employ a multidisciplinary team approach to their practice. Marshfield Clinic offers a competitive compensation package.
If you are interested in these opportunities please contact:
Beth Albee
Marshfield Clinic
1000 N. Oak Avenue
Marshfield, WI 54449
(800) 782-8581 ext. 19775
Fax (715) 221-9779
albee.beth@marshfieldclinic.org
www.marshfieldclinic.org

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

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Gen. Adult - Child & Adoles. - Forensics
Locum Tenens or Permanent Jobs
Salaries of up to 350,000 per annum
www.IMRpsychiatry.com

Fellowships

FELLOWSHIP
PUBLIC PSYCHIATRY at YALE

The Connecticut Mental Health Center - Yale University School of Medicine is accepting applications for a one-year Fellowship in Public Psychiatry for July 2010. CMHC is a major site for training, research and clinical service within the Yale and State systems. As a state-funded, academic, urban mental health center it provides a unique setting for psychiatrists to obtain advanced training as they pursue careers as leaders in the field. Fellows spend 50% time in seminars, supervision, and administrative/policy meetings of CMHC and the CT Dept. of Mental Health and Addiction Services; and up to 50% effort providing direct clinical service and/or consultation within public mental health settings in New Haven. Candidates must be eligible for board certification and CT licensure. Minority applicants are encouraged to apply. For further information contact Jeanne Steiner, D.O. Medical Director, CMHC - Yale Univ., 34 Park St New Haven, CT 06519 or Jeanne.Steiner@yale.edu.

UMass Fellowship in Addiction Psychiatry

This accredited Addiction Psychiatry fellowship, offered through the Department of Psychiatry at the University of Massachusetts Medical School/UMass Memorial Healthcare System, provides advanced training in state-of-the-art recognition, diagnosis, and treatment of addictive disorders in an academic environment with many clinical and translational research opportunities.

The overall goal of the program is to provide fellows with the education and learning experience to become an expert in the assessment and bio-psycho-social formulation, treatment and coordination of comprehensive care for individuals with substance use disorder. The training also provides fellows with experience in co-occurring mental illness and addiction; experience in rehabilitation and longer term residential services for individuals with co-occurring psychiatric and medical conditions; and experience with several psychotherapy modalities, including group treatment programs and integration of family counseling services. AA/EOE

To apply or for more details about the program, please visit our website: www.umassmed.edu/psychiatry/AddictionPsychiatryFellowship.aspx . For more information or to send your completed application with a current CV and personal statement, please contact Sarah Baker, Addiction Psychiatry Fellowship Coordinator at 508-334-2704 or sarah.baker@umassmed.edu. You may also contact Gerardo Gonzalez, MD, Training Director at 508-856-6480 or gerardo.gonzalez@umassmed.edu.

FELLOWSHIP IN COLLEGE MENTAL HEALTH

The Ohio State University Counseling and Consultation Service offers a Psychiatry Fellowship in College Mental Health for the 2010-11 academic year with training specific to a culturally and clinically diverse student population of over 53,000. This full-time, salaried position has benefits and no call or weekend duties. Candidates must be eligible for board certification and Ohio medical licensure. Mail CV, letter of interest and 3 letters of recommendation including letter from residency training director to: **Denise Deschenes, M.D., Counseling and Consultation Service, 4th Floor, Younkin Success Center, 1640 Neil Ave., Columbus, OH, 43201-2333, (614) 292-5766, www.ccs.osu.edu.**

Addiction Psychiatry/Medicine Fellowships
Univ. of Cincinnati top teaching, clinical sites. VA Nat'l Center of Excellence. NIDA CTN, NIAAA trials. 1 (ACGME-accredited) or 2 yr. Robust benefits/pay. Dir: Shannon Miller, MD. www.psychiatry.uc.edu, kathleen.peak@va.gov

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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.

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.

ADDICTION PSYCHIATRY FELLOWSHIP

The Albert Einstein College of Medicine Addiction Psychiatry Fellowship is seeking PGY-5 level psychiatry residents for July 2010. This is a 1 to 2 year program with ACGME accreditation and is under the auspices of the Division of Substance Abuse of the Albert Einstein College of Medicine. The Division of Substance Abuse is the largest medical school affiliated addiction treatment program in the United States and currently treats over 4200 patients in its various sites throughout the Bronx. The Fellowship provides clinical experience in all aspects of addiction treatment, including opioid treatment, outpatient rehabilitation, inpatient alcohol and drug detoxification, and consultation-liaison psychiatry leading to eligibility for the added qualifications in Addiction Psychiatry ABPN certification.

Clinical and basic research is encouraged, with particular focus on the neurobiology of drug addiction, as well as research in enhancing the care of drug abusers with HIV disease. Trainees will have the opportunity to participate in one of the ongoing research projects of their choice.

The Fellowship includes a mentoring program for those interested in academic careers. Competitive salary with full benefits package. Please send letter of interest, curriculum vitae and 3 letters of reference to:
Merrill Herman, M.D., Department of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Jack and Pearl Resnick Campus, 1300 Morris Park Ave, Befer Hall 403, Bronx, New York 10461; Tel: (718) 430-3080; Fax: (718) 430-8987. EOE

FELLOWSHIP IN GERIATRIC PSYCHIATRY NYC

ACGME approved 1 or 2 year fellowships in geriatric psychiatry. HRSA funding provides opportunities for academic development including MPH courses, pedagogy, IT training, and research. No night/weekend calls. Must be NYS license eligible and permanent resident/citizen (for HRSA track). Salary up to $130,000. Contact: Carl Cohen, MD, SUNY Downstate Medical Center, Box 1203, 450 Clarkson Avenue, Brooklyn, NY 11203; carl.cohen@downstate.edu; 718-270-1750

NEWLY ACCREDITED FORENSIC PSYCHIATRY FELLOWSHIP

University of California, San Diego is recruiting Fellows for start date 7/1/10 or before. For detailed description go to: http://www.aapl.org/fellow.php#UN_UCSD. Send e-mail indicating interest to: kstuart@ucsd.edu

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.

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Cost-effective strategies for busy clinicians. Over 90 vignettes!
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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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