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

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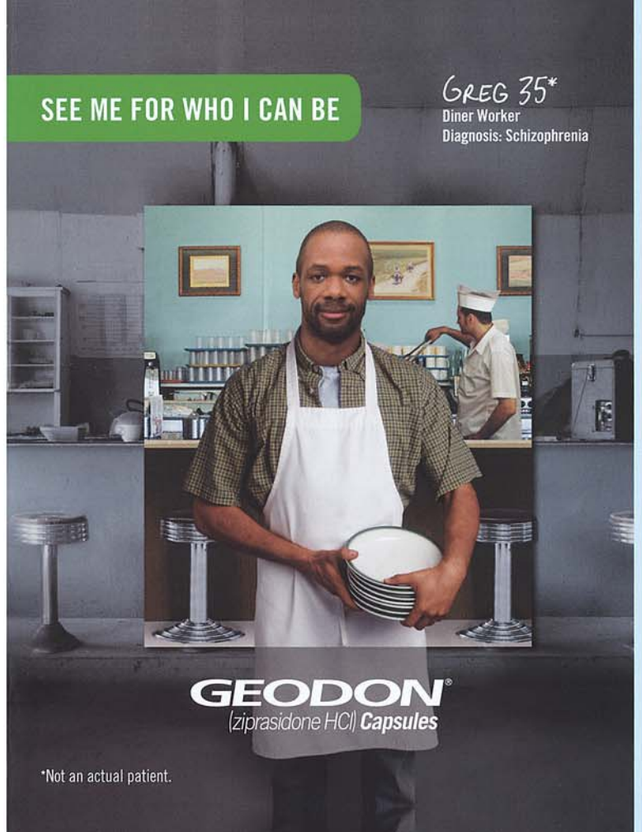

GEODON is indicated for the treatment of schizophrenia.

Important Safety Information

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

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

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

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

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

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

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

Please see brief summary of prescribing information on adjacent page.

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

BRIEF SUMMARY. See package insert for full prescribing information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis—Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of seventeen placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. GEODON® (ziprasidone HCl) is not approved for the treatment of patients with Dementia-Related Psychosis (see WARNINGS).

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

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

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PERIODICALS:
TIME-SENSITIVE MATERIALS

Imaging, Genetics on Verge Of Transforming Psychiatry

Fast-changing landscapes in genetics, imaging, and technology combine to create a new language that the most experienced and the newest members of the profession must learn.

BY AARON LEVIN

Advances in genetics and technology to diagnose and treat depression will inevitably lead to changes in psychiatric training and practice, APA President Alan Schatzberg, M.D., told attendees at the Institute on Psychiatric Services in New York in October.

"Psychiatry must learn a new language," said Schatzberg. "This is not the language I was taught 40 years ago."

Genetics continues its prominent role in the exploration of treatments for depression, as well as for a host of other medical illnesses. Pharmacogenetics is a developing field, but it is not ready to be applied for routine screening, said Schatzberg, a professor and chair of psychiatry at Stanford University School of Medicine. Researchers have hoped to be able to predict responses to medications, he said. "In fact, side effects seem to be better predicted than positive response for specific agents."

He noted people with certain alleles of the 5HTT serotonin transporter polymorphism or the 5HT-2A receptor have had positive or negative responses to SSRIs as well as high dropout rates in some antidepressant treatment trials, often indicating intolerance to the drugs. Capturing that kind of information in future trials will require collecting DNA at baseline to avoid losing genetic data on people who drop out.

Eventually, it may be possible for a clinician to order a quick test of perhaps 50 alleles and then use an algorithm to determine the proper drug and dose for individual patients. Clinicians will have to greatly increase their knowledge about genes and the biological processes they control so as to anticipate a new schema for diagnosis as well as to assess genes' effects on drug response, he said.

Alternatively, it may be possible to insert a virus into a gene promoter region and use a fiber-optic laser with a different colored light to turn the gene on and off.

"It's not just genetics," he added. "We'll

please see ***Transforming*** *on page 30*

Credit: Ellen Dallager

Scientific Program Chair Stephen Goldfinger, M.D., officially opens APA's 2009 Institute on Psychiatric Services in New York City with the traditional bell-ringing ceremony. This year's institute attracted the highest number of attendees ever—2,033. See articles at left and on pages 8, 9, 14, 17, and 23.

Psychiatrist Helped Demonstrate Psychotherapy Is Cost-Effective

Whether psychotherapy is cost-effective was an important question during President Clinton's health care reform effort. Lessons from that era remain relevant during current health reform debates.

BY MARK MORAN

If psychotherapy has a place in the American health care system of tomorrow, give some credit to psychiatrist Susan Lazar, M.D., and other clinician-researchers who helped establish the evidence base for the cost-effectiveness of psychotherapy beginning more than 16 years ago.

That was when Hillary Rodham Clinton's Health Care Task Force was at work. Though the exact content of health insurance benefit packages hasn't yet been a focus of today's health care debates, a decade and a half ago task force members were weighing the relative value of any health care service as a criterion for inclusion in mandated benefits.

And "value" meant cost-effectiveness—the cost of providing the service compared with the benefits derived from the service.

"My own work on establishing the cost-effectiveness of psychotherapy really began in 1992 during the presidential campaign when people were worried about what Clinton was thinking about for health system reform," said Lazar, a clinical professor of psychiatry at Georgetown University School of Medicine, George Washington University School of Medicine, and Uniformed Services University of the Health Sciences and a supervising and training analyst at the Washington

please see ***Psychotherapy*** *on page 31*

Who Will Be APA's Next Leaders?

It's up to you to decide the answer to that question, and the December 4 issue of *Psychiatric News* will help you choose. That issue will contain information on the candidates running in APA's 2010 election. If you would like to receive an electronic ballot in future elections and forego the clutter of receiving a paper ballot, please log in to <www.psych.org/options> and opt-in to only receive an electronic ballot. All ballots must be received by 5 p.m. on February 5, 2010.

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Medical Journal Editors Issue Uniform Disclosure Standard

Journal authors can now use one standard form to report financial and other conflicts of interest, including commercial ties involving family members, to many biomedical journals.

BY JUN YAN

Mainstream medical journals may be moving toward a common standard for authors to report their financial and other conflicts of interest following an October announcement by a group of prominent medical journal editors.

Most peer-reviewed biomedical journals have already imposed explicit requirements for authors of submitted manuscripts to report their financial interests, including funding and employment. These requirements are often similar but may differ in how the conflicts of interest are defined and should be reported.

Now, the International Committee of Medical Journal Editors (ICMJE) has put forth a uniform standard for reporting authors' potential conflicts of interest for manuscript submissions. The standard was approved and adopted by all ICMJE members, consisting of the editors of 12 general medical journals in nine countries and two representatives from the World Association of Medical Editors and the National Library of Medicine.

In recent years, controversies over ethical research reporting and conflicts of interest have plagued the medical journal and research communities. The new disclosure standard requires each study author to report four types of financial or other ties: (1) commercial funding sources of the work described in the manuscripts, (2) commercial entities "that could be viewed as having an interest in the general area of the submitted manuscript" within 36 months before the submission, (3) financial ties involving the author's spouse or children under age 18, and (4) any nonfinancial associations that "may be relevant" to the manuscript.

To ensure consistency across journals, the ICMJE developed a standard Uniform Disclosure Form for Potential Conflicts of Interest, which authors can fill out online in a PDF file and submit to any of the ICMJE member journals. The form asks each author to identify the type of his or her financial relationships with commercial entities, such as consultancies, gifts, and grants.

Among the dozen members of the ICMJE are the *New England Journal of Medicine*, *BMJ*, *Journal of the American Medical Association*, and *The Lancet*. The organization is an extremely influential force in setting the standard for manuscript submissions to peer-reviewed biomedical journals. A large number of biomedical journals adapt or follow the ICMJE's guidelines and principles.

The American Journal of Psychiatry (AJP) is among the journals that follow the ICMJE "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" and had implemented similar or more stringent disclosure requirements

please see ***Editors*** *on page 30*

Important Annual Meeting Announcements

- **For APA Members Only: Register Early!**
  APA members now have an exclusive opportunity to register and make their hotel reservations for APA's 2010 annual meeting in New Orleans. Nonmembers will not be able to do so until December 17. Meeting and hotel information, including hotel rates and descriptions and course information, can be accessed on APA's Web site at <www.psych.org/MainMenu/EducationCareerDevelopment/Meetings/AnnualMeeting.aspx>.

- **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.

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

APA RESOURCES

- ***Psychiatric News* Web Site:** pn.psychiatryonline.org/
- **APA and the APA Answer Center:**
  (888) 35-PSYCH in the U.S. and Canada; in other countries: (703) 907-3700. The Answer Center is open Monday through Friday, 8:30 a.m. to 6 p.m. Eastern time. All APA departments and staff may be reached through the Answer Center.
  Fax: (703) 907-1085
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  Web Site: www.PsychFoundation.org

APA's Institute Looks to Future

BY ALAN F. SCHATZBERG, M.D.

APA's 2009 Institute on Psychiatric Services, which was held in New York City in early October, had its largest attendance ever—over 2,000 professional registrants. That's almost twice as many attendees as in 2008 and surpasses the previous high of 1,971 for the 2006 institute in New York. The record attendance may be due to the expanded scope of this year's program—it was broadened from its traditional community psychiatry focus to address the range of clinical issues in psychiatric care. Coverage of the institute begins in this issue of *Psychiatric News*.

Under the leadership of Dr. Steve Goldfinger, the Scientific Program Committee developed a rich and exciting program. New this year was a series of special lectures by national leaders from various disciplines in our field. These were well attended, as were special courses addressing topics such as psychopharmacology, buprenorphine, and cognitive-behavioral therapy for psychosis. Our psychopharmacology update session drew some 300 attendees.

Jill Gruber, Cathy Nash, and other APA staff did a terrific job on the arrangements for the institute. Although we were all encouraged by the success of the meeting this year, we need to be vigilant about continuing our efforts to make it an enduringly successful meeting, particularly because of the difficult, current economic times.

One question that arises annually in the budget discussions is whether we should continue the Institute on Psychiatric Services. Financially, the meeting usually loses some money, particularly when the overhead costs and staff support are figured into the analysis. Some advocate for doing away with it altogether and incorporating the institute into the annual meeting as a community track. That is certainly one possibility. Another is to continue what the Scientific Program Committee did this year—namely, broaden the content to make it more clinically relevant to a wide range of practitioners. This would make the institute a more extensive educational experience.

Along these lines, we have considered changing the name of the Institute on Psychiatric Services to add "and Clinical Practice." We would then make the institute more of a continuing education meeting that is held each fall in a major metropolitan area that would be attractive to not only the members at large but also to members residing in strong regional bases, for example, the New York City area this year, Boston and New England next, San Francisco and the West Coast later on. Of course, having the meeting in Dr. Goldfinger's backyard (he chairs the Department of Psychiatry at SUNY Downstate Medical Center in Brooklyn) certainly helped in his impressive success in having a large turnout of residents at the institute.

Those who wish to discontinue the institute make cogent arguments about, for example, its cost and appeal to a relatively small minority of our members. However, it does seem that a fall meeting that meets the professional needs of a broader group of psychiatrists beyond its strong—but relatively small—community base and is accessible to more of our members could work. The Budget and Finance Committee discussed this at length at its recent meeting, and the issue will no doubt come up at the Board of Trustees meeting next month.

To this end, the changes made by this year's Scientific Program Committee should be considered for retention in future institutes. The program chair for the 2010 institute is Dr. Anita Everett, and we need to ensure that she and her committee have sufficient representation and input from members in a wide range of subspecialties who can help plan the program. We should also consider how to finance the meeting and set appropriate fees for courses, registration, and so on. If we are to have a viable enterprise, commitment on the part of many members is required. I look forward to helping Dr. Carol Bernstein, APA's president-elect, and Dr. Everett in their work to build on the next exciting institute, which will be held October 14 to 17 in Boston.

Incidentally, the committee welcomes submissions for next year's institute. The deadline for all formats except posters is December 15; the poster submission deadline is May 19, 2010. More information is posted at <www.psych.org/IPS>.

I welcome your comments and suggestions about the future of the institute, as well as other areas in which your Association is active. Please write me at aschatzberg@psych.org. ■

EHR Incentives for Physicians

Robert Plovnick, M.D., director of APA's Department of Quality Improvement and Psychiatric Services, has posted important information on APA's Web site at <www.psych.org/ehrincentive> regarding physician adoption of electronic health records (EHR). Physicians who treat outpatient Medicare patients and demonstrate that they are using a "certified" EHR in a "meaningful" way will be eligible for incentive payments distributed through Medicare for up to $44,000 per physician over five years. The details of the incentive program will be established through regulation starting in December.

Children With Various Illnesses Benefit From Horsing Around

Maryland Therapeutic Riding Inc. would like to find a psychiatric researcher to help it study the therapeutic effects of horseback riding, since little research has been conducted on the subject.

BY JOAN AREHART-TREICHEL

Credit: Joan Arehart-Treichel

Two children with autism play "Simon says" on horseback. The goal is to get them to focus, interact, and follow instructions.

Not long ago, on a Saturday morning in Crownsville, Md., a handful of horses were bridled and blanketed or bridled and saddled for a noble quest.

It was to help children with various psychiatric or other medical illnesses heal—children with autism, attention-deficit/hyperactivity disorder (ADHD), cerebral palsy, multiple sclerosis, muscular dystrophy, severe brain trauma, and other disorders.

The horses live on a 25-acre farm in Crownsville, located in Anne Arundel County, Md., near Annapolis.

The farm is called Maryland Therapeutic Riding Inc. (MTR). It was founded in 1996 as a nonprofit charitable organization by Naomi Parry, who had recovered from a severe car accident with the help of what she came to believe was the healing influence (physical and emotional) of horseback riding. The farm is accredited as a premier therapeutic riding center by the North American Riding for the Handicapped Association (NARHA). Although some 700 therapeutic riding centers are located throughout the United States, not all have received NARHA accreditation, especially its premier accreditation.

So on this recent Saturday morning, the youngsters were helped to mount the horses after they were bridled, blanketed, and led out of the barn. Volunteers led the horses around the arena, while other volunteers walked alongside the horses to make sure that the children didn't fall off. In some cases, the children received what is referred to as "therapeutic riding." Other children received hippotherapy, which consists of using a horse's rhythmic movement to achieve therapeutic gains—for example, to improve balance, coordination, or motor development.

For instance, MTR's physical therapist, Michele Seanger, worked with some of the children on strengthening their trunks and rotating their pelvises, while guiding them around the arena as they sat upright, with their backs as straight as possible. People need to have control of their torsos to speak, and they need to be able to rotate their pelvises to walk, Seanger explained in an interview with *Psychiatric News*.

Eventually some of the children and their horses were taken outside the arena to practice various skills. For instance, one volunteer instructor played the game "Simon says" with two children with autism as they rode around a corral—"Simon says raise your arms" or "Simon says turn your horse to the left." The goal is to get the children to focus, interact, and follow instructions.

MTR also offers therapeutic riding and hippotherapy to adults with various psychiatric or other medical illnesses. For instance, it has a Horses for Heroes Program on Wednesday evenings, which some soldiers from Fort Meade, Md., attend. All of the soldiers have posttraumatic stress disorder (PTSD) and some physical injuries. MTR has also launched a Horses for Hope Program for women in crisis—say, victims of domestic violence or sexual abuse, or women battling substance abuse or anorexia nervosa or bulimia.

Credit: Joan Arehart-Treichel

MTR's headquarters building.

Credit: Joan Arehart-Treichel

Naomi Parry is the founder of Maryland Therapeutic Riding Inc.

Horse Healing Garners Praise

Numerous people have praise for MTR and what its healing horses can accomplish.

The mother of a boy with ADHD who was receiving therapeutic riding at MTR on a recent Saturday morning said in an interview that the riding has helped him focus better and become less shy.

"Last December, I started doing hippotherapy with a 7-year-old boy with a rare brain disorder," said Seanger. "He could only crawl and sit; he couldn't talk. He can now sit on a horse and hold himself up. He can now stand, walk with a walker, and talk some. That's profound; that's huge."

Megan Buck, a graduate student in social work who is doing some volunteer work at MTR, had this to say: "Three women with severe autism have started riding with us. One usually doesn't speak, but when she rides a horse around the ring, she looks over at us and says, 'Hi. Happy!' "

"We've had children with autism speak for the first time," Anne Joyner, MTR's development director, also noted.

As for the soldiers with PTSD who have been coming to MTR, "at first they were nervous, a little shy," Kelly Stepstone, MTR program director, reported. "But after two or three weeks, they were looking forward to it; they were excited about getting on a horse. Some of them are now volunteering with us, giving back. They feel comfortable and safe here."

Staff Sgt. Dan Miller, who is stationed at Fort Meade, Md., and is the superior of some of the soldiers who have visited MTR, commented: "I have personally seen the changes in the attitudes of the soldiers after coming to MTR."

But Where Is Hard Evidence?

Some scientific studies also confirm the value of horse healing, Joyner pointed out.

For example, in a pilot study conducted by Central Michigan University researchers, multiple sclerosis subjects who exhibited postural instability received 14 weeks of hippotherapy. They showed a statistically significant improvement in balance at the end of therapy. Control subjects did not. Results were published in the June 2007 *Journal of Neurologic Physical Therapy*.

In a 2008 pilot study conducted by Washington University researchers, children with cerebral palsy were given 12 weeks of hippotherapy. At the end of that time, the children experienced statistically significant improvement in head and trunk stability and upper-extremity function. The children were also found to sustain these improvements for several months after hippotherapy ended.

Margaret Bass, Ph.D., of the Good Hope Equestrian Training Center in Homestead, Fla., and coworkers, with the help of a grant from the Horse and Humans Research Foundation, conducted a study to determine whether therapeutic riding could benefit children with autism.

Nineteen subjects were randomly assigned to an experimental group and 15 to a control group. The experimental group received therapeutic riding once a week for 12 weeks, the control group did not. The subjects' parents completed two instruments before and after the 12-week period. One was the Social Responsiveness Scale, a 65-item questionnaire that measures the severity of autism symptoms. The other was the Sensory Profile, a 125-item questionnaire that addresses overall social functioning and the degree to which children exhibit problems in sensory processing and behavioral and emotional responses. Outcomes for the experimental group were compared with those of the control one. The experimental group was found to exhibit significantly greater attention and focus than the control group. In fact, it showed "a sustained level of directed attention and focus that is usually not seen in children with autism spectrum disorders," the researchers noted in their paper, which was published in the September *Journal of Autism and Developmental Disorders*. The experimental group was also found to exhibit significantly greater sensory seeking, sensory sensitivity, social motivation, and physical activity than the control group.

"But quite frankly, much more research on therapeutic riding or hippotherapy is needed," Joyner said. "We at MTR would love to find a psychiatric researcher or another type of scientist who would be willing to study horse healing at our center to determine which types of clients it helps, how it works—for instance, is it physical, psychological, or spiritual, or perhaps a combination of all three elements—and whether short-term benefits translate into long-term ones. We would be happy to jointly fund such research or to share our resources and contacts to find funding for such research."

In the meantime, it looks as though MTR will continue to prosper. In addition to a paid staff of nine people, some 150 individuals volunteer at the center each week in various capacities. This year MTR will serve about 300 clients.

"Whether they are soldiers in our Horses for Heroes Program, women in our Horses for Hope Program, or children with autism or severe brain trauma, they don't realize how hard they are working when they come here because it's so much fun," Joyner observed. "Isn't that a great way to make healing happen?"

The Web site of the North American Riding for the Handicapped Association is <www.narha.org>. The Web site for the American Hippotherapy Association is <www.americanhippotherapyassociation.org>. ■

Long-Term-Care Insurance Finds Place in Reform Bills

The measure could benefit the more than 10 million Americans who require long-term care but who struggle to afford such assistance, such as the $70,000 average annual price of nursing homes.

BY RICH DALY

A controversial proposal has been added to some health care reform measures to provide the first national government insurance program to cover long-term care for people whose incomes disqualify them from Medicaid assistance.

Democratic leaders in the House added the long-term-care insurance program to their health care overhaul bill (HR 3200) in October after a Senate committee added similar language to a bill in July.

The voluntary insurance program would provide cash benefits to help cover the cost of a home-care attendant, equipment and supplies, home improvements to aid disabled beneficiaries, and nursing-home care.

"What we are doing here is relieving a burden on individuals so they can be fully functional and independent," said Sen. Bob Casey (D-Pa.) in an October floor speech.

The proposal is based on the Community Living Assistance Services and Supports Act (CLASS Act, S 697 and HR 1721), which has already been introduced and has the support of President Obama.

Under the program, all workers who pay federal income taxes would be automatically enrolled; however, they could choose to opt out. It would charge a premium in exchange for cash benefits to help cover the cost of long-term care after participants were enrolled for at least five years. Federal regulators would decide the program's premiums and benefit levels.

The program could have a significant impact on people with disabilities, including the more than 10 million Americans who need long-term services and supports to assist them in daily activities, according to the proposal's supporters. That number is expected to grow as the U.S. population ages and the number of people with disabilities increases.

MH Advocates See Pressing Need

Some mental health advocates are among the measure's supporters, and in March they sent a letter to the Obama administration urging the White House to support the CLASS Act and push for health care reform that includes its provisions.

"We must create a public program that allows all people, including individuals with disabilities and those near retirement, the opportunity to contribute to and prepare for the costs of long-term services and supports," wrote the advocacy groups, which included Mental Health America and the Bazelon Center for Mental Health Law. APA also supports the long-term-care insurance program.

The insurance program aims to expand on Medicaid's support for comprehensive long-term services and supports, which is limited to low-income Americans. Medicare covers only short-term, skilled nursing and home-health programs.

Advocates of the proposed program said that it is needed to keep the soaring cost of long-term services from wiping out the savings of elderly people and younger ones who are disabled. Lower- and middle-income people are rarely able to afford long-term nursing-home costs, for example, which average more than $70,000 each year, according to a 2008 estimate by the Department of Health and Human Services.

The insurance program was promoted for many years by the late Sen. Edward Kennedy (D-Mass.), who pushed to have it added to the health care overhaul bill that passed the Senate Health, Education, Labor, and Pensions Committee in July.

Lawmakers Anxious About Price Tag

While it has strong support among some lawmakers, the measure has drawn significant opposition, including from fiscally conservative Democrats, because they worry that its long-term costs could far outstrip premiums and add to the budget deficit.

Seven moderate Democrats wrote Senate Majority Leader Harry Reid (D-Nev.) in October asking him not to include CLASS Act provisions in the chamber's final health care bill due to concerns about long-term costs.

The Congressional Budget Office (CBO) estimated, however, that in its first 10 years the program as currently proposed would bring in more money than it pays out and reduce the federal budget deficit by about $73 billion. Critics noted that the initial 10-year period includes 10 years of premium collections and only five years of benefit payouts. The program would begin collecting premiums in 2011 but would not begin paying benefits until 2016. The CBO also estimated that the program would remain fiscally solvent over a 75-year period, assuming an initial monthly premium of $123 and a $75 daily benefit.

Another analysis of the CLASS Act by the American Academy of Actuaries concluded that a combination of factors would make the program insolvent by 2021 and require massive federal subsidies to provide even limited benefits. The costs of the program would further rise, according to critics, under pressure from beneficiaries to raise the low annual benefit of $27,000—far less than needed for nursing-home care.

If the cost concerns over the long-term-care proposal lead to significant Democratic opposition to the health care reform bills in either chamber of Congress, that opposition could endanger passage of the final reform package, according to critics of the proposed insurance program.

The Community Living Assistance Services and Supports Act can be accessed at <http://thomas.loc.gov> by searching on the bill numbers, S 697 and HR 1721. ■

Data Dampen Enthusiasm For Effectiveness Research

Proponents of health care reform have consistently hailed the potential of "comparative effectiveness" as a key feature that will help control accelerating cost growth, but that's now in question.

BY RICH DALY

Will vastly expanding research to determine the most effective treatments for various ailments produce big health care cost savings? Many proponents of health care reform claim it will, but a recent analysis raises serious doubts.

An analysis released in September by the Rand Corporation, an independent health policy research group, examined the likely cost savings from nationwide use of comparative effectiveness research (CER), which examines health outcomes from alternative treatments for the same health problem. CER can be used in several ways, such as providing information on treatment options to physicians and patients and helping to design insurance benefits, determine coverage, and decide on payments.

The researchers found that the voluntary use of CER findings won't necessarily lead to reductions in spending and waste or improvements in health.

"While increasing research aimed at determining the most effective treatments for a wide array of diseases should have benefits, there is not enough evidence at this point to predict exactly what the result might be for the cost of the nation's health care system," said Elizabeth McGlynn, co-director of Rand Compare, a subsidiary of Rand.

The conclusions of the analysis were based on an examination of the existing body of data on CER, as well as how CER is used both in the United States and internationally. It is particularly significant in some other countries where it is used to determine whether certain types of treatment should be covered and, if so, at what amount.

The conclusion is at sharp odds with the position of many advocates of health care reform. The various health care reform bills have included massive expansions in CER as a way to help hold down future health care spending and improve patient health outcomes.

"Investing in research on best practices will drive down health care costs over the long run and will be an essential part of our effort to overhaul the health care system this year," said Sen. Max Baucus (D-Mont.), chair of the Senate Finance Committee and a major player in health care reform, in a statement in June.

Baucus's $829 billion health care reform bill, approved by the Finance Committee in October, included major expansions in funding for conducting and disseminating CER *(Psychiatric News*, October 16). However, the Congressional Budget Office (CBO) estimated that the implementation of CER would cost private insurers a net $2.6 billion over savings and produce net cuts of only $300 million in Medicare costs over the next 10 years.

That estimate fit with the Rand conclusion that in the near term, any reduction in spending created from CER would be offset by the upfront costs associated with generating, coordinating, and disseminating the research findings.

Congress made the down payment for an expanded federal role in this area earlier this year when $1.1 billion was included for CER in the $787 billion economic stimulus package that President Obama signed into law in February.

The Rand researchers found CER programs can have benefits. For instance, they provide better information for doctors and patients about what works best in treating different health problems. The researchers also concluded that under some circumstances, CER might reduce spending for certain diseases by producing clear guidelines that point to superior and potentially less costly medical treatments.

However, the researchers said CER's effectiveness is limited by the extent to which it encourages both clinicians and patients to change their behavior. Previous successful efforts showed that incentives or "other mechanisms" were needed to change behavior. For instance, CER cost-saving studies by the CBO and the Commonwealth Fund in recent years concluded that billions of dollars in annual savings could result if public and private insurers used the research findings to make payment decisions.

However, the stimulus bill specifically prohibited the use of CER results to guide payment policy or benefit design, and the final health care reform measure

please see ***Effectiveness*** *on page 9*

Nadelson Honored for Contributions to Medicine

Twenty-five years ago, Carol Nadelson, M.D., was elected APA's first woman president. Since then, seven women have been elected to that post. That's just one of her notable accomplishments.

BY JOAN AREHART-TREICHEL

On October 9, Carol Nadelson, M.D., a professor of psychiatry at Harvard Medical School and director of the Office for Women's Careers at Brigham and Women's Hospital, received the 10th annual Alma Dea Morani, M.D., Renaissance Woman Award at Harvard's Center for the History of Medicine. She is the second psychiatrist ever to receive the award.

The award honors a woman physician "who has provided a uniquely valuable influence in medicine and the sciences, who challenges the status quo, . . . and whose dedicated service has enhanced the practice and understanding of medicine and humanities in our lifetime."

And indeed, Nadelson's achievements, especially in the domain of women and psychiatry, have been extensive and impressive. Or as Carolyn Robinowitz, M.D., a former APA president who nominated Nadelson for the award, put it: "Most people have no idea what challenges Carol has faced and overcome in her career, what ground she has broken, and the impact she has had nationally on so many young women psychiatrists."

Photo courtesy of Carol Nadelson, M.D.

Carol Nadelson, M.D.

In 1961, she received her medical degree from the University of Rochester, where she was only one of two women in her class. Subsequently she worked as an instructor in psychiatry at Harvard Medical School, advancing to the rank of associate professor of psychiatry. In 1979, she became a professor of psychiatry at Tufts University School of Medicine and vice chair of psychiatry at New England Medical Center.

In 1984, she was elected the first woman president of APA. From 1986 to 2001, she was chief executive officer and editor in chief of American Psychiatric Press Inc. (APPI, now know as American Psychiatric Publishing Inc.).

She was appointed founding director of the Office for Women's Careers at Brigham and Women's Hospital in 1998. In this role she has had a tremendous influence at Harvard on the advancement and success of women physicians, especially of women psychiatrists.

Nadelson launched a new field of study—women's mental health—in collaboration with Malkah Notman, M.D. Her early publications included those on psychological responses to rape, pregnancy, adoption, and abortion. She and her colleagues identified rape as a risk factor for posttraumatic stress disorder. In addition, she was codirector of a longitudinal study that explored the stresses that medical students face.

She is the author of nearly 250 scientific publications, clinical contributions, book chapters, and tapes, and editor of 24 books.

Nadelson has been invited to the White House and the U.S. Congress, where she discussed mental health issues as well as women's roles in medicine and research.

In conjunction with Nadelson's receiving the award, *Psychiatric News* interviewed her to learn how she views her career, notably her time at APA and her work with women psychiatrists, and what she foresees for APA and for women psychiatrists.

Q. What were one or two of your greatest achievements as APA president?

A. One was opening APA to more diversity. Some other major achievements of my APA presidency were organizing a landmark conference on the future of education, with Carolyn Robinowitz, M.D.; working with other medical specialties; and addressing changing values in medicine, with medicine becoming more of a

please see ***Nadelson*** *on page 31*

Psychiatrists Urged to Reframe Conflict-of-Interest Issues

A problem commonly framed in economic or political terms may suggest solutions to a dilemma that is occupying many in the medical profession. As in economics and politics, the solutions all have limitations and costs.

BY MARK MORAN

The subject of industry influence on medicine in general and psychiatry in particular appears to have turned into a toxic one for many physicians, like the clinician who stood up after a lecture on the subject by past APA President Paul Appelbaum, M.D., at the APA Institute on Psychiatric Services last month. He protested that it was all a grand "overreaction" to a nonproblem that had caused physicians, and especially psychiatrists, to become scared and defensive.

That the subject had become a polarizing one was a point that Appelbaum had already acknowledged. He opened his address by citing the words of Harvard physician Thomas Stossel, M.D., who called the persistent demand for regulation of financial conflicts of interest in medicine "a damaging solution in search of a problem." (Stossel's words came from a 2007 article in the journal *Perspectives in Biology and Medicine*, "Regulation of Financial Conflicts of Interest in Medical Practice and Medical Research: A Damaging Solution in Search of a Problem.")

Yet however angry and beleaguered physicians may feel, Appelbaum said the high tide of oversight and regulation rising around industry-physician relations is unlikely to turn. "Psychiatrists and other physicians are caught in a quickly changing regulatory and ethical landscape with simultaneous flux in professional standards, institutional policies, and statutory requirements," he emphasized at the institute.

For this reason, he suggested that physicians, as well as policymakers and medical organizations, might do well to reconceptualize the issue not as an ethical one, with its implications of bad faith and bad behavior, but as a public-policy problem. And as with any public-policy dilemma, working out how physicians will relate to industry in the future will require weighing costs and benefits of a variety of possible solutions and a realization that there is likely to be no perfect solution.

"It may detoxify the issue to view it less as a matter of ethics and more an issue of policy, allowing us to shun reflexive judgment and engage instead in a systematic analysis of options," Appelbaum said. "We need to weigh options against each other and against the option of doing nothing at all. Sometimes we will have data [to back up our decisions] and sometimes not. In all cases, there will be costs associated with our choices, so we need to conceptualize our goal as finding the best approach, not the perfect approach."

As a model of how physician conflicts of interest associated with pharmaceutical-industry relationships might be more dispassionately arbitrated, Appelbaum offered the "principal-agent" problem—a ubiquitous scenario in economics in which any hired "agent" may have interests that diverge from those of the principal, or the hiring party.

The principal-agent problem arises in the most prosaic situations: a department-store clerk is hired to induce as many customers as possible to make purchases, but the clerk may have any number of divergent interests—from taking breaks, to answering text messages, to managing a side business on eBay—that conflict with what he or she was hired to do.

So, too, can conflicts of interest arising from physician relationships with industry be viewed as a variation of the principal-agent problem. Appelbaum summarized evidence showing how financial relationships with the pharmaceutical industry can create potentially conflicting interests for doctors in continuing medical education, clinical practice, and research.

He cited, for example, industry-supported presentations that can influence physicians' prescribing in the direction desired by the companies, sometimes contrary to the interests of patients. Or,

> **"Cutting off relationships with industry inhibits flow of clinical input to the development of therapeutics and eliminates industry support for potentially beneficial programs."**

he noted, a review of studies on meetings with drug-company representatives found increased requests from physicians for formulary additions for promoted drugs and altered prescribing practices by both residents and practicing physicians. These actions favored newly promoted drugs despite their additional cost and sometimes despite evidence suggesting that they may have been inappropriate.

Meta-analyses and reviews consistently indicate that research supported by industry is more likely to report positive findings than studies with other sources of funding. Papers in which at least one author had financial ties to sponsors of psychiatric clinical trials also show a higher rate of positive findings, Appelbaum said.

Possible solutions for resolving principal-agent problems that can be applied to medicine include education, disclosure, management, and alignment of interests.

Education has an intrinsic appeal, but its effectiveness as a tool in resolving or preventing conflicts may be limited, according to Appelbaum.

Reviews of education with house staff about the impact of meetings with drug reps showed some short-term effects on perceptions and behavior. What may be the only study in psychiatry found that a one-hour educational program led to no change in residents' attitudes toward drug reps, but a reduced acceptance of noneducational gifts, he said.

Disclosure, a response to the popular demand for "transparency," operates essentially as a proxy for monitoring whose interests the doctor is serving and is the most ubiquitous strategy for managing potential conflicts. Today, presenters at sessions sponsored by the Accreditation Council for Continuing Medical Education (ACCME) must reveal companies from which they have received funding; journals routinely require authors to divulge financial ties with industry; the National Institutes of Health now asks institutions to report whether researchers' income from a company exceeds $10,000; and state and federal "sunshine"

please see ***Conflict of Interest*** *on page 30*

Nobel Winners' Findings Opened New Area of Illness Study

Although vital discoveries have been made about the molecular caps on chromosomes, the best may be yet to come regarding their roles in aging, cancer, and mental illness.

BY JOAN AREHART-TREICHEL

Major discoveries about telomeres—those DNA-protein complexes that cap the end of chromosomes—have garnered three scientists the 2009 Nobel Prize in Physiology or Medicine.

The announcement was made by the Nobel Assembly at the Karolinska Institute in Stockholm on October 5. The scientists are Elizabeth Blackburn, Ph.D., a professor of biology and physiology at the University of California, San Francisco; Carol Greider, Ph.D., a professor of molecular biology and genetics at Johns Hopkins University; and Jack Szostak, Ph.D., a professor of genetics at Massachusetts General Hospital.

As early as the 1930s, telomeres had already been observed by scientists, though nothing was known about their function. In 1982, however, Blackburn and Szostak reported that telomeres taken from one organism—a unicellular organism called *Tetrahymena*—could protect chromosomes in an entirely different organism—yeast—from degradation. Thus, it looked as if this might be telomeres' *raison d'etre*—to protect chromosomes from degradation.

please see ***Nobel*** *on page 32*

Suicide Rates Disappointing Marker Of Access to MH Services

The newest "report card" began tracking suicide rates as a measure of the availability of mental health care and found a majority of states had worsening rates in recent years.

BY RICH DALY

States have improved overall in recent years in both their provision of needed mental health care for children and in reducing the use of physical restraints in nursing homes, according to an analysis of U.S. health trends.

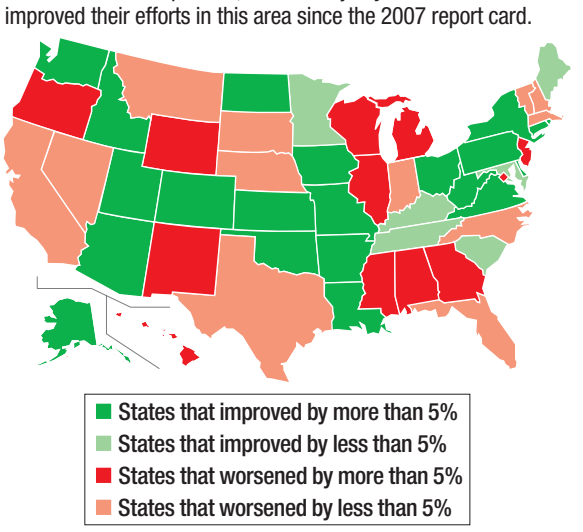
The findings came from the Commonwealth Fund Commission on a High Performance Health System's second state scorecard report released on October 8. The follow-up report to the 2007 report card uses public-health data to rank states on 38 health indicators in the areas of access, prevention, treatment, avoidable hospital use and costs, and healthy lives. Among its major findings: health insurance coverage for adults declined, health care costs rose, and quality improved in areas in which outcomes were reported to the public.

In the few mental health measures that were examined, the report noted that children were slightly more likely to receive needed mental health care, with 27 states improving their standing in this area since the 2007 report. The authors noted that only 21 states "substantially improved"

please see ***Report Card*** *on facing page*

States Improve Children's Mental Health Care Access

Nationally, the rate of children receiving needed mental health care increased 2.2 percent, while a majority of states also improved their efforts in this area since the 2007 report card.



Source: *Aiming Higher: Results From a State Scorecard on Health System Performance, 2009*, Commonwealth Fund Commission on a High Performance Health System, October 2009

Police Crisis Teams Promising, But Final Verdict Not In

Law enforcement crisis intervention teams, trained to intercede in situations with individuals who may be mentally ill, are multiplying, but research on their effectiveness is only now becoming available.

BY AARON LEVIN

Crisis intervention team (CIT) training for police forces seems like a good idea, yet little is known about the outcomes of such training despite 20 years of experience.

At the APA Institute on Psychiatric Services in New York in October, researchers from Georgia and Illinois began to fill in that gap, reporting results from early studies of CIT programs.

An estimated 10 percent of police contacts with the public involve people with mental illness, turning officers into de-facto triage personnel. Traditionally, police cadets get only an average of one to two hours of information about mental illness during their training, leaving them poorly equipped to judge the behavior of mentally ill individuals in a confrontation.

CITs began in 1987 after officers killed a mentally ill man in Memphis. The Memphis Police Department and the local branch of the organization now known as the National Alliance on Mental Illness worked with mental health professionals and community members to teach the police better ways to manage their interactions with people with mental illness. The concept proved popular. Today, there are an estimated 400 CIT programs for local and state law enforcement units in the United States.

"The goal is to get the subjects medical treatment rather than criminal incarceration, reduce stigma, and improve safety," said Michael Compton, M.D., M.P.H., of Emory University in Atlanta. He and Beth Broussard, M.P.H., reported on the Georgia program, which has trained about 3,000 officers in at least 50 of the state's 159 counties.

Typically, officers volunteer for CIT training. The training usually consists of 40 hours of course work and field experience that include the science of mental illness, visits with mentally ill people, and techniques to deescalate potentially violent encounters. Some of the training includes role playing by the police or actors who are mental health consumers. Police dispatchers also undergo special training so they know when to send a CIT team.

Effectiveness Assessed

Compton and his colleagues performed nine small pilot studies to lay the groundwork for a larger study funded by the National Institute of Mental Health (NIMH) that is now under way. Several of these studies showed that officers who took the CIT training displayed a scientifically informed understanding of mental illness, a greater knowledge of mental health issues, less stigma, and less social distancing from people with mental illness.

The researchers also hypothesized that as more police officers got CIT training, the use of special weapons and tactics (SWAT) teams might decline. In fact, they found no correlation between the two in a study of administrative data from 1999 to 2007.

"SWAT teams and CIT address different situations," said Compton. "When the SWAT team is called, the situation has already developed beyond what the CIT is trained for."

Another survey of 88 police officers, taken an average of two years after the training, found a slight but significant decline in their knowledge. That decline correlated not with time elapsed since the training, as Compton expected, but inversely with the number of years an officer had been on the force. The longer they had served, the less decline in knowledge they displayed.

"Perhaps longer-serving officers may be better choices for joining a CIT," he suggested.

Another study of 48 officers with CIT training and 87 without used several escalating vignettes to evaluate when they were likely to resort to physical force to control a subject. The untrained officers were more likely to choose physical force sooner in the escalating scenario, and CIT-trained officers rated the value of nonphysical force more highly.

However, whether that is due to training is still unclear, said Compton. "The key may be who chooses to enter CIT training."

For one, among the volunteers for CIT training, there were higher proportions of women officers and of officers who knew someone who had received psychiatric treatment compared with police personnel who had not volunteered for the training.

The Emory researchers have received an NIMH grant to determine how CIT training relates to behavioral attitudes and intentions, deescalation skills, and actual mental health referrals. In the future, they also hope to look at both officer-level and patient-level outcomes.

Impact of CIT Training on Arrests

Chicago's CIT program began in two police districts in 2005, training 30 to 40 officers and supervisors in each district, said Amy Watson, Ph.D., an assistant professor in the Jane Addams College of Social Work at the University of Illinois at Chicago. The program expanded to all 25 of the city's districts a year later. Close to 1,000 officers have now been trained.

CIT-trained officers have increased referral of individuals to mental health services by 18 percent. However, there was no difference in the rates of arrest between trained and untrained officers. Regardless of their training or lack of it, all officers seemed to know when it was more appropriate to arrest than to refer for treatment.

CIT training may not be the only factor influencing an officer who has to decide between arresting subjects and sending them to a mental health service site, said Watson. If a supervisor is pressing officers to resolve a situation quickly so they can move on to another call, they may resort more quickly to arrest rather than take the time to talk with a subject to determine the ideal approach to the problem.

Watson, too, expects future research to reveal the effects of CIT training on the experience of mentally ill people in contacts with the police. In the meantime, CIT training will remain just one tool to help police reduce the risk of harm to themselves and to those with mental illness.

"CIT is not the only or even the best approach for dealing with these people," said Compton. "Mobile crisis teams may be the best approach because CIT is a police-based response when other systems don't exist or are not available." ■

Report Card

continued from facing page

in the rate at which children living there were able to receive needed mental health care, while 11 states and the District of Columbia "declined substantially."

"Key indicators of nursing-home and home-health-care quality improved substantially in nearly all states, with declines in rates of pressure ulcers, physical restraints, and pain for nursing home residents and improved mobility for home care patients," wrote the authors.

The decline in the use of restraints came after years of efforts by government health officials and health advocates, including APA, to reduce their use among patients in general and nursing-home residents with mental illnesses in particular.

For example, the Centers for Medicare and Medicaid Services (CMS) enacted regulations in February 2007 that sought to minimize the use of seclusion and restraints by physicians and health care workers who treat patients in hospitals that participate in Medicare or Medicaid (*Psychiatric News*, January 19, 2007).

Although the Commonwealth Fund researchers addressed only physical restraints, the CMS guidelines applied to "any manual method, physical or mechanical device, material, or equipment that immobilizes or reduces the ability of a patient to move his or her arms, legs, body, or head freely; or a drug or medication when it is used as a restriction to manage the patient's behavior or restrict the patient's freedom of movement and is not a standard treatment or dosage for the patient's condition."

In 2003, APA and other organizations issued a 42-page booklet, "Learning From Each Other: Success Stories and Ideas for Reducing Restraint/Seclusion in Behavioral Health," which described strategies for reducing the use of seclusion and restraint (*Psychiatric News*, February 7, 2003).

The Commonwealth Fund researchers began tracking suicide rates in the latest report card as a shorthand method of quantifying the availability of mental health services in the states. Although federal and state funding of mental health services has generally increased in the last decade, the researchers found, the national suicide rate also has increased.

Paula Clayton, M.D., medical director of the American Foundation for Suicide Prevention, agreed that using suicide rates is a valid indicator of the availability of mental health care, because 90 percent of suicide victims are suffering from a mental disorder at the time of their death.

"The only way that we can change suicide [rates] is to recognize the disorders and see that [the people with these disorders] get treatment," Clayton told *Psychiatric News*.

The report stated that age-adjusted suicide rates were the lowest in New York and New Jersey and highest in Montana, Alaska, and Nevada. Suicide rates are generally highest in Mountain region states and lowest in the Northeast.

Those findings largely dovetail with regional differences in the availability of mental health care, Clayton said. And the high rates in the less-populated Mountain states reflect research linking suicide and loneliness in the elderly.

"Aiming Higher: Results From the 2009 State Scorecard on Health System Performance" is posted at <www.commonwealthfund.org/Content/Publications/Fund-Reports/2009/Oct/2009-State-Scorecard.aspx>.■

Effectiveness

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is expected to include a similar caveat. The result is that it is "considerably less likely" that federal health officials will develop strong incentives to implement CER results and drive down spending, according to the Rand authors.

The fear of mandatory use of CER to determine coverage and payments has made it highly controversial. Critics of CER, including many physicians, worry that it could eventually be used by policymakers, insurers, or hospital administrators to limit options for patients and their physicians.

"Making a blanket coverage denial based on comparative effectiveness studies if the two treatments are safe and effective—I think it's wrong," said David Nexon, a vice president of the Advanced Medical Technology Association and a longtime congressional health care expert. "It's wrong for patients. It's wrong for doctors. It's wrong for our health care system."

Further information on the analysis is posted at <www.randcompare.org>. ■

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

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62-1014307R R2 03/09

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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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APA Seeks Ideas to Sever Mental Illness, Delinquency Link

APA's OMNA on Tour stops in Seattle, where the link between child mental illness and juvenile delinquency is put under the microscope by experts.

BY STEPHANIE WHYCHE

Credit: Alison Bondurant

Participating in one of the OMNA on Tour–Seattle panel discussions were (from left) Betty Wane, peer mentor for foster children in Pierce County, Wash.; Sabrena Roddy, a parent/child advocate; Deborah Stake, with Seattle's Therapeutic Health Services; Mariko Kakiuchi, with Career Educational Options at Shoreline Community College; and Marcus Stubblefield, with King County (Wash.) Systems Integration Initiative.

Jeanette Barnes has volunteered her time over the years to myriad child mental health endeavors at the local, state, and national levels. She is the founder of A Village Project II, a grassroots enterprise designed to strengthen child/family relations. She is employed as the family liaison for the state of Washington's Division of Behavioral Health and Recovery.

But Barnes, who is of Lakota, Sioux, and Winnebago tribal descent, did not plan this career path—she wanted to be an accountant. Her interest in child mental health stems from another hat she wears: that of mother. The youngest of her three children was diagnosed at age 4 with attention-deficit/hyperactivity disorder (ADHD). By age 11 he was diagnosed with bipolar disorder, and by age 12 with posttraumatic stress disorder (PTSD).

In first grade he was placed in a special-education class, she said, diagnosed with conduct disorder. He stayed on that track through the fifth grade. Next came substance use, followed by gang membership, followed by entry into the juvenile-justice system at age 16 for first-degree robbery.

Credit: Alison Bondurant

Sandra Walker, M.D., a Seattle-based psychiatrist and chair of APA's Council on Minority Mental Health and Health Disparities, introduces Bruce Gage, M.D., director of psychiatric services for the Washington State Department of Corrections, at OMNA on Tour–Seattle.

Barnes said she is convinced that had her son received early in his life a needs-specific, multidisciplinary range of support services and treatment—and not medication-driven care—he might not have found himself locked in a facility for two years where the lack of good mental health care continued.

"Our juvenile-justice system is punitive," Barnes said in Seattle during an interview with *Psychiatric News.* "It's not rehabilitation. It doesn't recognize that mental health plays a role in the events leading up to [a child's] incarceration."

Earlier Intervention Needed

Barnes shared her child's story, what she calls their "life journey," during the sixth stop in four years of APA's OMNA on Tour in Seattle in September (see box below left). The theme of the meeting was "Diverse Youth in Transition: Navigating a Difficult Passage."

About 90 people from the Seattle metropolitan area, King County (the jurisdiction the city is in), and around the state attended the multidisciplinary meeting. They included psychiatrists, mental health and other health care professionals; city, county, and state mental health officials; social-service and child-welfare personnel; homeless-shelter workers; and child educators. The eight panel discussions around which the day-long program was designed included former at-risk youth and family members.

The overarching question with which participants wrestled was this: How can children who live in and around Seattle and are at risk of developing a mental illness be identified (and identified early) to prevent them from becoming statistics of the juvenile-justice or adult-correctional systems? And how can youth already in the system be helped to live full and healthful lives in the community?

Speakers at the meeting agreed that undiagnosed and untreated mental health problems such as depression, anxiety, ADHD, oppositional defiant disorder, and PTSD from exposure to life-threatening experiences can lead to poor choices, which can lead to interruption in a child's schooling, which can lead to antisocial behavior such as illicit drug use, crime, and incarceration in a juvenile-delinquency or adult-correctional facility. Such troubled youth may die as victims of crime or suicide. In the meantime, the child's family is typically also under pressure and may experience worry, anxiety, stress, work disruption, and legal costs.

According to the National Conference of State Legislators, "nearly 70

please see ***Delinquency*** *on page 24*

APA Program Works To Reduce MH Disparities

OMNA on Tour, hosted by APA's Office of Minority and National Affairs (OMNA), is in its fourth year. This on-the-move, community-education program reaches out to diverse, underserved communities around the United States to help them wage a more effective war against mental illness—from stigma and lack of information to the languishing racial, ethnic, and economic disparities in its prevention, early diagnosis, and treatment.

To help eliminate such disparities, the tour facilitates multidisciplinary collaboration among a community's stakeholders with the goal that they will develop or enhance local action plans and implement them.

Annelle Primm, M.D., M.P.H., director of OMNA and creator of the tour program, launched it in 2005; the first stop was Washington, D.C. *(Psychiatric News,* March 4, 2005). Since then, she and her staff have crisscrossed the country making stops in Philadelphia, Chicago, New Orleans, Los Angeles, and Seattle (see story above).AThe cosponsors of the Seattle tour were the Washington State Psychiatric Association (WSPA), a district branch of APA, and the King County Mental Health, Chemical Abuse, and Dependency Services. WSPA President James Peacey, M.D., a child and adolescent psychiatrist and medical director of the Seattle Children's Home, opened the meeting.

The meeting's local planning committee was led by Charles Huffine, M.D., a Seattle child and adolescent psychiatrist who serves as medical director of the child and adolescent programs at the King County Mental Health, Chemical Abuse, and Dependency Division. He helped found Youth 'N Action, a King County youth and family support and self-advocacy initiative funded in part by a federal grant from the Substance Abuse and Mental Health Services Administration.

Other members of the planning committee, who along with Huffine also served as chairs of various panel discussions, were Ray Hsiao, M.D., who teaches psychiatry and behavioral sciences at the University of Washington School of Medicine and is codirector of the Adolescent Substance Abuse Program at Children's Hospital in Seattle; William Womack, M.D., an associate professor emeritus of psychiatry at the University of Washington School of Medicine and a member of APA's Board of Trustees; and Sandra Walker, M.D., a Seattle-based psychiatrist and psychiatric consultant and chair of APA's Council on Minority Mental Health and Health Disparities.

"They have been an extremely active planning group, making this OMNA on Tour possible and customized to the specific needs of the community," Primm told *Psychiatric News.*

At the same time, the state psychiatric association, overall, is "doing a lot of outreach to the broader mental health community," said Marlis Korber, executive director of WSPA. "They are not just psychiatrists talking to other psychiatrists. They are talking to adjudicators, educators, social workers, and the like."

Credit: Alison Bondurant

At a reception preceding the OMNA on Tour–Seattle meeting, OMNA Director Annelle Primm, M.D., M.P.H., chats with (center) James Peacey, M.D., president of the Washington State Psychiatric Association, and William Womack, M.D., an associate professor emeritus at the University of Washington and a member of APA's Board of Trustees.

Recovery Model Needs More Adherents, Says Psychiatrist

SAMHSA's push for psychiatry to embrace the recovery care model for people with serious mental illness aims to spur action by late adopters of a strategy that emphasizes goals over symptoms.

BY RICH DALY

Federal mental health leaders have a message for psychiatrists: Give "recovery" another look.

That is, psychiatrists and mental health professionals should move from an approach that emphasizes recommending disease treatments to one that focuses on asking patients what they want from treatment and discussing ways to meet those goals.

Leaders from the Substance Abuse and Mental Health Services Administration (SAMHSA) met with about 40 psychiatrists in October to discuss ways to move psychiatry into the "recovery-focused" movement long espoused by patient-advocacy groups. A big focus of the meeting in Washington, D.C., on October 5 and 6 was on developing explicit clinical instructions on the use of "recovery" approaches and ways to promote those strategies to psychiatrists.

Kenneth Thompson, M.D., associate director for medical affairs at SAMHSA's Center for Mental Health Services, helped organize the event and shared some of his clinical experiences using a recovery-based approach. Such approaches have made many of his patients "more engaged" in their treatment and produced better overall outcomes, he said.

"I find practice more fulfilling and less deadening," said Thompson in an interview with *Psychiatric News*.

Recovery has been used to denote amelioration of symptoms along with a reduction of the impact of serious mental illness on patients' lives. Patient advocates emphasize an understanding of recovery that focuses less on a remission of symptoms and more on helping patients overcome the effects of mental illness on their lives, including difficulties with employment, housing, and a lack of hope about their future.

A shift of emphasis to a recovery approach "creates tension with a system created to treat people's illnesses," Wayne Katon, M.D., a professor and vice chair of psychiatry at the University of Washington, told *Psychiatric News*. "There are things that we have to learn from that perspective that have been ignored by the national mental health professions."

Urged by Presidential Commission

The recovery approach has a long history in general health care and has been widely used by many who provide care for people with psychiatric illness. The New Freedom Commission on Mental Health endorsed the recovery approach when it called for a "fundamental transformation of the nation's approach to mental health care" in its report to President George W. Bush in July 2003. The commission recommended a focus on "promoting recovery and building resilience."

A 2005 APA position statement titled "Use of the Concept of Recovery" described the recovery approach as one that "enriches and supports medical and rehabilitation models."

"By applying the concept of recovery as well as rehabilitation techniques and by encouraging other mental health professionals to adopt the concept of recovery, psychiatrists can enhance the care of all clinical populations served within the community-based and other public-sector mental health and behavioral health systems," said the statement.

The SAMHSA meeting "signaled to me that the issue of recovery is beginning to be seriously considered," said Annelle Primm, M.D., M.P.H., director of the APA Office of Minority and National Affairs.

Specific Help Planned

The challenge to implementing wide adoption by psychiatrists of a recovery model may come in the transition from concept to practice.

The SAMHSA effort aims to move beyond previous educational efforts about recovery to create specific instructions, possibly by next spring, that psychiatrists can use as guidelines for integrating recovery models into their practices. Such training materials are needed in the same way that training is required to perform mental status exams and cognitive-behavioral therapy, said Joseph Parks, M.D., director of the Division of Comprehensive Psychiatric Services at Missouri's Department of Mental Health, in an interview with *Psychiatric News*.

"If we're going to learn to do a recovery-oriented interaction with patients, it's going to be that same kind of very explicit

please see ***Recovery*** *on page 32*

PAROXETINE HYDROCHLORIDE EXTENDED-RELEASE TABLETS 12.5 mg and 25 mg

℞ only

BRIEF SUMMARY: Please see package insert for full prescribing information.

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 paroxetine 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. Paroxetine is not approved for use in pediatric patients. (See WARNINGS: Clinical Worsening and Suicide Risk, PRECAUTIONS: Information for Patients and PRECAUTIONS: Pediatric Use.)

INDICATIONS AND USAGE: Major Depressive Disorder: Paroxetine hydrochloride extended-release tablets are indicated for the treatment of major depressive disorder.

The efficacy of paroxetine hydrochloride extended-release tablets in the treatment of a major depressive episode was established in two 12 week controlled trials of outpatients whose diagnoses corresponded to the DSM-IV category of major depressive disorder (see CLINICAL PHARMACOLOGY: Clinical Trials in full prescribing information).

A major depressive episode (DSM-IV) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed mood or loss of interest or pleasure in nearly all activities, representing a change from previous functioning, and includes the presence of at least 5 of the following 9 symptoms during the same 2 week period: Depressed mood, markedly diminished interest or pleasure 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.

The antidepressant action of paroxetine in hospitalized depressed patients has not been adequately studied.

Paroxetine hydrochloride extended-release tablets have not been systematically evaluated beyond 12 weeks in controlled clinical trials; however, the effectiveness of immediate-release paroxetine hydrochloride in maintaining a response in major depressive disorder for up to one year has been demonstrated in a placebo-controlled trial (see CLINICAL PHARMACOLOGY: Clinical Trials in full prescribing information). The physician who elects to use paroxetine hydrochloride extended-release tablets for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS: Concomitant use in patients taking either monoamine oxidase inhibitors (MAOIs), including linezolid, an antibiotic which is a reversible non-selective MAOI, or thioridazine is contraindicated (see WARNINGS and PRECAUTIONS).

Concomitant use in patients taking pimozide is contraindicated (see PRECAUTIONS).

Paroxetine hydrochloride extended-release tablets are contraindicated in patients with a hypersensitivity to paroxetine or to any of the inactive ingredients in paroxetine hydrochloride extended-release tablets.

WARNINGS: 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 to 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 4,400 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 1,000 patients treated) are provided in Table 1.

Table 1

Age Range	Drug-Placebo Difference in Number of Cases of Suicidality Per 1,000 Patients Treated
Increases Compared to Placebo	
< 18	14 additional cases
18 to 24	5 additional cases
Decreases Compared to Placebo	
25 to 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 PRECAUTIONS and DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets, for a description of the risks of discontinuation of paroxetine).

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 healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for paroxetine 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 paroxetine is not approved for use in treating bipolar depression.

Potential for Interaction With Monoamine Oxidase Inhibitors: In patients receiving another serotonin reuptake inhibitor drug in combination with an MAOI, there have been reports of serious, sometimes fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued that drug and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. While there are no human data showing such an interaction with paroxetine hydrochloride, limited animal data on the effects of combined use of paroxetine and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that paroxetine hydrochloride extended-release tablets not be used in combination with an MAOI (including linezolid, an antibiotic which is a reversible non-selective MAOI), or within 14 days of discontinuing treatment with an MAOI (see CONTRAINDICATIONS). At least 2 weeks should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

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 paroxetine hydrochloride extended-release tablets 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 paroxetine hydrochloride extended-release tablets with MAOIs intended to treat depression is contraindicated.

If concomitant treatment of paroxetine hydrochloride extended-release tablets 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 paroxetine hydrochloride extended-release tablets with serotonin precursors (such as tryptophan) is not recommended.

Treatment with paroxetine hydrochloride extended-release tablets 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.

Potential Interaction with Thioridazine: Thioridazine administration alone produces prolongation of the QTc interval, which is associated with serious ventricular arrhythmias, such as Torsade de pointes-type arrhythmias, and sudden death. This effect appears to be dose related.

An *in vivo* study suggests that drugs which inhibit CYP2D6, such as paroxetine, will elevate plasma levels of thioridazine. Therefore, it is recommended that paroxetine not be used in combination with thioridazine (see CONTRAINDICATIONS and PRECAUTIONS).

Usage in Pregnancy: ***Teratogenic Effects:*** Epidemiological studies have shown that infants born to women who had first trimester paroxetine exposure had an increased risk of cardiovascular malformations, primarily ventricular and atrial septal defects (VSDs and ASDs). In general, septal defects range from those that are symptomatic and may require surgery to those that are asymptomatic and may resolve spontaneously. If a patient becomes pregnant while taking paroxetine, she should be advised of the potential harm to the fetus. Unless the benefits of paroxetine to the mother justify continuing treatment, consideration should be given to either discontinuing paroxetine therapy or switching to another antidepressant (see PRECAUTIONS: General: *Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets*). For women who intend to become pregnant or are in their first trimester of pregnancy, paroxetine should only be initiated after consideration of the other available treatment options.

A study based on Swedish national registry data evaluated infants of 6,896 women exposed to antidepressants in early pregnancy (5,123 women exposed to SSRIs; including 815 for paroxetine). Infants exposed to paroxetine in early pregnancy had an increased risk of cardiovascular malformations (primarily VSDs and ASDs) compared to the entire registry population (OR 1.8; 95% confidence interval 1.1 to 2.8). The rate of cardiovascular malformations following early pregnancy paroxetine exposure was 2% vs. 1% in the entire registry population. Among the same paroxetine exposed infants, an examination of the data showed no increase in the overall risk for congenital malformations.

A separate retrospective cohort study using U.S. United Healthcare data evaluated 5,956 infants of mothers dispensed paroxetine or other antidepressants during the first trimester (n = 815 for paroxetine). This study showed a trend towards an increased risk for cardiovascular malformations for paroxetine compared to other antidepressants (OR 1.5; 95% confidence interval 0.8 to 2.9). The prevalence of cardiovascular malformations following first trimester dispensing was 1.5% for paroxetine vs. 1% for other antidepressants. Nine out of 12 infants with cardiovascular malformations whose mothers were dispensed paroxetine in the first trimester had VSDs. This study also suggested an increased risk of overall major congenital malformations (inclusive of the cardiovascular defects) for paroxetine compared to other antidepressants (OR 1.8; 95% confidence interval 1.2 to 2.8). The prevalence of all congenital malformations following first trimester exposure was 4% for paroxetine vs. 2% for other antidepressants.

Animal Findings: Reproduction studies were performed at doses up to 50 mg/kg/day in rats and 6 mg/kg/day in rabbits administered during organogenesis. These doses are approximately 8 (rat) and 2 (rabbit) times the maximum recommended human dose (MRHD) on a mg/m^2 basis. These studies have revealed no evidence of teratogenic effects. However, in rats, there was an increase in pup deaths during the first 4 days of lactation when dosing occurred during the last trimester of gestation and continued throughout lactation. This effect occurred at a dose of 1 mg/kg/day or approximately one-sixth of the MRHD on a mg/m^2 basis. The no effect dose for rat pup mortality was not determined. The cause of these deaths is not known.

Nonteratogenic Effects: Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or serotonin and norepinephrine reuptake inhibitors (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: Potential for Interaction with Monoamine Oxidase Inhibitors).

Infants exposed to SSRIs in late pregnancy may have an increased risk for persistent pulmonary hypertension of the newborn (PPHN). PPHN occurs in 1 to 2 per 1,000 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 6-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 collaborative 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.

There have also been post-marketing reports of premature births in pregnant women exposed to paroxetine or other SSRIs.

When treating a pregnant woman with paroxetine 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.

PRECAUTIONS: General: ***Activation of Mania/Hypomania:*** During premarketing testing of immediate-release paroxetine hydrochloride, hypomania or mania occurred in approximately 1% of paroxetine-treated unipolar patients compared to 1.1% of active control and 0.3% of placebo-treated unipolar patients. In a subset of patients classified as bipolar, the rate of manic episodes was 2.2% for immediate-release paroxetine and 11.6% for the combined active control groups. Among 1,627 patients with major depressive disorder, panic disorder, social anxiety disorder, or PMDD treated with paroxetine hydrochloride extended-release tablets in controlled clinical studies, there were no reports of mania or hypomania. As with all drugs effective in the treatment of major depressive disorder, paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of mania.

Seizures: During premarketing testing of immediate-release paroxetine hydrochloride, seizures occurred in 0.1% of paroxetine treated patients, a rate similar to that associated with other drugs effective in the treatment of major depressive disorder. Among 1,627 patients who received paroxetine hydrochloride extended-release tablets in controlled clinical trials in major depressive disorder, panic disorder, social anxiety disorder, or PMDD, one patient (0.1%) experienced a seizure. Paroxetine hydrochloride extended-release tablets should be used cautiously in patients with a history of seizures. It should be discontinued in any patient who develops seizures.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were not systematically evaluated in most clinical trials; however, in recent placebo-controlled clinical trials utilizing daily doses of paroxetine hydrochloride extended-release tablets up to 37.5 mg/day, spontaneously reported adverse events while discontinuing therapy with paroxetine hydrochloride extended-release tablets were evaluated. Patients receiving 37.5 mg/day underwent an incremental decrease in the daily dose by 12.5 mg/day to a dose of 25 mg/day for one week before treatment was stopped. For patients receiving 25 mg/day or 12.5 mg/day, treatment was stopped without an incremental decrease in dose. With this regimen in those studies, the following adverse events were reported for paroxetine hydrochloride extended-release tablets, at an incidence of 2% or greater for paroxetine hydrochloride extended-release tablets and were at least twice that reported for placebo: Dizziness, nausea, nervousness, and additional symptoms described by the investigator as associated with tapering or discontinuing paroxetine hydrochloride extended-release tablets (e.g., emotional lability, headache, agitation, electric shock sensations, fatigue, and sleep disturbances). These events were reported as serious in 0.3% of patients who discontinued therapy with paroxetine hydrochloride extended-release tablets.

During marketing of paroxetine hydrochloride extended-release tablets and other SSRIs and SNRIs, 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 and tinnitus), 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 paroxetine hydrochloride extended release tablets. 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).

See also PRECAUTIONS: Pediatric Use, for adverse events reported upon discontinuation of treatment with paroxetine in pediatric patients.

Akathisia: The use of paroxetine or other SSRIs has been associated with the development of akathisia, which is characterized by an inner sense of restlessness and psychomotor agitation such as an inability to sit or stand still usually associated with subjective distress. This is most likely to occur within the first few weeks of treatment.

Hyponatremia: Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including paroxetine hydrochloride extended-release tablets. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). 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 paroxetine hydrochloride extended-release tablets 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 paroxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants may add to this 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 paroxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Use in Patients with Concomitant Illness: Clinical experience with immediate-release paroxetine hydrochloride in patients with certain concomitant systemic illness is limited. Caution is advisable in using paroxetine hydrochloride extended-release tablets in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

As with other SSRIs, mydriasis has been infrequently reported in premarketing studies with paroxetine hydrochloride. A few cases of acute angle closure glaucoma associated with therapy with immediate-release paroxetine have been reported in the literature. As mydriasis can cause acute angle closure in patients with narrow angle glaucoma, caution should be used when paroxetine hydrochloride extended-release tablets are prescribed for patients with narrow angle glaucoma.

Paroxetine hydrochloride extended-release tablet or the immediate-release formulation 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 clinical studies during premarket testing. Evaluation of electrocardiograms of 682 patients who received immediate-release paroxetine hydrochloride in double-blind, placebo-controlled trials, however, did not indicate that paroxetine is associated with the development of significant ECG abnormalities. Similarly, paroxetine hydrochloride does not cause any clinically important changes in heart rate or blood pressure.

Increased plasma concentrations of paroxetine occur in patients with severe renal impairment (creatinine clearance < 30 mL/min.) or severe hepatic impairment. A lower starting dose should be used in such patients (see DOSAGE AND ADMINISTRATION).

Drug Interactions: ***Tryptophan:*** As with other serotonin reuptake inhibitors, an interaction between paroxetine and tryptophan may occur when they are coadministered. Adverse experiences, consisting primarily of headache, nausea, sweating, and dizziness, have been reported when tryptophan was administered to patients taking immediate-release paroxetine. Consequently, concomitant use of paroxetine hydrochloride extended-release tablets with tryptophan is not recommended (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*).

Monoamine Oxidase Inhibitors: See CONTRAINDICATIONS and WARNINGS.

Pimozide: In a controlled study of healthy volunteers, after immediate-release paroxetine hydrochloride was titrated to 60 mg daily, coadministration of a single-dose of 2 mg pimozide was associated with mean increases in pimozide AUC of 151% and C_{max} of 62%, compared to pimozide administered alone. The increase in pimozide AUC and C_{max} is due to the CYP2D6 inhibitory properties of paroxetine. Due to the narrow therapeutic index of pimozide and its known ability to prolong the QT interval, concomitant use of pimozide and paroxetine hydrochloride extended-release tablets are contraindicated (see CONTRAINDICATIONS).

Serotonergic Drugs: Based on the mechanism of action of SNRIs and SSRIs, including paroxetine hydrochloride and the potential for serotonin syndrome, caution is advised when paroxetine hydrochloride extended-release tablets are coadministered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible nonselective MAOI), lithium, tramadol, or St. John's Wort (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*). The concomitant use of paroxetine extended-release tablets with MAOIs (including linezolid) is contraindicated (see CONTRAINDICATIONS). The concomitant use of paroxetine extended-release tablets with other SSRI's, SNRIs or tryptophan is not recommended (see PRECAUTIONS: Drug Interactions: *Trytophan*).

Thioridazine: See CONTRAINDICATIONS and WARNINGS.

Warfarin: Preliminary data suggest that there may be a pharmacodynamic interaction (that causes an increased bleeding diathesis in the face of unaltered prothrombin time) between paroxetine and warfarin. Since there is little clinical experience, the concomitant administration of paroxetine hydrochloride extended-release tablets and warfarin should be undertaken with caution (see PRECAUTIONS: Information for Patients: *Drugs That Interfere with Hemostasis*).

Triptans: There have been rare post-marketing reports of serotonin syndrome with the use of an SSRI and a triptan. If concomitant use of paroxetine hydrochloride extended-release tablets with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases (see WARNINGS: Potential for Interaction with Monoamine Oxidase Inhibitors: *Serotonin Syndrome*).

Drugs Affecting Hepatic Metabolism: The metabolism and pharmacokinetics of paroxetine may be affected by the induction or inhibition of drug metabolizing enzymes.

Cimetidine: Cimetidine inhibits many cytochrome P450 (oxidative) enzymes. In a study where immediate-release paroxetine (30 mg once daily) was dosed orally for 4 weeks, steady-state plasma concentrations of paroxetine were increased by approximately 50% during coadministration with oral cimetidine (300 mg three times daily) for the final week. Therefore, when these drugs are administered concurrently, dosage adjustment of paroxetine hydrochloride extended-release tablets after the starting dose should be guided by clinical effect. The effect of paroxetine on cimetidine's pharmacokinetics was not studied.

Phenobarbital: Phenobarbital induces many cytochrome P_{450} (oxidative) enzymes. When a single oral 30 mg dose of immediate-release paroxetine was administered at phenobarbital steady-state (100 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 25% and 38%, respectively) compared to paroxetine administered alone. The effect of paroxetine on phenobarbital pharmacokinetics was not studied. Since paroxetine exhibits nonlinear pharmacokinetics, the results of this study may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustment with paroxetine hydrochloride extended-release tablets are considered necessary when coadministered with phenobarbital; any subsequent adjustment should be guided by clinical effect.

Phenytoin: When a single oral 30 mg dose of immediate-release paroxetine was administered at phenytoin steady-state (300 mg once daily for 14 days), paroxetine AUC and $T_{1/2}$ were reduced (by an average of 50% and 35%, respectively) compared to immediate-release paroxetine administered alone. In a separate study, when a single oral 300 mg dose of phenytoin was administered at paroxetine steady-state (30 mg once daily for 14 days), phenytoin AUC was slightly reduced (12% on average) compared to phenytoin administered alone. Since both drugs exhibit nonlinear pharmacokinetics, the above studies may not address the case where the 2 drugs are both being chronically dosed. No initial dosage adjustments are considered necessary when paroxetine hydrochloride extended-release tablets are coadministered with phenytoin; any subsequent adjustments should be guided by clinical effect (see ADVERSE REACTIONS: Post-marketing Reports).

Drugs Metabolized by CYP2D6: Many drugs, including most drugs effective in the treatment of major depressive disorder (paroxetine, other SSRIs, and many tricyclics), are metabolized by the cytochrome P_{450} isozyme CYP2D6. Like other agents that are metabolized by CYP2D6, paroxetine may significantly inhibit the activity of this isozyme. In most patients (> 90%), this CYP2D6 isozyme is saturated early during paroxetine dosing. In one study, daily dosing of immediate-release paroxetine (20 mg once daily) under steady-state conditions increased single-dose desipramine (100 mg) C_{max}, AUC, and $T_{1/2}$ by an average of approximately 2-, 5-, and 3-fold, respectively. Concomitant use of paroxetine with risperidone, a CYP2D6 substrate has also been evaluated. In one study, daily dosing of paroxetine 20 mg in patients stabilized on risperidone (4 to 8 mg/day) increased mean plasma concentrations of risperidone approximately 4-fold, decreased 9-hydroxy-risperidone concentrations approximately 10%, and increased concentrations of the active moiety (the sum of risperidone plus 9-hydroxyrisperidone) approximately 1.4-fold. The effect of paroxetine on the pharmacokinetics of atomoxetine has been evaluated when both drugs were at steady-state. In healthy volunteers who were extensive metabolizers of CYP2D6, paroxetine 20 mg daily was given in combination with 20 mg atomoxetine every 12 hours. This resulted in increases in steady-state atomoxetine AUC values that were 6- to 8-fold greater and in atomoxetine C_{max} values that were 3- to 4-fold greater than when atomoxetine was given alone. Dosage adjustment of atomoxetine may be necessary and it is recommended that atomoxetine be initiated at a reduced dose when given with paroxetine.

Concomitant use of paroxetine hydrochloride extended-release tablets with other drugs metabolized by cytochrome CYP2D6 has not been formally studied but may re quire lower doses than usually prescribed for either paroxetine hydrochloride extended-release tablets or the other drug.

Therefore, coadministration of paroxetine hydrochloride extended-release tablets with other drugs that are metabolized by this isozyme, including certain drugs effective in the treatment of major depressive disorder (e.g., nortriptyline, amitriptyline, imipramine, desipramine, and fluoxetine), phenothiazines, risperidone, tamoxifen, and Type 1C antiarrhythmics (e.g., propafenone, flecainide, and encainide), or that inhibit this enzyme (e.g., quinidine), should be approached with caution.

However, due to the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, paroxetine and thioridazine should not be coadministered (see CONTRAINDICATIONS and WARNINGS).

Tamoxifen is a pro-drug requiring metabolic activation by CYP2D6. Inhibition of CYP2D6 by paroxetine may lead to reduced plasma concentrations of an active metabolite and hence reduced efficacy of tamoxifen.

At steady-state, when the CYP2D6 pathway is essentially saturated, paroxetine clearance is governed by

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alternative P_{450} isozymes that, unlike CYP2D6, show no evidence of saturation (see PRECAUTIONS: Drug Interactions: *Tricyclic Antidepressants*).

Drugs Metabolized by Cytochrome CYP3A4: An *in vivo* interaction study involving the coadministration under steady-state conditions of paroxetine and terfenadine, a substrate for CYP3A4, revealed no effect of paroxetine on terfenadine pharmacokinetics. In addition, *in vitro* studies have shown ketoconazole, a potent inhibitor of CYP3A4 activity, to be at least 100 times more potent than paroxetine as an inhibitor of the metabolism of several substrates for this enzyme, including terfenadine, astemizole, cisapride, triazolam, and cyclosporine. Based on the assumption that the relationship between paroxetine's *in vitro* K_i and its lack of effect on terfenadine's *in vivo* clearance predicts its effect on other CYP3A4 substrates, paroxetine's extent of inhibition of CYP3A4 activity is not likely to be of clinical significance.

Tricyclic Antidepressants (TCAs): Caution is indicated in the coadministration of TCAs with paroxetine hydrochloride extended-release tablets, because paroxetine may inhibit TCA metabolism. Plasma TCA concentrations may need to be monitored, and the dose of TCA may need to be reduced, if a TCA is coadministered with paroxetine hydrochloride extended-release tablets (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CYP2D6*).

Drugs Highly Bound to Plasma Protein: Because paroxetine is highly bound to plasma protein, administration of paroxetine hydrochloride extended-release tablets to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse events. Conversely, adverse effects could result from displacement of paroxetine by other highly bound drugs.

Drugs That Interfere with Hemostasis (e.g., NSAIDs, Aspirin and Warfarin): 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 this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when paroxetine is initiated or discontinued.

Alcohol: Although paroxetine does not increase the impairment of mental and motor skills caused by alcohol, patients should be advised to avoid alcohol while taking paroxetine hydrochloride extended-release tablets.

Lithium: A multiple-dose study with immediate-release paroxetine hydrochloride has shown that there is no pharmacokinetic interaction between paroxetine and lithium carbonate. However, due to the potential for serotonin syndrome, caution is advised when immediate-release paroxetine hydrochloride is coadministered with lithium.

Digoxin: The steady-state pharmacokinetics of paroxetine was not altered when administered with digoxin at steady-state. Mean digoxin AUC at steady-state decreased by 15% in the presence of paroxetine. Since there is little clinical experience, the concurrent administration of paroxetine hydrochloride extended-release tablets and digoxin should be undertaken with caution.

Diazepam: Under steady-state conditions, diazepam does not appear to affect paroxetine kinetics. The effects of paroxetine on diazepam were not evaluated.

Procyclidine: Daily oral dosing of immediate-release paroxetine (30 mg once daily) increased steady-state $AUC_{0\text{-}24}$, C_{max}, and C_{min} values of procyclidine (5 mg oral once daily) by 35%, 37%, and 67%, respectively, compared to procyclidine alone at steady-state. If anticholinergic effects are seen, the dose of procyclidine should be reduced.

Beta-Blockers: In a study where propranolol (80 mg twice daily) was dosed orally for 18 days, the established steady-state plasma concentrations of propranolol were unaltered during coadministration with immediate-release paroxetine (30 mg once daily) for the final 10 days. The effects of propranolol on paroxetine have not been evaluated (see ADVERSE REACTIONS: Post-marketing Reports).

Theophylline: Reports of elevated theophylline levels associated with immediate-release paroxetine treatment have been reported. While this interaction has not been formally studied, it is recommended that theophylline levels be monitored when these drugs are concurrently administered.

Fosamprenavir/Ritonavir: Coadministration of fosamprenavir/ritonavir with paroxetine significantly decreased plasma levels of paroxetine. Any dose adjustment should be guided by clinical effect (tolerability and efficacy).

Electroconvulsive Therapy (ECT): There are no clinical studies of the combined use of ECT and paroxetine hydrochloride extended-release tablets.

Carcinogenesis, Mutagenesis, Impairment of Fertility: ***Carcinogenesis:*** Two year carcinogenicity studies were conducted in rodents given paroxetine in the diet at 1, 5, and 25 mg/kg/day (mice) and 1, 5, and 20 mg/kg/day (rats). These doses are up to approximately 2 (mouse) and 3 (rat) times the (MRHD on an mg/m^2 basis. There was a significantly greater number of male rats in the high-dose group with reticulum cell sarcomas (1/100, 0/50, 0/50, and 4/50 for control, low-, middle-, and high-dose groups, respectively) and a significantly increased linear trend across dose groups for the occurrence of lymphoreticular tumors in male rats. Female rats were not affected. Although there was a dose related increase in the number of tumors in mice, there was no drug related increase in the number of mice with tumors. The relevance of these findings to humans is unknown.

Mutagenesis: Paroxetine produced no genotoxic effects in a battery of five *in vitro* and two *in vivo* assays that included the following: Bacterial mutation assay, mouse lymphoma mutation assay, unscheduled DNA synthesis assay, and tests for cytogenetic aberrations *in vivo* in mouse bone marrow and *in vitro* in human lymphocytes and in a dominant lethal test in rats.

Impairment of Fertility: A reduced pregnancy rate was found in reproduction studies in rats at a dose of paroxetine of 15 mg/kg/day, which is approximately twice the MRHD on a mg/m^2 basis. Irreversible lesions occurred in the reproductive tract of male rats after dosing in toxicity studies for 2 to 52 weeks. These lesions consisted of vacuolation of epididymal tubular epithelium at 50 mg/kg/day and atrophic changes in the seminiferous tubules of the testes with arrested spermatogenesis at 25 mg/kg/day (approximately 8 and 4 times the MRHD on a mg/m^2 basis).

Pregnancy: ***Pregnancy Category D:*** See WARNINGS: Usage in Pregnancy: *Teratogenic Effects:*.

Labor and Delivery: The effect of paroxetine on labor and delivery in humans is unknown.

Nursing Mothers: Like many other drugs, paroxetine is secreted in human milk, and caution should be exercised when paroxetine hydrochloride extended-release tablets are administered to a nursing woman.

Pediatric Use: Safety and effectiveness in the pediatric population have not been established (see BOX WARNING and WARNINGS: Clinical Worsening and Suicide Risk). Three placebo-controlled trials in 752 pediatric patients with MDD have been conducted with paroxetine hydrochloride and the data were not sufficient to support a claim for use in pediatric patients. Anyone considering the use of paroxetine hydrochloride extended-release tablets in a child or adolescent must balance the potential risks with the clinical need.

In placebo-controlled clinical trials conducted with pediatric patients, the following adverse events were reported in at least 2% of pediatric patients treated with immediate-release paroxetine hydrochloride and occurred at a rate at least twice that for pediatric patients receiving placebo: emotional lability (including self harm, suicidal thoughts, attempted suicide, crying, and mood fluctuations), hostility, decreased appetite, tremor, sweating, hyperkinesia, and agitation.

Events reported upon discontinuation of treatment with immediate-release paroxetine hydrochloride in the pediatric clinical trials that included a taper phase regimen, which occurred in at least 2% of patients who received immediate-release paroxetine hydrochloride and which occurred at a rate at least twice that of placebo, were: emotional lability (including suicidal ideation, suicide attempt, mood changes, and tearfulness), nervousness, dizziness, nausea, and abdominal pain (see DOSAGE AND ADMINISTRATION: Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets).

Geriatric Use: SSRIs and SNRIs, including paroxetine, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event (see PRECAUTIONS: Hyponatremia).

In worldwide premarketing clinical trials with immediate-release paroxetine hydrochloride, 17% of paroxetine-treated patients (approximately 700) were 65 years or older. Pharmacokinetic studies revealed a decreased clearance in the elderly, and a lower starting dose is recommended; there were, however, no overall differences in the adverse event profile between elderly and younger patients, and effectiveness was similar in younger and older patients (see CLINICAL PHARMACOLOGY in full prescribing information and DOSAGE AND ADMINISTRATION).

In a controlled study focusing specifically on elderly patients with major depressive disorder, paroxetine hydrochloride extended-release tablets were demonstrated to be safe and effective in the treatment of elderly patients (> 60 years) with major depressive disorder. (See CLINICAL PHARMACOLOGY: Clinical Trials in full prescribing information and ADVERSE REACTIONS: Table 3.)

ADVERSE REACTIONS: The information included under the "Adverse Findings Observed in Short-Term, Placebo-Controlled Trials with Paroxetine Hydrochloride Extended-Release Tablets" subsection of ADVERSE REACTIONS is based on data from eleven placebo-controlled clinical trials. Three of these studies were conducted in patients with major depressive disorder, three studies were done in patients with panic disorder and one study was conducted in patients with social anxiety disorder. Two of the studies in major depressive disorder, which enrolled patients in the age range 18 to 65 years, are pooled. Information from a third study of major depressive disorder, which focused on elderly patients (60 to 88 years), is presented separately as is the information from the panic disorder studies. Information on additional adverse events associated with paroxetine hydrochloride extended-release tablet and the immediate-release formulation of paroxetine hydrochloride is included in a separate subsection (see Other Events Observed During the Clinical Development of Paroxetine).

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials With Paroxetine Hydrochloride Extended-Release Tablets: ***Adverse Events Associated With Discontinuation of Treatment:*** *Major Depressive Disorder:* Ten percent (21/212) of patients treated with paroxetine hydrochloride extended-release tablets discontinued treatment due to an adverse event in a pool of two studies of patients with major depressive disorder. The most common events (≥ 1%) associated with discontinuation and considered to be drug-related (i.e., those events associated with dropout at a rate approximately twice or greater for paroxetine hydrochloride extended-release tablets compared to placebo) included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 212)	Placebo (n = 211)
Nausea	3.7%	0.5%
Asthenia	1.9%	0.5%
Dizziness	1.4%	0.0%
Somnolence	1.4%	0.0%

In a placebo-controlled study of elderly patients with major depressive disorder, 13% (13/104) of patients treated with paroxetine hydrochloride extended-release tablets discontinued due to an adverse event. Events meeting the above criteria included the following:

	Paroxetine Hydrochloride Extended-Release Tablets (n = 104)	Placebo (n = 109)
Nausea	2.9%	0.0%
Headache	1.9%	0.9%
Depression	1.9%	0.0%
LFT's abnormal	1.9%	0.0%

Commonly Observed Adverse Events: ***Major Depressive Disorder:*** The most commonly observed adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a pool of two trials (incidence of 5% or greater and incidence for paroxetine hydrochloride extended-release tablets at least twice that for placebo, derived from Table 2) were: Abnormal ejaculation, abnormal vision, constipation, decreased libido, diarrhea, dizziness, female genital disorders, nausea, somnolence, sweating, trauma, tremor, and yawning.

Using the same criteria, the adverse events associated with the use of paroxetine hydrochloride extended-release tablets in a study of elderly patients with major depressive disorder were: Abnormal ejaculation, constipation, decreased appetite, dry mouth, impotence, infection, libido decreased, sweating, and tremor.

Incidence in Controlled Clinical Trials: Table 2 enumerates adverse events that occurred at an incidence of 1% or more among patients treated with paroxetine hydrochloride extended-release tablets, aged 18 to 65, who participated in two short-term (12 week) placebo-controlled trials in major depressive disorder in which patients were dosed in a range of 25 mg to 62.5 mg/day. Table 3 enumerates adverse events reported at an incidence of 5% or greater among elderly patients (ages 60 to 88) treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week) placebo-controlled trial in major depressive disorder in which patients were dosed in a range of 12.5 mg to 50 mg/day. Table 4 enumerates adverse events reported at an incidence of 1% or greater among patients (19 to 72 years) treated with paroxetine hydrochloride extended-release tablets who participated in short-term (10 week) placebo-controlled trials in panic disorder in which patients were dosed in a range of 12.5 mg to 75 mg/day. Table 5 enumerates adverse events reported at an incidence of 1% or greater among adult patients treated with paroxetine hydrochloride extended-release tablets who participated in a short-term (12 week), double-blind, placebo-controlled trial in social anxiety disorder in which patients were dosed in a range of 12.5 to 37.5 mg/day.

The prescriber should be aware that these figures cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence rate in the population studied.

Table 2. Treatment Emergent Adverse Events Occurring in ≥1% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Pool of Two Studies in Major Depressive Disorder[1,2]

	% Reporting Event	
Body System/Adverse Event	**Paroxetine Hydrochloride Extended-Release Tablets (n = 212)**	**Placebo (n = 211)**
Body as a Whole		
Headache	27%	20%
Asthenia	14%	9%
Infection[3]	8%	5%
Abdominal Pain	7%	4%
Back Pain	5%	3%
Trauma[4]	5%	1%
Pain[5]	3%	1%
Allergic Reaction[6]	2%	1%
Cardiovascular System		
Tachycardia	1%	0%
Vasodilatation[7]	2%	0%
Digestive System		
Nausea	22%	10%
Diarrhea	18%	7%
Dry Mouth	15%	8%
Constipation	10%	4%
Flatulence	6%	4%
Decreased Appetite	4%	2%
Vomiting	2%	1%
Nervous System		
Somnolence	22%	8%
Insomnia	17%	9%
Dizziness	14%	4%
Libido Decreased	7%	3%
Tremor	7%	1%
Hypertonia	3%	1%
Paresthesia	3%	1%
Agitation	2%	1%
Confusion	1%	0%
Respiratory System		
Yawn	5%	0%
Rhinitis	4%	1%
Cough Increased	2%	1%
Bronchitis	1%	0%
Skin and Appendages		
Sweating	6%	2%
Photosensitivity	2%	0%
Special Senses		
Abnormal Vision[8]	5%	1%
Taste Perversion	2%	0%
Urogenital System		
Abnormal Ejaculation[9,10]	26%	1%
Female Genital Disorder[9,11]	10%	< 1%
Impotence[9]	5%	3%
Urinary Tract Infection	3%	1%
Menstrual Disorder[9]	2%	< 1%
Vaginitis[9]	2%	0%

1. Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are: Abnormal dreams, anxiety, arthralgia, depersonalization, dysmenorrhea, dyspepsia, hyperkinesia, increased appetite, myalgia, nervousness, pharyngitis, purpura, rash, respiratory disorder, sinusitis, urinary frequency, and weight gain.
2. < 1% means greater than zero and less than 1%.
3. Mostly flu.
4. A wide variety of injuries with no obvious pattern.
5. Pain in a variety of locations with no obvious pattern.
6. Most frequently seasonal allergic symptoms.
7. Usually flushing.
8. Mostly blurred vision.
9. Based on the number of males or females.
10. Mostly anorgasmia or delayed ejaculation.
11. Mostly anorgasmia or delayed orgasm.

Table 3. Treatment Emergent Adverse Events Occurring in ≥ 5% of Patients Treated with Paroxetine Hydrochloride Extended-Release Tablets in a Study of Elderly Patients with Major Depressive Disorder[1,2]

	% Reporting Event	
Body System/Adverse Event	**Paroxetine Hydrochloride Extended-Release Tablets (n = 104)**	**Placebo (n = 109)**
Body as a Whole		
Headache	17%	13%
Asthenia	15%	14%
Trauma	8%	5%
Infection	6%	2%
Digestive System		
Dry Mouth	18%	7%
Diarrhea	15%	9%
Constipation	13%	5%
Dyspepsia	13%	10%
Decreased Appetite	12%	5%
Flatulence	8%	7%
Nervous System		
Somnolence	21%	12%
Insomnia	10%	8%
Dizziness	9%	5%
Libido Decreased	8%	< 1%
Tremor	7%	0%
Skin and Appendages		
Sweating	10%	< 1%
Urogenital System		
Abnormal Ejaculation[3,4]	17%	3%
Impotence[3]	9%	3%

1. Adverse events for which the paroxetine hydrochloride extended-release tablets reporting incidence was less than or equal to the placebo incidence are not included. These events are nausea and respiratory disorder.
2. < 1% means greater than zero and less than 1%.
3. Based on the number of males.
4. Mostly anorgasmia or delayed ejaculation.

A comparison of adverse event rates in a fixed dose study comparing immediate-release paroxetine with placebo in the treatment of major depressive disorder revealed a clear dose dependency for some of the more common adverse events associated with the use of immediate-release paroxetine.

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.

The percentage of patients reporting symptoms of sexual dysfunction in the pool of two placebo-controlled trials in nonelderly patients with major depressive disorder, in the pool of three placebo-controlled trials in patients with panic disorder, and in the placebo-controlled trial in patients with social anxiety disorder, are as follows:

	Major Depressive Disorder	
	Paroxetine HCl Extended-Release Tablets	**Placebo**
n (males)	**78**	**78**
Decreased Libido	10%	5%
Ejaculatory Disturbance	26%	1%
Impotence	5%	3%
n (females)	**134**	**133**
Decreased Libido	4%	2%
Orgasmic Disturbance	10%	<1%

There are no adequate, controlled studies examining sexual dysfunction with paroxetine treatment.

Paroxetine treatment has been associated with several cases of priapism. In those cases with a known outcome, patients recovered without sequelae.

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.

Weight and Vital Sign Changes: Significant weight loss may be an undesirable result of treatment with paroxetine for some patients but, on average, patients in controlled trials with paroxetine hydrochloride extended-release tablet or the immediate-release formulation, had minimal weight loss (about 1 pound). No significant changes in vital signs (systolic and diastolic blood pressure, pulse, and temperature) were observed in patients treated with paroxetine hydrochloride extended-release tablets, or immediate-release paroxetine hydrochloride, in controlled clinical trials.

ECG Changes: In an analysis of ECGs obtained in 682 patients treated with immediate-release paroxetine and 415 patients treated with placebo in controlled clinical trials, no clinically significant changes were seen in the ECGs of either group.

Liver Function Tests: In a pool of two placebo-controlled clinical trials, patients treated with paroxetine hydrochloride extended-release tablets or placebo exhibited abnormal values on liver function tests at comparable rates. In particular, the extended-release paroxetine versus placebo comparisons for alkaline phosphatase, SGOT, SGPT, and bilirubin revealed no differences in the percentage of patients with marked abnormalities.

In a study of elderly patients with major depressive disorder, 3 of 104 patients treated with paroxetine hydrochloride extended-release tablets and none of 109 placebo patients experienced liver transaminase elevations of potential clinical concern.

Two of the patients treated with paroxetine hydrochloride extended-release tablets dropped out of the study due to abnormal liver function tests; the third patient experienced normalization of transaminase levels with continued treatment. Also, in the pool of three studies of patients with panic disorder, 4 of 444 patients treated with paroxetine hydrochloride extended-release tablets and none of 445 placebo patients experienced liver transaminase elevations of potential clinical concern. Elevations in all four patients decreased substantially after discontinuation of paroxetine hydrochloride extended-release tablets. The clinical significance of these findings is unknown.

In placebo-controlled clinical trials with the immediate-release formulation of paroxetine, patients exhibited abnormal values on liver function tests at no greater rate than that seen in placebo-treated patients.

Hallucinations: In pooled clinical trials of immediate-release paroxetine hydrochloride, hallucinations were observed in 22 of 9,089 patients receiving drug and in 4 of 3,187 patients receiving placebo.

Other Events Observed During the Clinical Development of Paroxetine: The following adverse events were reported during the clinical development of paroxetine hydrochloride extended-release tablet and/or the clinical development of the immediate-release formulation of paroxetine.

Adverse events for which frequencies are provided below occurred in clinical trials with the extended-release formulation of paroxetine. During its premarketing assessment in major depressive disorder, panic disorder and social anxiety disorder, multiple doses of paroxetine hydrochloride extended-release tablets were administered to 1,627 patients in phase three double-blind, controlled, outpatient studies. Untoward events associated with this exposure were 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 untoward events into a smaller number of standardized event categories.

In the tabulations that follow, reported adverse events were classified using a COSTART based dictionary. The frequencies presented, therefore, represent the proportion of the 1,627 patients exposed to paroxetine hydrochloride extended-release tablets who experienced an event of the type cited on at least one occasion while receiving paroxetine hydrochloride extended-release tablets. All reported events are included except those already listed in Tables one through four and those events where a drug cause was remote. If the COSTART term for an event was so general as to be uninformative, it was deleted or, when possible, replaced with a more informative term. It is important to emphasize that although the events reported occurred during treatment with paroxetine, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: Frequent adverse events are those occurring on one or more occasions in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1,000 patients; rare events are those occurring in fewer than 1/1,000 patients.

Adverse events for which frequencies are not provided occurred during the premarketing assessment of immediate-release paroxetine in phase two and three studies of major depressive disorder, obsessive compulsive disorder, panic disorder, social anxiety disorder, generalized anxiety disorder, and posttraumatic stress disorder. The conditions and duration of exposure to immediate release paroxetine varied greatly and included (in overlapping categories) open and double-blind studies, uncontrolled and controlled studies, inpatient and outpatient studies, and fixed dose and titration studies. Only those events not previously listed for extended-release paroxetine are included. The extent to which these events may be associated with paroxetine hydrochloride extended-release tablets is unknown.

Events are listed alphabetically within the respective body system. Events of major clinical importance are also described in the PRECAUTIONS section.

Body as a Whole: Infrequent were chills, face edema, fever, flu syndrome, malaise; rare were abscess, anaphylactoid reaction, anticholinergic syndrome, hypothermia; also observed were adrenergic syndrome, neck rigidity, sepsis.

Cardiovascular System: Infrequent were angina pectoris, bradycardia, hematoma, hypertension, hypotension, palpitation, postural hypotension, supraventricular tachycardia, syncope; rare were bundle branch block; also observed were arrhythmia nodal, atrial fibrillation, cerebrovascular accident, congestive heart failure, low cardiac output, myocardial infarct, myocardial ischemia, pallor, phlebitis, pulmonary embolus, supraventricular extrasystoles, thrombophlebitis, thrombosis, vascular headache, ventricular extrasystoles.

Digestive System: Infrequent were bruxism, dysphagia, eructation, gastritis, gastroenteritis, gastroesophageal reflux, gingivitis, hemorrhoids, liver function test abnormal, melena, pancreatitis, rectal hemorrhage, toothache, ulcerative stomatitis; rare were colitis, glossitis, gum hyperplasia, hepatosplenomegaly, increased salivation, intestinal obstruction, peptic ulcer, stomach ulcer, throat tightness; also observed were aphthous stomatitis, bloody diarrhea, bulimia, cardiospasm, cholelithiasis, duodenitis, enteritis, esophagitis, fecal impactions, fecal incontinence, gum hemorrhage, hematemesis, hepatitis, ileitis, ileus, jaundice, mouth ulceration, salivary gland enlargement, sialadenitis, stomatitis, tongue discoloration, tongue edema.

Endocrine System: Infrequent were ovarian cyst, testes pain; rare were diabetes mellitus, hyperthyroidism; also observed were goiter, hypothyroidism, thyroiditis.

Hemic and Lymphatic System: Infrequent were anemia, eosinophilia, hypochromic anemia, leukocytosis, leukopenia, lymphadenopathy, purpura; rare were thrombocytopenia; also observed were anisocytosis, basophilia, bleeding time increased, lymphedema, lymphocytosis, lymphopenia, microcytic anemia, monocytosis, normocytic anemia, thrombocythemia.

Metabolic and Nutritional Disorders: Infrequent were generalized edema, hyperglycemia, hypokalemia, peripheral edema, SGOT increased, SGPT increased, thirst; rare were bilirubinemia, dehydration, hyperkalemia, obesity; also observed were alkaline phosphatase increased, BUN increased, creatinine phosphokinase increased, gamma globulins increased, gout, hypercalcemia, hypercholesteremia, hyperphosphatemia, hypocalcemia, hypoglycemia, hyponatremia, ketosis, lactic dehydrogenase increased, nonprotein nitrogen (NPN) increased.

Musculoskeletal System: Infrequent were arthritis, bursitis, tendonitis; rare were myasthenia, myopathy, myositis; also observed were generalized spasm, osteoporosis, tenosynovitis, tetany.

Nervous System: Frequent were depression; infrequent were amnesia, convulsion, depersonalization, dystonia, emotional lability, hallucinations, hyperkinesia, hypesthesia, hypokinesia, incoordination, libido increased, neuralgia, neuropathy, nystagmus, paralysis, vertigo; rare were ataxia, coma, diplopia, dyskinesia, hostility, paranoid reaction, torticollis, withdrawal syndrome; also observed were abnormal gait, akathisia, akinesia, aphasia, choreoathetosis, circumoral paresthesia, delirium, delusions, dysarthria, euphoria, extrapyramidal syndrome, fasciculations, grand mal convulsion, hyperalgesia, irritability, manic reaction,

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manic-depressive reaction, meningitis, myelitis, peripheral neuritis, psychosis, psychotic depression, reflexes decreased, reflexes increased, stupor, trismus.

Respiratory System: Frequent were pharyngitis; infrequent were asthma, dyspnea, epistaxis, laryngitis, pneumonia; rare were stridor; also observed were dysphonia, emphysema, hemoptysis, hiccups, hyperventilation, lung fibrosis, pulmonary edema, respiratory flu, sputum increased.

Skin and Appendages: Frequent were rash; infrequent were acne, alopecia, dry skin, eczema, pruritus, urticaria; rare were exfoliative dermatitis, furunculosis, pustular rash, seborrhea; also observed were angioedema, ecchymosis, erythema multiforme, erythema nodosum, hirsutism, maculopapular rash, skin discoloration, skin hypertrophy, skin ulcer, sweating decreased, vesiculobullous rash.

Special Senses: Infrequent were conjunctivitis, earache, keratoconjunctivitis, mydriasis, photophobia, retinal hemorrhage, tinnitus; rare were blepharitis, visual field defect; also observed were amblyopia, anisocoria, blurred vision, cataract, conjunctival edema, corneal ulcer, deafness, exophthalmos, glaucoma, hyperacusis, night blindness, parosmia, ptosis, taste loss.

Urogenital System: Frequent were dysmenorrhea*; infrequent were albuminuria, amenorrhea*, breast pain*, cystitis, dysuria, prostatitis*, urinary retention; rare were breast enlargement*, breast neoplasm*, female lactation, hematuria, kidney calculus, metrorrhagia*, nephritis, nocturia, pregnancy and puerperal disorders*, salpingitis, urinary incontinence, uterine fibroids enlarged*; also observed were breast atrophy, ejaculatory disturbance, endometrial disorder, epididymitis, fibrocystic breast, leukorrhea, mastitis, oliguria, polyuria, pyuria, urethritis, urinary casts, urinary urgency, urolith, uterine spasm, vaginal hemorrhage.

*Based on the number of men and women as appropriate.

Post-Marketing Reports: Voluntary reports of adverse events in patients taking immediate-release paroxetine hydrochloride that have been received since market introduction and not listed above that may have no causal relationship with the drug include acute pancreatitis, elevated liver function tests (the most severe cases were deaths due to liver necrosis, and grossly elevated transaminases associated with severe liver dysfunction), Guillain-Barré syndrome, toxic epidermal necrolysis, priapism, syndrome of inappropriate ADH secretion, symptoms suggestive of prolactinemia and galactorrhea; extrapyramidal symptoms which have included akathisia, bradykinesia, cogwheel rigidity, dystonia, hypertonia, oculogyric crisis which has been associated with concomitant use of pimozide; tremor and trismus; status epilepticus, acute renal failure, pulmonary hypertension, allergic alveolitis, anaphylaxis, eclampsia, laryngismus, optic neuritis, porphyria, ventricular fibrillation, ventricular tachycardia (including Torsade de pointes), thrombocytopenia, hemolytic anemia, events related to impaired hematopoiesis (including aplastic anemia, pancytopenia, bone marrow aplasia, and agranulocytosis), and vasculitic syndromes (such as Henoch-Schönlein purpura). There has been a case report of an elevated phenytoin level after 4 weeks of immediate-release paroxetine and phenytoin coadministration. There has been a case report of severe hypotension when immediate-release paroxetine was added to chronic metoprolol treatment.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: Paroxetine hydrochloride is not a controlled substance.

Physical and Psychologic Dependence: Paroxetine hydrochloride extended-release tablets have not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug seeking behavior, 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, patients should be evaluated carefully for history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of paroxetine hydrochloride extended-release tablets (e.g., development of tolerance, incrementations of dose, drug seeking behavior).

OVERDOSAGE: Human Experience: Since the introduction of immediate-release paroxetine hydrochloride in the United States, 342 spontaneous cases of deliberate or accidental overdosage during paroxetine treatment have been reported worldwide (circa 1999). These include overdoses with paroxetine alone and in combination with other substances. Of these, 48 cases were fatal and of the fatalities, 17 appeared to involve paroxetine alone. Eight fatal cases that documented the amount of paroxetine ingested were generally confounded by the ingestion of other drugs or alcohol or the presence of significant comorbid conditions. Of 145 nonfatal cases with known outcome, most recovered without sequelae. The largest known ingestion involved 2000 mg of paroxetine (33 times the maximum recommended daily dose) in a patient who recovered.

Commonly reported adverse events associated with paroxetine overdosage include somnolence, coma, nausea, tremor, tachycardia, confusion, vomiting, and dizziness. Other notable signs and symptoms observed with overdoses involving paroxetine (alone or with other substances) include mydriasis, convulsions (including status epilepticus), ventricular dysrhythmias (including Torsade de pointes), hypertension, aggressive reactions, syncope, hypotension, stupor, bradycardia, dystonia, rhabdomyolysis, symptoms of hepatic dysfunction (including hepatic failure, hepatic necrosis, jaundice, hepatitis, and hepatic steatosis), serotonin syndrome, manic reactions, myoclonus, acute renal failure, and urinary retention.

Overdosage Management: Treatment should consist of those general measures employed in the management of overdosage with any drugs effective in the treatment of major depressive disorder.

Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion, or in symptomatic patients.

Activated charcoal should be administered. Due to the large volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for paroxetine are known.

A specific caution involves patients taking or recently having taken paroxetine who might ingest excessive quantities of a tricyclic antidepressant. In such a case, accumulation of the parent tricyclic and an active metabolite may increase the possibility of clinically significant sequelae and extend the time needed for close medical observation (see PRECAUTIONS: Drug Interactions: *Drugs Metabolized by Cytochrome CPY2D6*).

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. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

DOSAGE AND ADMINISTRATION: Major Depressive Disorder: *Usual Initial Dosage:* Paroxetine hydrochloride extended-release tablets should be administered as a single daily dose, usually in the morning, with or without food. The recommended initial dose is 25 mg/day. Patients were dosed in a range of 25 mg to 62.5 mg/day in the clinical trials demonstrating the effectiveness of paroxetine hydrochloride extended-release tablets in the treatment of major depressive disorder. As with all drugs effective in the treatment of major depressive disorder, the full effect may be delayed. Some patients not responding to a 25 mg dose may benefit from dose increases, in 12.5 mg/day increments, up to a maximum of 62.5 mg/day. Dose changes should occur at intervals of at least one week.

Patients should be cautioned that paroxetine hydrochloride extended-release tablets should not be chewed or crushed, and should be swallowed whole.

Maintenance Therapy: There is no body of evidence available to answer the question of how long the patient treated with paroxetine hydrochloride extended-release tablets should remain on it. It is generally agreed that acute episodes of major depressive disorder require several months or longer of sustained pharmacologic therapy. Whether the dose of an antidepressant needed to induce remission is identical to the dose needed to maintain and/or sustain euthymia is unknown.

Systematic evaluation of the efficacy of immediate-release paroxetine hydrochloride has shown that efficacy is maintained for periods of up to one year with doses that averaged about 30 mg, which corresponds to a 37.5 mg dose of paroxetine hydrochloride extended-release tablets, based on relative bioavailability considerations (see CLINICAL PHARMACOLOGY: Pharmacokinetics in full prescribing information).

Special Populations: *Treatment of Pregnant Women During the Third Trimester:* Neonates exposed to paroxetine hydrochloride extended-release tablets and other SSRIs or SNRIs, late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding (see WARNINGS). When treating pregnant women with paroxetine during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering paroxetine in the third trimester.

Dosage for Elderly or Debilitated Patients, and Patients with Severe Renal or Hepatic Impairment: The recommended initial dose of paroxetine hydrochloride extended-release tablets is 12.5 mg/day for elderly patients, debilitated patients, and/or patients with severe renal or hepatic impairment. Increases may be made if indicated. Dosage should not exceed 50 mg/day.

Switching Patients to or From a Monoamine Oxidase Inhibitor: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with paroxetine hydrochloride extended-release tablets. Similarly, at least 14 days should be allowed after stopping paroxetine hydrochloride extended-release tablets before starting an MAOI.

Discontinuation of Treatment with Paroxetine Hydrochloride Extended-Release Tablets: Symptoms associated with discontinuation of immediate-release paroxetine hydrochloride or paroxetine hydrochloride extended-release tablets have been reported (see PRECAUTIONS). Patients should be monitored for these symptoms when discontinuing treatment, regardless of the indication for which paroxetine hydrochloride extended-release tablets are being prescribed. 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.

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Son's Mental Illness Sets Father On Harrowing Journey

Pete Earley believes psychiatrists need to take a more forceful stance against a legal system that criminalizes seriously mentally ill people.

BY MARK MORAN

Pete Earley's son has a severe and persistent mental illness, but the author and journalist, who spent a year residing in the jail system of a large American city to tell the story of mentally ill people warehoused there, has his own diagnosis for America's mental health system—"Crazy."

That's the title of Earley's latest book, whose subtitle is "A Father's Search Through America's Mental Health Madness."

Credit: Ellen Dallager

Pete Earley discusses his book about the criminalization of mental illness during the "Conversations" event sponsored by the American Psychiatric Foundation.

At last month's APA Institute on Psychiatric Services in New York, Earley was the guest discussant for "Conversations," an event sponsored by the American Psychiatric Foundation, where he talked about his book and the harrowing family saga that led him to write it.

An investigative journalist whose previous work included a biography of Aldrich Ames, the American spy convicted in 1994, and a behind-the-scenes account of the Federal Witness Protection Program, Earley was thrust into a murky world of another kind when his son, Mike, was diagnosed with bipolar disorder.

Refusing to take his medication, Mike quickly decompensated. When Pete Earley tried to get his son admitted to a hospital for treatment, he was told repeatedly that Mike couldn't be admitted against his will until he became dangerous to himself or others; it was only after Mike committed a criminal offense that he was able to get the treatment his father had been seeking for him.

The event served as a catalyst for the senior Earley to do what he does best—go on a journalistic hunt for the story behind America's criminalization of mentally ill people. He sought to spend time in the jail systems of several major cities—including Los Angeles, Chicago, New York, and Washington, D.C.—before he was successful in being

please see ***Earley*** *on page 31*

The Lifers Want You!

The APA Lifers are seeking new members. The Lifers consist of APA members who have achieved life member, life fellow, or distinguished life fellow status. The dues are $50 a year and provide member benefits that include events at APA's annual meeting in May, a chance to have their voices heard by the APA leadership, representation at the APA Assembly, the opportunity to volunteer at the Lifers display at the annual meeting, and receive *LifersLine,* the newsletter of the Lifers, according to Bernard Katz, M.D., a member of the Lifers Executive Committee.

The Lifers' events at APA's annual meetings include the Business Meeting/Educational Forum on Tuesday morning and a workshop. (The submission for the workshop for APA's 2010 annual meeting in May is titled "From Narrative and Theory to Evidence-Based Support for Psychiatrists Working Under Extreme Stress.") The Lifers reception, at which the Harold E. Berson, M.D., Lifers Award is presented, completes the day.

"Perhaps one of the greatest benefits of joining the Lifers," said Katz, "is an opportunity to stay relevant within the profession, to share ideas with many APA leaders from the recent and distant past, and to bring our collective wisdom to the organization, particularly during troubled times. The current APA leadership does take our counsel seriously and welcomes our input. We are looking to *all* eligible members to come and join us. You will be glad you did. The dues are minimal, and you'll find the Lifers group is an energetic and stimulating way to stay connected."

Sheila Hafter Gray, M.D., is the president of the Lifers. In addition to Gray and Katz, the members of the Lifers Executive Committee are Edward Hanin, M.D., Maria Lymberis, M.D., Paul Wick, M.D., Stephen Scheiber, M.D., Pierre Loebel, M.D., Captane Thomson, M.D., Philip Margolis, M.D., Arthur Meyerson, M.D., Norman Clemens, M.D., Bert Warren, M.D., and Herb Peyser, M.D.

Members of the Executive Committee would be pleased to hear from other Lifers with ideas of projects, programs, and ways that the Lifers can continue to be of assistance to and impact APA.

Membership information is available from Captane Thomson, M.D., at *cpthomson @comcast.net* or (530) 753-7223.

PSYCHIATRIC PRACTICE & MANAGED CARE
APA OFFICE OF HEALTHCARE SYSTEMS AND FINANCING

New Medicare Audit Program To Launch in January 2010

Starting in January 2010, Medicare's Recovery Audit Contractors (RACs) will begin conducting audits of Medicare fee-for-service claims throughout the United States. The RACs were created by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA), and from 2005 to 2008, the RACs conducted a demonstration project. The audits of provider and supplier claims that were part of the demonstration project began in New York, California, and Florida in 2005 and were expanded to include South Carolina and Arizona in 2007.

On the basis of the demonstration project, the RACs were deemed to be a success. They are funded by contingency fees, or, in lay terms, on a bounty system: the RACs get a percentage of the overpayments they uncover, but they also report underpayments as well. In 2007 they collected $124.6 million in Medicare overpayments and refunded $14.3 million in underpayments to Medicare providers.

For 2010, the country has been divided into four regions (A to D), each one with a different RAC assigned to it.

The RACs conduct two kinds of audits: automated and review. The automated audits are done electronically and can be expected to capture the "low-hanging fruit"—such as payments for the same procedure for the same patient on the same day (the example that the Centers for Medicare and Medicaid Services [CMS] provides in a press release is three colonoscopies on the same patient on the same day), duplicate claims that were both paid, and claims that were paid using an outdated fee schedule. In the beginning, it is expected most audits will be of this type.

The review audits will be done on the basis of examining claims documentation. CMS, which contracts with the RACs, has set limits on the number of documentation requests a RAC can make in a 45-day period. A solo practitioner can be asked for only 10 medical records, while a partnership of two to five physicians, for example, can be asked for 20 records.

If you have a claim denied on the basis of a RAC audit, you will have the same appeals process available to you as when the Medicare contractor (carrier or fiscal intermediary) that paid the claim issues a denial. In fact, the appeals of a RAC denial will revert to the Medicare contractor that originally paid the claim.

If you believe a claim has been inappropriately denied, APA's Office of Healthcare Systems and Financing advises you to appeal—experience has shown that it is usually worth the effort. With appropriate documentation, it is very likely that you will win your appeal, although you may have to go through several levels of the process to reach this outcome. The good news is that neither the RAC nor your Medicare contractor may collect monies it says you owe if an appeal is in process, although if you lose your appeal, you will have to pay interest on the money owed.

This topic presents a good opportunity to once again remind APA members of the need to maintain appropriate documentation. Although all physicians understand the importance of accurate and thorough documentation as part of providing quality patient care, documentation is also essential for protecting you in a claims audit.

If your claims are audited by a RAC or Medicare and you lack the documentation for the services provided, as far as the auditors are concerned, the services never occurred.

More information about RACs is posted at <www.cms.hhs.gov/RAC/01_Overview.asp#TopOfPage>. Information on Medicare audits is posted on APA's Web site at <http://psych.org/MainMenu/PsychiatricPractice/MedicareMedicaid/AppealingMedicareCarrierDecisions.aspx>. You can also contact APA's Managed Care HelpLine at (800) 343-7924. ■

Psychiatric Practice & Managed Care (PP&MC) provides news and updates on practice management issues to APA members. PP&MC is printed bimonthly in *Psychiatric News* and is posted in PDF format under "Psychiatric Practice" on APA's Web site.

Q&A From APA's HelpLine Database: Billing For Phone Psychotherapy

Q. One of my patients has moved to another city, but wants to continue psychotherapy with me over the telephone. How do I code for this?

A. There is no *CPT* code for conducting psychotherapy over the telephone. All the psychotherapy codes are described as face to face with the patient. The only appropriate code to use would be 90899, "unlisted psychiatric service or procedure." If you use this code, you should provide documentation describing that it is for psychotherapy over the telephone. There are timed codes for E/M services provided on the telephone (99441: 5-10 minutes; 99442: 11-20 minutes; 99443: 21-30 minutes). These codes can be used for medical discussion with a patient for whom you have not provided an E/M service within the past seven days and whom you would not be seeing for the reason discussed in the call.

Have Policy Changes Due to Parity Had an Impact on Your Practice?

The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act of 2008 (PL 110-343), which became law on October 3, 2008, goes into effect on January 1, 2010. Generally, the law requires that any group health plan that covers more than 50 employees and offers mental health and/or substance use disorders coverage must provide that coverage with no greater financial requirements (that is, copays, deductibles, and annual or lifetime dollar limits) or treatment limitations (that is, number of visits) than the *predominant* requirements that it applies to *substantially all* medical/surgical benefits.

There is some ambiguity about what the terms *predominant* and *substantially all* mean and whether such significant practices as requiring prior authorization and applying other utilization management tools are considered treatment limitations and subject to the requirements of the law. It is also unclear whether there can be a separate but equal deductible requirement for mental health and substance abuse coverage—that is, a deductible that is separate from the one for medical/surgical benefits.

Also, many states already have mental health insurance mandates or parity laws in place, and there is some ambiguity about whether the state or federal law takes precedence. The law that is meant to take precedence, however, is the one most protective of consumers' access to care.

Federal guidance and regulations that clarify the terms and intent of a law are usually issued before the law goes into effect. In this case, the regulations for the new parity law are being written by staff from the three cabinet departments that oversee it: the departments of Labor, Health and Human Services, and Treasury. It had been projected that the regulations would be released by October 3, but that deadline was missed. They are now expected in January 2010, even though insurers have already been making changes for 2010 plans based on what they believe the law requires and permits.

APA's Office of Healthcare Systems and Financing (OHSF) has been talking to officials of health plans and large insurers in an attempt to determine any changes in coverage that may result from the law and what the law will mean for the practice of psychiatry in the short run.

Numerous insurers and employers have begun announcing new coverage requirements for 2010, many of which OHSF staff think are onerous and in conflict with the intent of the law.

For example, recently Blue Cross/Blue Shield has presented its psychiatrist providers in Florida and Illinois with new prior-authorization requirements for psychiatric care for 2010. The Florida and Illinois district branches, with the assistance of the OHSF staff, have begun negotiations with BC/BS to try to mitigate these requirements.

Irvin "Sam" Muszynski, J.D., director of OHSF, asks that you contact APA with any information about changes in policy coverage for 2010 that you believe have resulted from implementation of the parity law and that will impact negatively on patient care or your practice.

"It's vital that we know what's happening on the ground if we are to be able to provide any assistance," said Muszynski.

APA's Managed Care HelpLine can be reached at (800) 343-4671 or at bsf@psych.org. ■

Medicare News

• Discriminatory Copay Begins Phase Out

Starting on January 1, 2010, Medicare will begin reimbursing providers for outpatient psychiatric services at 55 percent, while the patient copay will drop to 45 percent from the current 50 percent copay. Mandated by the Medicare Improvements for Patients and Providers Act of 2008, the new rates are the first step in the gradual elimination of the discriminatory copayment rate for outpatient mental health treatment. In 2012 the reimbursement rate to providers will increase to 60 percent, in 2013 it will be 65 percent, and in 2014 it will be 80 percent—the same as for all other medical services.

• Reminder About Retroactive Billing

Please note that you don't have less time to do retroactive billing for Medicare than in the past. Here's the new rule: If the service occurs in the first nine months of the year, you have until December 31 of the following year to file your claim. Thus, if you see a patient on or before September 30, 2009, you must file the claim for that service before December 31, 2010, or the claim will be denied automatically. If the service occurs in the last three months of the year, you have until December 31 of the second year after the service occurs to file the claim. Thus, claims for services provided from October through December 2009 must be filed by December 31, 2011.

• NPI Reminder From CMS

When writing prescriptions, be sure to use your provider NPI rather than your practice number.

Babies of Recovered Anorexics Show Few Negative Outcomes

While women who had recovered from teenage anorexia nervosa had surprisingly good reproductive histories, their babies had a lower birth weight and more sleeping problems than did babies of control subjects.

BY JOAN AREHART-TREICHEL

Although anorexia nervosa is a serious mental disorder for many, a study out of Sweden offers hope to female teens who have it—recovery is possible.

The study was headed by Elisabet Wentz, M.D., Ph.D., an associate professor of child and adolescent psychiatry at the University of Gothenburg in Sweden. It included 48 women, average age 32, whom the researchers had diagnosed with anorexia as teens. It also included 48 women matched on age and school attended, but whom the researchers had not diagnosed with anorexia as teens. The latter served as a control group. The researchers had been following the outcomes of both groups since the subjects were teens.

Of the 48 subjects with a history of anorexia, only six still had an eating disorder by the time of the study—three with anorexia and three with another type. In their paper, published in the September *International Journal of Eating Disorders*, the researchers referred to this finding as "encouraging" and pointed out that it was comparable to what some other studies on the subject have found in recent years.

Other results from this new study should offer encouragement to teens with anorexia regarding later reproduction. Over half the women with an anorexia history had given birth to at least one child.

Moreover, as far as weight gain during pregnancy, delivery complications, or severe infant-feeding problems were concerned, there were no statistically significant differences between subjects who had been diagnosed with anorexia and the control subjects. And complications during the neonatal period were rare among children in both the anorexia and control groups.

Still, the study did find that anorexia subjects bore babies who, on average, were of lower weight than were the babies born to control mothers. The difference was statistically significant. Women who had experienced anorexia were also significantly more likely to have infants with sleeping problems than control subjects.

Perhaps most notably, none of the six subjects who still had an eating disorder at the time of the study had become a mother.

On the whole, though, "The outcome regarding fertility, pregnancy, and delivery was better than expected in women with a history of teenage-onset anorexia nervosa," Wentz told *Psychiatric News*. "Previous studies have reported many serious complications."

One reason why she and her colleagues obtained more positive results than previous researchers have, she conjectured, may have been because "clinical studies often include severe cases with several inpatient episodes, whereas in our group, where all the participants had met *DSM-III-R* and *DSM-IV* criteria for anorexia nervosa, only 1 in 4 had ever received inpatient treatment."

Infants Born to the Anorexia Group Fared Well After Birth

Regarding complications during infancy and developmental problems during childhood, only one significant difference was found between children born to the anorexia group and children born to the control group: sleeping problems were significantly more prevalent in the former.

	Children of anorexia group (n = 57)	Children of control group (n = 51)	p-value
Severe feeding problems	4	5	
Selective eating	6	4	
Colic	12	14	
Sleeping problems	16 (28%)	7 (14%)	0.05
Attention problems	4 (7%)	0 (0%)	0.12
Hyperactivity	2	0	
Delayed motor skills	1	0	
Speech delay	0	1	
Reading and/or writing problems	3	1	
One or more psychomotor developmental problems	7 (12%)	2 (4%)	0.17
Support at child care and/or at school	5	2	

Source: Elisabet Wentz, M.D., Ph.D., et al., *International Journal of Eating Disorders*, September 2009

The study was funded by the Swedish Council, Swedish Institute for Health Sciences, and Soderstrom-Konigska Nursing Home Foundation.

An abstract of "Reproduction and Offspring Status 18 Years After Teenage-Onset Anorexia Nervosa—A Controlled Community-Based Study" is posted at <www3.interscience.wiley.com/journal/121683460/abstract>. ■

CBT Proves Its Value In an Unusual Setting

CBT not only improved the mental health of Iranian prisoners, but also seemed to help keep them from committing more crimes once they were out of prison.

BY JOAN AREHART-TREICHEL

Cognitive-behavioral therapy (CBT) has been found to benefit the mental health of Iranian prisoners, new research shows.

The study was conducted by Gregory Hamot, Ph.D., director of the University of Iowa Center for Human Rights, in conjunction with two Iranian colleagues who are associate professors of psychology at the University of Tehran.

Results were published online August 31 in the *International Journal of Offender Therapy and Comparative Criminology*.

The study's goal was to learn whether individual or group CBT could improve the psychological status of Iranian prisoners. The type of CBT offered was called Reasoning and Rehabilitation (R & R), a corrective intervention that is already being offered to prisoners in a number of countries, including the United States. The main objective of the intervention, which involves 36 two-hour sessions, is to develop cognitive skills in a progressive (accelerated) manner. The program covers topics such as interpersonal problem-solving, stress-coping skills, anger control, risk-taking skills, and positive thinking.

A random sample of 180 male inmates was studied. About a third of the inmates had committed robbery, about a fourth assault and battery, and about a fifth murder. Nine percent had committed fraud, 8 percent rape, and 8 percent drug dealing. Nearly a third had mental disorders prior to conviction (notably anxiety, depression, somatization, and obsessive-compulsive disorder), and nearly half had a history of illicit drug use. A number of the subjects were receiving psychotropic medications prescribed by psychiatrists for their mental disorders.

Subjects were randomly assigned to one of three groups. One group received individual R & R, the second group received both individual and group R & R, and the third group served as controls. Subjects were evaluated psychologically both before and after the intervention periods with the General Health Questionnaire, Symptom Checklist-90-Revised, and diagnostic interviews based on *DSM-IV*. The researchers compared outcomes for the three groups.

Individual and Group R & R Ideal

Subjects who received individual R & R or individual plus group R & R improved significantly more psychologically than control subjects did, and especially as far as somatization, depression, anxiety, and hostility were concerned, the researchers found. However, subjects who had received individual and group R & R improved even more than did subjects who had received individual R & R only.

The reason why, the researchers speculated, may have been because "by attending group therapy sessions and being exposed to other participants' experiences and contributions to group dynamics, the inmates started to analyze and scrutinize their own problems. In addition, the participants in this group might have benefited from individual therapy, which provided an opportunity for them to discuss the problems and issues that they did not or could not discuss in group settings."

In any event, the study's results are not surprising to psychiatrist Cassandra Newkirk, M.D., vice president of Correctional Mental Health Services and chief medical officer of GEO Care Inc. The reason, she told *Psychiatric News*, is because CBT has already been demonstrated to benefit American prisoners.

For example, she said, "CBT is widely used in substance abuse programs that are prison-based with very good results. . . . The programs focus on thinking prior to acting and understanding how thinking affects one's actions. . . . From personal experience I have [also] noted that many inmates in [CBT] groups that teach them how to think have often said that they wished they had learned such skills in school. Educational systems teach 'theories and facts,' but not much about feelings and the influence that thought has on those feelings."

CBT May Also Reduce Recidivism

The Iranian study also suggests that CBT—or more specifically R & R—can reduce recidivism once prisoners are released from prison. In a one-year follow-up after inmate release, recidivism in the individual R & R subjects and in the individual-plus-group subjects who received R & R was zero, whereas it was 15 percent in the control group.

Other studies have also implied that R & R CBT can reduce recidivism, Hamot and his coworkers noted in their paper. In one study, for instance, one group of subjects had received R & R, a second had been given life-skills training, and a third had received no training. Results showed that whereas the rate of recidivism was 48 percent and 70 percent in the second and third groups, respectively, it was only 18 percent in the R & R group.

But even though psychological group therapy is offered to American prisoners, it's not clear how much of it is CBT based and what impact CBT therapy might have on American prisoners' overall recidivism rates, Newkirk pointed out. "It would be well worth the effort of psychiatrists working in correctional settings," she suggested, "to note the models of group therapy that are being provided, usually by psychologists and master's-level clinicians, and review recidivism rates for inmates living with mental illnesses and having been exposed to CBT-type groups while incarcerated."

The study was funded by the University of Tehran and the Tehran Prisons Organization.

An abstract of "Effects of Individual and Group Cognitive-Behavioral Therapy for Male Prisoners in Iran" is posted at <http://ijo.sagepub.com/cgi/content/abstract/0306624X09344840v1>. ■

Could 'Smart' Pillbox Solve Medication Adherence Problem?

Changing systems or technology advances may uncover new approaches to helping patients adhere to the medication regimens their physicians have prescribed.

BY AARON LEVIN

Writing a prescription takes only a stroke of the pen, but ensuring that patients take prescribed medications is a never-ending struggle.

"Putting cameras in pills is the only way to know if patients are actually taking their meds," said Dawn Velligan, Ph.D., a professor of psychiatry at the University of Texas Health Science Center in San Antonio, at APA's Institute on Psychiatric Services (IPS) in New York in October.

For decades, studies have shown that adherence is particularly poor among those with persistent disorders, whether physical or psychiatric; where medications serve to prevent symptom onset or recurrence; or where stopping treatment causes no immediate negative consequences, said Velligan, one of several speakers who suggested new ways of improving adherence.

Practitioners sometimes wrongly assume that a good working relationship with a patient equates with medication compliance. "When you ask, clinicians all say 'Adherence is a problem, but not with my patients,' " said Velligan. "But just because patients engage doesn't mean that they're taking their meds."

Patients with schizophrenia may have considerable difficulty complying with medication regimens, said Velligan. Her research has found that less than 60 percent of medication doses were taken by one group of patients in the first 10 days after hospital discharge, and time is not on their side.

"As many as 75 percent of patients with schizophrenia or other serious mental illnesses become noncompliant within two years of hospital discharge," she said. Patients may be deterred by adverse side effects, poor understanding of their illness, lack of insight, poor ability to comply, or system problems, she said. They may be confused, forgetful, or distracted. Some may not understand instructions or may be unable to establish daily routines that lead to taking their drugs.

One solution has been to develop compensatory strategies. External supports such as signs, checklists, alarms, or regularly straightening up personal belongings can help overcome cognitive deficits and remind patients when to take their medications. Velligan also published research in the May 2008 *Schizophrenia Bulletin* showing that intensive social and cognitive interventions, coupled with attention to medication and appointment adherence, can improve functioning, adherence, and time to relapse.

But such interventions don't work for all patients.

One new solution may be the "smart" pill container. The electronic device holds a one-week to one-month supply of pills, depending on pill size. A voice tells patients when to take the pill, alerts them if they take the wrong pill or take it at the wrong time, and can even ask if they have taken the pill.

The container can send data to the clinic where the patient is treated and e-mail alerts to providers, prompting a telephone call from the clinic to ask if the patient is taking the medication and, if not, why not, said Velligan. That contact can then lead to motivational interviewing and problem-solving by clinic staff.

Can a $1,500 pillbox do a better job than a team of psychiatrists, nurses, and social workers? Velligan will find out in five years when she completes a study, funded by the National Institute of Mental Health, of 150 patients. At the three-month mark, however, the electronic monitoring system recorded 99 percent adherence, compared with 95 percent for a study group receiving the combination of psychosocial interventions at home visits, and 70 percent for a group receiving treatment as usual.

A second approach shows what can be done within a huge, centrally directed health care organization like the Veterans Health Administration (VA), said Marcia Valenstein, M.D., M.S., an associate professor of psychiatry at the University of Michigan Medical School and a research scientist and staff physician at the Veterans Affairs Ann Arbor Health System, who spoke at the same session.

Valenstein and her colleagues have been looking at VA pharmacy data for clues to improving adherence and found that 40 percent of patients had less than 80 percent of the medications needed for outpatient treatment. That was just a statistical aggregate, however.

"Objective measures show we don't know which patients are taking their medication," she said.

please see ***Adherence*** *on page 30*

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.

Let There Be Light in Depression, Bipolar Illness

Researchers in the United States and Canada are investigating whether the type of light therapy used to treat seasonal affective disorder could be effective in treating major depression and bipolar disorder.

BY LYNNE LAMBERG

As hours of daylight dip to annual lows in the northern hemisphere, psychiatrists can expect to hear more patients report seasonal mood disturbances.

Some patients have seasonal affective disorder (SAD), which affects an estimated 1 in 35 people in Canada and 1 in 200 in the United States.

Beyond having pervasive low mood and other common depressive symptoms, some patients sleep and eat more and gain weight. Their symptoms commonly emerge in October and November, peak in January, and remit in the spring. In the southern hemisphere, SAD also occurs in winter months.

Diagnosing SAD is challenging because the clinician must characterize depressive episodes that go back many years, noted Raymond Lam, M.D, a professor of psychiatry and head of clinical neuroscience at the University of British Columbia in Vancouver. Indeed, the typical patient diagnosed with SAD at his clinic, a 38-year-old woman, reports 10 previous episodes of winter depression. Light therapy, starting in late fall, can prevent or minimize such episodes.

Seasonal worsening of moods may complicate nonseasonal depression, Lam said. Up to 15 percent of patients with recurrent depression seen in outpatient psychiatric clinics describe a seasonal winter pattern.

Level 1 evidence supports light therapy's use for SAD (also known as seasonal major depressive disorder [MDD]), according to a report by the Canadian Network for Mood and Anxiety Treatments published in a supplement to the October *Journal of Affective Disorders*. Lam was among its authors.

Research in progress aims to see if light therapy also benefits patients with nonseasonal MDD, bipolar disorder, attention-deficit/hyperactivity disorder (ADHD), and other psychiatric disorders, Lam said.

He and colleagues, for example, are conducting a randomized, double-blind, placebo-controlled clinical trial to assess efficacy of both light therapy and ion therapy in combination with the antidepressant fluoxetine in the treatment of MDD. High-density ion therapy delivered by a negative ion generator, like light therapy, has been found to relieve symptoms of SAD.

Various Combinations Under Study

The researchers plan to enroll 216 patients with nonseasonal MDD at six Canadian centers over three years. Study participants will take a pill and use either a light-therapy or ion-therapy device for eight weeks. Half the patients will receive a placebo pill, and half will use an inactivated treatment device, enabling researchers to assess outcomes of the various treatment combinations.

The investigators will use standard validated scales, including the Hamilton Rating Scale for Depression, to measure treatment outcomes. They also will examine moderators and mediators of treatment response. Funding comes from the Canadian Institutes of Health Research.

Light therapy generally works best for SAD when used in the morning, soon after awakening. Morning light may, however, have destabilizing effects in people with bipolar disorder, noted Dorothy Sit, M.D., an assistant professor of psychiatry at the Western Psychiatric Institute and Clinic at the University of Pittsburgh. It may trigger a switch from depression to hypomania or mania, ultrarapid cycling between states, or suicidality.

Will Bipolar Patients Benefit?

In a pilot study, Sit and colleagues assessed safety and efficacy of differing doses of light therapy for depression in nine women with bipolar I or II disorder. "We were surprised by our patients' exqui-

please see ***Light Therapy*** *on page 32*

Psychiatrists Develop Therapy Guide

Two-thirds of patients with seasonal affective disorder (SAD) improve with light therapy, often starting within one week. Most find the 15- to 30-minute regimen easy to fit into daily life, and with the recent introduction of light boxes costing about $100, regard treatment as affordable.

Despite demonstration of light therapy's benefits over the past 25 years, many psychiatrists have yet to incorporate it into their practice, Raymond Lam, M.D., a professor of psychiatry at the University of British Columbia in Vancouver, told *Psychiatric News*.

Aiming to change that, he and Edwin Tam, M.D., a clinical associate professor of psychiatry at the University of British Columbia, developed *A Clinician's Guide to Using Light Therapy* (Cambridge University Press, 2009).

Lam and Tam describe clinical features and differential diagnosis of SAD and discuss who should and should not use light therapy. They offer advice on selecting light devices, monitoring clinical response, managing side effects, and combining light therapy with antidepressants and other treatments. They also provide clinician resources, including patient questionnaires, instruction sheets, rating scales, and a sample insurance reimbursement letter.

In addition, they discuss light treatment for nonseasonal depression and other psychiatric disorders.

Psychiatrist Challenges Usual Care For First Psychosis Episode

Evidence from neuroleptic-free treatment programs in continental Europe, the United Kingdom, and North America indicate that first-episode patients may be treated successfully with intensive psychosocial interventions.

BY MARK MORAN

Can some patients experiencing a first psychotic episode be treated without neuroleptics and hospitalization? Yes, according to psychiatrist Peter Stastny, M.D., who challenged the prevailing wisdom that all first-episode patients require inpatient hospitalization and antipsychotic medication at APA's Institute on Psychiatric Services in New York last month. He presented the lecture "Starting From Scratch: How to Promote Recovery From Early Psychotic Episodes."

Stastny, whose views are at variance with much of mainstream psychiatric research and thinking, cited a body of data from experimental programs in the United Kingdom, continental Europe, and North America showing successful treatment of psychosis using alternative approaches.

These alternatives included outpatient and in-home services; small, highly staffed, and unlocked residential programs designed specifically for patients with first-episode psychosis; and/or acute day services. Clinical management in these alternative settings included supportive crisis planning, emotional support and information for the family, regular and liberal doses of anxiolytics, and a focus on avoiding extrapyramidal symptoms associated with antipsychotic medication.

"Emergency rooms and acute hospital units weren't developed to treat first-episode psychosis," Stastny told *Psychiatric News*. "They basically exist for their own reasons and over time, like a force of nature, have magnetically attracted individuals with all kinds of needs. Going back to the 1960s, community mental health centers never developed the capacity, as they were supposed to, to include crisis and family interventions. So if you look around the country, crisis intervention is not an integrated element of community services and has largely been replaced by crisis management and triage in emergency departments attached to hospitals."

Stastny is a senior psychiatrist at South Beach Psychiatric Center in Staten Island, N.Y., and consults with several community-based residential programs. Known as a critic of mainstream approaches to treatment, he has written and spoken widely about psychosocial treatments, recovery, self-help and empowerment, and subjective experiences of mental illness.

He is also a member of the planning committee for the conference "Rethinking Psychiatric Crisis: Alternatives to 'First Breaks,' " sponsored by the International Network Toward Alternatives and Recovery, the Center to Study Recovery in Social Contexts, and Community Access Inc. The conference will be held November 23 at the Kimmel Center at New York University. More information is posted at <www.intar.org>.

Poor Outcomes From Standard Treatment

In his lecture, Stastny challenged the conventional wisdom that insists that all patients presenting with an acute psychosis be hospitalized and treated quickly with antipsychotic medication.

He presented data showing the poor outcomes and high rates of patient dissatisfaction associated with conventional treatment. For instance, a research report in the March 2004 *American Journal of Psychiatry* titled "Symptomatic and Functional Recovery From a First Episode of Schizophrenia or Schizoaffective Disorder" showed that after five years only 13.7 percent of subjects met full recovery criteria for two years or longer.

(Recovery measures in that study were derived from the University of California at Los Angeles recovery criteria, as published in the *International Review of Psychiatry* in November 2002, in the article "Operational Criteria and Factors Related to Recovery From Schizophrenia." Full recovery required that subject ratings covering the same period fulfill criteria for both symptom remission and adequate social/vocational functioning.)

Treatment May Compound Trauma

Moreover, Stastny said that patients experience trauma associated with standard treatment that compounds the trauma often accompanying a first psychotic episode. He presented data from a report in the January 2007 *Social Psychiatry and Psychiatric Epidemiology* by Nicholas Tarrier and colleagues showing that 80 percent of first-episode patients felt they had been traumatized by their treatment and 38 percent were diagnosed with symptomatic PTSD as a consequence.

Stastny also presented data from three projects—the Swedish Parachute Project, the Finnish Open Dialogues Program, and the Soteria Programs in North America and Europe—showing that first-episode patients can be treated successfully without hospitalization and neuroleptics.

For instance, the Parachute project is based on the following principles:

- Intervention without delay, preferably in the patient's home.
- Immediate and recurrent family meetings with the patient present.
- Accessibility to a stable, specialized treatment team of up to five years.
- Lowest optimal doses of neuroleptic medication with an attempt to avoid neuroleptic medication during the first one to two weeks.

A follow-up study of outcomes published in the October 2002 *Acta Psychiatrica Scandinavica* showed that Global Assessment of Functioning values were significantly higher for patients in the pro-

please see ***Psychosis*** *on page 32*

Roots of Impulsive Behavior May Lie in Opioid System

Could receptors in the brain that latch onto morphine or other opioids and create a sense of euphoria, serenity, and pain relief have anything to do with why certain people act rashly?

BY JOAN AREHART-TREICHEL

The personality trait of impulsivity has been linked to such negative behaviors as binge eating, drug abuse, problem gambling, reckless driving, and suicide.

But what causes certain people to be impulsive? Probably genes, experts say. And very likely brain biology. Indeed, the serotonin neurotransmitter system and the dopamine neurotransmitter system have already been linked with impulsivity. And now the opioid neurotransmitter system has as well.

The research demonstrating this finding was headed by Jon-Kar Zubieta, M.D., Ph.D., a professor of psychiatry and radiology at the University of Michigan. Results were published in the October *Archives of General Psychiatry*.

Zubieta and his coworkers had 19 young, healthy male volunteers complete a personality questionnaire—the NEO Personality Inventory, Revised. The researchers wanted to learn how the subjects scored on scales in the questionnaire that measure impulsivity. Nine of the subjects, it turned out, scored above the population average on impulsivity; the remaining 10 scored below it.

The researchers then gave the subjects a radioactive material that makes mu opioid receptors visible on PET scans. After that, they examined the subjects' brains with PET scans. Finally, they looked to see whether mu opioid receptors in the brains of the impulsive subjects differed from those in the brains of nonimpulsive subjects.

The answer was yes, as the researchers obtained two notable findings. One was that impulsive subjects had significantly more opioid receptors than nonimpulsive subjects did and thus were more capable of releasing endogenous opioids than the latter. The other finding was that under the influence of stress, impulsive subjects showed a significantly greater activation of opioid receptors and thus released more endogenous opioids.

Moreover, the opioid receptor results obtained were observed in multiple brain regions, including in the amygdala, nucleus accumbens, and prefrontal cortex. These regions are known to be involved in impulsivity and have, in published research, been implicated in disorders associated with impulsive behaviors, such as pathological gambling and substance abuse.

But what are the larger implications of these results?

"People who are impulsive also have a greater opioid system function and particularly so during stress," Zubieta told *Psychiatric News*. In other words, there is an association between impulsivity and the opioid system. Whether impulsivity impacts the opioid system, or whether the opioid system impacts impulsivity, or whether other factors unite the two remains to be discovered.

For example, said Zubieta, "It can simply mean that people who are impulsive are more able to tolerate stress, and, in fact, that stress may make them more impulsive—they may seek the thrill of novelty or be less likely to think through before acting."

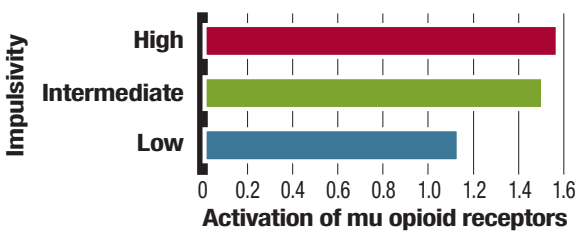
In any event, since impulsivity is associated with drug and sex experimentation, problem gambling, reckless driving, binge eating, and suicide, the results have clinical implications, Zubieta believes. "It means that the opioid system may be involved in those behaviors. In fact, we know it is, either directly or indirectly. This discovery may suggest possible novel therapeutic targets [for such behaviors]."

The study was funded by the National Institute on Drug Abuse.

An abstract of "Positron Emission Tomography Measures of Endogenous Opioid Neurotransmission and Impulsiveness Traits in Humans" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/66/10/1124>. ■

Could Opioid Receptors Fuel Impulsivity?

Subjects who measured highest in impulsivity had the most activated mu opioid receptors under stress. The opioid receptor results were observed in multiple brain regions, including in the amygdala, nucleus accumbens, and prefrontal cortex—regions known to be involved in impulsivity.



Source: Jon-Kar Zubieta, M.D., Ph.D., et al., *Archives of General Psychiatry*, October 2009

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 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*** beat 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 for 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>.*** ■

professional news

Delinquency

continued from page 10

percent of youth in the juvenile justice system have a diagnosable mental health disorder," said Annelle Primm, M.D., M.P.H., director of OMNA and creator of OMNA on Tour, during her introductory remarks at the meeting. Among these youth, minorities are overrepresented, she said, making up a third of all youth in America but representing more than two-thirds of youth in juvenile correctional facilities.

> **"Nearly 70 percent of youth in the juvenile justice system have a diagnosable mental health disorder."**

Youth crime in Seattle is reported as staying constant at around 800 cases a year between 2003 and 2008. While the number doesn't appear to be increasing, the concern is that it is entrenched. Speakers and audience members agreed that to lower the number, education is needed for those who care and are responsible for the welfare of children—parents, guardians, school teachers, social workers, pediatricians, police, judges, and so on—about the immediate and long-term effects that untreated mental illness can have on a child's physical and emotional development.

Wraparound Approach Praised

"We have to build partnerships between the systems that serve our youth and families," including the juvenile-justice systems, said Barnes.

She said her son, now 29, is still healing but doing well. "He is not in trouble, hasn't been in jail for three years, and he's directing his own care," she said.

What happened? At age 14, he and his family embarked on a journey of healing with help from a local "wraparound" program. Barnes said it was through this experience that she first became involved in child mental health treatment and advocacy. The intervention offered her child the emotional support, family bonding, survival skills, and sense of physical protection that he needed and that he had previously sought through his gang affiliation.

The wraparound process was one of a number of strategies that received a thumbs up by former at-risk youth and their families at the Seattle meeting. The multidisciplinary intervention almost literally "wraps" a troubled youth and his or her family in supportive care that is culturally sensitive, strength based, needs driven, and collaborative; it's a committed network of medical and mental health professionals, immediate and extended family, peer-to-peer counseling, and an array of other community service providers.

The principles of wraparound have been practiced in various forms for years around the country. Efforts are under way to establish uniform, evidence-based, best-practice standards of care.

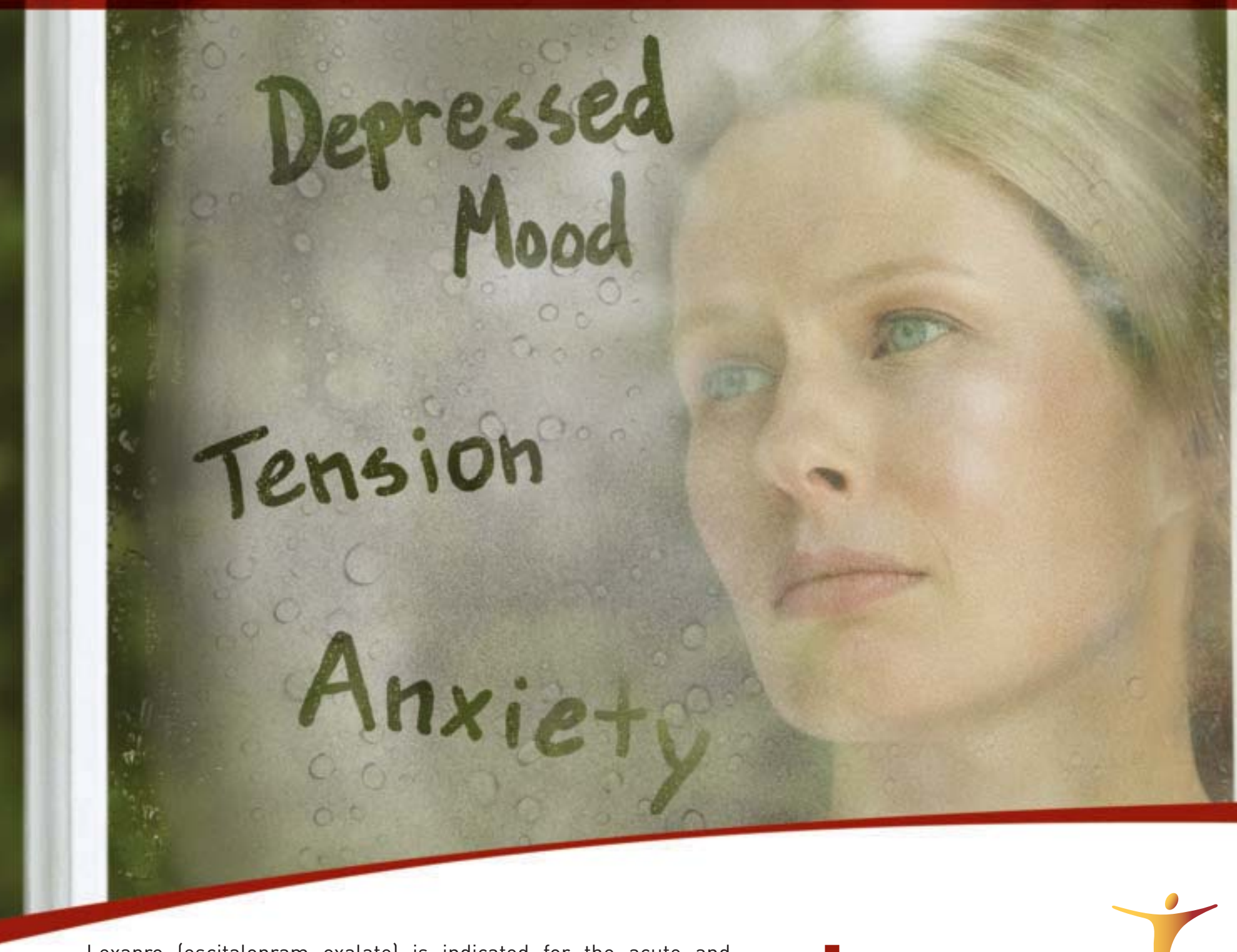
Seattle's government is employing some wraparound principles in its Youth Violence Prevention Initiative, a relatively new multimillion-dollar program. City officials hope to reach out to 800 children and adolescents a year who are at risk of developing emotional problems that could lead to violent behavior and a jail sentence. Program staff "will identify these children and surround them with services tailored to their specific needs," a press statement said.

"Next year's goal is to cut violence in the targeted area by one half," said Mariko Lockhart, director of the Youth Violence Prevention Initiative.

More information about OMNA on Tour and the Seattle stop is posted at <www.psych.org/share/OMNA/omnaontour.aspx>. More information about wraparound intervention—and the effort funded by the Substance Abuse and Mental Health Services Administration and others to develop standards for it—is posted at <www.rtc.pdx.edu/nwi/>. ■

Treat core symptoms[1,2]

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



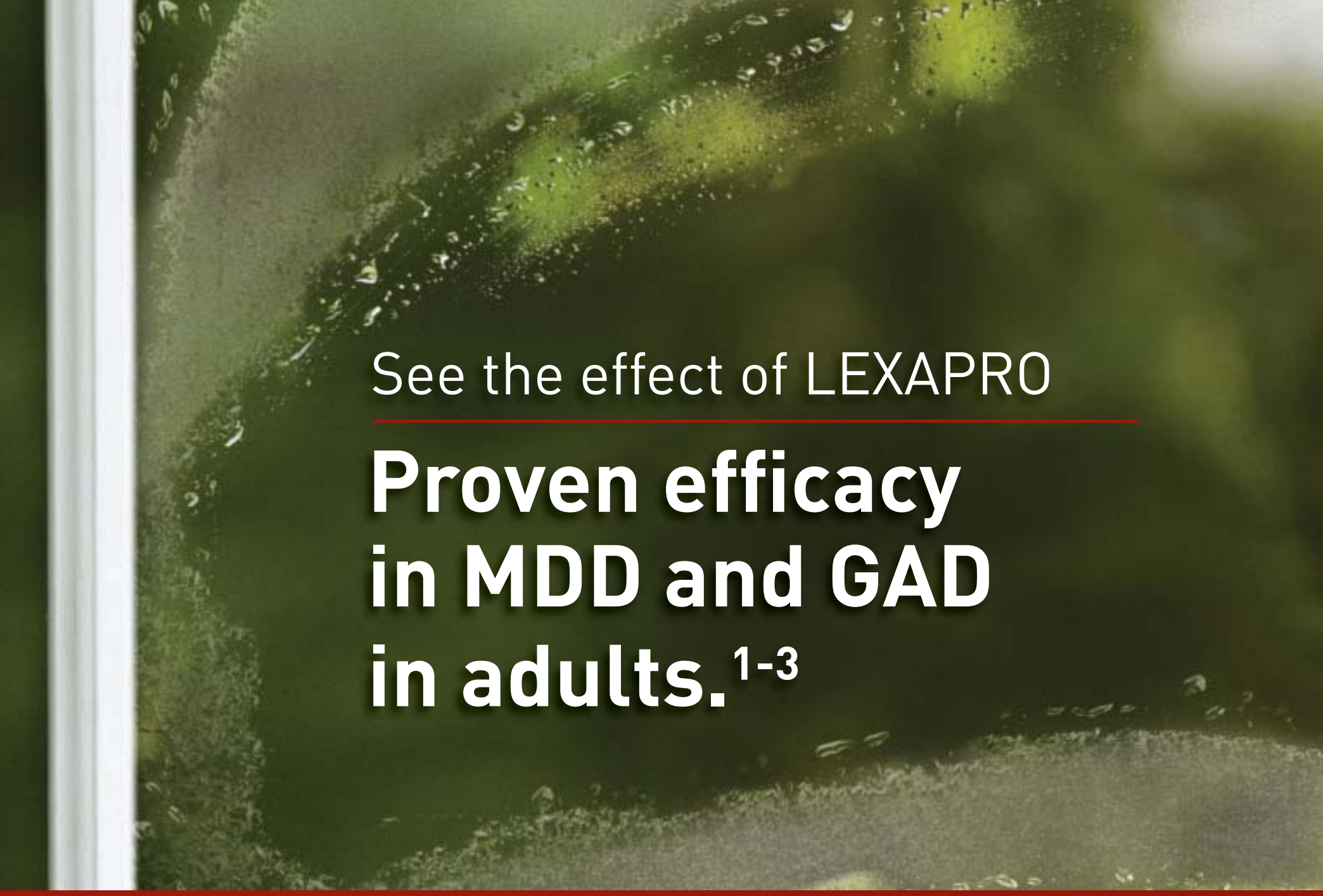
Lexapro (escitalopram oxalate) is indicated for the acute and maintenance treatment of major depressive disorder (MDD) in adults and adolescents aged 12-17 years. Lexapro is also indicated for the acute treatment of generalized anxiety disorder (GAD) in adults.

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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Transforming

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have to put genetics into the context of neuroanatomy."

Many areas of the brain are involved in mood regulation—the prefrontal cortex, orbitofrontal cortex, anterior cingulate cortex, amygdala, and the hippocampus. Already, genotyping can reveal patterns of response on facial-emotion tests, he said. "When you put individuals with the S/S alleles for the 5HTT promoter in an MRI machine and show them faces with various expressions, he or she appears more emotional."

The brain's anatomy is central to new technologies such as vagal nerve stimulation, transcranial magnetic stimulation, and deep brain stimulation.

Vagal nerve stimulation was originally developed to treat refractory epilepsy. Early clinical trials resulted in about a 15 percent response, not much better than the 10 percent registered for placebo. The FDA had rejected its use for the treatment of depression until follow-up studies indicated a 30 percent response rate by one-year follow-up. Vagal nerve stimulation remains controversial, however.

"The FDA has approved it, but Medicare won't pay for it," said Schatzberg. "We'll need large-scale trials to know its efficacy."

Transcranial magnetic stimulation (TMS), developed originally for chronic pain, is applied for 40 minutes a day, five days a week, for six weeks. The effect penetrates about one inch into the brain. It has produced response rates of 20 percent to 25 percent, better than placebo (10 percent). It has been approved for use by the FDA for patients with mild-to-moderate refractory depression but is not yet covered by Medicare.

Deep brain stimulation (DBS) uses an implantable device to trigger response in specific brain areas. Studies using a small number of patients have shown response rates of 40 percent to 60 percent, but many questions remain. It is not yet approved by the FDA and not covered by Medicare for psychiatric conditions.

Credit: Ellen Dallager

Alan Schatzberg, M.D., tells psychiatrists at APA's 2009 Institute on Psychiatric Services that they need to prepare for a future in which genetic information and technology will play an ever-growing role.

DBS has abeen tested in different areas of the brain. The key to success with all these technologies may be more accurate brain mapping plus a better understanding not just of the regions but also of the circuitry that connects them, said Schatzberg. That understanding might not only improve treatment but also make the technology more efficient, he said.

"Right now, the problem is that the battery eventually dies, and the patient needs a second surgery to recharge it," he said. "But a more accurate signal point would demand less power and lead to longer battery life."

The hypothalamic-pituitary-adrenal (HPA) axis is another target of current investigation. Corticotropin-releasing hormone antagonists have been tested in double-blind studies with little success to date.

Tests of mifepristone (RU486)—a glucocorticoid receptor antagonist in the brain—have been well tolerated by subjects. There are both positive and failed trials in psychotic major depression and a recent positive trial in bipolar depression. The drug may work by "resetting" the HPA axis, a strategy that, if proven successful, may eventually have wider applications. It is given for one week, but the effects last eight weeks or longer, suggesting that a "pulsing" approach for some treatments may become the norm.

Much of this new science will affect existing approaches to treatment as well.

"Once we understand the biology of these illnesses, we'll be able to predict the responses to psychotherapy based on genetics," he said. "There is a science to psychotherapy. To think that biological psychiatry would do away with psychosocial treatment is naïve. We'll do it in a more informed way."

To keep up with these and other developments, psychiatry training will have to include more about imaging, genetics, and electrical stimulation, along with better integration of stress physiology and brain circuitry, said Schatzberg. However, psychiatry should not be combined with neurology into a single clinical neuroscience discipline, as some have suggested.

"Neurologists are less interested in affect and behavior, which is what drives psychiatry," he said. "We will always need a discipline based on behavior and affect; however, we will be stronger and better when we incorporate these new ideas and techniques."

Schatzberg has been a consultant to Neuronetics, manufacturer of an r-TMS device; a cofounder of Corcept Therapeutics, which is developing mifepristone for psychotic depression; and a named inventor on Stanford's use patents on mifepristone and genetic markers for antidepressant drug response. ■

professional news

Conflict of Interest

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bills seek Web-based disclosure of industry payments.

Similarly, "management" is a strategy that is growing in popularity. ACCME accreditation standards mandate that program content be determined independently of the program's funder, and speakers can be required to balance their presentations. In addition, hospitals require drug reps to make appointments to see physicians, restrict them from distributing literature to residents, and bar them from patient-care areas. Meanwhile by 2004 more than three-fourths of U.S. medical schools had established committees to review and manage researchers' relationships with industry, Appelbaum reported.

"Alignment of interests" tends to be the strategy most commonly favored by economists in other principal-agent scenarios, and it consists essentially of eliminating the divergent or conflicting interests of the agent. "In the context of medicine this means abstaining from certain relationships so we are not confused by multiple sources of influence on our behavior," Appelbaum said.

For instance, the Association of American Medical Colleges (AAMC) and Institute of Medicine of the National Academy of Sciences have recommended that physicians not accept personal gifts or food from industry, and the AAMC recommends that researchers with financial interests related to a study not be allowed to participate unless they give up those interests. Academic medical centers have banned presentations by pharma employees and restricted faculty from joining industry speaking bureaus.

Appelbaum emphasized that the principal-agent model is useful not so much as a means of arriving at the perfect solution to conflicts of interest as for understanding that there is no perfect solution: all strategies will have limitations and costs, a fact that may dampen the ardor of those who would eliminate all industry involvement with medicine.

"Cutting off relationships with industry inhibits flow of clinical input to the development of therapeutics and eliminates industry support for potentially beneficial programs," Appelbaum stated.

"Viewing the issue as a principal-agent problem can focus everyone on the questions that need to be asked: What is the undesirable behavior we are trying to prevent? How serious are the consequences? How effective are solutions, and what are the costs? And are they really going to work?" ■

clinical & research news

Adherence

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In response to these findings, the VA researchers designed a trial intervention to improve adherence that minimized complexity, coercion, and cost; did not add to the burdens of busy clinicians; decreased barriers to and costs of adherence; and provided cues to action by patients.

The key to their plan lay in simplifying the provision of medications to patients. They aligned all medication refills to the same day of the month. Pharmacy technicians then placed the pills in refillable, one-month packs divided into breakfast/lunch/dinner/bedtime sections for each day. The patients could pick up the packs at the VA or have them mailed to their homes.

This "unit-of-use" packaging is like a pillbox, but doesn't require patients to sort out drugs on their own and can serve as a reminder system as well. Each patient is assigned a pharmacy contact person to answer questions, and doctors are notified if a patient fails to pick up a refill pack.

Preliminary research among patients using unit-of-use packs has measured their adherence though prescription-refill monitoring, blood samples, and self-report. Patients found the approach generally acceptable, and it has improved adherence, but the system has not yet made a significant difference in reducing symptoms, said Valenstein.

Short of putting cameras in pills, adherence problems will continue to be complex, and clinicians will continue to mobilize a variety of psychosocial, technological, and system tools to help keep patients on their prescribed medications, the speakers agreed. ■

Editors

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even before this ICMJE announcement, Michael Roy, the editorial director of *AJP*, told *Psychiatric News*.

"We appreciate and applaud the ICMJE for its efforts in setting standards for disclosure of financial relationships," Roy said. "As this new form is being tested, we are currently working with the ICMJE on achieving agreement with our current guidelines, since in some areas we request more information than that set forth in the ICMJE form."

AJP's requirement for author disclosure of financial relationships states that "financial support for the study is always disclosed, whether from governmental, nonprofit, or commercial sources" and that authors must report all financial relationships, "whether or not directly related to the subject of their paper. Such reporting must include all equity ownership, profit-sharing agreements, royalties, patents, and research or other grants from private industry or closely affiliated nonprofit funds."

The *AJP* financial-disclosure requirement previously covered the 12-month period before the manuscript submission, but will be expanded to 36 months to be consistent with the new ICMJE standard, according to *AJP* Editor-in-Chief Robert Freedman, M.D.

The ICMJE editorial "Uniform Format for Disclosure of Competing Interests in ICMJE Journals" is posted at <www.icmje.org/format.pdf>. The online "ICMJE Uniform Disclosure Form for Potential Conflicts of Interest" is posted at <www.icmje.org/coi_disclosure.pdf>. ■

Psychotherapy

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Psychoanalytic Institute. "I said, 'Let's study it to see if we can justify it.' That led to the study group at the Washington Psychoanalytic Society to which I belonged beginning to read the mainstream medical, psychiatric, and psychological literature for cost-effectiveness studies."

In fact, there was a fledgling literature on the subject going back to before the early 1980s. And in time Lazar's work on the subject earned her a role as a consultant to Bernard Arons, M.D., who was named the chair of the Work Group for Mental Health of the Health Care Task Force. And so Lazar became a regular at the task force's White House meetings.

"I soon realized that when you called researchers who had looked at cost-effectiveness of psychotherapy, they were eager to contribute what they had," Lazar told *Psychiatric News*. "We created a network of interested researchers and clinicians."

> **"We learned that you had to talk about the effect of a specific service on a specific medical budget within a given period of time."**

This included leading lights in research on all kinds of psychotherapy and psychiatric services such as Kenneth Wells, M.D., of Rand; Willard Manning, Ph.D., then of the University of Minnesota; Myrna Weissman, Ph.D., of Columbia University; Glen Gabbard, M.D., then with the Menninger Foundation; Lenore Terr, M.D., of the University of California, San Francisco; Jacob Lindy, M.D., of Cincinnati; Judith Herman, M.D., of Cambridge Hospital; and David Spiegel, M.D., of Stanford University, who had done research on psychotherapy and group therapy for women with breast cancer.

"They came on their own nickel to present data about cost-effectiveness," Lazar said.

As they went along, they learned how to argue their case. "We learned that you had to talk about the effect of a specific service on a specific medical budget within a given period of time," Lazar said, a feat that was difficult when discussing psychotherapy because the benefits might accrue many years out. "Most budget people can't think in terms of five or 10 years, only the next budget year."

Lazar said she and her colleagues were able to present data about "cost-offset"—that is, data showing that psychotherapy saves money elsewhere, such as medical costs for disorders exacerbated by untreated depression. It was ultimately more meaningful, however, to present data reflecting cost-effectiveness, a measure of the economic value of a service obtained per dollar spent, she said.

"Cost-offset is interesting, but it is not a moral standard," Lazar said. "It holds psychotherapy to a more stringent standard if you need to demonstrate cost-offset before you will provide psychotherapy benefits. You would not ask a surgeon or internist to prove they will lower other medical costs before you would reimburse for their care, especially for urgent services."

The group's message began to be heard. "We found that in speaking with people and to staffers, when you make a cost-effectiveness argument with good data, you are really making two points at once," she said. "So many people said, 'Wait—you mean it works at all?' "

Since that time, the study of the cost-effectiveness of psychotherapy has matured. Today, Lazar is the editor and coauthor of *Psychotherapy Is Worth It: A Comprehensive Review of Its Cost-Effectiveness* with other members of the Committee on Psychotherapy of the Group for the Advancement of Psychiatry (GAP). The book is in press with American Psychiatric Publishing Inc.

(GAP's Web site describes the organization as a "think tank" for psychiatry. "The goal of GAP is to continue to germinate new and exciting ideas which will impact on the thinking and practice of mental health clinicians," according to the Web site.)

The book includes chapters reviewing the literature on the cost-effectiveness of all kinds of psychotherapy in the treatment of schizophrenia, borderline personality disorder, posttraumatic stress disorder, anxiety disorders, depression, substance abuse, and psychotherapy of patients with medical illness. The book also covers psychotherapy for children and adolescents and the place of long-term and intensive psychodynamic psychotherapy and psychoanalysis.

"While there are perhaps still too few large-scale studies addressing the cost-effectiveness of psychotherapy for specific diagnostic groups of patients, we can arrive at some important impressions from the studies that we do have," Lazar and colleagues write in their book. "Those that exist do confirm that, for many conditions, psychotherapy works, is cost-effective, can at times provide a significant cost-offset in other medical and hospital expenses, and is not overused or 'abused' by those not truly in need. Also, it is important to understand that a treatment that is cost-effective is not 'cheap', may not save money in other treatment costs, but does provide effective medical help at a cost acceptable to society, both in comparison to other effective treatments for the same condition and to medical treatments for other classes of medical disorder."

Following the collapse of the Clinton health reform effort, Lazar continued to publish on the subject of psychotherapy and cost. In one publication in 1997, she joined Gabbard, Spiegel, and Jeffrey Hornberger, M.D., M.S., in writing "The Economic Impact of Psychotherapy," which was the cover article for the February 1997 *American Journal of Psychiatry.*

Lazar said she believes the new book represents an up-to-date compendium of what has been learned about costs, cost-effectiveness, and psychotherapy since the subject first began to be studied in a formal way.

"What you see in the past 10 years is a much more sophisticated measure of cost-effectiveness, including measures of work productivity, and such measures as quality-adjusted life years," she pointed out.

(Quality-adjusted life years is a measure of disease burden, including both the quality and the quantity of life lived.)

And she believes the book presents a case that will be difficult to ignore. "I think it can be a very powerful tool if you are talking to those designing medical insurance benefits," she said. "It presents an unassailable argument."

"The Economic Impact of Psychotherapy: A Review" is posted at <http://ajp.psychiatryonline.org/cgi/reprint/154/2/147>. GAP's Web site is <www.ourgap.org/default.aspx>. ■

Earley

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given unrestricted access to the Miami-Dade County Jail by officials there.

Earley's book tells the story of five mentally ill patients in the Miami-Dade County jail system, including one patient whose parents literally had to frame her for a crime to get her treated. In between, he weaves in his own family story in a passionate attack on the way many with mental illness are criminalized.

Earley had blunt words for clinicians attending the event during the institute last month. "Psychiatrists really need to step it up and take a more forceful role," he said. "I don't think I have ever met a group that is more modest."

In an interview with *Psychiatric News*, Earley reiterated his belief that psychiatry needs to take on both a health-insurance system that has relegated psychiatrists to being "pill pushers" and a legal system that has allowed an average of 16 percent of the population of an average large-city prison system to be composed of people with a serious mental illness.

"When you have a heart problem, you don't go to a lawyer to see if you need heart surgery," he said. "Yet that is what we do with mental illness. You have to go to a lawyer to decide if someone is dangerous enough to get any kind of help. I think that is fundamentally wrong."

It's a message Earley has delivered before, when he was awarded APA's Patient Advocacy Award at last year's annual meeting in Washington, D.C.

"I love my son," he said then of the young man who is now training to be a peer-to-peer counselor for other patients with serious mental illness. "And I want his civil rights safeguarded. And I know the dreadful history of how we have treated people with mental disorders in our country. But it does not do either an ill person or our society any good to tell a father 'come back after your son tries to kill himself or you.' We must find a better way to help ensure civil rights but also get persons who are clearly psychotic meaningful help rather than waiting until they become dangerous, while preventing avoidable long-term damage, such as metabolic syndrome and foreshortened lives."

More information about Pete Earley is posted at <www.peteearley.com>. ■

Nadelson

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business. That was a tough—and will continue to be a tough—problem for us.

Q. What advice do you have for future APA presidents?

A. One piece of advice is to work more actively with primary care physicians to provide mental health care to patients. Another is to bring the subject of mental health more to the forefront in the debate over changing the American health care system. I think it needs to be addressed through APA's government relations and public affairs offices and via better communication with our colleagues. It needs to receive attention not only from APA, but from other medical specialties. We also need to focus on what APA is accomplishing. I think our members sometimes view us as focusing too much on structure and not enough on accomplishments.

Q. Can you comment on the years when you headed APPI and what you think APPI's future will be when its current director, Ron McMillen, retires in 2010?

A. When I started with APPI it was very, very small. You can see what it has grown into—the largest psychiatric publisher in the world. I am very proud of that. However, it was quite a challenge, and I think it is still a challenge. The book-publishing industry is changing so much, and APPI is going to have to change with it—for instance, we have to look at how the electronic market will work. The person who takes over from Ron will have a major challenge and needs to come with a lot of experience.

Q. It has been 25 years since you were elected the first woman president of APA, and APA will have its eighth woman president next year. What is your reaction to that?

A. I think it's wonderful and important. I think psychiatry leads the way among medical specialties in having women involved in the executive process. However, I'd like to see more women psychiatrists in specific areas of APA leadership—the district branches and Assembly—and in academia and research. ■

Erratum

An article in the October 16 issue on a ruling in the New York case *Disability Advocates Inc. v. David A. Paterson* incorrectly said that the judge's ruling rejected as a violation of the Americans With Disability Act the state's practice of placing nonviolent mentally ill individuals in nursing homes. In fact, the ruling applied to adult board-and-care homes, not nursing homes. ■

Psychosis

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gram than for those in a historical comparison group but similar to those for the prospective group.

Psychiatric inpatient care was lower, as was prescription of neuroleptic medications. Satisfaction with care was generally high in the Parachute group, according to the report.

Doctors Would Rather Be 'Safe Than Sorry'

Stastny underscored his belief that what is now considered the standard of treatment for first-episode psychosis is largely an artifact of imperatives created by the fragmentation of services in the United States.

In addition, Stastny said he believes an increasingly biological approach in American psychiatry combined with fears of liability has resulted in an overreliance on antipsychotic medication.

Because of the legal standard of dangerousness to self and others, doctors would "rather be safe than sorry," Stastny said, and hospitalization has become the reflexive fallback. "I've personally seen many patients who had been admitted but who obviously didn't need hospitalization," he said.

Stastny also addressed the issue of "duration of untreated psychosis" (DUP) and the considerable body of research showing that a longer DUP—typically interpreted as duration of time before treatment with antipsychotic medication—is associated with poorer outcomes.

He said he believes that the assumption is based largely on observations of those patients who typically have had a long, insidious onset of psychosis with prodromal symptoms existing for many years prior to what is designated as the first break. Such patients might be vulnerable to a more severe form of psychosis and tend to develop the overt disorder in ways that lead to later identification and treatment, and hence to poorer outcomes.

Many other patients presenting with a more acute first-episode psychosis, not properly reflected in studies of DUP, will not be so predisposed and may not require coercive inpatient treatment and treatment with neuroleptics, Stastny said.

Neuroleptic-Free Period Beneficial

He cited a summary of five studies of psychosocial treatment for first-episode psychosis in the March *Psychosis* showing that a neuroleptic-free period of two to three weeks in the early phases of a first psychotic episode along with the use of anxiolytics appears safe and likely to help distinguish those individuals who might need ongoing or intermittent low-dose neuroleptics from those who can recover without them altogether.

"All persons experiencing a first psychotic episode should be given the opportunity to recover without neuroleptics within the context of an intensive psychosocial intervention in the community that involves team work, short-term residential alternatives, continuity of care, and family support," Stastny told *Psychiatric News*. "This is not only a prudent course of action, but it is likely to help us further differentiate patient groups and their needs while preventing avoidable long-term damages, such as metabolic syndrome and foreshortened lives."

"Symptomatic and Functional Recovery From a First-Episode Schizophrenia or Schizoaffective Disorder" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/161/3/473?ck=nck>. An abstract of "The Subjective Consequences of Suffering a First-Episode Psychosis: Trauma and Suicide Behavior" is posted at <www.springerlink.com/content/l8261p7w84581871/?p=4bb2c3080a774ad48c6b98b90a1087bf&pi=4>.

An abstract of "One-Year Outcome in First-Episode Psychosis Patients in the Swedish Parachutes Project" is posted at <www3.interscience.wiley.com/journal/120697858/abstract>. An abstract of "Operational Criteria and Factors Related to Recovery From Schizophrenia" is posted at <www.informaworld.com/smpp/content~db=all?content=10.1080/09540260210000169 05>. "Psychosocial Treatment, Antipsychotic Postponement, and Low-Dose Medication Strategies in First-Episode Psychosis" is posted at <http://psychrights.org/Research/Digest/Effective/PsychoSocialMoreEffective2009Psychosis.pdf>. ■

Light Therapy

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site sensitivity to morning light," Sit said.

Three of four subjects receiving morning light therapy developed mixed states, the researchers reported in *Bipolar Disorders* in September 2007. Of the five women with bipolar I or II disorder treated with midday light, however, four achieved stable sustained improvement.

Positive results from light therapy would be especially welcome in bipolar disorder, Sit said, because the effectiveness of existing therapies for this disorder is limited, and treatment resistance is common.

In October, Sit and colleagues began enrollment of a planned 80 subjects in a randomized, double-blind, controlled trial to assess the efficacy of midday light therapy in women and men with bipolar I or II disorder during an acute or chronic depressive episode. The National Institute of Mental Health funded this four-year study.

The light dose will be titrated over six weeks, starting with 15 minutes daily between noon and 2 p.m. for one week, adding 15 minutes each week for three weeks, and continuing with 60 minutes daily for weeks 4 to 6. Half of the subjects will use an active light-therapy unit, and half will use an inactive comparator.

Responders will remain on the dose of response in the acute phase of the study and in the 18-week continuation phase, Sit said, permitting researchers to assess the durability of response. Subjects on a stable dose of antidepressant and antimanic medications will stay on them throughout the study. The researchers will evaluate changes in depression and manic symptoms.

In a Canadian study, 29 adults with ADHD, some of whom had mild SAD, received morning light therapy in a three-week open trial in fall and winter. Subjects' sleep and activity preference shifted to an earlier time.

This shift was strongly correlated with alleviating subjective and objective deficits in maintaining effort and arousal and improving problems with inattention, independently of changes in mood, according to Robert Levitan, M.D., a professor of psychiatry at the University of Toronto. This finding, he said, suggests that light therapy may offer clinical benefits beyond treatment of SAD.

More information on light therapy is posted at <www.cet.org> and at <http://sltbr.org>. ■

Nobel

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Then on Christmas Day 1984, Blackburn and Greider identified an enzyme that makes telomeres. They named it telomerase.

In brief, the scientists had discovered a function for telomeres as well as an enzyme that makes them—discoveries that would ultimately bring them a Nobel Prize.

Moreover, their findings launched a new subfield of study—the exploration of telomeres in aging and cancer. Here, too, there have been some intriguing discoveries.

For example, the older a person is, the fewer times his or her cells divide when cultured in the lab, and the reason is because the telomeres shorten a bit during each cell division. Finally the telomeres become so short that the cell cannot divide any more and dies.

Conversely, if telomerase activity is high, telomere length is maintained, and cellular senescence is delayed. Cancer cells often have increased telomerase activity. Thus some scientists proposed that cancer might be treated by eradicating telomeres. Several studies are now under way in this area, including clinical trials evaluating vaccines directed against cells with elevated telomerase activity.

Telomere research has also segued into the field of mental health and illness.

For instance, in 2004 Elissa Epel, Ph.D., an assistant professor of psychiatry at the University of California, San Francisco, and colleagues reported that chronically psychologically stressed subjects had significantly shorter telomeres than did subjects who were not chronically stressed. This finding suggested that psychological stress might hasten the telomere-shortening process that occurs with normal aging (*Psychiatric News*, January 7, 2005).

In 2006 Naomi Simon, M.D., associate director of Massachusetts General Hospital's Center for Anxiety and Traumatic Stress Disorders, and colleagues reported telomere shortening in subjects with major depression or bipolar disorder. "Our study is the first to demonstrate accelerated telomere shortening in mood disorders, or in any chronic psychiatric disorder," they noted, "and suggests that chronic mood disorders contribute to acceleration of aging processes" (*Psychiatric News*, June 2, 2006).

And recently, Audrey Tyrka, M.D., Ph.D., an assistant professor of psychiatry at Brown University, and colleagues found that subjects who had been emotionally, physically, or sexually abused as children had significantly shorter telomeres than did subjects who had not been so abused. Moreover, these results held even when age, gender, level of education, smoking status, and body mass index were considered. The results were reported online October 15 in *Biological Psychiatry*.

That Blackburn, Greider, and Szostak have received this year's Nobel Prize in medicine "is extremely well deserved," Epel told *Psychiatric News*. "Their scientific discoveries . . . have sprouted new fields in many disease areas. More significantly, the cell-aging system is important across diseases, and we think especially important to brain aging and psychiatric disease." ■

Recovery

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instruction and feedback to us as individuals," Parks said. "We'll never get there by [recovery] just being a general philosophy."

Recovery-orientation training should include the types of questions psychiatrists need to ask certain patients and even how to ask those questions, he said.

The recovery approach is one in which many community psychiatrists have recently expressed great interest, Parks said. The biggest challenge to implementing the change in approach will be the development of more explicit training and broad commitments from psychiatrists to complete the training.

"Most of us now are familiar with doing motivation enhancement-type of interviews and a brief medication check in 15 minutes; it's hard to pack it in, but we know how to do that," Parks said. "And we can get the same way with the recovery-oriented interaction. We just need that level of explicit instruction."

Payment structures are unlikely to prevent a move toward broader adoption of a recovery model in psychiatric care, Parks suggested.

"We can do more recovery-oriented things even during the medication visit; we can certainly do it during medical psychotherapy—a therapy visit that includes a medication element," he said. Payers "don't really constrain exactly how we interact with the person in the room; they just list a few elements that we need to get through. But most of the interaction we can do what we will with."

The specifics of those approaches should become clear through the SAMHSA-led effort to provide "explicit, actionable instructions" for psychiatrists, he said. ■

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Send CV by December 21, 2009 to:

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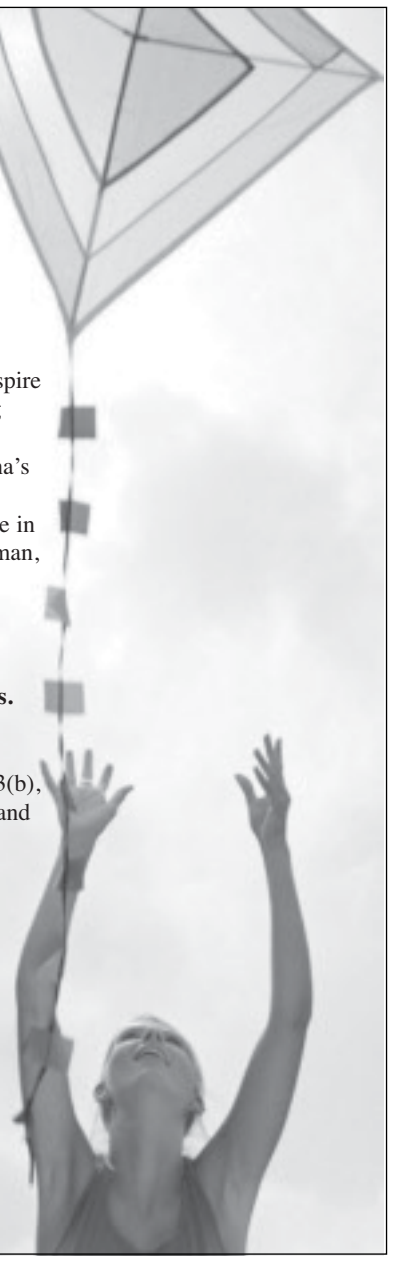

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- 1 line = approximately 43 characters
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- Classified rates are non-commissionable
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Psychiatric News classified ads are posted on **pn.psychiatryonline.org** as each issue is published on the first and third Friday of each month.

EMAIL AND WEB PAGE LINKS: For an additional $50 your prospects can e-mail a response to your ad in seconds. A web link transports prospects directly to your web site in just one click.

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ATTN.: Box P-XXX
Psychiatric News Classifieds
American Psychiatric Publishing Inc.
1000 Wilson Blvd, Suite 1825
Arlington, Virginia 22209-3901

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American Psychiatric Publishing Inc.
1000 Wilson Blvd, Suite 1825
Arlington, Virginia 22209-3901
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classads@psych.org

All advertising copy, changes and cancellations received after the deadline will be placed in the next available issue. We do not provide proofs of ads before publication.

DEADLINES: All new advertising copy, changes, and cancellations must be received *in writing* by Friday, 2 p.m. (E.T) two weeks prior to publication date. Publication dates are the first and third Fridays of every month. Specific deadline dates for upcoming issues are as follows:

Issue	Deadline (Friday, 2 p.m. E.T.)
December 18	December 4
January 1	December 16

The publisher reserves the right to accept or reject advertisements for Psychiatric News. All advertisers in this section must employ without regard for race, sex, age, nationality, or religion in accordance with the law. APA policy also prohibits discrimination based on sexual orientation or country of origin. Readers are urged to report any violations immediately to the executive editor.

Nationwide

Neuroleptic Malignant Syndrome Information Service Presents the 6th Annual NMSIS Promising New Investigators Travel Scholarship Program. Residents, fellows, and students are invited to submit a manuscript on psychotropic drug safety and side effects by February 6, 2010. Prizes of $2000 and $1000 will be awarded at the American Psychiatric Association Meeting in May 2010. Papers may be submitted info@nmsis.org or faxed to 1-607-674-7910. For more information, go to www.nmsis.org. Supported by an educational grant from Janssen, L.P., administered by Ortho-McNeil Scientific Affairs, LLC.

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FCS

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Over 400 permanent searches nationwide.
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ALABAMA

Taylor Hardin Secure Medical, a 115-bed state forensic psychiatric hospital, seeking licensed/or eligible in Alabama psychiatrists for adult patients committed by the circuit courts. BC in psychiatry required. Experience in forensic psychiatry preferred.
Psychiatrist III - 72 months+ experience in psychiatry with administrative experience ($134,968 - 205,792). See APA Job Bank related ad.
Psychiatrist II - graduation from an accredited school of medicine and Board Certified by ABPN. ($125,316 - 191,044)
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

ARKANSAS

LITTLE ROCK & FAYETTEVILLE-General & Child Psychiatrists. Admin/Clinical & Staff positions. Inpatient & partial programs. Fulltime or part-time positions offering highly competitive salary, benefits & bonus. Student loan assistance. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

CALIFORNIA

Contract psychiatrist needed at Coalinga State Hospital, CA. Schedule options - Five 8 hours; Four 10 hours & Three 12 hours weekly. Rate $180/hour when you contact us directly. Call 800-758-7012; fax 800-758-7013 & e-mail hahacorp@gmail.com. We work with recruiters for fee.

Psychiatrist needed for Adults and Pediatric Subspecialty.

Part-time (12 to 24 hours per week), Outpatient Position available.

If you are interested in practicing quality psychiatric care in a challenging and diverse setting, consider Mission City Community Network, Inc. (MCCN), a non-profit community health clinic located in Mission Hills, CA. MCCN seeks a Board-Certified/Eligible Psychiatrist with an interest in the comprehensive treatment of adolescents and adults. The position requires excellence in psychiatric care, interdisciplinary collaboration, coordination of resources and cultural competence in working with the underserved and culturally diverse populations.

Bilingual/cultural abilities in Spanish language are highly desirable. California license is essential for appointment. Applicants may qualify for student loan repayment through N.H.S.C.

Salary range $ 125 - $ 185 per hour, DOE. MCCN is an EOE.

Please e-mail CV to Jacqueline Guinn, M.D., Medical Director at jackieg@mccn.org, hr@MCCN.org or fax to (818)892-3982

Intuitive Health Services, Inc.
Atascadero State Hospital $185 per hr
CA Corrections $170 per hr, on-call $42 by phone
4/10's and week-ends available
www.intuitivehealthservices.com
intuitivehealthservices@intuitivehealthservices.com
Office (805) 703-3729 Fax (925) 462-2583

Southern CA - Lancaster: Join an established private practice. Combined inpatient & outpatient practice. Competitive compensation with partnership. Contact Kimberly Lanzillotti at 866-227-5415 or email Kimberly.lanzillotti@uhsinc.com

PSYCHIATRISTS (Southern California): At **Kaiser Permanente Southern California**, we believe our physicians' time should be spent working with patients, not paper. That's why we provide you with comprehensive administrative support, so you're free to spend the time you need with each person you treat. And the advantages of working with us reach far beyond our comprehensive network of support and state-of-the-art electronic medical records system. As part of our cross-specialty team, you'll also have access to a compensation and benefits package that's designed to impress you. And our surroundings are equally inspiring. Breathtaking natural beauty, year-round recreational amenities, an amazing climate and more will greet you when you arrive at Kaiser Permanente in Southern California. Please email your CV to: Joan.X.Little@kp.org. You may also call Joan Little at (800) 541-7946 or (661) 864-3320. We are an AAP/EEO employer. **http://physiciancareers.kp.org/scal.**

San Diego County needs psychiatrist for hospital, possible ER and telepsychiatry. Salary extremely competitive for San Diego - up to 170K plus 10% Boards and extra 5% second Boards. CV to Marshall Lewis, MD, Clinical Dir, County Behavioral Health Div, Marshall.Lewis@sdcounty.ca.gov. Apply now at www.sdcounty.ca.gov/hr.

California Department of Mental Health

CALIFORNIA
BC/BE STAFF PSYCHIATRIST

Patton State Hospital is recruiting board certified/eligible psychiatrists. Patton is a Joint Commission accredited, 1500 bed, adult forensic psychiatric hospital, with an extremely interesting and challenging patient population. The hospital is nestled below Arrowhead and the San Bernardino Mountains, 65 miles east of Los Angeles; an hour's drive to beaches, Palm Springs, or mountain lakes and skiing. Salary with Board Certification starts at **$18,622 and goes to $21,311 monthly.** Salary for Board Eligible starts at **$18,146 and goes to $20,711 monthly.** In addition, Patton offers excellent benefits (health, dental, and vision; license renewal; malpractice insurance; tax-deferred compensation; paid annual leave and 12 holidays (plus one personal holiday), as well as seven days per fiscal year of Continuing Medical Education leave). Voluntary on call duty is compensated on an hourly basis over and above base salary. We provide civil service security and retirement plans (including safety retirement). For confidential consideration, send CV to George Christison, M.D., (A) Medical Director, 3102 East Highland Avenue, Patton, California 92369, (909) 425-7326 or Fax (909) 425-6635.

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.

COLORADO

Experienced Psychiatrist Wanted To Care for Our Nation's Finest at Evans Army Community Hospital - Fort Carson

Humana Military Healthcare Services is seeking a Psychiatrist to provide full time services to military personnel and their dependents in the Adult Behavioral Health Department of Evans Army Community Hospital in Colorado Springs. Provider will work full-time days, Monday - Friday and will share evening/weekend on-call rotation with other providers. Requirements include board certification by the American Board of Psychiatry and Neurology, current, unrestricted licensure to practice as a Psychiatrist in any U.S. State, current DEA registration and a minimum of 6 months practice experience within the past year. U.S. citizenship and current BCLS certification are also required prior to start. Competitive remuneration package available including paid time off and sign-on bonus. For confidential consideration please send your CV to: cfitzpatrick@humana.com or fax to (954)785-6508, or you may call Mrs. Fitzpatrick toll-free at 1-888-241-1475.

CONNECTICUT

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.

FULL-TIME/PART-TIME/PER DIEM ADULT PSYCHIATRIST
Central Connecticut

Full-time/Part-time/Per Diem opportunity for BC/BE adult psychiatrist at Saint Francis Hospital and Medical Center. You'll work in the adult psychiatric unit with a skilled, multidisciplinary team of Master's-level therapists, nurses and mental health workers treating a broad spectrum of psychiatric patients. Additional responsibilities may include treating adult patients in a partial hospital or intensive outpatient setting. We offer flexible hours with an opportunity for permanent PT/FT position.

Our central Connecticut location offers a wide range of upscale suburban living choices and all the amenities of the New England region, including first-rate schools, and the pleasures of country and coastal environments. Close proximity to professional sporting events, concerts, ballet, theatres, skiing and boating, and less than two hours to Boston and New York.

For more information about this opportunity, please contact Christine Bourbeau in the Recruitment Office at 800.892.3846 or fax/email your CV to 860.714.8835

Email address: cdoughti@stfranciscare.org
Please visit our website at:
www.saintfranciscare.com

EEO/AA - A/F/D/V, pre-employment drug testing

Department of Psychiatry, Yale School of Medicine, is recruiting a Staff Psychiatrist to function as an inpatient attending at the VA Connecticut Healthcare System, West Haven Campus. This position carries an academic appointment at the rank of Assistant Professor of Psychiatry with a targeted effective date of January 1, 2010. Salary will be commensurate with experience. The candidate would be responsible for the psychiatric evaluation and management in an outpatient setting of patients within the Mental Hygiene Clinic of VA Connecticut Healthcare System, in the Anxiety Disorders and Post Traumatic Stress Disorders clinic and in the Errera Community Care Center. Duties include working with a multidisciplinary team, providing medical coverage for other mental health professionals and supervision to trainees, such as residents, medical students and others, who rotate through the clinic. Applicants must have successfully completed psychiatric residency training in an accredited, U.S. program, be board certified (or eligible), licensed to practice in CT and legally employable. Interested applicants send CV and 3 letters of recommendation no later than December 20, 2009 to Dr. Ismene Petrakis, Professor of Psychiatry, Yale School of Medicine, Acting Chief of Psychiatry and Mental Health Service Line Manager, VA Connecticut Healthcare System, 950 Campbell Avenue, West Haven, CT, 06516. Yale University is an equal opportunity, affirmative action employer. Applications from women and minority group members are requested.

FULL TIME ADULT PSYCHIATRIST
CENTRAL CONNECTICUT

Full time (40 hour) opportunity for adult psychiatrist to work in a combination of inpatient and outpatient settings at Saint Francis Hospital and Medical Center, a 617-bed tertiary hospital located in Hartford, Connecticut. As a Saint Francis psychiatrist, you would be part of a multidisciplinary team of psychiatrists, psychiatric nurse practitioners, psychologists, licensed clinical social workers and licensed professional counselors. Our psychiatric service at Saint Francis Hospital includes 4 inpatient units and a large multi-site outpatient psychiatric service. Enjoy flexibility and well-defined scheduling so you can pursue other career or life interests. Additional work hours are available through the other components of our psychiatric service, for candidates that have interest in such an arrangement.

Our central Connecticut offers a wide range of upscale suburban living choices and all the amenities of the New England region, including first-rate schools, and the pleasures of country and coastal environments. Close proximity to professional sporting events, concerts, ballet, theatres, skiing and boating, and less than 2 hours to Boston and New York.

For more information about this opportunity, please contact Christine Bourbeau in the Recruitment Office at 800.892.3846 or fax/email your CV to 860.714.8894.

Email address: CBourbea@stfranciscare.org
Visit our Website at:
www.saintfranciscare.com

EEO/AA-M/F/D/V, Pre-employment drug testing

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.

DELAWARE

WILMINGTON / NEWARK & DOVER: Child and General Psychiatrists. Inpatient/partial programs. Very competitive salary, benefits & incentive plans. J1 eligibility for Dover. 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

Job Details:
Full time Psychiatrist position available at Bayview Mental Health Center, in Sunny Miami Florida. Since 1979, Bayview Center for Mental Health has been providing comprehensive substance abuse and mental health services to the community.

Description:
The psychiatrist provides evaluation, diagnosis, and treatment to Bayview Center clients on the FACT/ACT team. Services are provided primarily in client's home or in other community settings.

Minimum Qualifications:
- Board Eligible/Certified Adult Psychiatrist (MD/DO) with active Florida Medical and DEA licenses.
- Minimum of three years of psychiatric practice, including extensive work with acutely and chronically psychiatrically disabled individuals, and Crisis Stabilization Unit experience preferred.
- Working knowledge of rules and regulations, governing services provided in a community mental health center.
- Strong clinical skills and experience providing treatment to adults with persistent mental illness and co-occurring disorders, in community settings.

Please fax resume to HR recruiter at (305) 493-0814 or e-mail resume to hr@bayviewcenter.com

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ORLANDO - General or Child Psychiatrist. Fulltime position for inpatient & partial programs. Potential Admin/clinical duties. Very competitive salary & benefits. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

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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

MEDICAL DIRECTOR - BEAUTIFUL AREA - CLOSE TO TALLAHASSEE, FL - Seeking Psychiatrist to head up the very impressive adult and geropsychiatric services (inpatient, PHP & outpatient) in a general hospital in south GA. Opportunity for telepsychiatry if desired. Offering very attractive salary w/benefits and bonus plan. Great quality of life: great climate; great opportunity-have it all. Please **call Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

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.

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

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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.

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.

HAWAII

HAWAII PSYCHIATRISTS

This is your opportunity to live and work in Hawaii! The Adult Mental Health Division of the State of Hawaii Department of Health is recruiting psychiatrists. We have openings for psychiatrists to work full or part time at a Community Mental Health Center on the Island of Hawaii.

Employment with the State of Hawaii offers competitive salaries and generous benefits. Benefits include 21 days of vacation per year, 21 days of sick leave per year, 13 paid state holidays, liability insurance, medical/vision/dental insurance, and a pension plan with vesting after 5 years of service.

For more information about us, please see our website at: www.amhd.org.
Please send a CV to Ms. Val Low at: Valerie.low@doh.hawaii.gov or call 808-586-4691.

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.

KANSAS

Full-time Child/Adolescent and Adult Psychiatrist for Community Mental Health Center

Johnson County Mental Health Center (located in a suburb of Kansas City) has an opening effective 2-1-10 for a full-time Child, Adolescent and Adult Psychiatrist for outpatient and corrections work. Req. a medical degree; (M.D. or D.O.); successful completion of ACGME accredited General Psychiatry and Child and Adolescent Psychiatry Residency Programs; must be eligible for licensure to practice in KS. Must have board eligibility or certification through the ABPN; compensation commensurate with experience. This position has been posted as open until filled. For the current recruitment status, please visit our website. Interested applicants should apply online at http://hr.jocogov.org/ or contact: Dr. Jane Lauchland. Johnson County Mental Health Center, 6000 Lamar, Suite 130, Mission, KS 66202; 913-831-2550; FAX to 913-826-1594; Jane.Lauchland@jocogov.org EOE M/F/D.

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

CHILD PSYCHIATRISTS - DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for BE/BC child psychiatrists at the instructor or assistant professor level, salary commensurate with experience. Clinical responsibilities available in the areas of inpatient psychiatry, community based child and adolescent psychiatry, and early childhood mental health. Teaching responsibilities include the supervision of residents, clinical psychology fellows and interns, and medical students rotating through the clinical facilities serviced by this position as well as the presentation of grand rounds and participation in the didactic series in child psychiatry. Clinical research is strongly encouraged. The persons selected must be professionally competent and be board eligible/certified in general psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until a suitable qualified candidate is found. Send CV and list of professional/academic references to Charley Zeanah, Jr, MD, Professor and Vice Chair, Child and Adolescent Psychiatry, Tulane University School of Medicine, Department of Psychiatry and Neurology, 1440 Canal Street TB52, New Orleans, LA 70112 (czeanah@tulane.edu). Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

DEPARTMENT OF PSYCHIATRY AND NEUROLOGY, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for several general and forensic psychiatrists (clinical track) for our growing department, at the Assistant/Associate Professor level. Candidates must have completed an approved general psychiatry residency and be board certified/eligible in general psychiatry and forensic psychiatry, respectively. Responsibilities will include direct patient care, teaching of medical students and house officers, and research (clinical and basic science) at various state hospitals, state correctional institutions, and at Tulane University Health Sciences Center. Time allocations will be based upon individual situations. Applicants must be eligible to obtain a Louisiana medical license. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until suitable qualified candidates are found. Send CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, Department of Psychiatry and Neurology, Tulane University School of Medicine, 1440 Canal Street TB48, New Orleans, LA 70112. For further information, you may contact Dr. Winstead, at 504-988-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admission and in employment.

The 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.

MAINE

Adult inpatient psychiatrist. Mid Coast Hospital is an independent, non-profit community hospital located in beautiful coastal Maine one of Maine's most desirable regions. We are searching for an inpatient psychiatrist for our 12-bed unit. Our team uses a multi-disciplinary approach to treat both voluntary and involuntary patients. This is a full-time position for a BC/BE psychiatrist. Must have or be willing to obtain certification for ECT and a waiver for suboxone management. Share on-call responsibilities with eight other physicians. 40-hour week. Generous benefits, excellent work environment. Please send letter of introduction with CV to: mmackellar@midcoasthealth.com.

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

MARYLAND

The VA Maryland Health Care System (VAMHCS), Mental Health Clinical Center (MHCC) is actively recruiting for psychiatrists to provide after hours (evening, night weekend, and holiday) psychiatric coverage at the **Baltimore Medical Center, located in downtown Baltimore.** These positions do not include any eligibility for benefits such as health insurance, life insurance, etc. nor paid leave. Please mail CV to **Joseph Liberto, M.D., Director, Mental Health Clinical Center, 10 North Greene Street, Baltimore, Md. 21201.** The VAMHCS is an Equal Opportunity Employer.

The VA Maryland Health Care System (VAMHCS), Mental Health Clinical Center (MHCC) is actively recruiting for full time and/or part time psychiatrists at the following locations: The Baltimore Medical Center, located in downtown Baltimore; The Perry Point Medical Center located on the Chesapeake Bay about 35 miles north of Baltimore City; three community based outpatient clinics in the Baltimore metropolitan area; and two community based outpatient clinics on the Eastern Shore of Maryland located in Cambridge and Pocomoke City. The Mental Health Clinical Center is organized into four Sub-Product lines: Inpatient Mental Health; Residential Treatment; Community (outpatient) Mental Health; and Special Programs (Addictions and Trauma). Mental health activities are conducted at all divisions and sites. Mental health professionals assigned across the various Sub-Product Lines consist of a staff of approximately 425 individuals, including psychiatrists, psychologists, social workers, nurses, nurse practitioners, addiction therapists, vocational rehabilitation specialists, physician assistants. The VAMHCS has inpatient, outpatient, and residential programs for substance abuse, PTSD, and the chronically mentally ill. It also has a program in schizophrenia affiliated with the University of Maryland. Opportunities for research and teaching are available but not required. The VAMHCS offers competitive salary rates, health and life insurance, retirement planning including Thrift Savings Plan, generous paid leave and educational opportunities plus the satisfaction of serving those who served. Please mail CV to Joseph Liberto, M.D., Director, Mental Health Clinical Center, 10 North Greene Street, Baltimore, MD 21201. The VAMHCS is an Equal Opportunity Employer.

UNIVERSITY OF MARYLAND MEDICAL SYSTEM

Psychiatrist

The Baltimore Washington Medical Center located in Anne Arundel County, Maryland is seeking a full time hospital based Psychiatrist as the Director of Adult Partial Hospitalization Program. This FT position requires some inpatient work with no outpatients; and extra for weekend call. Opportunities for ED, med-surge consultation and faculty teaching appointments at University of Maryland and Sheppard Pratt are possible.

With us, you will participate as a member of the medical staff of Baltimore Washington Medical Center, an affiliate of the University of Maryland Medical System (UMMS). Baltimore Washington Medical Center is a 311 bed suburban community hospital consisting of 600+ physicians to include resident rotation and faculty affiliation with the University of Maryland. Located near the Chesapeake Bay, Anne Arundel County is an enticing place to live, play and work because of the diversified lifestyles that are offered. The Hospital is located between Baltimore, Washington and Annapolis thus providing easy access to cultural, recreational and education opportunities.

Come see why UMMS is the place for physicians to practice. We offer excellent benefits and compensation. For more information about a rewarding career at UMMS, please email your cover letter an electronic CV to Sharee Selah, sselah@umm.edu

UMMS hospitals and health care facilities are equal opportunity employers and proud of an environment of diversity.

MASSACHUSETTS

BOSTON - Central & Suburb locations. NO CALL. Inpatient/partial programs. Very competitive salaries, benefits & incentive plans. Weekend moonlighting also available. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com

Massachusetts. Lifestyle practice. Top notch colleagues.

Alex Sabo, MD, Chair, Berkshire Medical Center's Department of Psychiatry and Behavioral Science would like you to consider this opportunity to become part of their highly integrated clinical collaboration between Berkshire Medical Center and the Brien Center for Mental Health and Substance Abuse Services. Combined there are two inpatient psychiatry units, one inpatient chemical dependency unit, a partial hospitalization program, a child crisis stabilization unit, two adult crisis houses, half-way houses, rehabilitation programs, seven outpatient clinics, a memory disorders clinic and a crisis team. On average, this unique and highly effective program treats close to 12,000 patients each year. We seek a full time, general inpatient psychiatrist. Flexibility in designing a position exists if your interest also lies in acute primary care outreach services, inpatient chemical dependency services, community crisis services, or community outpatient mental health psychiatry. Monday-Friday, 8:00 am - 5:00 pm with no required call and resident and medical student teaching opportunities.

Berkshire Health Systems is fortunate to serve not only a diverse population, but to be located in the midst of the spectacular natural beauty that is the Berkshire Hills of Western Massachusetts. Berkshire County is home to some of the most scenic vistas in the Northeast as well as world renowned cultural attractions, exceptional centers of higher education, some of the biggest names in retail, outstanding restaurants and much more. ID#30577PY.

Contact Ashley McNeil at 800-678-7858 x64465; amcneil@cejkasearch.com; or visit www.cejkasearch.com.

CAMBRIDGE: Outpatient Psychiatry

OUTPATIENT PSYCHIATRIST: Cambridge Health Alliance is seeking a half-to-full-time psychiatrist, to join our adult outpatient service with integrated addictions and dual diagnosis programs serving a multi-ethnic and diverse patient population. The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School. Our public health commitment to improving the health of our communities, coupled with a strong academic tradition, make this an ideal opportunity for candidates interested in caring for underserved populations in a rich clinical environment. We have strong adult and child residency training programs which provide many opportunities for teaching, as well as innovative programs for HMS students. Academic appointment is anticipated, as determined by the criteria of Harvard Medical School.

Qualifications: BC, strong clinical skills, commitment to public sector populations, team oriented, problem solver, interested in working closely with primary care. Bilingual and/or bicultural abilities are desirable. Interest and experience with dual diagnosis and/or substance use disorders preferred. We offer competitive compensation and excellent benefits package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply. CV & letter to Susan Lewis, Department of Psychiatry, 1493 Cambridge Street, Cambridge, MA; Fax: 617-665-1204. **Email preferred: SLewis@challiance.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 bi-lingual in Spanish. Opportunity for multi-cultural 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.

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.

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.

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

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.

MICHIGAN

Medical Director - An Easy Income of $220k to $240k (Or More) - No long workdays necessary to make a great income. Seeking Psychiatrist for clinical and part-time administrative responsibilities on Psychiatric Services in a hospital in Saginaw, MI. Adult and C/A psychiatric services. Salary w/benefits is also an option. Very close to Bay City on Lake Huron and Flint. Only an hour and a half to Detroit and Ann Arbor. Please call **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

GRAND RAPIDS - Staff Psychiatrist. Inpatient and Outpatient practice position. Collegial clinical care & work environment. Highly competitive salary & benefits & bonus offered. Contact Joy Lankswert @ 866-227-5415 or email joy.lankswert@uhsinc.com

MISSOURI

Medical Director - Base Salary $220k to $240k - Can easily make well over base with Very Generous Bonus Plan - Close to Springfield - Extremely lucrative opportunity. 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.

KANSAS CITY - Staff and potential Admin/ Clinical positions. General and specialty inpatient and partial programs. Fulltime position s offering salary, benefits and incentive plan. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

MONTANA

Helena, MT
Queen City of the Rockies

Horizon Health invites you to consider an exciting new **Medical Director** opportunities for two NEW distinct **Adult** and **Geriatric** Inpatient Psychiatric Units, comprised of **26** total beds in **Helena, MT.** Nestled beneath the foothills of the Montana Rockies, **Helena,** the Capital of Montana, is alive with history and culture. This charming and beautiful Victorian city of 70,000 people provides a diverse attraction with many street festivals, theater, museums, symphonies, fairs and rodeos. There is truly something for everyone here! Excellent practice opportunity with great income ($200K+) and unparalleled quality of life! For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

NEW JERSEY

Westampton Township - Just East of Philadelphia. Addiction Psychiatrist or General Psychiatrist with interest in dual diagnoses. Very competitive compensation and benefits. No on site weekend call required. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 or email joy.lankswert@uhsinc.com

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CHILD & ADOLESCENT PSYCHIATRIST
PRINCETON

to join Princeton office of successful private fee for service comprehensive child, adolescent and adult therapy Center with locations in Princeton, Cedar Knolls, Westfield and Ridgewood. Candidate will be part of a multi-disciplinary team and will provide psychiatric evaluation, medication management and, if desired, psychotherapy. He/She will also clinically oversee treatment at the Center. Salary and benefit package is generous and includes medical/dental insurance, retirement plan, professional liability coverage and substantial continuing education and vacation. Supportive collegial atmosphere. Candidate must be board certified or board eligible in child/adolescent psychiatry. E-mail CV to abbazn@aol.com.

Crisis and/or Inpatient Psychiatry - Central New Jersey: Join an established behavioral health program undergoing a fresh new start. New Chairman, newly renovated inpatient facility and new offices. Call 1:5. The energetic salary-based team is growing and serving the expanding community. Hospital is affiliated with Robert Wood Johnson. Wanda Parker, The HealthField Alliance, 866-232-2333, healthfield@mindspring.com

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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 MEXICO

MEDICAL DIRECTOR
Salaried Opportunity

Horizon Health, in partnership with client hospital in Artesia, New Mexico seeks a Medical Director for a 15-bed Geriatric Inpatient Psychiatric program. Hospital is a full service facility using state-of-the art equipment. Artesia is located in southeastern New Mexico, nestled between the two larger cities of Roswell to the north and Carlsbad to the south. Offering competitive salary and benefits. For more information please contact Diane Odom, Horizon Health, 972-921-9707, fax 972-499-1842, or email diane.odom@psysolutions.com. EOE

NEW YORK CITY & AREA

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.

BC/BE Psychiatrists to provide Consultation-Liaison services in Long Term Care settings (NH, SNF).
Facilities Located in NYC Metro area, Long Island and Westchester, Putnam, Dutchess, Rockland, Orange and Ulster Counties.
Priority positions for: Staten Island, Duchess and Orange Counties.
PT/FT Well above average salaries/benefits, flexible hours.
Recent graduates encouraged to apply.

Please contact: Carlos Rueda, M.D. at Tel: 718-239-0030 or via fax: 718-239-0032 E-mail: crueda@neuropsychllp.com

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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

NEW YORK STATE

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.

NORTH CAROLINA

Medical Director - Inpatient Services
Open Rank
Department of Psychiatric Medicine
The Brody School of Medicine at East Carolina University

The Department of Psychiatric Medicine at the Brody School of Medicine at ECU is accepting applications for a full-time faculty position to serve as Medical Director for Inpatient Services, one of our major teaching sites. The position emphasizes a clinical leadership role and an active interest in educational and scholarly activities. This 52 bed service houses acute beds, combined MI-DD beds, and combined Med-Psych beds in an 800 bed tertiary care hospital serving Eastern and coastal North Carolina. The hospital provides acute, intermediate, rehabilitation, and outpatient health services to more than 1.2 million people in 29 counties. Requirements include MD or equivalent degree, completion of accredited psychiatric residency training in psychiatry, and board certification in Psychiatry. Five years progressive experience in administrative psychiatry, with experience in an inpatient setting is preferred. Salary and academic rank commensurate with experience and academic background. Please send letters of interest and a CV to: John M. Diamond, M.D., Chair Search Committee, Department of Psychiatric Medicine, Brody School of Medicine at ECU, 4E-94B Brody Building, 600 Moye Blvd., Greenville, NC 27834, telephone 252-744-2673, e-mail: diamondj@ecu.edu Additionally, applicants are required to submit an on-line application to **www.jobs.ecu.edu** (position #966016) with attached cover letter, CV, and list of references. East Carolina University is an AA/EO Employer.

OHIO

Psychiatrist, BC/BE. $133-$150K/yr, paid malpractice insurance, health, vision, 401K & more. OH medical license. CV to HR, Community Counseling Center of Ashtabula County at 1201 'C' Court, Ashtabula, OH 44004.

PENNSYLVANIA

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.

Great Opportunity for Psychiatrist in Practice in or near Montgomery County, PA near Bucks Cty line - Increase income/Capture new market. Geropsychiatric Unit in general hospital. Associate Medical Director position with annual stipend. Position nicely compliments already existing private practice and we'll market your practice as well. Please **call Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

Greater Philadelphia Area

Horizon Health, in partnership with **Lower Bucks Hospital** in **Bristol, PA,** has an exciting opportunity for an **Associate Medical Director** for a **24-bed** Adult Inpatient Psychiatric Program. Excellent practice opportunity and income potential for local physician. Call coverage shared - 1:3 weekends, or less, and 1-2 nights per week.
For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

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.

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.

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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Hospitalist, Psychiatric

Outstanding practice opportunity! KidsPeace, a national leader in acute psychiatric care for emotionally & behaviorally challenged children, seeks qualified FT Psychiatric Hospitalist for our modern, state of the art facilities in the Lehigh Valley, PA area (suburban Allentown). Working with a clinically diverse population, we provide comprehensive inpatient services as part of our extensive continuum. Our Hospitalists provide dynamic leadership for a truly integrated treatment team using evidence-based approaches. Compensation is highly competitive. Both BE/BC Child and Adolescent Psychiatrists and BE/BC General Psychiatrists w/ significant adolescent experience are encouraged to apply. An outstanding benefits package is also provided. Please visit our web site for more information at www.kidspeace.org

KidsPeace is located in Pennsylvania's beautiful Lehigh Valley. The area is central to family-oriented communities with excellent school systems. Within easy access to Philadelphia, NYC & the Pocono Mountains recreation region, this culturally rich area boasts 11 area colleges & universities. Come enjoy the beauty and diversity of Eastern PA while working in a challenging and rewarding hospital setting. For immediate & confidential consideration, please submit CV with cover letter to: Herbert Mandell, MD, KidsPeace Medical Director, 5300 KidsPeace Drive, Orefield PA, 18069, email to (hmandell@kidspeace.org), or phone 610.799.8877. EOE-M/F/D/V

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.

TENNESSEE

Horizon Health, in partnership with **Jamestown Regional Medical Center** in **Jamestown, TN,** has an exciting opportunity for a **Medical Director** for a **10-bed** Geriatric Inpatient Psychiatric Program. Excellent practice opportunity and income potential with attractive Medical Director's Stipend.
For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

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

NURSES

Come join the specialists in behavioral health. We're hiring experienced RN's & LVN's for MH, MR/DD and Substance Abuse programs. Requires current RN, LVN certification to practice in the State of Texas. One year MHMR experience and bilingual (English/Spanish) preferred. Apply online at www.chcsbc.org/jobs.html Sign-on Incentive

The Center for Health Care Services
EOE

The Center for Health Care Services
3031 IH 10 West
San Antonio, Texas 78201
Attn: HR Department

MEDICAL DIRECTOR

Horizon Health, in partnership with **Muleshoe Area Medical Center** in **Muleshoe, Texas** seeks a **Medical Director** for a **NEW 10-bed Geriatric Inpatient Psychiatric** Program. Offering competitive Medical Director Stipend. Located near Lubbock and Plainview, TX. Telemedicine may be a possibility at this location. For more information please contact Diane Odom, Horizon Health, 972-921-9707, fax 972-499-1842, or email diane.odom@psysolutions.com. EOE

PSYCHIATRISTS: Mental Health Mental Retardation Authority of Harris County (MHMRA) in Houston, Texas is one of the largest mental health centers in the United States. Demands have created the need for additional BC/BE Psychiatrists throughout the Agency.

Outpatient Clinic
Part-time Adult position available
Perform psychiatric evaluations
& treatment in clinic setting
Flexible day hours
No on call

Psychiatric Emergency Center
24/7 Mental Health Crisis Unit
Full & Part-time positions available

Harris County Jail
Second & third shifts available
Perform psychiatric evaluations
& medication management
Some on call at 24/7 facility

Texas licensure is required for all positions

MHMRA offers competitive salary plus a generous benefit package. Houston offers excellent quality of life, lower than average cost of living, no state sales tax and exciting cultural, entertainment, sporting and tourists venues.

Contact Charlotte Simmons at (713) 970-7397, or submit your C.V. to charlotte.simmons@mhmraharris.org or fax: 713-970-3386

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

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Psychiatrist. Senior Staff Position providing psychiatric services at a multidisciplinary counseling center. Conducts psychiatric assessments and diagnostic evaluations of university students. Determines and administers psychiatric treatment, including prescribing and monitoring medications. Works collaboratively and cooperatively with other mental health professionals on CMHC's multidisciplinary staff. Consults with physicians and mid level practitioners of University Health Services. Doctoral Degree in Medicine (M.D. or D.O.) required, and at least 3 years experience after active board certification preferred. Please access the full job description at http://utdirect.utexas.edu/pnjobs/pnjobsvw.WBX?job_nbr=08-05-22-01-0510. Applications must be made on-line at www.utexas.edu/hr/empl. Review of applications may be considered after the deadline if the position remains unfilled. The University of Texas is an AA/EEO employer.

Assistant Associate Professor

The Department of Psychiatry at the University of Texas Medical Branch in Galveston is seeking an Assistant 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: In-house Night Call Physician. Monday - Thursday schedule. Independent contractor compensation.
DALLAS area - Sherman. General Psychiatrist - 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

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The Center for Health Care Services, an APA Gold Award winning behavioral health organization, is actively seeking full-time & part-time psychiatrists for our Adult & Child Mental Health Programs. Our psychiatrists are at the leading edge of the delivery of mental health service, providing assessment and treatment of residents of Bexar County, Texas. The psychiatrists provide leadership of a team of skilled and dedicated mental health professionals. Must be board eligible, prefer board certified.
Attractive compensation and benefits package, including retirement.
San Antonio offers a beautiful subtropical climate, lower than average cost of living, with higher than average infrastructure, Four Time Champions - San Antonio Spurs NBA basketball, exciting cultural, entertainment and tourists attractions. International airport for ease of travel to any destination.
Please visit our website: www.chcsbc.org for more information about the organization. You may submit your confidential C.V. to The Center for Health Care Services Attn: HR Department, 3031 IH 10 West San Antonio, Texas 78201 EOE

Salaried Opportunities for Adult Psychiatrists - San Antonio, TX

Vericare (www.vericare.com) is the leader in providing mental health services to residents of long term care. We have immediate, salaried positions for Adult or Geriatric Psychiatrists in San Antonio. We offer flexible scheduling, 100% paid malpractice, administrative support, no on call/weekend requirement and a complete benefits package. Board Certified preferred. **Call Sanel Lekic at 800-257-8715 x1166 or email your resume/inquiry to slekic@vericare.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

VERMONT

Springfield Medical Care Systems is pleased to announce an opening for a general adult psychiatrist at the Windham Center for Psychiatric Care in Bellows Falls, Vermont.

The Windham Center is recognized throughout Vermont for its leadership in recovery- oriented services, integrated programming for individuals with mental health and substance use disorders, and utilization of DBT throughout the continuum. The Windham Center includes a 10 bed designated hospital inpatient unit, a partial hospital program, a DBT program, an intensive outpatient program, a buprenorphine program, and an outpatient program.

We are seeking a dynamic Psychiatrist who is Board Eligible or Board Certified in psychiatry to work with other members of the psychiatry department to build a strong future. We have the flexibility to negotiate job descriptions, hours, and responsibilities to meet the needs of candidates who are interested in partnering with us, and who would enjoy working in our setting with our philosophy.

SMCS has the flexibility to offer a variety of salary packages that can be negotiated to meet the needs of the applicant, as well as an outstanding benefit package.

Please contact Janet Sherer, RN, BSN, MBA, Chief of Patient Care Services, at 802-885-7582 or jsherer@springfieldmed.org.

VIRGINIA

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.

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: 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 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.

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.

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

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Fellowships

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.

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

Geropsychiatry Fellowship, Portland Oregon, Recruiting for July 1, 2010 ACGME-accr PGY5 level, at Ore Hlth Sci Univ and Portland VA Med Center. Flexible program with either research or clinical emphasis. Training sites include inpatient, outpatient, nursing home and community. Research and clinical strengths in end-of-life/palliative care, ethics, mood disorders, dementias, Parkinson's disease, and substance abuse. Opportunity, support and mentoring will be provided to fellow for research training. Contact Linda Ganzini, MD, MPH, Director of Geriatric Psychiatry Training, Mental Health Div, R & D 66 , PO box 1034, Portland, OR 97207 or at Linda.ganzini@va.gov EOE.

PSYCHOSOMATIC MEDICINE FELLOWSHIP UNIVERSITY OF MICHIGAN

Our ACGME accredited one-year fellowship program (PGY-5) provides a broad-based clinical experience, with a strong multidisciplinary emphasis, and opportunities to achieve skills in education, administration, and research, in a rich academic environment; no night or weekend on-call. Elective experiences in many areas including an academic psychiatric emergency service can be arranged. Supervision is provided by full-time attendings with board certification in Psychosomatic Medicine. The position begins on July 1, 2010. Candidates must have completed an approved U.S. residency in Psychiatry and be eligible for an unlimited medical license in the State of Michigan, prior to entry into program. Excellent salary and benefits. Contact: Michelle Riba, MD, Director, Psychosomatic Medicine Fellowship, Tel: 734-764-6879; Email:gacioch@umich.edu ; web: http://www.med.umich.edu/psych/education/psychosomatic/.

The University of Michigan is an equal opportunity/affirmative action employer.

Residencies

PGY 2 and PGY 4/5 Residency Positions at Yale University

Each year the Yale University Department of Psychiatry admits four residents at the PGY2 level.

The Department also has PGY 4 and 5 positions available. Sites include the Connecticut Mental Health Center, Silver Hill Hospital, VA Connecticut Healthcare System, Yale New Haven Hospital and Yale University Health Services. Positions include inpatient, outpatient, ER and C-L. Each position offers clinical and academic opportunities. Applicants interested in PGY 2 or 4/5 positions should contact Ann Cohen DePalma at 203.785.2095.

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