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PSYCHIATRIC NEWS

The First and Last Word in Psychiatry

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Jennifer Dart

Former Rep. Patrick Kennedy speaks with reporter Andrea Mitchell on MSNBC about obstacles that prevent individuals from accessing quality mental health care, stressing that "an ounce of prevention is worth a pound of care."

Kennedy Makes Suicide Concerns Focus of National Media Tour

Former Rep. Patrick Kennedy continues his strong advocacy for mental health care as he partners with APA on a cross-country tour stressing the value of suicide-prevention efforts.

BY VABREN WATTS

As this month marks the beginning of enrollment for the insurance exchanges created through the Affordable Care Act and the 50th anniversary of President John Kennedy's signing of the Community Mental Health Act, APA spokesperson and former member of Congress Patrick Kennedy is taking steps to ensure that the case for providing adequate care for those with mental illness is being heard by Americans throughout the country.

In September, Kennedy, along with APA, led a two-day national media tour as part of the activities of National Suicide Prevention Month. The former Rhode Island congressional representative and son of the late Sen. Edward Kennedy, is a senior strategic advisor to APA.

"An ounce of prevention is worth a pound of care," said Kennedy on the MSNBC show "Andrea Mitchell Reports." Kennedy explained that suicide was the second-leading cause of death among adolescents aged 12 to 17 in 2010 and that nearly 40,000 Americans are expected to take their lives this year alone. "This is inexcusable," said Kennedy, emphasizing that the best way to prevent suicides "is to treat the underlying mental health issue."

The tour launched September 4 with an interview that took place on the website of the *Fiscal Times* newspaper and continued across 23 television, radio, and digital outlets—including Boston's WBZ News, among other—until noon the next day.

In addition to suicide prevention,

see ***Kennedy*** *on page 30*

Readiness Leads to Fast MH Response At Navy Yard

A mass shooting at the Washington, D.C., Navy Yard prompts quick deployment of well-prepared mental health services for employees and families of victims.

BY AARON LEVIN

The shooting deaths of 12 employees at the Washington, D.C., Navy Yard on Monday, September 16, set in motion a rapid response from area mental health professionals to help those affected by the tragedy.

APA President Jeffery Lieberman, M.D., sent a letter to the Washington Psychiatric Society expressing sympathy for victims and their families and offering APA's help. "We know our colleagues may be called upon to deal with the mental health consequences that may arise from this traumatic event, and we are confident they will meet this challenge," said Lieberman.

The Washington Psychiatric Society also sent its members a toolkit with information on communicating with the public and the media about trauma, as well as advice on how parents might talk to children about such tragic events, said Steven Epstein, M.D., the district branch's president-elect and a professor and chair of psychiatry at MedStar Georgetown University Hospital and Georgetown University School of Medicine.

see ***Navy Yard*** *on page 31*

PERIODICALS: TIME SENSITIVE MATERIALS

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DISCOVER A NEW TREATMENT OPTION FOR BIPOLAR DEPRESSION

PSYCHIATRIC NEWS

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If so, you have an exclusive opportunity to register for APA's 2014 annual meeting in New York City and reserve your hotel room

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Departments

NOW APPROVED FOR YOUR ADULT PATIENTS WITH

BIPOLAR DEPRESSION

Latuda®

(lurasidone HCl) tablets

20mg | 40mg | 80mg | 120mg

INDICATIONS

LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNINGS: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for use in patients with dementia-related psychosis.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.**

Please see additional Important Safety Information, including **Boxed Warnings**, and Brief Summary of Prescribing Information on adjacent pages.

SUNOVION

IMPORTANT SAFETY INFORMATION AND INDICATIONS FOR LATUDA

WARNINGS:

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for use in patients with dementia-related psychosis.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.**

CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke: In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA 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 administration of antipsychotic drugs, including LATUDA. NMS can cause 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. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes

Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. 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 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.

Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer's dementia).

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

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 LATUDA for patients who will be experiencing conditions that 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.

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

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

ADVERSE REACTIONS

Commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA:

- Adult patients with bipolar depression: akathisia, extrapyramidal symptoms, and somnolence
- Adult patients with schizophrenia: somnolence, akathisia, extrapyramidal symptoms, and nausea

INDICATIONS

LATUDA is indicated for:

- Treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults
- Treatment of schizophrenia in adults

Please see Brief Summary of Prescribing Information, including **Boxed Warnings**, on adjacent pages.

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

WARNINGS:

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS; AND SUICIDAL THOUGHTS AND BEHAVIORS

- **Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death *[see Warnings and Precautions (5.1)]*.**
- **LATUDA is not approved for use in patients with dementia-related psychosis *[see Warnings and Precautions (5.1)]*.**
- **Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older *[see Warnings and Precautions (5.2)]*.**
- **In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber *[see Warnings and Precautions (5.2]*.**

1 INDICATIONS AND USAGE

1.1 Schizophrenia

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia *[see Clinical Studies (14.1)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2)]*.

1.2 Depressive Episodes Associated with Bipolar I Disorder

Monotherapy: LATUDA is indicated as monotherapy for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week monotherapy study in adult patients with bipolar depression *[see Clinical Studies (14.2)]*.

Adjunctive Therapy with Lithium or Valproate: LATUDA is indicated as adjunctive therapy with either lithium or valproate for the treatment of patients with major depressive episodes associated with bipolar I disorder (bipolar depression). The efficacy of LATUDA was established in a 6-week study in adult patients with bipolar depression who were treated adjunctively with lithium or valproate *[see Clinical Studies (14.2)]*.

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient *[see Dosage and Administration (2.2)]*.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

4 CONTRAINDICATIONS

- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone *[see Adverse Reactions (6.1)]*.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) *[see Drug Interactions (7.1)]*.
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 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. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

5.2 Suicidal Thoughts and Behaviors in Adolescents and Young Adults

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 of 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.

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 suicidal thoughts and behaviors, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for LATUDA should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.

5.3 Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks), including fatalities, compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.4 Neuroleptic Malignant Syndrome

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

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. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) 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 NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

5.5 Tardive Dyskinesia

Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to 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 are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

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

Given these considerations, LATUDA 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 (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. 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 on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.

5.6 Metabolic Changes

Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

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

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 2.

Table 2: Change in Fasting Glucose in Schizophrenia Studies

		LATUDA				
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
	Mean Change from Baseline (mg/dL)					
	n=680	n=71	n=478	n=508	n=283	n=113
Serum Glucose	-0.0	-0.6	+2.6	-0.4	+2.5	+2.5
	Proportion of Patients with Shifts to ≥ 126 mg/dL					
Serum Glucose (≥ 126 mg/dL)	8.3% (52/628)	11.7% (7/60)	12.7% (57/449)	6.8% (32/472)	10.0% (26/260)	5.6% (6/108)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 3.

Table 3: Change in Fasting Glucose in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	20 to 60 mg/day	80 to 120 mg/day
Mean Change from Baseline (mg/dL)			
	n=148	n=140	n=143
Serum Glucose	+1.8	-0.8	+1.8
Proportion of Patients with Shifts to ≥ 126 mg/dL			
Serum Glucose (≥ 126 mg/dL)	4.3% (6/141)	2.2% (3/138)	6.4% (9/141)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 4.

Table 4: Change in Fasting Glucose in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=302	n=319
Serum Glucose	-0.9	+1.2
Proportion of Patients with Shifts to ≥ 126 mg/dL		
Serum Glucose (≥ 126 mg/dL)	1.0% (3/290)	1.3% (4/316)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 5.

Table 5: Change in Fasting Lipids in Schizophrenia Studies

		LATUDA				
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
Mean Change from Baseline (mg/dL)						
	n=660	n=71	n=466	n=499	n=268	n=115
Total Cholesterol	-5.8	-12.3	-5.7	-6.2	-3.8	-6.9
Triglycerides	-13.4	-29.1	-5.1	-13.0	-3.1	-10.6
Proportion of Patients with Shifts						
Total Cholesterol (≥ 240 mg/dL)	5.3% (30/571)	13.8% (8/58)	6.2% (25/402)	5.3% (23/434)	3.8% (9/238)	4.0% (4/101)
Triglycerides (≥ 200 mg/dL)	10.1% (53/526)	14.3% (7/49)	10.8% (41/379)	6.3% (25/400)	10.5% (22/209)	7.0% (7/100)

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=356) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 6.

Table 6: Change in Fasting Lipids in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	20 to 60 mg/day	80 to 120 mg/day
Mean Change from Baseline (mg/dL)			
	n=147	n=140	n=144
Total cholesterol	-3.2	+1.2	-4.6
Triglycerides	+6.0	+5.6	+0.4
Proportion of Patients with Shifts			
Total cholesterol (≥ 240 mg/dL)	4.2% (5/118)	4.4% (5/113)	4.4% (5/114)
Triglycerides (≥ 200 mg/dL)	4.8% (6/126)	10.1% (12/119)	9.8% (12/122)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n=130) and -1.0 (n=130) mg/dL at week 24, respectively.

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled, adjunctive therapy bipolar depression studies are presented in Table 7.

Table 7: Change in Fasting Lipids in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	20 to 120 mg/day
Mean Change from Baseline (mg/dL)		
	n=303	n=321
Total cholesterol	-2.9	-3.1
Triglycerides	-4.6	+4.6
Proportion of Patients with Shifts		
Total cholesterol (≥ 240 mg/dL)	5.7% (15/263)	5.4% (15/276)
Triglycerides (≥ 200 mg/dL)	8.6% (21/243)	10.8% (28/260)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA, as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and 5.3 (n=88) mg/dL at week 24, respectively.

Weight Gain

Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was 0.43 kg for LATUDA-treated patients compared to -0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 *[see Clinical Studies (14.1)]*, respectively. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

Table 8: Mean Change in Weight (kg) from Baseline in Schizophrenia Studies

		LATUDA				
	Placebo (n=696)	20 mg/day (n=71)	40 mg/day (n=484)	80 mg/day (n=526)	120 mg/day (n=291)	160 mg/day (n=114)
All Patients	-0.02	-0.15	+0.22	+0.54	+0.68	+0.60

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.59 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Bipolar Depression

Monotherapy

Data from the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study are presented in Table 9. The mean weight gain was 0.29 kg for LATUDA-treated patients compared to -0.04 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 2.4% for LATUDA-treated patients versus 0.7% for placebo-treated patients.

Table 9: Mean Change in Weight (kg) from Baseline in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo (n=151)	20 to 60 mg/day (n=143)	80 to 120 mg/day (n=147)
All Patients	0.0	+0.56	+0.02

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in weight of -0.02 kg at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

Data from the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 10. The mean weight gain was 0.11 kg for LATUDA-treated patients compared to 0.16 kg for placebo-treated patients. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 3.1% for LATUDA-treated patients versus 0.3% for placebo-treated patients.

Table 10: Mean Change in Weight (kg) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

	Placebo (n=334)	LATUDA 20 to 120 mg/day (n=327)
All Patients	+0.16	+0.11

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate in the short-term and continued in the longer-term study, had a mean change in weight of +1.28 kg at week 24 (n=86).

5.7 Hyperprolactinemia

As with other drugs that antagonize dopamine D_2 receptors, LATUDA elevates prolactin levels.

Hyperprolactinemia 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 with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients *[see Adverse Reactions (6)]*.

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. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a LATUDA carcinogenicity study conducted in rats and mice *[see Nonclinical Toxicology (13)]*. 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.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 11.

Table 11: Median Change in Prolactin (ng/mL) from Baseline in Schizophrenia Studies

		LATUDA				
	Placebo	20 mg/day	40 mg/day	80 mg/day	120 mg/day	160 mg/day
All Patients	-1.9 (n=672)	-1.1 (n=70)	-1.4 (n=476)	-0.2 (n=495)	+3.3 (n=284)	+3.3 (n=115)
Females	-5.1 (n=200)	-0.7 (n=19)	-4.0 (n=149)	-0.2 (n=150)	+6.7 (n=70)	+7.1 (n=36)
Males	-1.3 (n=472)	-1.2 (n=51)	-0.7 (n=327)	-0.2 (n=345)	+3.1 (n=214)	+2.4 (n=79)

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -0.9 ng/mL at week 24 (n=357), -5.3 ng/mL at week 36 (n=190) and -2.2 ng/mL at week 52 (n=307).

Bipolar Depression

Monotherapy

The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively compared to +0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 12.

Table 12: Median Change in Prolactin (ng/mL) from Baseline in the Monotherapy Bipolar Depression Study

		LATUDA	
	Placebo	20 to 60 mg/day	80 to 120 mg/day
All Patients	+0.3 (n=147)	+1.7 (n=140)	+3.5 (n=144)
Females	0.0 (n=82)	+1.8 (n=78)	+5.3 (n=88)
Males	0.4 (n=65)	+1.2 (n=62)	+1.9 (n=56)

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day or placebo

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate
The median change from baseline to endpoint in prolactin levels, in the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.8 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in Table 13.

Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Adjunctive Therapy Bipolar Depression Studies

		LATUDA
	Placebo	20 to 120 mg/day
All Patients	0.0 (n=301)	+2.8 (n=321)
Females	+0.4 (n=156)	+3.2 (n=162)
Males	-0.1 (n=145)	+2.4 (n=159)

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

The proportion of patients with prolactin elevations ≥ 5x upper limit of normal (ULN) was 0.0% for LATUDA-treated patients versus 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 0% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.9 ng/mL at week 24 (n=88).

5.8 Leukopenia, Neutropenia and Agranulocytosis
Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class.

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 pre-existing low WBC or a history of drug-induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy and LATUDA should be discontinued at the first sign of decline in WBC, in the absence of other causative factors.

Patients with 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 LATUDA and have their WBC followed until recovery.

5.9 Orthostatic Hypotension and Syncope
LATUDA may cause orthostatic hypotension and syncope, perhaps due to its α1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antihypertensive medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥ 20 mm Hg decrease in systolic blood pressure and ≥ 10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia
The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Bipolar Depression

Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.6% with LATUDA 80 to 120 mg compared to 0% with placebo.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

5.10 Seizures
As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

Schizophrenia
In short-term, placebo-controlled schizophrenia studies, seizures/convulsions occurred in 0.1% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) placebo-treated patients.

Bipolar Depression

Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, no patient experienced seizures/convulsions.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

5.11 Potential for Cognitive and Motor Impairment
LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Schizophrenia
In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Bipolar Depression

Monotherapy
In the short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, somnolence was reported by 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 to 60 mg and 80 to120 mg, respectively compared to 6.5% (11/168) of placebo patients.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/360) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

5.12 Body Temperature Dysregulation
Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that 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 *[see Patient Counseling Information (17.9)]*.

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

Schizophrenia
In short-term, placebo-controlled schizophrenia studies, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

Bipolar Depression

Monotherapy
In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the incidence of treatment-emergent suicidal ideation was 0.0% (0/331) with LATUDA-treated patients compared to 0.0% (0/168) with placebo-treated patients. No suicide attempts or completed suicides were reported in this study.

Adjunctive Therapy with Lithium or Valproate
In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, the incidence of treatment-emergent suicidal ideation was 1.1% (4/360) for LATUDA-treated patients compared to 0.3% (1/334) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.14 Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

5.15 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. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

5.16 Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies
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.

6 ADVERSE REACTIONS
The following adverse reactions 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 (5.1)]*
- Suicidal Thoughts and Behaviors *[see Boxed Warning and Warnings and Precautions (5.2)]*
- Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis *[see Warnings and Precautions (5.3)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.4)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.5)]*
- Metabolic Changes (Hyperglycemia and Diabetes Mellitus, Dyslipidemia, and Weight Gain) *[see Warnings and Precautions (5.6)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.7)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.8)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.9)]*
- Seizures *[see Warnings and Precautions (5.10)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.11)]*
- Body Temperature Dysregulation *[see Warnings and Precautions (5.12)]*
- Suicide *[see Warnings and Precautions (5.13)]*
- Activation of Mania/Hypomania *[see Warnings and Precautions (5.14)]*
- Dysphagia *[see Warnings and Precautions (5.15)]*
- Neurological Adverse Reactions in Patients with Parkinson's Disease or Dementia with Lewy Bodies *[see Warnings and Precautions (5.16)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in 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 information below is derived from an integrated clinical study database for LATUDA consisting of 3799 patients exposed to one or more doses of LATUDA for the treatment of schizophrenia and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.9 patient-years. A total of 1106 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

Schizophrenia
The following findings are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, extrapyramidal symptoms, and nausea.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 14.

Table 14: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction						
		LATUDA					
Body System or Organ Class	Placebo (N=708) (%)	20 mg/day (N=71) (%)	40 mg/day (N=487) (%)	80 mg/day (N=538) (%)	120 mg/day (N=291) (%)	160 mg/day (N=121) (%)	All LATUDA (N=1508) (%)
Gastrointestinal Disorders							
Nausea	5	11	10	9	13	7	10
Vomiting	6	7	6	9	9	7	8
Dyspepsia	5	11	6	5	8	6	6
Salivary Hypersecretion	<1	1	1	2	4	2	2
Musculoskeletal and Connective Tissue Disorders							
Back Pain	2	0	4	3	4	0	3
Nervous System Disorders							
Akathisia	3	6	11	12	22	7	13
Extrapyramidal Disorder	6	6	11	12	22	13	14
Dizziness	2	6	4	4	5	6	4
Somnolence**	7	15	16	15	26	8	17
Psychiatric Disorders							
Insomnia	8	8	10	11	9	7	10
Agitation	4	10	7	3	6	5	5
Anxiety	4	3	6	4	7	3	5
Restlessness	1	1	3	1	3	2	2

Note: Figures rounded to the nearest integer
*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus
**Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following findings are based on the short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5%, in either dose group, and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 15.

Table 15: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in a Short-term Monotherapy Bipolar Depression Study

	Percentage of Patients Reporting Reaction			
Body System or Organ Class Dictionary-derived Term	Placebo (N=168) (%)	LATUDA 20-60 mg/day (N=164) (%)	LATUDA 80-120 mg/day (N=167) (%)	All LATUDA (N=331) (%)
Gastrointestinal Disorders				
Nausea	8	10	17	14
Dry Mouth	4	6	4	5
Vomiting	2	2	6	4
Diarrhea	2	5	3	4
Infections and Infestations				
Nasopharyngitis	1	4	4	4
Influenza	1	<1	2	2
Urinary Tract Infection	<1	2	2	2
Musculoskeletal and Connective Tissue Disorders				
Back Pain	<1	3	<1	2
Nervous System Disorders				
Extrapyramidal Symptoms*	2	5	9	7
Somnolence**	7	7	14	11
Akathisia	2	8	11	9
Psychiatric Disorders				
Anxiety	1	4	5	4

Note: Figures rounded to the nearest integer
*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus
**Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Dose-Related Adverse Reactions in the Monotherapy Study:

In the short-term, placebo-controlled study (involving lower and higher LATUDA dose ranges) [see Clinical Studies (14.2)] the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA in any dose group and greater than placebo in both groups were nausea (10.4%, 17.4%), somnolence (7.3%, 13.8%), akathisia (7.9%, 10.8%), and extrapyramidal symptoms (4.9%, 9.0%) for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively.

Bipolar Depression

Adjunctive Therapy with Lithium or Valproate

The following findings are based on two short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions: The most common adverse reactions (incidence ≥ 5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with bipolar depression) are shown in Table 16.

Table 16: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Short-term Adjunctive Therapy Bipolar Depression Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	Placebo (N=334) (%)	LATUDA 20 to 120 mg/day (N=360) (%)
Gastrointestinal Disorders		
Nausea	10	14
Vomiting	1	4
General Disorders		
Fatigue	2	3
Infections and Infestations		
Nasopharyngitis	2	4
Investigations		
Weight Increased	1	3
Metabolism and Nutrition Disorders		
Increased Appetite	2	3
Nervous System Disorders		
Extrapyramidal Symptoms*	9	14
Somnolence**	5	11
Akathisia	5	11
Psychiatric Disorders		
Restlessness	1	3

Note: Figures rounded to the nearest integer
*Extrapyramidal symptoms includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus
**Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

Extrapyramidal Symptoms

Schizophrenia

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 17.

Table 17: Incidence of EPS Compared to Placebo in Schizophrenia Studies

		LATUDA				
Adverse Event Term	Placebo (N=708) (%)	20 mg/day (N=71) (%)	40 mg/day (N=487) (%)	80 mg/day (N=538) (%)	120 mg/day (N=291) (%)	160 mg/day (N=121) (%)
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/ Restlessness	**6**	**6**	**11**	**12**	**22**	**13**
Akathisia	3	6	11	12	22	7
Dystonia*	<1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Bipolar Depression

Monotherapy

In the short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% versus 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% versus 2.4% for placebo-treated patients. Incidence of EPS by dose groups is provided in Table 18.

Table 18: Incidence of EPS Compared to Placebo in the Monotherapy Bipolar Depression Study

		LATUDA	
Adverse Event Term	Placebo (N=168) (%)	20 to 60 mg/day (N=164) (%)	80 to 120 mg/day (N=167) (%)
All EPS events	5	12	20
All EPS events, excluding Akathisia/Restlessness	2	5	9
Akathisia	2	8	11
Dystonia*	0	0	2
Parkinsonism**	2	5	8
Restlessness	<1	0	3

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

Adjunctive Therapy with Lithium or Valproate

In the short-term, placebo-controlled adjunctive therapy bipolar depression studies, for LATUDA-treated patients, the incidence of EPS, excluding akathisia and restlessness, was 15.3% versus 9.8% for placebo. The incidence of akathisia for LATUDA-treated patients was 7.7% versus 4.3% for placebo-treated patients. Incidence of EPS is provided in Table 19.

Table 19: Incidence of EPS Compared to Placebo in the Adjunctive Therapy Bipolar Depression Studies

Adverse Event Term	Placebo (N=334) (%)	LATUDA 20 to 120 mg/day (N=360) (%)
All EPS events	**13**	**24**
All EPS events, excluding Akathisia/Restlessness	**9**	**14**
Akathisia	5	11
Dystonia*	1	1
Parkinsonism**	8	13
Restlessness	1	4

Note: Figures rounded to the nearest integer
*Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus
**Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia and bipolar depression studies, data was objectively collected on the Simpson Angus Rating Scale (SAS) for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (BAS) for akathisia and the Abnormal Involuntary Movement Scale (AIMS) for dyskinesias.

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.0%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Bipolar Depression

Monotherapy

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate

The mean change from baseline for LATUDA-treated patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

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.

Schizophrenia

In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5%, 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Bipolar Depression

Monotherapy

In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 14 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: ***Infrequent:*** *anemia*

Cardiac Disorders: ***Frequent:*** *tachycardia;* ***Infrequent:*** *AV block 1st degree, angina pectoris, bradycardia*

Ear and Labyrinth Disorders: ***Infrequent:*** *vertigo*

Eye Disorders: ***Frequent:*** *blurred vision*

Gastrointestinal Disorders: ***Frequent:*** *abdominal pain, diarrhea;* ***Infrequent:*** *gastritis*

General Disorders and Administrative Site Conditions: ***Rare:*** *sudden death*

Investigations: ***Frequent:*** *CPK increased*

Metabolism and Nutritional System Disorders: ***Frequent:*** *decreased appetite*

Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*

Nervous System Disorders: ***Infrequent:*** *cerebrovascular accident, dysarthria*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder*

Renal and Urinary Disorders: ***Infrequent:*** *dysuria;* ***Rare:*** *renal failure*

Reproductive System and Breast Disorders: ***Infrequent:*** *amenorrhea, dysmenorrhea;* ***Rare:*** *breast enlargement, breast pain, galactorrhea, erectile dysfunction*

Skin and Subcutaneous Tissue Disorders: ***Frequent:*** *rash, pruritus;* ***Rare:*** *angioedema*

Vascular Disorders: ***Frequent:*** *hypertension*

Clinical Laboratory Changes

Schizophrenia

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from > 0.79 to > 1.3 mg/dL based on the centralized laboratory definition for each study (Table 20).

Table 20: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Schizophrenia Studies

Laboratory Parameter	Placebo (N=708)	LATUDA 20 mg/day (N=71)	LATUDA 40 mg/day (N=487)	LATUDA 80 mg/day (N=538)	LATUDA 120 mg/day (N=291)	LATUDA 160 mg/day (N=121)
Serum Creatinine Elevated	2%	1%	2%	2%	5%	7%

Bipolar Depression

Monotherapy

Serum Creatinine: In the short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to -0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/162) on placebo (Table 21).

Table 21: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in a Monotherapy Bipolar Depression Study

Laboratory Parameter	Placebo (N=168)	LATUDA 20 to 60 mg/day (N=164)	LATUDA 80 to 120 mg/day (N=167)
Serum Creatinine Elevated	<1%	2%	4%

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In short-term, placebo-controlled premarketing adjunctive studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 22).

Table 22: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adjunctive Therapy Bipolar Depression Studies

Laboratory Parameter	Placebo (N=334)	LATUDA 20 to 120 mg/day (N=360)
Serum Creatinine Elevated	2%	4%

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

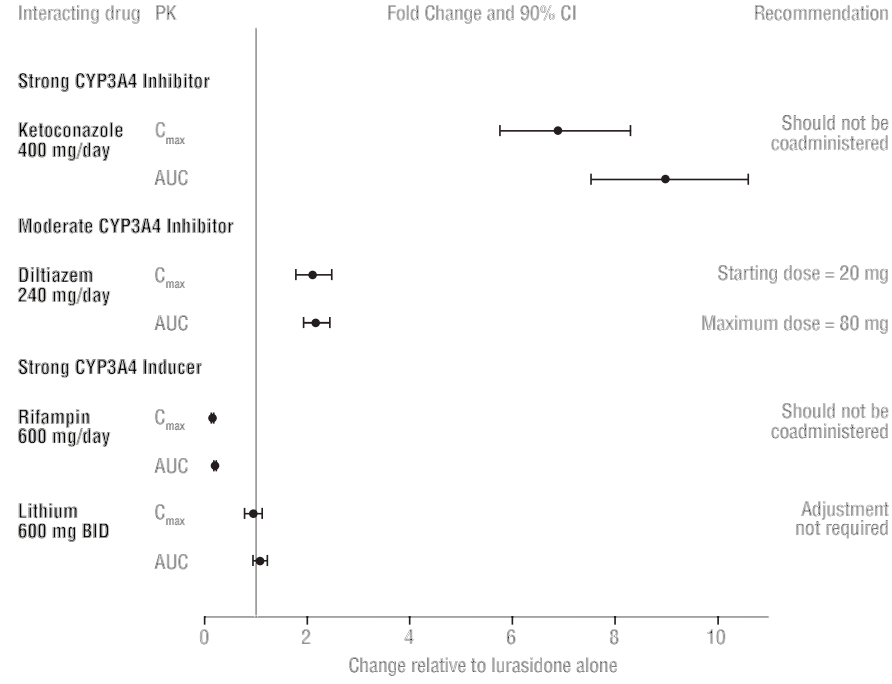
LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used concomitantly with strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil, etc.) or strong CYP3A4 inducers (e.g., rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine, etc.) *[see Contraindications (4)]*. The LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4 (e.g., diltiazem, atazanavir, erythromycin, fluconazole, verapamil, etc.). If LATUDA is used concomitantly with a moderate CYP3A4 inducer, it may be necessary to increase the LATUDA dose *[see Dosage and Administration (2.5)]*.

Lithium: It is not necessary to adjust the LATUDA dose when used concomitantly with lithium (Figure 1).

Valproate: It is not necessary to adjust the LATUDA dose when used concomitantly with valproate. A dedicated drug-drug interaction study has not been conducted with valproate and LATUDA. Based on pharmacokinetic data from the bipolar depression studies valproate levels were not affected by lurasidone, and lurasidone concentrations were not affected by valproate.

Grapefruit: Grapefruit and grapefruit juice should be avoided in patients taking LATUDA *[see Dosage and Administration (2.5)]*.

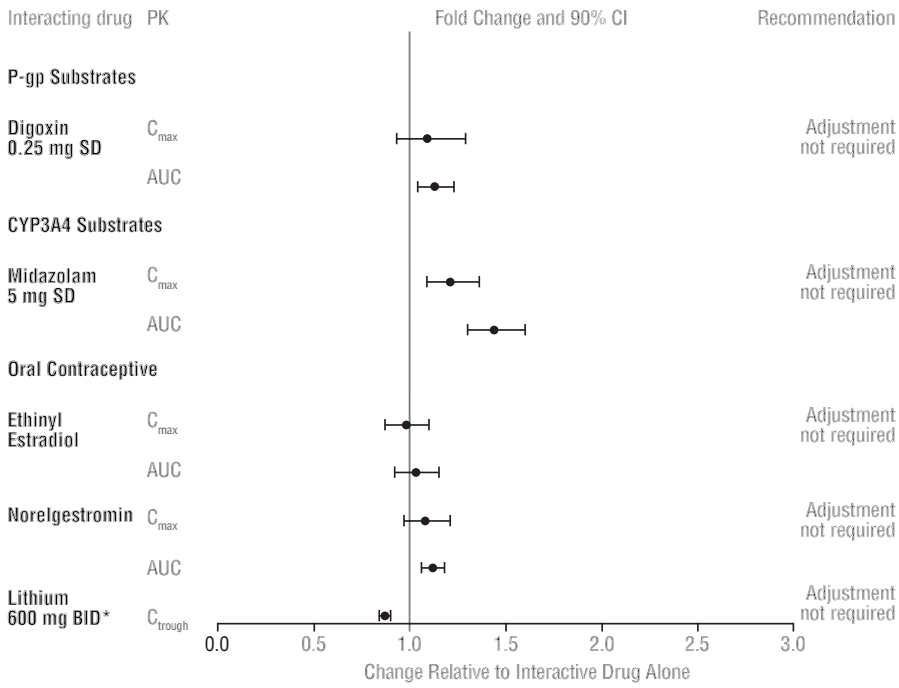
Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



7.2 Potential for LATUDA to Affect Other Drugs

No adjustment is needed on the dose of lithium, valproate, or substrates of P-gp or CYP3A4 when coadministered with LATUDA (Figure 2).

Figure 2: Impact of LATUDA on Other Drugs



*Steady state lithium Ctrough on Day 4 vs Day 8 when lithium was coadministered with lurasidone at steady state

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category B

Risk Summary

There are no adequate and well controlled studies of LATUDA use in pregnant women. Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Human Data

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data

No adverse developmental effects were observed in a study in which pregnant rats were given lurasidone during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day, which is approximately half of the maximum recommended human dose (MRHD) of 160 mg/day, based on mg/m^2 body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given lurasidone during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-times, in rats and rabbits, respectively, the MRHD of 160 mg/day based on mg/m^2 body surface area.

8.3 Nursing Mothers

LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering the risk of drug discontinuation to the mother.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

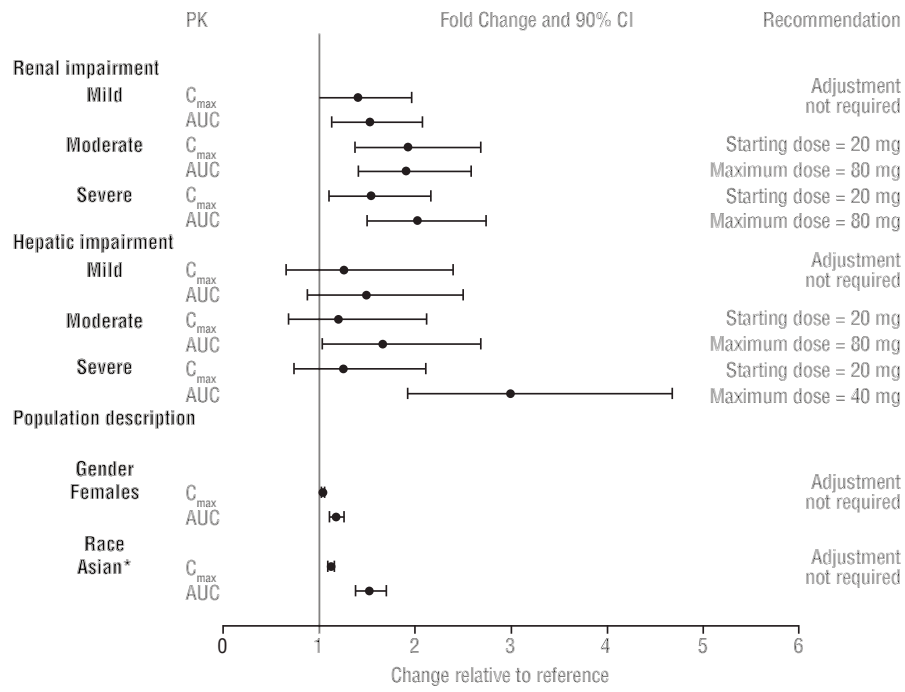
Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

Elderly patients with dementia-related psychosis treated with LATUDA are at an increased risk of death compared to placebo. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

8.6 Other Patient Factors

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics



*Compare to Caucasian

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers. Consider the possibility of multiple-drug overdose.

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

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered.

Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered.

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

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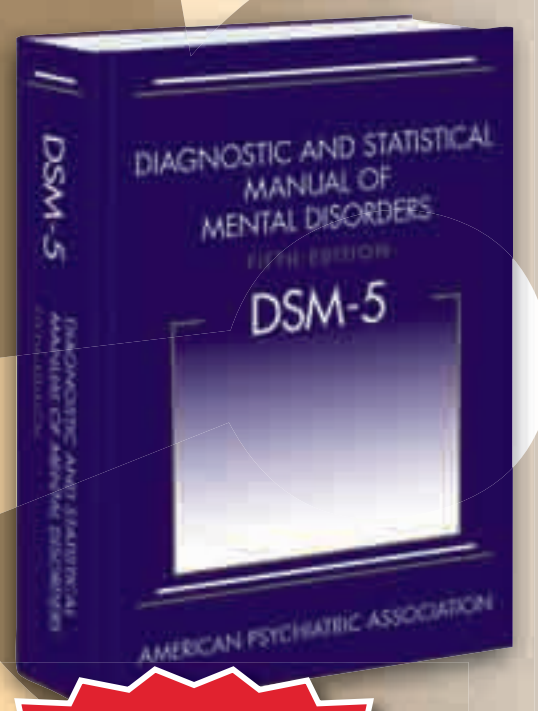

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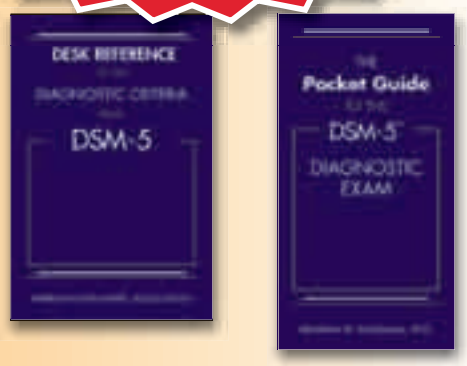

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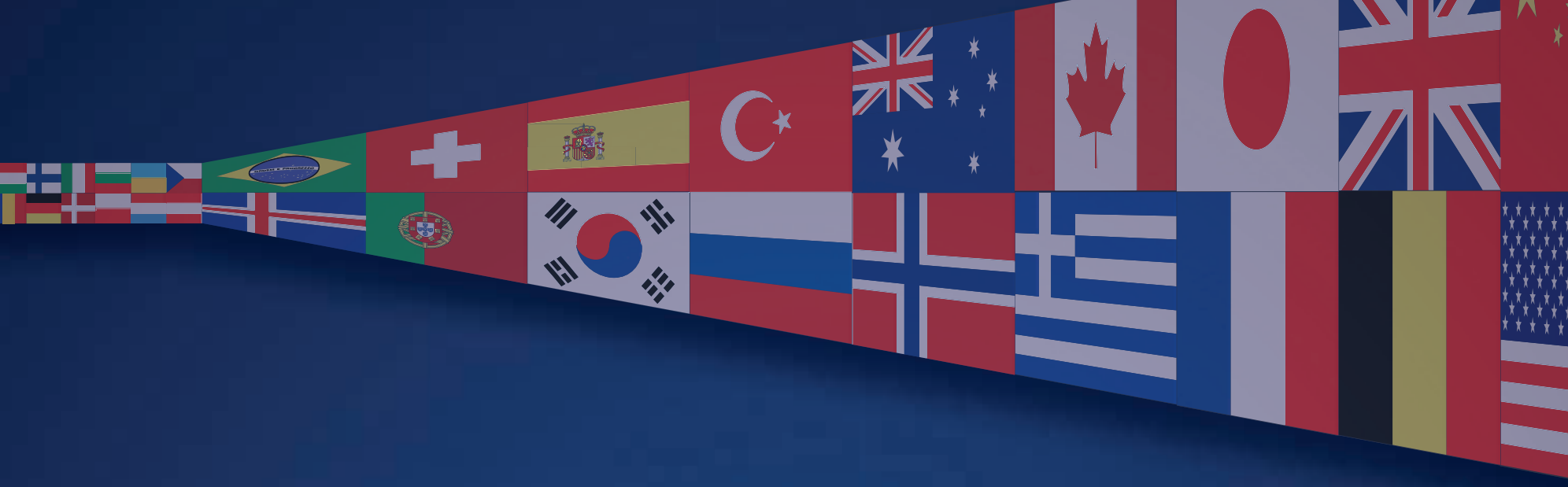

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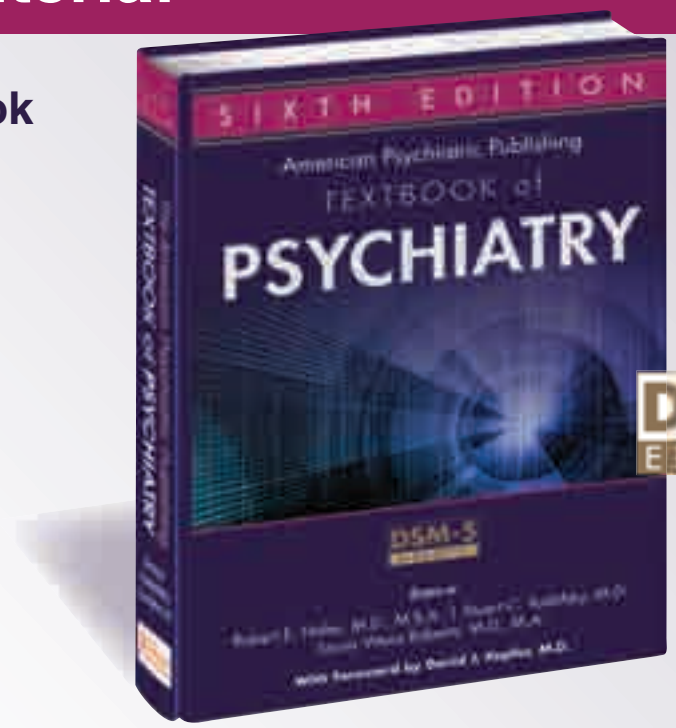

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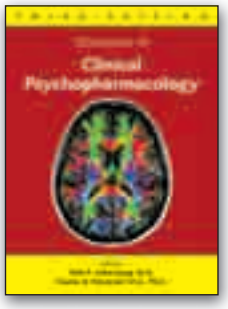

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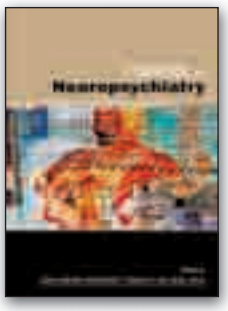

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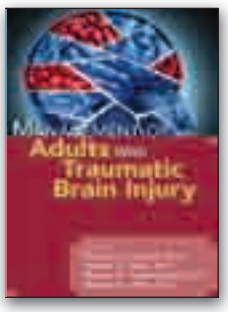

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FROM THE PRESIDENT

Change, Challenge, and Opportunity: Psychiatry in the Age of Health Care Reform

BY JEFFREY LIEBERMAN, M.D., AND HOWARD GOLDMAN, M.D., PH.D.

And keep your eyes wide
The chance won't come again
And don't speak too soon
For the wheel's still in spin
—Bob Dylan
"The Times They Are a-Changin' "

The wheel of health care reform is in full spin as we await implementation of the 2014 health insurance changes mandated by the Patient Protection and Affordable Care Act (ACA). Although some reforms have already begun to occur, the majority of changes loom ahead as the law goes into effect in the coming years. These reforms hold important implications for psychiatrists, our allied mental health care providers, and, most importantly, our patients. This article will summarize the key elements of health care reform (HCR) and describe what APA is doing in response.

We can divide the provisions of the ACA into those focused on health care service reform and those focused on health insurance reform. Some of the latter have been in place almost from the passage of the ground-breaking law (for example, ending certain underwriting restrictions for preexisting conditions), while some begin this month or soon (enrollment in health insurance exchanges, Medicaid expansion), and still others have been postponed (for example, the employer mandate will not begin until 2015). The reforms in health care services, though under way, are more slowly affecting practice and the financing of behavioral health services.

Many of us have already benefited from changes in health insurance underwriting associated with the ACA. Children under 19 years old cannot be denied health insurance on the basis of a preexisting condition, and underwriting for all health insurance benefits has become more closely regulated. As of 2014, no one will be denied coverage on the basis of preexisting conditions. Children may remain on parental health insurance policies until they are 26, even if they are no longer full-time students. They will not lose eligibility for health insurance, even if they develop one of the many mental disorders that have their onset around that age.

The most ambitious aspects of the ACA are also the most controversial. The law creates an individual mandate for health insurance, with federal subsidies for individuals who cannot afford the cost and tax penalties for individuals who do not buy insurance. Health insurance exchanges in each state are offering a carefully regulated array of

health insurance plans to certain individuals who are not part of employer health insurance schemes. The federal government is subsidizing the premiums on a sliding scale for individuals with incomes between 133 percent and 400 percent of the poverty level. Implementing the health exchanges is a monumental task and will be a challenge for the states and federal government in 2014 and beyond.

While the Supreme Court upheld the principle of the federal health insurance mandate and its tax penalties, it also struck down the requirement that every state expand its Medicaid program to provide nearly universal health insurance coverage for individuals with incomes below 133 percent of the poverty level. Some states are taking advantage of the complete federal subsidy of the Medicaid expansion, but others are not participating in that part of the law. In an effort to improve the coverage afforded by Medicaid, the ACA calls for an increase in Medicaid physician fees, which have historically been so low that many physicians will not accept Medicaid beneficiaries as patients. Except for states that opt out of the Medicaid expansion, the implementation of the ACA in 2014 will bring near-universal health insurance to the United States.

So what does this mean for psychiatrists and patients seeking mental health care? The near-universal health insurance coverage should mean that patients and their families will have lower out-of-pocket costs and should expect a broader choice of doctors and health care programs. It may also create an increase in the demand for psychiatric services and more resources to help pay for them.

Universal coverage is also paired with a mandate that health insurance cover treatment for mental disorders, including substance use disorders, and that the coverage will be at parity in the cost-sharing and managed care provisions of their health insurance policies. The historic Mental Health Parity and Addiction Equity Act (MHPAEA) of 2008 applies to the ACA, making this health insurance legislation a triple victory for our field in terms of universal coverage, a behavioral health mandate, and parity.

This victory, however, is not without some concerns. First of all, not everyone in every state will be insured. Some will fail to sign up, some undocumented immigrants will not be covered, and very poor people in some states will not be covered because their state chose not to participate in the Medicaid expansion. Second, not all behavioral health services will be covered. Some support services for individuals with disabling conditions or certain rehabilitation services may not be covered, even in the broader array of Medicaid services. Even there, however, the ACA offers new opportunities in a provision for states to elect to cover some of these home- and community-based services by modifying their Medicaid plans. And finally, even if the main outlines of the policy are known and beneficial, many of the details of parity coverage and regulation have still not yet been worked out, awaiting the issuance of the final rule on the MHPAEA, which is expected imminently.

Health care reform will also change the types of mental health services and ways that they are provided. Among other innovative services, the ACA provides an opportunity for supporting prevention services and early intervention. The law authorizes spending for early interventions in populations at risk for behavioral health conditions. Accountable care organizations (ACOs) and patient-centered medical (or health care) homes offer new opportunities for psychiatrists to practice in "integrated health care" arrangements with new financing schemes. Integrated care creates new opportunities for patients to get holistic care, addressing their co-occurring general medical conditions (see page 13). It also offers new settings for psychiatrists to practice in the mainstream of medical care. To highlight this for APA members, the APA journal *Psychiatric Services* has launched a new column on integrated care, edited by Ben Druss, M.D., and *Psychiatric News* devoted the Septem-

see ***From the President*** *on page 30*

What Is a Psychiatrist's Role In Treating Patients on Disability?

An expert on depression and workplace disability urges psychiatrists to view employers as partners in restoring workers with depression to mental good health.

BY JOAN AREHART-TREICHEL

Psychiatrists often evaluate and treat patients who have depression that is interfering with their ability to continue in their jobs, at least temporarily. An expert on depression in the workplace and workplace disability offers guidance to psychiatrists involved in the disability-evaluation process.

That expert is Paul Pendler, Psy.D., a vice president at J.P. Morgan Chase and Co. in the firm's Employee Assistance and Work Life Program, an assistant professor of psychiatry and behavioral sciences at Northwestern University Feinberg School of Medicine, and a member of the advisory council for the American Psychiatric Foundation's Partnership for Workplace Mental Health.

During the APA Assembly's May meeting in San Francisco, then-APA Assembly Speaker Scott Benson, M.D., invited Pendler to talk about depression in the workplace and workplace disability.

Psychiatric News recently interviewed Pendler about the subject. The following are highlights from the interview:

Q *How many American workers are impacted by depression in the course of a year?*

A Research has shown that 6 percent to 7 percent of the American workforce meets diagnostic criteria for major depression annually. It is important to point out, though, that just because someone has a clinical depression, it does not necessarily mean that he or she is unable to work. That is one of the points I made before the APA Assembly.

Q *What are important issues that psychiatrists should know about impairment in job performance due to depression?*

A First, since a depression diagnosis is not necessarily the same as being impaired, psychiatrists should evaluate depressed patients for functional limitations that might interfere with their work. For example, someone who is depressed and periodically tearful because of it might have difficulty functioning in a position where she has to have a lot of contact with customers.

Another important concern is that once a patient reaches the point where he is so severely impaired in function that he would be better off not going to work, then he should receive aggressive treatment. By this I mean he should not just receive psychotropic medications and/or psychotherapy, but be encouraged to maintain a daily routine that approximates his work schedule—for example, getting up at a certain time, getting dressed, and so on.

Paul Pendler, Psy.D.

Paul Pendler, Psy.D.: "We rely on the clinical judgment of the psychiatrist to determine when a depressed patient on short-term disability is capable of returning to work. But there is also the question of whether the patient's symptoms have been reduced enough that he can handle his job demands."

Q *When should a psychiatrist suggest to a patient with depression that he or she may want or need to apply for disability leave?*

A All too often we've seen psychiatrists and mental health professionals recommend that patients be put on disability without knowing what their tasks at work are. It could be that perhaps they don't need to be off work—that they simply need some of their existing coping strategies bolstered.

Q *How is disability leave defined—a specific time off from work with pay?*

A Often people think about permanent disability, which is a federally managed program under the Social Security Administration. But many companies offer a temporary, short-term period of paid disability leave, which has nothing to do with permanent disability. It is sometimes managed through private insurance companies, or in our case at J.P. Morgan Chase, we manage it ourselves.

Q *How does an employee with depression go about obtaining short-term disability leave? Does the person talk to his or her supervisor or to the human resources department?*

A Each company has its own policy. It is usually a user-friendly system, and the employee takes the initiative. However, he usually has to provide documentation from his psychiatrist, another physician, or mental health professional that he is unable to function in specific ways because of his depression.

Q *Once a patient is on short-term disability leave, does his psychiatrist have to make progress reports to the insurance company?*

A Depending on how disability is managed, there are usually some narrative reports required. The disability timeline varies based on the diagnosis, level of impairment indicated, and specific symptoms that are being targeted. While there may be guidelines such as approximate time period for time off due to depression, each case needs to be examined on a case-by-case basis.

Q *And each time, does the psychiatrist have to get permission from the patient to release the information?*

A This relates more to medical practice of the practitioner. Typically a disability entity will have a release initially, but I would think it's sound clinical practice to ensure that the patient authorizes the release of new information each time.

Q *At any point do the patient's psychiatric records have to be evaluated by an independent psychiatrist?*

A Depending on the insurance company, chart notes may be required if forms are not filled out in a timely manner, and the disability company wants to learn more about the frequency of visits and specific symptoms being targeted. If there is a determination for an independent review, then of course the request for notes would be made.

The recommendation for an independent review is made on a case-by-case basis. It relates to the exact short-term disability benefit that a company has. So if a physician recommends the maximum time off without supporting evidence, there could be a recommendation for an independent evaluation.

Q *A patient already in treatment with a psychiatrist for depression can use that psychiatrist for the disability evaluation and necessary periodic evalutions. But suppose the psychiatrist doesn't want to get involved with the disability process?*

A Yes, some clinicians elect not to "contaminate their treatment" by placing themselves in an evaluative capacity for off-work determination. That is the psychiatrist's right.

Q *What are some issues surrounding return to work for patients with depression on disability leave?*

A In today's workforce, almost all jobs require people to manage multiple expectations at the same time. Thus, if patients with depression who are out on disability leave could return to work on a reduced schedule, that would probably be ideal to [get an idea of] how well they can handle the various demands on them. And if they were making good progress, then they would eventually be expected to return full time.

Q *Do patients on disability leave sometimes malinger?*

A Yes, sometimes they do. The psychiatrist needs to tell them up front, "I'm going to be exchanging information with your disability company about your functional limitations. And once we see signs of progress, we will probably encourage you to come back to work—perhaps even sooner than you estimate."

On the other hand, when patients with depression are reluctant to return to work, it may be because there are things going on at work that they want to avoid—say, a boss they don't like. You need to have a frank conversation with patients about such matters and perhaps suggest that they contact their human resources department or employee assistance program for help in this regard.

Q *If an employee is impaired because of substance abuse, can the employer request that he be evaluated, and if so, can he see any psychiatrist, or must it be an employer-selected psychiatrist?*

A Every company has its own drug-free-workplace policies. In our experience, we encourage a patient with a substance abuse problem to get evaluated

see ***Disability*** *on page 20*

Psychiatrist Focuses on Populations In Health Delivery Services

While many thought leaders in integrated care have concentrated on bringing mental health services to primary care patients with chronic medical conditions, Benjamin Druss, M.D., has focused on improving health status for patients with serious mental illness in the public sector.

INTEGRATED CARE
Putting Together the Puzzle

BY MARK MORAN

As a public-health expert and a health-services researcher, Benjamin Druss, M.D., is something of a rarity for a psychiatrist.

Trained initially in both primary care and psychiatry, he began his clinical work as a consultation-liaison psychiatrist and soon realized that in many cases—and especially for patients in the public mental health system—the problems that patients were confronting went beyond the traditional clinical skills for which he was trained.

"As a clinician, what brought me to thinking about system-level issues was the fact that it seemed as though what I was trained for was not matching up with what I needed to be doing for patients," he said. "Deciding what dose of risperidone a patient should be on was the easy part. But getting them a follow-up appointment if I saw them in the emergency room was a problem. I just didn't feel like I could do it alone, and I realized that many of these problems required fixes at the system level."

It's a phenomenon he says he sees in young psychiatrists today. "I was talking recently to residents working in a community mental health center," he told *Psychiatric News*. "I think a lot of them were feeling overwhelmed by what they were doing. What they were trained to do and competent to do at this point was to write prescriptions for psychiatric medications and do psychotherapy. But that didn't really match up with what their patients needed, many of whom were coming with enormous stresses in their lives—abuse, homelessness, and other psychosocial issues."

Benjamin Druss, M.D.

Benjamin Druss, M.D., says an emphasis on population-based care is the thread that runs through many of the movements in health care today, including accountable care organizations and medical homes.

So following his residency, Druss received a public-health degree at Yale and spent 10 years there as a health-services researcher. In 2003, Druss came to Emory University in Atlanta, where he has become a leading researcher in integrated care. But while many of the thought leaders of this movement have focused on bringing mental health services to the primary care setting for patients with chronic medical conditions, Druss has specialized in bringing primary care services to individuals with serious and persistent mental illness in the public sector.

His perspective has caused him to look beyond simply merging mental health and primary care to a broader vision that can include a range of social and rehabilitative services—and for that reason, Druss said that he prefers the term "population-based care."

"We call it integration," he said, "but what we really mean to do is to make sure that patients get all the kinds of services they need and that those services extend across whole populations of people, even those who aren't presenting for services."

Program Provides Greater Access

At Emory, Druss's research has been a mix of mining large datasets for information about health-service utilization patterns and intervention studies focused around the issue of improving physical health and health status in people with serious mental illness.

An example of the latter is the PCARE (Primary Care Access, Referral, and Evaluation) model, which employs a medical nurse/care manager to provide education and care coordination to help patients with serious and persistent mental illness engage in primary care.

In a study published in the *American Journal of Psychiatry*, care managers provided communication and advocacy with medical providers, health education, and support services in overcoming system-level fragmentation and barriers to primary medical care. At a 12-month follow-up evaluation, the intervention group received an average of 58.7 percent of recommended preventive services compared with a rate of 21.8 percent in the usual-care group. They also received a significantly higher proportion of evidence-based services for cardiometabolic conditions and were more likely to have a primary care provider.

"Several features of the PCARE study management model make it an appealing approach for community mental health clinics seeking to improve their patients' medical care," Druss and colleagues wrote. "Compared with co-located approaches, care management is relatively inexpensive to implement and practical for even relatively small sites that do not have the financial or staffing resources to establish fully functioning medical clinics on site. Existing mental health care managers can be retrained to add medical services to their scope of activities. Finally, a rationale for CMHCs to address primary care services among their clients may be provided by the fact that improving medical care might be associated with better mental health outcomes."

Future Is Population-Based Care

Another ongoing project is the HOME (Health Outcome Management Evaluation) Study, which involves a partnership between a federally qualified health center in Atlanta and a local community mental health center (CMHC). The health center has set up a satellite clinic in the CMHC and employs team-based care for patients with serious mental illness and one or more active cardiometabolic problems (such as diabetes, hypertension, and hyperlipidemia). The study uses standardized, validated instruments to assess the impact of integrated community care on quality and outcomes of cardiometabolic and general medical care.

Such projects may seem visionary, but Druss echoes other leaders in the integrated/collaborative care movement in urging individual psychiatrists to reach out to their own hospitals and health sys-

see ***Populations*** *on page 31*

Accreditation Programs Launched for Integrated Care, ACOs

URAC (formerly the Utilization Review Accreditation Commission) is launching two new accreditation programs for physician groups and health systems moving toward clinical integration and accountable care. The programs are designed to assist provider organizations as they move from physician practice groups to fully functioning "medical homes," from loosely organized networks to clinically integrated networks, and from clinically integrated networks to population-based health care delivery through accountable care entities.

"URAC's new accreditation programs are a roadmap for providers to successfully navigate the complex structural and cultural changes required under the Affordable Care Act to succeed in a new environment focused on quality and accountability," said Kylanne Green, president and CEO of URAC, in a statement. "Accreditation provides a competitive advantage for health care organizations by distinguishing themselves in the market while meeting industry needs at a crucial time of change."

The first program, Clinical Integration Accreditation, offers education and guidance for health care providers to achieve interdependent operations, care coordination, clinical management, and improved performance measures. The program focuses on the development of the organizational structure needed for clinical integration and applying evidence-based guidelines and best practices.

The second program, Accountable Care Accreditation, supports an advanced level of operations with a focus on total population health and improving health outcomes through care coordination of population groups. The program helps providers address patient centeredness and engagement, health information technology, quality management, population-based risk management, and case management.

To earn the accreditation, providers are independently evaluated, ensuring the achievement of accountability and quality under industry-vetted standards. URAC's clinical integration standards also align with Federal Trade Commission antitrust regulations. More information is available at www.urac.org or (202) 216-9010.

PSYCHIATRIC PRACTICE & MANAGED CARE

What to Consider When Contracting With Insurers

As you negotiate contracts with insurers, don't hesitate to ask for what you want, and be sure to read the final document before signing.

BY ELLEN JAFFE AND COLLEEN COYLE, J.D.

The changes to the psychiatry CPT codes that occurred at the start of this year present an excellent reason to renegotiate any insurance contracts that you're not entirely happy with. Even if the insurance plans provided crosswalks to accommodate the new codes for 2013, since most contracts stipulate which CPT codes will be covered by the health plan and the reimbursement for these codes, the possibility that the codes in your original contract no longer exist creates an ideal opportunity to reopen contract negotiations and perhaps improve the terms. (If instead of wanting to renegotiate, you feel you no longer want to do business with a particular insurance company, now is also a good time to affirmatively terminate your contract using the process specified in that contract.)

Keep in mind that until a contract is signed, its terms are open to negotiation. And don't worry about what others have told you about their experiences in talking with insurers. Each contract is different—even from the same company. A contract with one physician may be written at a time and under circumstances different from those for another physician.

APA's Practice Management HelpLine has heard from many members who didn't like the reimbursement rates they were offered by an insurer, but felt obligated to accept the contract because the insurer covered a large percentage of their current and potential patients. HelpLine staff have also heard from members who balked at the reimbursement they were being offered, refused to sign the contract, and were surprised (and gratified) to find the insurer then offered them a higher reimbursement rate. They may not have gotten the fees they wanted on the first "no", but they got way more than they were originally offered. Sometimes you have to be willing to say "no" more than once.

Contract Negotiation and Termination

Most health insurance companies operate as businesses, with the goal of minimizing expenses while maintaining or maximizing income and maintaining an adequate provider network for their subscribers. There is a shortage of psychiatrists willing to participate in insurance panels, so you may find that you have more leverage in negotiating a contract than you think. Remember, too, that a psychiatric practice is also a business. While your primary goal may be the successful treatment of your patients, your practice is your livelihood, and you shouldn't hesitate to make the best deal you can. Your ability to negotiate specific contract terms is really a function of supply and demand in your geographical area and your willingness to try to achieve better terms for yourself.

Even though you may feel uncomfortable rejecting the terms an insurer is offering, you should never agree to terms that you find onerous or fees that you find unsatisfactory—at least not at first. There is no risk in indicating your unwillingness to accept the terms being offered. If you do that and find that the insurer does not proffer anything more agreeable, don't feel embarrassed to say that you've changed your mind and are willing to accept the terms being offered.

If your negotiation fails to end in the terms you require and you no longer want to be part of an insurer's network, you must follow the process laid out in the contract for terminating your relationship. Most networks require formal written notice that you will no longer be a participating provider. Failure to provide this notice and refusing to take new network patients can be considered a breach of your contract. Also, your failure to terminate your relationship formally may hinder other psychiatrists' ability to negotiate their agreements with the insurer because the supply of available psychiatrists appears to be greater than it is. This can also create access problems for patients since the insurer will continue to claim you as a provider, and it will not add new providers because on paper its network seems adequate—even though in reality it is not.

Because many insurance companies are having trouble maintaining enough psychiatrists in their networks to meet enrollees' needs, they may make it difficult for psychiatrists to sever their relationship. APA's Practice Management HelpLine has received calls from members who were unable to get out of their contracts for months because an insurer maintained that it hadn't received faxes or e-mails in which the members' change in status was conveyed. We recommend that any notifications about a change in status with an insurer be done in writing, according to the terms set forth in the contract, and be sent by registered mail, return-receipt requested. This way you will have a record of the company's having received your request.

Sergey Ivanov

Contract Terms You Need to Know

- **Time:** Most contracts stipulate the fees that will be paid to in-network physicians for specific procedure (CPT) codes and which physicians will be paid for which CPT codes. For instance, prior to this year, some insurers reimbursed psychiatrists only for the psychiatry CPT codes, even though it was just as appropriate for psychiatrists to use the evaluation and management (E/M) codes (the 992xx series). Now that psychiatrists are required to use the E/M codes to code their medical work, it is essential that not only the codes in the psychiatry section of CPT be covered, but the E/M codes as well. The information about specific codes and their reimbursement rates is rarely found in the body of the contract you sign, but should be available in either the appendixes or attachments. Before you sign an initial contract or continue a current contract, be sure you find out which CPT codes you're permitted to use and how much you'll be paid for each code. Many contracts are "evergreen," meaning they automatically renew unless you affirmatively terminate, even if an insurer unilaterally changes the rates to your detriment.

- **Place :** Contracts should also stipulate the physician's status with the insurer in various settings. Some contracts provide that an in-network psychiatrist is in-network at every place of service, while others may just be for a specific setting. This is an issue that has proved problematic for some APA members who practice in clinics where many forms of insurance are accepted and who also have private practices in which they do not accept insurance. If the clinic's contract with an insurer says it covers the psychiatrist in all settings, and the psychiatrist sees a patient covered by that insurer in his or her private practice, the psychiatrist is an in-network provider and may be paid the in-network fees that were negotiated under the clinic contract. Even if the clinic's contract with the insurer does not stipulate that all places of service are covered, a psychiatrist who wants to be considered out-of-network in another setting must notify the insurer in writing of that desire.

- **Products:** Besides indicating which codes and places of service are covered, contracts also should indicate which specific products of the insurer are covered (that is, the HMO or PPO). Some contracts may state they are for "all products," present and future, and those products may or may not have different fee schedules. When you sign one of these agreements, you accept all products and all future products without actually knowing the terms of the future products or the fee schedules for them. With the advent of health exchanges, this provision could pose a problem. If the insurer creates a new health exchange product, you may inadvertently become part of that network as well and will be required to accept the fee schedule. You should review your contracts to determine whether such a clause is present and how it impacts you.

- **Arbitration and 'Choice of Law':** Other contract issues to watch out for are arbitration provisions and "choice of law." Contracts often contain provisions requiring you to arbitrate a dispute. In effect, you give up your right to have a court determine the resolution. Contracts also have a "choice of law" provision; typically, the company decides to follow the law in the jurisdiction where it is located and requires that arbitration take place there rather than where you are located. You may not want to go to California to arbitrate a dispute if you practice in New York, so check that these provi-

*see **Insurers** on page 20*

Ellen Jaffe is a Medicare specialist in APA's Office of Healthcare Systems and Financing. Colleen Coyle, J.D., is APA's general counsel.

Call me for a quote.

Medical professional liability policies can vary widely from one company to the next. It is important for psychiatrists to know the full – and accurate – story on a policy. Whether it is reviewing the difference between occurrence and claims-made policies or explaining how another policy might leave the doctor with an uninsured risk, I have done my job when I help psychiatrists evaluate their options to make the right choice.

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GOVERNMENT NEWS

Psychiatrists Can Help Patients Qualify For ADA Accommodations

Psychiatrists can help their patients obtain adjustments at work in light of their disabilities, but must plan ahead to do it in the most effective way.

BY AARON LEVIN

Question: When is a note from the doctor a federal case?

Answer: When it serves to support a patient's claim for reasonable accommodation at work under the Americans With Disabilities Act (ADA).

This summer, the U.S. Equal Employment Opportunity Commission (EEOC) issued a fact sheet explaining what mental health care providers can do when patients request their help on this ADA issue.

"Reasonable accommodation" means some change in the usual way work is performed "that enables an individual to do a job, apply for a job, or enjoy equal access to a job's benefits and privileges," according to the fact sheet.

And the psychiatrist's role involves more than writing a note to the employer reporting on a diagnosis or treatment, said Colleen Coyle, J.D., APA's general counsel.

"The doctor must understand the essential responsibilities of the person's job and what, if any, disabilities affect performing that job," Coyle told *Psychiatric News*.

The ADA looks at patients "in their native state," as if they were untreated, to determine the existence of a disability and the need for accommodation, said Coyle. For instance, a patient may have difficulty paying attention for long periods of time and has a job stocking shelves: Does that symptom affect job performance? The two must relate.

The disability need not be extreme, according to the EEOC, just substantially limiting, meaning something that makes work activities "more difficult, uncomfortable, or time-consuming," compared with what most people experience. The EEOC was silent on what degree of difficulty, discomfort, or timing would be "substantially limiting," however.

Accommodation must be "reasonable" and not cause "significant financial or operational difficulty" to the employer. That might include (but not be limited to) time off work for the employee to receive treatment (to be made up later), modified work schedules, or changes in supervision such as providing written rather than oral instructions to the employee.

The psychiatrist needs the patient's permission to write to or talk with the employer, said Coyle. Information disclosed should concern only the matter of the disability and possible accommodation, because legal and ethical standards of patient confidentiality remain in place.

Upon the patient's request, the psychiatrist should discuss with the patient the nature of the job and suggest possible accommodations that would be sufficient to get work done. The psychiatrist's proposed accommodation is still just a suggestion, however. The employer and the patient may be able to arrange for an alternative that accomplishes the same goals, if they choose.

Documentation—in plain language—should describe the following factors, according to the EEOC:

- The clinician's professional qualifications and nature and length of the relationship with the patient.
- The patient's diagnosis,
- The patient's functional limitations in the absence of treatment.
- The need for reasonable accommodation.
- Suggested accommodations for the disability.

But that's not all, said Coyle.

"Show the patient the letter you're sending to the employer and get them to OK it," she said. "You don't want to recommend something the patient is unwilling to do or that would inhibit the patient from doing the job."

The clinician must strike a balance. If the bar is set too high for the patient's abilities and he or she cannot complete the tasks agreed to, or will not accept the reasonable accommodation offered, then the employer may have the right to terminate the employee, Coyle said.

Finally, while on the subject, psychiatrists might also take this moment to consider how well their own clinic settings and procedures accommodate patients and others with disabilities, Coyle added. PN

"The Mental Health Provider's Role in a Client's Request for a Reasonable Accommodation at Work" is posted at http://www1.eeoc.gov/eeoc/publications/ada_mental_health_provider.cfm.

RESIDENTS' FORUM

Building a Bridge Between Cardiology, Psychiatry

BY MICHAEL ASCHER, M.D., AND DAVID HSU, M.D.

At the World Psychiatric Association Thematic Conference on Intersectional Collaboration and 4th European Congress of the International Neuropsychiatric Association last December, Dr. Angelos Halaris, a professor of psychiatry at Loyola University School of Medicine in Chicago, proposed a new subspecialty called "psychocardiology."

While we recognize potential systemic limitations to creating such a specialty at this time, we applaud Dr. Halaris for proposing such a bold idea. As trainees in psychiatry, we appreciate that the two fields intersect in a formidable way, and the importance of collaboration between the two specialties cannot be overemphasized.

Research literature has shown that

patients who suffer from mental illness are at higher risk for developing cardiovascular disease (CVD). Studies have also shown that depressive symptoms may augment inflammatory markers (IL-6 and CRP), which may play a role in the progression of coronary artery disease.

While many of the risk factors for CVD—such as nicotine dependence, substance use disorders, depression, inactivity, poor primary medical care, obesity, diabetes, hyperlipidemia, and hypertension—are modifiable, engaging people with one or more of these factors in the most therapeutic way can be extremely challenging.

To make matters worse, many of the atypical neuroleptic medications that our patients rely on can lead to significant metabolic disturbances, QT prolongation, and torsades de pointes.

In addition, research has found that many individuals suffering from cardiovascular disease have increased levels of depression and anxiety symptoms. While the jury is still out regarding the causal pathways, the great need for more cardiac screening and preventative care for individuals living with mental illness is clear.

Engaging these vulnerable patients in conversations about health, the importance of medication adherence, and treatment planning is paramount. It is not uncommon for cardiologists to be the first clinicians to elicit symptoms of depression, anxiety, and other psychiatric symptoms from patients. These same patients may be hesitant to seek consultation from a psychiatrist for a more in-depth workup. Alternatively, psychiatric patients often have difficulty attending cardiology appointments and adhering to cardiac recommendations in a meaningful way.

Psychiatrists and cardiologists are in the position to develop relationships that are mutually beneficial resulting in improved patient outcomes. Specifically, psychiatrists can take the time to reach out to cardiologists and offer ways to quickly screen, assess, and facilitate mental health care with their patients in the most optimal way. Psychiatrists can also share the theory and basic techniques of motivational interviewing with cardiologists. This knowledge has the potential to increase patient adherence to treatment plans and facilitate their movement toward positive changes. APA and the American Heart Association have already published joint guidelines on management of depression in heart disease (http://m.circ.ahajournals.org/content/118/17/1768.short).

Since trainees often work in the general hospital and may be called to consult on patients, residency is a prime time for collaborative care and interdisciplinary education. We propose having a dialogue or a luncheon between the two special-

see ***Residents' Forum*** *on page 33*

Michael Ascher, M.D., is an addictions fellow at the University of Pennsylvania. David Hsu, M.D., is a geriatric psychiatry fellow at the Partners HealthCare Program through Harvard Medical School.

COMMUNITY NEWS

Blog Brings Doctors, Patients Together To Address MH Issues

An online forum helps clinicians and patients become better advocates during a period of dramatic change in the U.S. health care system.

BY VABREN WATTS

As preparations for the Affordable Care Act (ACA) rev up as more of the law goes into effect, some patients with mental illness and the clinicians who treat them are making sure that their voices are being heard—particularly by each other.

One vehicle they are using to communicate their needs and concerns is the Care for Your Mind (CFYM) blog, an online forum for people with mood disorders—along with their families and psychiatrists—to discuss the mental health care system and changes that may affect them under health care reform.

"Unfortunately, people living with mental illness do not have the political clout to address changes in their health care. Their voices are often stigmatized or dismissed," said William Gilmer, M.D., a mood disorder specialist and an associate professor of clinical psychiatry at Feinberg School of Medicine at Northwestern University. "CFYM provides an opportunity for mental health public-policy discussions between clinicians, patients, and other interested constituents so that we, as a unit, may provide the best insight to key stakeholders and lawmakers," he explained to *Psychiatric News*. Gilmer stressed that dialogue between all parties is important to ensure that the top priorities of those living with psychiatric disorders are met.

Launched May 1, CFYM is a joint venture by the Depression and Bipolar Support Alliance (DBSA) and Families for Depression Awareness (FFDA).

The blog has had close to 5,500 visitors, including 1,500 who arrived at the site via Facebook or Twitter referrals. "We wanted the CFYM blog to be accessible on as many platforms as possible—including Facebook and Twitter—in order to reach the masses of those most affected by mood disorders," said DBSA President Allen Doederlein, who noted that he has had a mood disorder diagnosis since age 17. He explained that the voices of people with mood disorders as well as the people who care for them need to be front and center in this transition period for the health care system.

According to the National Institute of Mental Health, mood disorders affect 21 million people in the United States annually, are linked to 90 percent of the nation's suicides, and cost $23 billion a year in lost workdays. Despite the prevalence of these illnesses and the serious sequelae, only about half who need care receive adequate treatment.

Susan Weinstein, J.D., director of programming and marketing for the FFDA, told *Psychiatric News,* "We are looking at the Affordable Care Act to open a lot of doors for people to get mental health care access. After we achieve access, then we are seeking quality."

Weinstein said that some of the issues often discussed on CFYM concern inadequate access to medication and health care providers, which is often amplified by geographical limitations, language barriers, and cultural challenges. "So we are really addressing a set of complex issues that our health care system is currently approaching," she said.

Cheryl Magrini, Ph.D., vice president of the DBSA Board of Directors, said the blog provides a wealth of valuable information. "The ACA can be so confusing. . . . I'm finally learning about what it means for people to get access to insurance and what actions to take that will lead us down the quickest road to access it," she told *Psychiatric News*. Magrini, who said she was diagnosed with bipolar I disorder in 2006, explained that she appreciates the blog for not being a platform for complaints by those with mood disorders or a "you [as a patient] should do this" website for psychiatric experts. "It is a true place for dialogue and conversation between patient, psychiatrist, and legislator," she said.

As for Gilmer, he said that physicians should be mindful of the intangible things that affect everyday lives of patients. "I think that clinicians should go to the website for issues that are concerns for our patients," he said. "It helps us, as clinicians, to become better advocates and to help our patients become better advocates for themselves during this transitional period of our health care system." PN

Information about Care for Your Mind is posted at http://careforyourmind.org/.

Women M.D.s Still Paid Less Than Male Colleagues

As more women enter high-paying, traditionally male-dominated specialties, such as orthopedic surgery, there may be more equalization of pay between them and their male counterparts.

BY JOAN AREHART-TREICHEL

There has been a substantial reduction in the size of the earnings gap separating male and female workers in the United States, from 30 percent in 1987 to 15 percent today. Thus, Anupam Jena, M.D., Ph.D., an assistant professor of health care policy and medicine at Harvard Medical School, anticipated that these positive findings would translate into closing the pay gap between male and female physicians as well.

This is, however, not what he and his colleagues found in a recent study, he told *Psychiatric News*. If anything, the pay gap has grown wider, they reported in research published online September 2 in *JAMA Internal Medicine.*

Using data from more than 6,000 physicians from 1987 through 2010, Jena and colleagues analyzed trends in average annual earnings from three time periods—1987 to 1990, 1996 to 2000, and 2006 to 2010. They took possibly confounding factors such as age, hours worked, years of experience, and state of residence into consideration. Dollar values were normalized to 2010 dollars.

They found that male physicians earned $33,840 (20 percent) more than female physicians in the 1987 to 1990 period; $34,620 (16 percent) more than female physicians in the 1996 to 2000 period, and $56,019 (25 percent) more in 2006 to 2010.

Assuming that these findings are an accurate picture of the physician pay situation, Jena suggested several possibilities for the persistence of the pay gap. The gap may be attributable, at least in part, to "different preferences of female physicians, such as a desire to work in jobs within a given specialty that are more lifestyle-friendly and that consequently require a tradeoff between income and lifestyle," he noted.

Another explanation could be "a relative lack of access to particular specialties or types of job opportunities. . . . We know that because women comprise a larger fraction of medical school graduates today than 20 years ago, women are more prevalent in all specialties. However, several are still heavily male-dominated, and these tend to be those that are higher paying, on average."

Molly Cooke, M.D., a professor of clinical medicine at the University of California, San Francisco, suggested in an accompanying commentary that traditional "old boys networks" could also be affecting the pay levels of women physicians.

All things considered, "The report and accompanying commentary provide more data in support of what I have experienced and observed in almost 50 years of medical practice," former APA President Carolyn Robinowitz, M.D., commented to *Psychiatric News*.

So what might women physicians do to close the pay gap?

"We first have to understand what the source of the gap is," Jena told *Psychiatric News*. "If the gap is simply due to differences in preferences between male and female physicians for the type of specialty to work in and the type of practice to join, this isn't necessarily an issue that needs addressing. However, we suspect that some of the gap we are seeing is unrelated to the choices women physicians would make if they did not perceive certain specialties to be male dominated. I think that the most important step has already been taken. Female physicians now comprise more than 50 percent of all medical graduates, and within the next decade will likely account for nearly 50

see ***Women*** *on page 31*

MEMBERS IN THE NEWS

Joan Arehart-Treichel

Layan Zhang, M.D., stands in front of the new St. Elizabeths Hospital in Washington, D.C., where she is a psychiatry resident.

Psychiatry Resident From China Makes Rewarding Transition to U.S. System

Whether she stays in the United States or returns to China, Layan Zhang, M.D., is passionately committed to becoming a good psychiatrist, and especially a good child and adolescent psychiatrist.

BY JOAN AREHART-TREICHEL

Layan Zhang, M.D., stands in front of historic St. Elizabeths Hospital in Washington, D.C., where Civil War soldiers were once quartered, the wind whipping through her hair and a pensive look on her face.

Yes, it is far from the village in the People's Republic of China where she was born and grew up. But here she is, a second-year psychiatry resident at the new St. Elizabeths Hospital, which is only a short walk away from the old one.

And, all things considered, she is pleased that her path in life has brought her here, she says.

Zhang is from Shanxi Province, which is in northwest China and separated on its northern flank from Inner Mongolia by the Great Wall of China. Her parents were farmers, and she recalls "walking through the fields, down a little path, I felt free and fresh." She also has a brother and sister. "The one-child policy applies to all citizens in China," she explains. "However, it was a bit flexible for people in the villages during the early 1980s." She adds that her parents were warm and supportive and did not drive her to succeed academically. She is very grateful for that, she says.

Because of her father's encouragement and her own interest, she applied to Shanxi Medical University after graduation from high school. One can go directly from high school into medical school in China, she points out. She graduated in 2003.

Training Followed at Yale's Sister School

After medical school graduation, she attended the Xiang-Ya Medical School of Central South University to study clinical psychology. The university was founded by the Yale-China Association in 1914. It is the only sister university of Yale University in China and a leading university in the mental health field in China. She earned a master's degree in clinical psychology in 2006.

From 2006 to 2008, she worked as a rehabilitation psychologist/psychiatrist at Beijing Bo-Ai Hospital of the China Rehabilitation Research Center, which is the largest rehabilitation facility in China.

In 2008, after her husband received his Ph.D. in molecular biochemistry from Peking University in Beijing, he was offered a research position at the University of Michigan. So Zhang and her husband moved to the United States. During the next several years, she worked hard to achieve her "American dream"—becoming a psychiatrist in the United States.

For example, she enrolled in a community college to improve her English and got involved in various community activities to learn about the local culture. She volunteered in a medical clinic as a nurse assistant and observed inpatient clinical practice to become familiar with the American medical system. She volunteered as a research assistant in the child subdivision of the University of Michigan's Department of Psychiatry. And, during this period, she gave birth to a boy.

In 2012, she was accepted into the psychiatry residency program at St. Elizabeths Hospital. She, her husband, and their son moved to Washington, D.C. In June her husband started work as a cancer researcher at the National Institutes of Health.

Good Things Have Happened

It is now a year since Zhang started her psychiatry residency at St. Elizabeths, and she reports many positive experiences.

St. Elizabeths is the District of Columbia's public psychiatric facility for individuals who have serious and persistent mental illness and need intensive inpatient care to support their recovery. In 2010, the hospital moved into a new state-of-the-art facility that incorporates best practices in inpatient mental health care. The new building's therapeutic design includes bright and airy living and treatment areas, green spaces off each patient unit, and enclosed courtyards. In brief, it is a congenial environment for doing a psychiatry residency.

Zhang is pleased with the supervision she is receiving at St. Elizabeths. For instance, "James Hutchinson, M.D., is a wonderful psychiatrist and psychoanalyst," she says. "He is my mentor and also supervising me on individual psychotherapy with a patient."

Exposure to different types of patients has been a valuable educational experience, she notes. There are about 300 psychiatric patients in St. Elizabeths, including patients with acute and chronic conditions, forensic and civil patients, adult and geriatric patients. "Here, one can learn pretty much all of the psychopharmacology knowledge you need as a psychiatry resident," she says.

Since she started her residency training last year, Zhang has been involved in several research projects. She began doing research with Teodor Postolache, M.D., of the University of Maryland on the "association between seasonality and evening chronotype in the Old Order Amish." She presented her study results at the APA annual meeting in San Francisco in May and during a poster session at the recent annual meeting of the Society of Biological Psychiatry. She is working on another project involving depression screening in a primary care setting in China, which is part of a research program in global mental health initiated by psychiatrist Eliot Sorel, M.D., of George Washington University.

But Zhang has faced challenges as well.

Sometimes she is too "soft," she admits. "Yet being pliable also helps her build good therapeutic alliances with patients," Farooq Mohyuddin, M.D., head of the psychiatry residency program at St. Elizabeths, told her. "It is a rare combination to have a resident who is well versed in research and also has excellent clinical acumen."

She also possesses other strengths that serve her well as a psychiatry resident, Hutchinson notes. "She is thoughtful and observant, adventurous in what she is willing to try, and passionately committed to what she is doing. She quietly and constantly tries to integrate her experiences in and out of the hospital."

As for the future, once she completes her residency training, Zhang plans on getting specialty training to become a child and adolescent psychiatrist.

And will she, her husband, and their little boy ultimately remain in the United States or return to China? "We're open to either," she says. "We'll see!" PN

To watch a video interview with Layan Zhang, M.D., on St. Elizabeths residency program, scan the QR code at left or go to http://youtu.be/jqHPypPuJg8.

APA, AADPRT Offer Course On Professionalism on Internet

This new course will help psychiatrists proactively navigate the Internet and use social media without worry.

BY MARK MORAN

An early career psychiatrist discovers a highly negative review of him on a physician-rating website. He is worried about what the review will do to his professional reputation and considers whether to fabricate several more positive reviews using pseudonyms.

A male psychotherapy patient angrily confronts his male therapist with material he found on the Internet, which reveals that the treating psychiatrist is homosexual. The psychiatrist is not "out" to his patients and had been unaware of the material on the Internet about him.

Those are two vignettes, drawn from real-life scenarios, that illustrate the ethical, legal, and clinical dilemmas raised by the interface between the practice of medicine and online technology. They are among the cases addressed in a new online continuing medical education course, "Professionalism and the Internet," available on APA's online learning management system, supplemented with the perils and pitfalls of the digital age in medical practice. (Other members of the task force were Sheldon Benjamin, M.D., Joan Anzia, M.D., Bob Boland, M.D., Nadyah John, M.D., Jim Lomax, M.D., and Tony Rostain, M.D.) What she and her colleagues came up with is a compilation of vignettes, 15 of which are in the online course on APA's learning

The course material was developed by a task force of the American Association of Directors of Psychiatric Residency Training (AADPRT). Revenue from the course, which costs $19, will be shared by AADPRT and APA.

"Online technology has become a part of all of medicine—not only administrative aspects, but in working with patients," said Sandra DeJong, M.D., chair of the AADPRT task force that developed the course material. "Patients can Google-search their physicians and vice-versa. And psychiatrists are communicating with their patients via text and e-mail. Yet there are very few guidelines for how to do this appropriately and professionally."

DeJong said that the course had its origins in a workshop at the 2010 AADPRT annual meeting after she and other training directors began hearing concerns from residents about the problems and dilemmas they experience related to digital technology. At the workshop, some general information was presented, and comments were invited from the audience.

It opened the floodgates, as audience members—residents, training directors, and program coordinators—related story after story about the legal, ethical, and clinical perils associated with online technology in psychiatric practice. "We were overwhelmed with vignettes," DeJong said.

In response to the outpouring, then-AADPRT President Sheldon Benjamin, M.D., appointed DeJong head of a task force charged with developing a curriculum to help psychiatrists navigate articles from scholarly journals as well as the lay media, PowerPoint slides, organizational guidelines, sample institutional policies, and other resources.

Clearly, too, the best venue to offer a curriculum about online technology would be, naturally, online. Present at the workshop in 2010 was APA Director of Education Deborah Hales, M.D., who saw a course on professionalism and the Internet as a natural offering for APA's online learning management system. So the partnership between AADPRT and APA was, as DeJong said, "a perfect fit."

Hales said the partnership is a model for what APA would like to do with other allied groups, offering APA's online learning management system as a portal for CME products of all kinds that would be useful to lifelong learning and maintenance of certification (MOC).

She also emphasized that the learning management system is a member benefit of significant value: it offers a convenient, easy-to-use system for archiving CME courses and credits for instant access and retrieval. The APA CME transcripts are sent regularly to the American Board of Psychiatry and Neurology (ABPN), so that those participating in MOC do not

see ***Internet*** *on page 20*

What Would You Do?

So about that psychiatrist who read the poor review of himself online and is considering writing a few rave reviews under a pseudonym? As part of the APA-AADPRT online CME course on "Professionalism and the Internet," psychiatrists are asked: "How should the psychiatrist proceed?" Here are your choices:

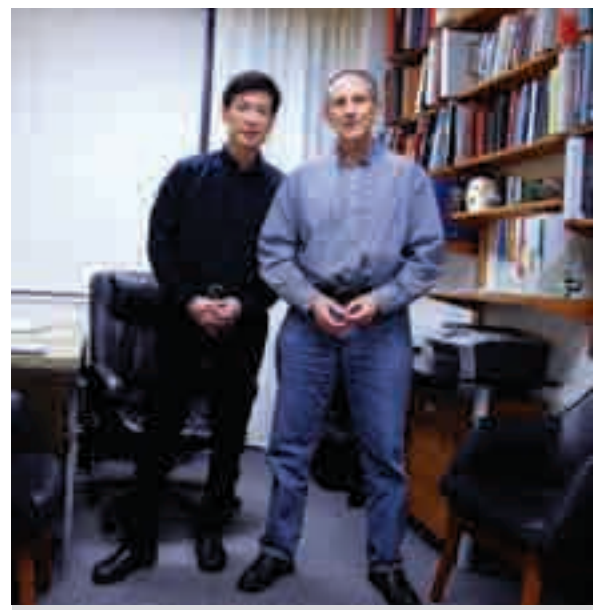
- Submit favorable reviews using pseudonyms.
- Request other patients to submit their own reviews.
- Contact the website and demand that the review be removed.
- Engage an attorney and begin legal action against the patient.
- Ignore the review and take no action.

FROM THE EXPERTS

Limbic Encephalitis: The Emperor Really Has New Clothes

BY TREVOR HURWITZ, M.B., CH.B., AND WARREN LEE, M.D., PH.D.

A 23-year-old woman presented to the emergency department with vague symptoms that began a week prior to admission. She was, however, unable to give much history. Her husband and mother reported that she was confused, had memory problems and poor concentration, and was unable to make decisions. She also appeared depressed, irritable, and anxious. She was noted to be talking to herself on more than one occasion. There was no medical or psychiatric history, no new psychosocial stressors, and no history of street-drug abuse. She was working at a desk job in a large corporation and was seen by the on-call psychiatry resident, who found her alert and responsive, but unwilling or unable to respond to questions.



Warren Lee, M.D., Ph.D., and Trevor Hurwitz, M.B., Ch.B.

She was admitted to a psychiatry ward with a differential diagnosis that included first-episode psychosis, depression with psychotic features, and anxiety NOS. She was started on olanzapine. Her confusion worsened, and she became stuporous, uncommunicative, and febrile, with a temperature of 38.7 degrees Celsius. An urgent neurological consultation was sought as her presentation at that point was now most consistent with a CNS inflammatory disease such as a meningoencephalitis.

She was started empirically on IV ceftriaxine, acyclovir, and metronidazole. However, blood and CSF chemistries and cytology were all normal, as were bacterial and viral studies. Her brain MRI was normal, and her EEG showed bilateral slowing but without epileptiform activity, a finding consistent with an organic encephalopathy. Blood and CSF samples then returned positive for anti-NMDA (N-methyl D-aspartate) receptor antibodies. She was started on IVIG and

see ***From the Experts*** *on page 30*

Trevor Hurwitz, M.B., Ch.B., and Warren Lee, M.D., Ph.D., are the coeditors of the *Casebook of Neuropsychiatry*, published by American Psychiatric Publishing. APA members may purchase the book at a discount at http://www.appi.org/SearchCenter/Pages/SearchDetail.aspx?ItemId=62431.

MED CHECK

BY VABREN WATTS

CVS Monitors Physicians Who Overprescribe Painkillers

Opioid prescriptions increased 300 percent from 1999 to 2010, and there was a 400 percent increase in deaths related to drug overdose during the same period. To combat the national prescription drug abuse epidemic, CVS Caremark has created a program that will monitor practices of clinicians who prescribe highly addictive drugs.

Reported in the *New England Journal of Medicine,* CVS Caremark evaluated its pharmacy submission records on 42 physicians with extreme and apparently unjustifiable practices of prescribing ***hydrocodone***, ***oxycodone***, ***alprazolam,*** or ***methadone***. The clinicians were asked to provide additional information about their prescription patterns.

Only six identified legitimate reasons for their unusual prescribing practices; the rest failed to respond or gave insufficient reasoning for their actions. As a result, CVS Caremark suspended controlled substance dispensing for 36 providers.

"While this program is not a comprehensive solution to prescription drug abuse, it is an important first step that is in line with the ethical duty pharmacists have to ensure that a prescription for a controlled substance is appropriate," said Mitch Betses, R.Ph., CVS's senior vice president of pharmacy services and a coauthor of the report. "We know there are many ways to fight prescription drug abuse, and we are committed to continuing to identify solutions to stop the improper use of controlled substances."

Betses M, Brennan T. "Abusive Prescribing of Controlled Substances—A Pharmacy View." 2013. NEJM. Aug 21 [Epub ahead of print] http://www.nejm.org/doi/full/10.1056/NEJMp1308222

Study Assesses Mortality Risk Of Numerous Psychotropics

There has been much debate on whether pharmacologic interventions increase mortality risk in patients with severe psychiatric illness. A study in *JAMA Psychiatry* attempted to clarify the issue.

Lead author Arif Khan, M.D., of the Northwest Clinical Research Center in Bellevue, Wash., and colleagues analyzed mortality rates of nearly 100,000 adults with mental illness who participated in 28 drug clinical trials submitted to the FDA from 1990 to 2011. The study examined mortality rates of individuals with or without mental illness and those receiving antipsychotics or placebo.

The results showed that patients with schizophrenia, depression, or bipolar disorder had the highest risk for mortality among individuals with psychiatric illnesses and those without psychiatric illness. In addition, the study found that administration of atypical antipsychotics, selective serotonin reuptake inhibitors, and selective serotonin-norepinephrine reuptake inhibitors did not increase risk of mortality when compared with placebo, whereas heterocyclic antidepressants, such as ***imipramine*** and ***amitryptiline***, did. Suicide accounted for 41 percent of the deaths.

The authors said that "the FDA may have data on more than 20,000 patients for individual psychotropic agents, but the SBA [Summary Basis of Approval] reports in general include data on approximately 3,000 to 5,000 patients, with even fewer data in supplemental new drug applications. Further detailed analysis of the clinical trial data by the FDA or the pharmaceutical companies is required before any firm conclusions can be drawn."

Khan A, Faucett J, Morrison S, Brown WA. "Comparative Mortality Risk in Adult Patients With Schizophrenia, Depression, Bipolar Disorder, Anxiety Disorders, and Attention-Deficit/Hyperactivity Disorder Participating in Psychopharmacology Clinical Trials." 2013. JAMA Psychiatry. Aug 28. [Epub ahead of print] http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/jamapsychiatry.2013.149

Mylan Granted FDA Approval For Generic Antidepressant

In August Mylan Inc. confirmed that it received Food and Drug Administration (FDA) approval of its bioequivalence study of 300 mg ***bupropion hydrocholoride (HCl) extended-release (ER) tablets***. Bupropion HCl ER tablets are the generic form of Wellbutrin and are used to treat depression.

Mylan submitted the study results in April in response to an FDA request for all generic drug companies marketing bupropion ER tablets to conduct a fasting-state comparison study with Wellbutrin. Mylan's bupropion HCl tablets were introduced to the United States market in 2010.

Reducing Antipsychotic Dosage Improves Cognitive Function in Some Schizophrenia Patients

Schizophrenia Bulletin published a study evaluating the impact of dose reductions of the atypical antipsychotics ***risperidone*** and ***olanzapine*** in 61 individuals with stable schizophrenia. The patients were divided into two groups: those receiving 50 percent less of their initial dose of risperidone or olanzapine, and those who maintained a constant dose. Cognitive decline was assessed with the Repeatable Battery for the Assessments of Neuropsychological Status (RBANS) and the Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).

At the six-month follow-up, the reduction group showed significantly greater improvement in total RBANS and DIEPSS scores than the constant-dose group.

According to the researchers, it was the first study to show how dose reduction of antipsychotics can be beneficial in improving cognitive function in patients with stable psychosis.

Takeuchi H, Suzuki T, Remington G, et al. "Effects of Risperidone and Olanzapine Dose Reduction on Cognitive Function in Stable Patients With Schizophrenia…." 2013 Schizophr Bull.;39(5):993-8. http://schizophreniabulletin.oxfordjournals.org/content/39/5/993.long PN

Disability

continued from page 12

and begin active treatment for it. Often this is done via a person's health insurance.

Q *Finally, if you could give psychiatrists only one piece of advice about workplace disability leave due to depression and return to work afterward, what would it be?*

A That the employer is not the enemy in the process. We employers are just as invested as psychiatrists in patients' feeling better and being functional. Actually, I tried to underscore this point before the APA Assembly—that if psychiatrists saw us employers as partners in the process of healing, it would probably be beneficial for everyone involved. PN

To watch this interview with Clare Miller, director of the Partnership for Workplace Mental Health, and for more information about Pendler and the partnership, scan the QR code at left or go to http://youtu.be/jLe7zJdrPyw.

Internet

continued from page 19

have to reenter credits needed to meet ABPN requirements. Moreover, CME credits automatically entered into the system through APA CME activities will not be audited by the ABPN. Psychiatrists are able to enter CME credits obtained elsewhere into their records, but self-reported credits may be subject to audit.

Participants enrolled in "Professionalism and the Internet" who wish to earn AMA PRA Category 1 Credit or a certificate of participation can do so by completing all sections in the course outline, including the evaluation. An opportunity for decision making is provided following each of the vignettes; a passing score of 60 percent must be achieved. Retakes are available for each assessment.

After evaluating the program, course participants will have an opportunity to claim hours of participation and print an official CME certificate showing the date of completion and hours earned. Based on anecdotal response, the course should be popular. And increasingly, issues around use of the Internet are becoming risk-management issues for physicians.

"Everywhere we go, we hear that people need help on how to manage these very difficult ethical, legal, and clinical issues that come up when using Internet technology in our clinical work as psychiatrists," DeJong told *Psychiatric News.* "A study of data from the Federation of State Medical Boards found that over 90 percent of state boards have had complaints filed around these issues, and they are increasingly taking action against physicians for these kinds of issues. So it's an important risk-management aspect of our ongoing continuing medical education." PN

APA's online learning management system can be accessed at www.apaeducation.org.

Insurers

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sions are not designed to make dispute resolution so inconvenient or expensive for you that you would be discouraged from using them.

Before You Sign a Contract

It is important that psychiatrists review and understand every aspect of a contract before signing it. This includes all attachments. Don't automatically accept what the insurer gives you as terms. Try to negotiate. Always check with your malpractice carrier to make sure nothing in the contract conflicts with your policy. And always check with your lawyer. Each psychiatrist's situation has its own nuances, and no one "model" contract can protect all of them equally. Don't sign any contract until you're sure you thoroughly understand what you're agreeing to. PN

If you have questions about contracting, contact APA's Practice Management HelpLine at (800) 343-4671 or hsf@psych.org.

Comorbid Illnesses Increase Service Use by Bipolar Patients

Additional psychiatric comorbidities among patients with bipolar disorder are found to increase the service utilization rate by 25 percent.

BY VABREN WATTS

People with bipolar disorder are three times more likely to have at least one medical comorbidity than are individuals with other psychiatric disorders. And neglect of counseling and medical services to alleviate impairments associated with the bipolar disorder often results in worse outcomes of both the psychiatric and general medical illnesses.

A study published online August 15 in *Psychiatric Services in Advance* investigated the use of medical and counseling services among outpatients with bipolar disorder in an effort to identify factors that contributed to service underutilization in this population.

According to the study, led by researchers at the departments of psychology and psychiatry at Massachusetts General Hospital (MGH), previous reports of therapeutic service utilization for individuals with bipolar disorder were inconsistent and limited to populations of military veterans.

"This study furthers the literature by examining predictors of service use in a broader [bipolar disorder] population at high risk for underutilizing services," said lead author Louisa Sylvia, Ph.D., an assistant director of psychology in the MGH Bipolar Clinic and Research Program. She told *Psychiatric News* that this is the first study to assess the differences in services utilization among individuals receiving personalized care in the presence or absence of the mood stabilizer, lithium.

The study was based on the Lithium Treatment–Moderate Dose Use Study (LiTMUS) design—a broad population-inclusion model used to assess the efficacy of moderate doses of lithium in the context of optimum personalized and guideline-informed care. The six-month multisite study collected data on 236 subjects with bipolar I disorder, diagnosed in accordance with *DSM-IV* criteria, to compare service use by those receiving or not receiving lithium treatment.

Service use was assessed by the Cornell Service Index, a standardized measure of health-service use among adults with cognitive impairment. Every medical and psychotherapeutic visit or hospitalization—regardless of duration—counted as one service used; also counted were visits with religious leaders, counselors, and peer supporters. In addition, the study took into account age, gender, duration in the United States, marital and employment statuses, and diagnoses of psychiatric and general medical comorbidities.

MGH Photo Lab

Louisa Sylvia, Ph.D., believes that clinicians treating individuals with bipolar disorder should be aware that there are certain demographic characteristics that may increase the likelihood that patients will not seek needed services.

The results showed no difference between services used by patients who took lithium and those who did not. However, severity of bipolar disorder as measured by the Clinical Global Impression Scale for Bipolar Disorder Severity was associated with a 13 percent increase in overall service utilization—including medical and counseling services.

In addition, outpatients with higher depressive and mania scores on the Montgomery-Asberg Depression Rating Scale and Young Mania Rating Scale had a 15 percent and 25 percent increase, respectively, in rates of service used. Interestingly, each additional psychiatric comorbid disorder resulted in a 25 percent higher rate of overall services used, a 35 percent increase in counseling services used, and an 11 percent increase in medical services used.

"Psychiatric comorbidities, particularly anxiety disorders, predicted higher rates of using all treatment services, further suggesting that individuals with more comorbid diagnoses have more insight into their need for help and thus seek more treatment services than individuals with just one diagnosis," the authors noted.

Sylvia told *Psychiatric News* that the study did have limitations, including using volunteer subjects who thus do not represent the entire population of patients with bipolar disorder, as well as using the Cornell Service Index, which cannot differentiate between use of multiple services and use of the same service multiple times.

"We hope the limitations highlighted in this paper are addressed by future researchers, as it seems clear that there are differences in service utilization among individuals with bipolar disorder, and thus, there is a need to better understand these differences to maximize equitable use of services in this clinical population," Sylvia concluded.

This research was funded by the National Institutes of Health. PN

"Use of Treatment Services in a Comparative Effectiveness Study of Bipolar Disorder" is posted at http://ps.psychiatryonline.org/article.aspx?articleid=1729158.

DSM-5 SELF-EXAM

Obsessive-Compulsive and Related Disorders

The chapter on obsessive-compulsive and related disorders is new in *DSM-5* and reflects the increasing evidence of these disorders' relatedness to one another in terms of a range of diagnostic validators as well as the clinical utility of grouping these disorders in the same chapter. New disorders include hoarding disorder, excoriation (skin picking) disorder, substance/medication-induced obsessive-compulsive and related disorder, and obsessive-compulsive and related disorder due to another medical condition.

The "insight" specifier for obsessive-compulsive disorder has been refined in *DSM-5* to allow a distinction between individuals with good or fair insight, poor insight, and "absent insight/delusional" obsessive-compulsive disorder beliefs (that is, complete conviction that obsessive-compulsive disorder beliefs are true). For body dysmorphic disorder, an additional diagnostic criterion describing repetitive behaviors or mental acts in response to preoccupations with perceived defects or flaws in physical appearance has been added to *DSM-5*, consistent with data indicating the prevalence and importance of this symptom. There is evidence for the diagnostic validity and clinical utility of a separate diagnosis of hoarding disorder, which reflects persistent difficulty discarding or parting with possessions due to a perceived need to save the items and distress associated with discarding them. Individuals with excoriation (skin picking) disorder present with recurrent picking of their skin, which results in skin lesions, and repeated attempts to decrease or stop skin picking. In *DSM-5,* other specified obsessive-compulsive and related disorder and unspecified obsessive-compulsive and related disorder diagnoses include conditions such as body-focused repetitive behavior disorder, olfactory reference syndrome, and obsessional jealousy.

The questions below are from *DSM-5 Self-Exam Questions: Test Questions for the Diagnostic Criteria,* which may be preordered from American Psychiatric Publishing at http://www.appi.org/SearchCenter/Pages/SearchDetail.aspx?ItemId=62467. The answers and rationales are posted at http://www.psychnews.org/pdfs/DSM-5_Self_Examination_QandA_13.pdf. The book, available in January 2014, contains 500 questions for all the categories of psychiatric disorders and includes Section III. The questions were developed under the leadership of Philip Muskin, M.D., a professor of clinical psychiatry at Columbia University College of Physicians and Surgeons. APA members may purchase the book at a discount.

1. A 52-year-old man presents to a psychiatrist on the advice of his primary care doctor with raw, chafed hands. He reports that he washes at least four hours a day, using abrasive cleansers and scalding hot water. Although he admits his hands are uncomfortable, he is entirely convinced that unless he washes in this manner, he will become gravely ill. Outside of his hands, a medical workup is unrevealing, and he takes no medications. Which of the following is the most appropriate diagnosis for this man?

a) delusional disorder, somatic type
b) illness anxiety disorder
c) obsessive-compulsive disorder with absent insight
d) obsessive-compulsive personality disorder
e) generalized anxiety disorder

see ***Self-Exam*** *on page 29*

CLINICAL & RESEARCH NEWS

Shared Decision Making Aids Parents Of Children With ADHD

Clinicians are urged to ask parents about their preferences and goals for their child's treatment for attention-deficit/hyperactivity disorder, a practice that is followed inconsistently.

BY VABREN WATTS

From organizations in New Hampshire to state mandates in California, the emphasis on involving patients and their families—alongside physicians—in making the best decisions for treating chronic illness has increased dramatically over the past decade. But is this the best practice for the well-being of patients? According to a study in the September 2 *Pediatrics*, it is.

Alexander Fiks, M.D., an assistant professor of pediatrics at the University of Pennsylvania, led a study investigating the impact of shared decision making in achieving parental goals for children with attention-deficit/hyperactivity disorder (ADHD).

"National guidelines for pediatrics, and more broadly 'good clinical practices,' have stressed the importance of asking families about their preferences and goals for treatment, but that's not being done consistently," Fiks told *Psychiatric News*.

Mark Wolraich, M.D., chief of the Section of Developmental and Behavioral Pediatrics at the University of Oklahoma Health Science Center, agreed. "Making sure to include patients and families in decision making is not a traditional role for clinicians, so it is still not very well done by many clinicians," he said in an interview.

As chair of the American Academy of Pediatrics (AAP) Clinical Practice Guideline Subcommittee on ADHD, Wolraich stated that the recent AAP toolkit for ADHD treatment—which strongly emphasizes ADHD as a chronic illness that requires shared decision making—included parental representatives from ADHD advocacy groups. He told *Psychiatric News* that "an important element is educating the patients and their families about ADHD and developing a treatment plan that best meets the patient's and their family's needs. The most effective way to do that is with [shared decision making]."

However, evidence to support the claim that shared decision making actually makes a difference in patients with ADHD is lacking, Fiks noted.

In the current study, Fiks and colleagues recruited 148 parents or guardians of children aged 6 to 12 with a diagnosis of ADHD. The children were not receiving combined medication and behavioral therapy at study initiation. To assess preferences and treatment goals, parents and guardians completed an ADHD Preference and Goal Instrument questionnaire at the start of the study and again after six months.

The questionnaire assessed the relationship between baseline treatment preferences and the decision to initiate pharmacological therapy (PT) or behavioral therapy (BT) in an effort to improve academic performance, behavioral compliance, and interpersonal relationships.

At the six-month follow-up, nearly 50 percent of children who were not receiving PT at baseline were taking medication—and 24 percent of those not receiving BT at baseline were being counseled for behavioral issues. The researchers found a correlation between parents whose baseline goals involved improving children's academic performance and initiation of PT in children, while those whose goals were to improve behavioral compliance and interpersonal relationships were more prone to initiate BT for their children.

Courtesy of Children's Hospital of Philadelphia

Alexander Fiks, M.D., says that clinicians should inquire about patients' preferences and goals for well-being during their initial visit.

Courtesy of University of Oklahoma Health Science Center

Mark Wolraich, M.D., believes that shared decision making is the most effective way of providing the best treatment to patients with ADHD.

At the study endpoint, concerns about academic and behavioral improvement were rated less important by parents whose children initiated PT and BT, suggesting that baseline goals were attained.

"Results suggest that assessing parents' preferences and goals, as prioritized in the AAP ADHD treatment guidelines, is useful for clinicians in understanding which treatment, if any, parents are likely to initiate for their children," the authors noted. Fiks added that the study also suggested that inquiring about patients' preferences and goals for treatment at baseline will help physicians choose a treatment that will promote better patient adherence.

R. Scott Benson, M.D., a child and adolescent psychiatrist and a member of the clinical faculty at Florida State University,

see ***Decision Making*** *on page 33*

Maternal Depression May Impact Brains of Unborn Children

Since depression in pregnancy has been linked with an abnormal right amygdala in newborns, and that brain region is involved in mood disorders, it's possible that depression can be transmitted from mother to child in utero.

BY JOAN AREHART-TREICHEL

Evidence that depression can be transmitted from a pregnant woman to her unborn child was published online August 21 in *Biological Psychiatry.*

Anqi Qiu, Ph.D., an associate professor of bioengineering at the National University of Singapore, and colleagues evaluated 157 women for depression when they were in the 26th week of pregnancy. The researchers used the Edinburgh Postnatal Depression Scale (EPDS), a 10-item self-report scale designed as a screening instrument for postnatal depression, but which also has been well validated for use in antenatal depression. The EPDS rates the intensity of depressive symptoms during the preceding seven days. Scores of 13 or higher indicate depression. Twenty-eight of the women scored within this range.

After the women's infants were born, the researchers used structural MRI imaging to evaluate the size of the amygdalae in the infants. They also used a technique called diffusion tensor imaging to determine the microstructure of the infants' amygdalae. The researchers were interested in evaluating this brain region in the infants because previous research has shown it to be associated with emotion regulation and depression. They reasoned that if maternal antenatal depression had an impact on the amygdala during gestation, it might make the fetus vulnerable to depression after birth.

Zffoto/Shutterstock

Maternal depression during pregnancy may alter the amygdala in the unborn child.

After taking household income, maternal age, maternal smoking exposure, postconceptual age at brain imaging, and birth weight into consideration, the researchers could find no difference in amygdala volume between the newborns of the 28 women who had been depressed during pregnancy and those of the 129 women who had not been depressed during pregnancy. However, they did find that nerve axons in the right amygdala in the newborns of the depressed mothers were significantly different from nerve axons in the right amygdala in the newborns of the nonde-

see ***Maternal*** *on page 33*

Keep It Simple

Forfivo™ XL provides a once-daily, bupropion 450 mg dose in a single tablet:

- Indicated for the treatment of major depressive disorder
- Forfivo XL is bioequivalent to three 150 mg tablets of Wellbutrin XL®[1]
- Most commercial drug plan patients expected to pay $28 or less for a 30-day supply[2]

Do not initiate bupropion therapy with Forfivo XL because the 450 mg tablet is the only available dosage strength. Use a lower-dose bupropion product for therapy initiation and dose titration.

ONCE-DAILY **450 MG**

Forfivo™ XL

(bupropion hydrochloride extended-release tablets)

Visit ForfivoXL.com to download Rx savings vouchers.

IMPORTANT SAFETY INFORMATION FOR FORFIVO XL

WARNING: SUICIDALITY and ANTIDEPRESSANT DRUGS; PSYCHIATRIC EVENTS and SMOKING CESSATION

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. 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. FORFIVO XL is not approved for use in pediatric patients.

PSYCHIATRIC EVENTS and SMOKING CESSATION: FORFIVO XL is not approved for smoking cessation treatment, but bupropion under the name ZYBAN® is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior.

CONTRAINDICATIONS

FORFIVO XL is contraindicated in:

- **Seizure disorder, because these patients may have a lower seizure threshold**
- **Patients treated currently with other bupropion products, because seizure incidence is dose-dependent**
- **A current or prior diagnosis of bulimia or anorexia nervosa**
- **Patients undergoing abrupt discontinuation of alcohol or sedatives**
- **Concurrent administration of monoamine oxidase (MAO) inhibitors.** At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with FORFIVO XL.
- **Known hypersensitivity to bupropion or the other ingredients of FORFIVO XL**

WARNINGS AND PRECAUTIONS

Activation of Mania/Hypomania A major depressive episode may be the initial presentation of bipolar disorder. 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 FORFIVO XL is not approved for use in treating bipolar depression. **Seizures** Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with FORFIVO XL. FORFIVO XL should be discontinued and not restarted in patients who experience a seizure while on treatment. Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if the total daily dose of bupropion does not exceed 450 mg and the rate of incrementation of the bupropion dose is gradual. **Psychosis and Other Neuropsychiatric Events** Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. It is recommended stopping bupropion when the symptoms occur. **Severe Hypertension** In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These reactions have been observed in both patients with and without evidence of preexisting hypertension. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement. **Agitation and Insomnia** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. In clinical studies of MDD, these symptoms (see **Table 2** of the full prescribing information) were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. Symptoms in these studies were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion hydrochloride sustained-release tablets and 0.8% of patients treated with placebo. **Altered Appetite and Weight** In placebo-controlled short-term studies of MDD using the sustained-release formulation of bupropion hydrochloride, patients experienced weight gain or weight loss (see **Table 3** of the full prescribing information). In studies conducted with the immediate-release formulation of bupropion hydrochloride, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion hydrochloride. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of FORFIVO XL tablets should be considered. **Hypersensitivity Reactions** Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking FORFIVO XL and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness [see ***Contraindications*** in the full prescribing information].

ADVERSE REACTIONS

Clinical Trials Experience: Commonly Observed Adverse Reactions in Controlled Clinical Trials The most common adverse reactions were (incidence ≥ 5%; ≥ 2 times placebo rate): Dry mouth, nausea, insomnia, dizziness, pharyngitis, abdominal pain, agitation, anxiety, tremor, palpitation, sweating, tinnitus, myalgia, anorexia, urinary frequency, and rash.

Please see brief summary of Prescribing Information, including complete Boxed Warnings, on the following pages.

[1]Wellbutrin XL is a registered trademark of GlaxoSmithKline.

[2]Cost estimate based on the lower of the copay amount or Rx Savings Program that covers patient cost above $28 for a 30-tablet prescription. Maximum savings benefit per Rx is as follows: ≤ 59 tablets is $100, 60-89 tablets is $200, ≥ 90 tablets is $300. Certain patient groups are not eligible for this Rx Savings Program (e.g., federal healthcare programs, including Medicare or Medicaid, Medicare Part D prescription drug plans, or by any similar federal or state program, including a state pharmaceutical assistance program, etc.). Cash-paying patients and Massachusetts patients are eligible but will require a physical Rx savings voucher.

FORFIVO is a trademark of IntelGenx Corp.

EDGEMONT® PHARMACEUTICALS

FFO-140_JA

FORFIVO XL (bupropion hydrochloride extended-release tablets), for oral use
Brief Summary: Consult package insert for full prescribing information

WARNING: SUICIDALITY and ANTIDEPRESSANT DRUGS; PSYCHIATRIC EVENTS and SMOKING CESSATION

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 FORFIVO XL 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. FORFIVO XL is not approved for use in pediatric patients *[see Warnings and Precautions]*.

PSYCHIATRIC EVENTS and SMOKING CESSATION: FORFIVO XL is not approved for smoking cessation treatment, but bupropion under the name ZYBAN® is approved for this use. Serious neuropsychiatric events, including but not limited to depression, suicidal ideation, suicide attempt, and completed suicide have been reported in patients taking bupropion for smoking cessation. Some cases may have been complicated by the symptoms of nicotine withdrawal in patients who stopped smoking. Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation, has been reported in smokers undergoing a smoking cessation attempt without medication. However, some of these symptoms have occurred in patients taking bupropion who continued to smoke. All patients being treated with bupropion for smoking cessation treatment should be observed for neuropsychiatric symptoms including changes in behavior, hostility, agitation, depressed mood, and suicide-related events, including ideation, behavior, and attempted suicide. These symptoms, as well as worsening of pre-existing psychiatric illness and completed suicide have been reported in some patients attempting to quit smoking while taking ZYBAN in the postmarketing experience. When symptoms were reported, most were during treatment with ZYBAN, but some were following discontinuation of treatment with ZYBAN. These events have occurred in patients with and without pre-existing psychiatric disease; some have experienced worsening of their psychiatric illnesses. Patients with serious psychiatric illness such as schizophrenia, bipolar disorder, and major depressive disorder did not participate in the premarketing studies of ZYBAN. Advise patients and caregivers that the patient using bupropion for smoking cessation should stop taking bupropion and contact a healthcare provider immediately if agitation, hostility, depressed mood, or changes in thinking or behavior that are not typical for the patient are observed, or if the patient develops suicidal ideation or suicidal behavior. In many postmarketing cases, resolution of symptoms after discontinuation of ZYBAN was reported, although in some cases the symptoms persisted; therefore, ongoing monitoring and supportive care should be provided until symptoms resolve. The risks of using bupropion for smoking cessation should be weighed against the benefits of its use. ZYBAN has been demonstrated to increase the likelihood of abstinence from smoking for as long as 6 months compared to treatment with placebo. The health benefits of quitting smoking are immediate and substantial *[see Warnings and Precautions and Patient Counseling Information]*.

INDICATIONS AND USAGE: FORFIVO XL (bupropion hydrochloride extended-release tablets) is indicated for the treatment of major depressive disorder (MDD). The efficacy in the treatment of MDD was established in two 4-week and one 6-week and one maintenance trial in adult patients whose diagnoses corresponded most closely to the Major Depression category of the APA Diagnostic and Statistical Manual (DSM) *[see Clinical Studies]*. A major depressive episode (DSM-IV) implies the presence of 1) depressed mood or 2) loss of interest or pleasure; in addition, at least 5 of the following symptoms have been present during the same 2-week period and represent a change from previous functioning: 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 efficacy of bupropion in pediatric population has not been established. The physician who elects to use FORFIVO XL for extended periods should periodically reevaluate the long-term usefulness of the drug for the individual patient. **CONTRAINDICATIONS:** FORFIVO XL is contraindicated in patients with the following: seizure disorder because these patients may have a lower seizure threshold; patients treated currently with other bupropion products because the incidence of seizure is dose dependent; a current or prior diagnosis of bulimia or anorexia nervosa because of a higher incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion in a pre-marketing clinical trial; patients undergoing abrupt discontinuation of alcohol or sedatives because of a lower seizure threshold in these conditions; concurrent administration of monoamine oxidase (MAO) inhibitors because MAOIs potentially can enhance the CNS toxicity, at least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with FORFIVO XL; and known hypersensitivity to bupropion or the other ingredients of FORFIVO XL tablets. Anaphylactoid/anaphylactic reactions and Stevens-Johnson syndrome have been reported *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk in Treating Psychiatric Disorder Patients with 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 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) show that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with 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. Drug-Placebo Difference in Number of Cases of Suicidality per 1000 Patients Treated

Age Range	
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 *[see Boxed Warning and Use in Specific Populations]*. 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 MDD 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. Families and caregivers of patients being treated with antidepressants for MDD 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 Patient Counseling Information]*. Prescriptions for FORFIVO XL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Neuropsychiatric Symptoms and Suicide Risk in Smoking Cessation Treatment** FORFIVO XL is not approved for smoking cessation treatment, but bupropion under the name ZYBAN is approved for this use. Serious neuropsychiatric symptoms have been reported in patients taking bupropion for smoking cessation *[see Boxed Warning and Adverse Reactions]*. These have included changes in mood (including depression and mania), psychosis, hallucinations, paranoia, delusions, homicidal ideation, hostility, agitation, aggression, anxiety, and panic, as well as suicidal ideation, suicide attempt, and completed suicide *[see Patient Counseling Information]*. **Activation of Mania/Hypomania** 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. 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 FORFIVO XL is not approved for use in treating bipolar depression. **Seizures** Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with FORFIVO XL. FORFIVO XL should be discontinued and not restarted in patients who experience a seizure while on treatment. Dose: At doses up to 300 mg/day of the sustained-release formulation of bupropion hydrochloride (WELLBUTRIN SR®), the incidence of seizure is approximately 0.1% (1/1,000). Data for the immediate-release formulation of bupropion hydrochloride revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. This seizure incidence (0.4%) may exceed that of some other marketed antidepressants. Additional data accumulated for the immediate-release formulation of bupropion hydrochloride suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of FORFIVO XL. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing. Patient Factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold. Clinical Situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives; addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin. Concomitant Medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, and systemic steroids) are known to lower seizure threshold. Recommendations for Reducing the Risk of Seizure: Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if the total daily dose of bupropion does not exceed 450 mg, the rate of incrementation of the bupropion dose is gradual. **Psychosis and Other Neuropsychiatric Events** Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. It is recommended stopping bupropion when the symptoms occurred. **Severe Hypertension** In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These reactions have been observed in both patients with and without evidence of preexisting hypertension. Data from a comparative study of the sustained-release formulation of bupropion hydrochloride (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion hydrochloride plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion hydrochloride and NTS. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement. There is no clinical experience establishing the safety of FORFIVO XL tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension. **Agitation and Insomnia** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials of MDD with sustained-release formulation of bupropion hydrochloride, experienced agitation, anxiety, and insomnia as shown in Table 2.

Table 2. Incidence of Agitation, Anxiety, and Insomnia in Placebo-Controlled Trials of Bupropion HCl Sustained-release Tablets for Major Depressive Disorder

Adverse Reactions Term	Bupropion HCl 300 mg/day (n = 376)	Bupropion HCl 400 mg/day (n = 114)	Placebo (n = 385)
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Insomnia	11%	16%	6%

In clinical studies of MDD, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. Symptoms in these studies were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion hydrochloride sustained-release tablets and 0.8% of patients treated with placebo. **Altered Appetite and Weight** In placebo-controlled short-term studies of MDD using the sustained-release formulation of bupropion hydrochloride, patients experienced weight gain or weight loss as shown in Table 3.

Table 3. Incidence of Weight Gain and Weight Loss in Placebo-Controlled Trials of Bupropion Hydrochloride Sustained-release tablets for Major Depressive Disorder

Weight Change	Bupropion HCl 300 mg/day (n = 339)	Bupropion HCl 400 mg/day (n = 112)	Placebo (n = 347)
Gained >5 lbs	3%	2%	4%
Lost >5 lbs	14%	19%	6%

In studies conducted with the immediate-release formulation of bupropion hydrochloride, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion hydrochloride. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of FORFIVO XL tablets should be considered. **Hypersensitivity Reactions** Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking FORFIVO XL and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness *[see Contraindications]*.

ADVERSE REACTIONS: The following risks are discussed in greater detail in other sections of the full prescribing information *[see Warnings and Precautions]*: clinical worsening and suicide risk, neuropsychiatric symptoms and suicide risk in smoking cessation treatment, activation of mania or hypomania, seizures, psychosis, and other neuropsychiatric events, severe hypertension, agitation and insomnia, altered appetite and weight, hypersensitivity reactions. **Clinical Trials Experience** Commonly Observed Adverse Reactions in Controlled Clinical Trials. Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. Adverse reactions from Table 5 occurring in at least 5% of patients treated with the sustained-release formulation of bupropion hydrochloride and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups. 300 mg/day of bupropion sustained release: anorexia, dry mouth, rash, sweating, tinnitus, and tremor. 400 mg/day of bupropion sustained release: abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency. FORFIVO XL is bioequivalent to three 150 mg tablets of WELLBUTRIN XL®, which has been demonstrated to have similar bioavailability both to the immediate-release formulation of bupropion and to the sustained-release formulation of bupropion. The information included under this subsection and under subsections 6.2 and 6.3 of the full prescribing information is based primarily on data from controlled clinical trials with the sustained-release formulation of bupropion hydrochloride. Adverse Reactions Leading to Discontinuation of Treatment with Bupropion Immediate Release or Bupropion Sustained Release. In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion hydrochloride and 4% of patients treated with placebo discontinued treatment due to adverse reactions. The specific adverse reactions in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of the sustained-release formulation of bupropion hydrochloride, and at a rate at least twice the placebo rate are listed in Table 4.

Table 4. Treatment Discontinuations Due to Adverse Reactions in Placebo-Controlled Trials for Major Depressive Disorder using Bupropion Hydrochloride Sustained Release Formulation

Adverse Reaction	Bupropion HCl 300 mg/day (n = 376)	Bupropion HCl 400 mg/day (n = 114)	Placebo (n = 385)
Rash	2.4%	0.9%	0.0%
Nausea	0.8%	1.8%	0.3%
Agitation	0.3%	1.8%	0.3%
Migraine	0.0%	1.8%	0.3%

In clinical trials with the immediate-release formulation of bupropion, 10% of patients and volunteers discontinued due to an adverse reaction. Reactions resulting in discontinuation, in addition to those listed above for the sustained-release formulation of bupropion hydrochloride, include vomiting, seizures, and sleep disturbances. Adverse Reactions Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion Immediate Release or Bupropion Sustained Release. Table 5 enumerates adverse reactions that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion hydrochloride and with placebo in controlled trials. Reactions that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse reactions were classified using a COSTART-based Dictionary. Accurate estimates of the incidence of adverse reactions associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward reactions in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions. Finally, it is important to emphasize that the tabulation does not reflect the relative severity and/or clinical importance of the reactions. A better perspective on the serious adverse reactions associated with the use of bupropion is provided in the **Warnings and Precautions**.

Table 5. Adverse Reactions in Placebo-Controlled Trials* for Major Depressive Disorder

Body System/Adverse Reaction	Bupropion HCl 300 mg/day (n = 376)	Bupropion HCl 400 mg/day (n = 114)	Placebo (n = 385)
Body (General)			
Headache	26%	25%	23%
Infection	8%	9%	6%
Abdominal pain	3%	9%	2%
Asthenia	2%	4%	2%

Chest pain	3%	4%	1%
Pain	2%	3%	2%
Fever	1%	2%	–
Cardiovascular			
Palpitation	2%	6%	2%
Flushing	1%	4%	–
Migraine	1%	4%	1%
Hot flashes	1%	3%	1%
Digestive			
Dry mouth	17%	24%	7%
Nausea	13%	18%	8%
Constipation	10%	5%	7%
Diarrhea	5%	7%	6%
Anorexia	5%	3%	2%
Vomiting	4%	2%	2%
Dysphagia	0%	2%	0%
Musculoskeletal			
Myalgia	2%	6%	3%
Arthralgia	1%	4%	1%
Arthritis	0%	2%	0%
Twitch	1%	2%	–
Nervous System			
Insomnia	11%	16%	6%
Dizziness	7%	11%	5%
Agitation	3%	9%	2%
Anxiety	5%	6%	3%
Tremor	6%	3%	1%
Nervousness	5%	3%	3%
Somnolence	2%	3%	2%
Irritability	3%	2%	2%
Memory decreased	–	3%	1%
Paresthesia	1%	2%	1%
Central nervous system stimulation	2%	1%	1%
Respiratory			
Pharyngitis	3%	11%	2%
Sinusitis	3%	1%	2%
Increased cough	1%	2%	1%
Skin			
Sweating	6%	5%	2%
Rash	5%	4%	1%
Pruritus	2%	4%	2%
Urticaria	2%	1%	0%
Special Senses			
Tinnitus	6%	6%	2%
Taste perversion	2%	4%	–
Blurred vision or diplopia	3%	2%	2%
Urogenital			
Urinary frequency	2%	5%	2%
Urinary urgency	–	2%	0%
Vaginal hemorrhage†	0%	2%	–
Urinary tract infection	1%	0%	–

* Adverse reactions that occurred in at least 1% of patients treated with either 300 or 400 mg/day of the sustained-release formulation of bupropion hydrochloride, but equally or more frequently in the placebo group, were: abnormal dreams, accidental injury, acne, appetite increased, back pain, bronchitis, dysmenorrhea, dyspepsia, flatulence, flu syndrome, hypertension, neck pain, respiratory disorder, rhinitis, and tooth disorder.

† Incidence based on the number of female patients.

— Hyphen denotes adverse reactions occurring in greater than 0 but less than 0.5% of patients.

Additional reactions to those listed in Table 5 that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion hydrochloride (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs. 4%), hypertension (4% vs. 2%), hypotension (3% vs. 2%), tachycardia (11% vs. 9%), appetite increase (4% vs. 2%), dyspepsia (3% vs. 2%), menstrual complaints (5% vs. 1%), akathisia (2% vs. 1%), impaired sleep quality (4% vs. 2%), sensory disturbance (4% vs. 3%), confusion (8% vs. 5%), decreased libido (3% vs. 2%), hostility (6% vs. 4%), auditory disturbance (5% vs. 3%), and gustatory disturbance (3% vs. 1%). Other adverse reactions occurring < 1% in clinical trials: Chills, facial edema, postural hypotension, stroke, syncope, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, mouth ulcers, stomatitis, edema of tongue, ecchymosis, edema, abnormal coordination, decreased libido, depersonalization, emotional lability, hyperkinesia, hypertonia, hypesthesia, ataxia, and derealization, bronchospasm, accommodation abnormality, dry eye, impotence, and prostate disorder. **Postmarketing Experience** The following adverse reactions have been identified during post-approval use of bupropion hydrochloride. Because these reactions are 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. Only those adverse reactions not previously listed for bupropion are included. The extent to which these reactions may be associated with FORFIVO XL is unknown. **Cardiovascular**—complete atrioventricular block, extrasystoles, myocardial infarction, phlebitis, and pulmonary embolism. **Gastrointestinal**—colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, intestinal perforation, pancreatitis, and stomach ulcer. **Endocrine**—hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone. **Hemic and Lymphatic**—anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. **Metabolic and Nutritional**—glycosuria. **Musculoskeletal**—muscle rigidity/fever/rhabdomyolysis and muscle weakness. **Nervous System**—abnormal electroencephalogram (EEG), aggression, akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, extrapyramidal syndrome, hypokinesia, increased libido, neuralgia, neuropathy, and unmasking tardive dyskinesia. **Skin**—alopecia, exfoliative dermatitis, and hirsutism. **Eye**—mydriasis. **Urogenital**—abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, painful erection, salpingitis, urinary incontinence, and urinary retention.

DRUG INTERACTIONS: Few systemic data have been collected on the metabolism of bupropion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs. **Potential for Other Drugs to Affect FORFIVO XL** Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. Substrates or Inhibitors/Inducers of Cytochrome P450IIB6 (CYP2B6): In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between FORFIVO XL and drugs that are substrates or inhibitors/inducers of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, cyclophosphamide, ticlopidine and clopidogrel). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, inhibit the hydroxylation of bupropion. *Ticlopidine, Clopidogrel:* In a study in healthy male volunteers, 75 mg clopidogrel once daily or 250 mg ticlopidine twice daily increased exposures (C_{max} and AUC) of bupropion by 40% and 60% for clopidogrel, by 38% and 85% for ticlopidine, respectively. The exposures of hydroxybupropion were decreased. This effect is thought to be due to the inhibition of the CYP2B6-catalyzed bupropion hydroxylation. Coadministration of FORFIVO XL with ticlopidine or clopidogrel is not recommended. *Prasugrel:* Prasugrel is a weak inhibitor of CYP2B6. In healthy subjects, prasugrel increased C_{max} and AUC values of bupropion by 14% and 18%, respectively, and decreased C_{max} and AUC values of hydroxybupropion, an active metabolite of bupropion, by 32% and 24%, respectively. The inhibition of prasugrel on bupropion metabolism is not considered clinically significant. *Ritonavir, Lopinavir, Efavirenz:* In a series of studies in healthy volunteers, ritonavir (100 mg twice daily or 600 mg twice daily) or ritonavir 100 mg plus lopinavir (KALETRA) 400 mg twice daily reduced the exposure of bupropion and its major metabolites in a dose dependent manner by approximately 20% to 80%. Similarly, efavirenz 600 mg once daily for 2 weeks reduced the exposure of bupropion by approximately 55%. This effect is thought to be due to the induction of bupropion metabolism. Patients receiving any of these drugs with bupropion may need increased doses of bupropion, but the maximum recommended dose of bupropion should not be exceeded *[see Clinical Pharmacology]*. *Cimetidine:* The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg tablets of the sustained-release formulation of bupropion hydrochloride with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion. *Carbamazepine, Phenobarbital, Phenytoin:* While not systematically studied, these drugs may induce the metabolism of bupropion. **Potential for FORFIVO XL to Affect Other Drugs** Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion hydrochloride, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs. Lamotrigine: Multiple oral doses of bupropion had no statistically significant effects on the single dose pharmacokinetics of lamotrigine in 12 healthy volunteers. Drugs Metabolized by Cytochrome P450IID6 (CYP2D6). Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of the CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion hydrochloride given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied. Therefore, coadministration of bupropion with drugs that are metabolized by the CYP2D6 isoenzyme including certain antidepressants (e.g., venlafaxine, nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, and sertraline), antipsychotics (e.g., haloperidol, risperidone, and thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone and flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index. CYP2D6 in order to be effective (e.g., tamoxifen) theoretically could have reduced efficacy when administered concomitantly with inhibitors of CYP2D6 such as bupropion. Although citalopram is not primarily metabolized by CYP2D6, in one study bupropion increased the C_{max} and AUC of citalopram by 30% and 40%, respectively. Citalopram did not affect the pharmacokinetics of bupropion and its three metabolites. **Nicotine Transdermal System** Data from a smoking cessation study suggest that a higher incidence of hypertension in patients who received the combination of sustained-release bupropion hydrochloride and NTS. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement *[see Warnings and Precautions]*. **Drug Laboratory Test Interactions** False-positive urine immunoassay screening tests for amphetamines have been reported in patients taking bupropion. This is due to lack of specificity of some screening tests. False-positive test results may result even following discontinuation of bupropion therapy. Confirmatory test such as gas chromatography/mass spectrometry, will distinguish bupropion from amphetamines. **MAO Inhibitors** Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine *[see Contraindications]*. **Drugs that Lower Seizure Threshold** Since there is no lower strength for FORFIVO XL, concurrent administration of FORFIVO XL tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with caution *[see Warnings and Precautions]*. **Alcohol** In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. Alcohol increased the release rate of FORFIVO XL in vitro. The consumption of alcohol during treatment with FORFIVO XL should be avoided. **Levodopa and Amantadine** Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Since there is no lower strength for FORFIVO XL, administration of FORFIVO XL tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution.

USE IN SPECIFIC POPULATIONS: Pregnancy Teratogenic Effects: **Pregnancy Category C**. In studies conducted in rats and rabbits, bupropion hydrochloride was administered orally at doses up to 450 and 150 mg/kg/day, respectively (approximately 11 and 7 times the maximum recommended human dose [MRHD], respectively, on a mg/m^2 basis), during the period of organogenesis. No clear evidence of teratogenic activity was found in either species; however, in rabbits, slightly increased incidences of fetal malformations and skeletal variations were observed at the lowest dose tested (25 mg/kg/day, approximately equal to the MRHD on a mg/m^2 basis) and greater. Decreased fetal weights were seen at 50 mg/kg and greater. When rats were administered bupropion hydrochloride at oral doses of up to 300 mg/kg/day (approximately 7 times the MRHD on a mg/m^2 basis) prior to mating and throughout pregnancy and lactation, there were no apparent adverse effects on offspring development. One study has been conducted in pregnant women. This retrospective, managed-care database study assessed the risk of congenital malformations overall, and cardiovascular malformations specifically, following exposure to bupropion in the first trimester compared to the risk of these malformations following exposure to other antidepressants in the first trimester and bupropion outside of the first trimester. This study included 7,005 infants with antidepressant exposure during pregnancy, 1,213 of whom were exposed to bupropion in the first trimester. The study showed no greater risk for congenital malformations overall, or cardiovascular malformations specifically, following first trimester bupropion exposure compared to exposure to all other antidepressants in the first trimester, or bupropion outside of the first trimester. The results of this study have not been corroborated. FORFIVO XL should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from FORFIVO XL tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** Safety and effectiveness in pediatric patients have not been established. Anyone considering the use of FORFIVO XL in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use** Of the approximately 6,000 patients who participated in clinical trials with bupropion hydrochloride sustained-release tablets (depression and smoking cessation studies), 275 were 65 years old and over and 47 were 75 years old and over. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion hydrochloride (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites *[see Clinical Pharmacology]*. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function *[see Dosage and Administration and Use in Specific Populations]*. **Renal Impairment** Since there is no lower dose strength for FORFIVO XL, FORFIVO XL is not recommended in patients with renal impairment *[see Clinical Pharmacology]*. **Hepatic Impairment** Since there is no lower dose strength for FORFIVO XL, FORFIVO XL is not recommended in patients with hepatic impairment *[see Clinical Pharmacology]*.

DRUG ABUSE AND DEPENDENCE: Controlled Substance Bupropion is not a controlled substance. **Abuse** Humans: Controlled clinical studies of bupropion hydrochloride (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement. In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion hydrochloride produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability. Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs. Animals: Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs.

OVERDOSAGE: Human Overdose Experience Overdoses of up to 30 g or more of bupropion have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of bupropion alone included hallucinations, loss of consciousness, sinus tachycardia, and ECG changes such as conduction disturbances or arrhythmias. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported mainly when bupropion was part of multiple drug overdoses. Although most patients recovered without sequelae, deaths associated with overdoses of bupropion alone have been reported in patients ingesting large doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients. **Overdosage Management** Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. 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. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known. Due to the dose-related risk of seizures with FORFIVO XL, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate. 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).

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CLINICAL & RESEARCH NEWS

Do Men Experience Depression Differently From Women?

Men appear to endorse "externalizing" symptoms—such as irritability, anger, risk taking, and substance abuse—more than women, but one expert says there is no evidence that those symptoms are equivalent to depression.

BY MARK MORAN

When certain alternative, "externalizing" symptoms of depression that appear to be more common among men are used to assess for depression, then men are more likely to meet depression criteria, and the long-established disparities in the prevalence of depression between men and women appear to be eliminated.

This is the conclusion of researchers at the University of Michigan who performed a secondary analysis of the National Comorbidity Study Replication (NCS-R) that appeared online August 28 in *JAMA Psychiatry*.

Subjects in the NCS-R were a national representative sample of 10,000 men and women.

"Although men were likely to endorse many traditional depression symptoms, men were significantly more likely to report symptoms of anger attacks/aggression, irritability, substance abuse, and risk-taking behaviors over symptoms such as withdrawal from friends, sleep problems, and feelings of complaintiveness," wrote Lisa Martin, Ph.D., of the Women's and Gender Studies and Health Policy Studies at the University of Michigan, and colleagues in the report. "These results suggest that relying only on men's disclosure of traditional symptoms could lead to an underdiagnosis of depression in men and that clinicians should consider other clues when assessing depression in men."

For the purposes of the analysis, Martin and colleagues developed two scales for assessing "externalizing" symptoms endorsed by subjects in the NCS-R. The two scales they developed—the Male Symptoms Scale (MSS) and the Gender Inclusive Depression Scale (GIDS)—were derived from two other scales tested and validated in Europe (the Gotland Male Depression Scale and the Masculine Depression Scale).

To create the new scales, researchers conducted an extensive literature review to construct a list of alternative male-type depression symptoms and then compared this list against the NCS-R questionnaire and dataset to determine whether appropriate variables capturing the desired symptoms could be identified. Symptoms were excluded from the scales for one of three possible reasons: symptoms were deemed inappropriate, equivalent items were not available, or the number of people for whom data were available for a symptom was too small to be useful for the analysis

The MSS included only the alternative male-type symptoms of depression: irritability, anger attacks/aggression, sleep disturbance, alcohol/other drug abuse, risk-taking behavior, hyperactivity, stress, and loss of interest in pleasurable activities. The GIDS combined these symptoms with six traditional symptoms of depression, including sad/depressed mood, loss of vitality, tiredness, ambivalence, anxiety/uneasiness, and complaintiveness.

The researchers found that when using the MSS scale for only alternative, male-type symptoms of depression, a higher proportion of men (26.3 percent) than women (21.9 percent) met criteria for depression. Analyses using the GIDS showed that men and women met criteria for depression in almost equal proportions: 30.6 percent of men and 33.3 percent of women.

Men endorsed the following items at significantly higher rates than did women: anger attacks/aggression, substance abuse, and risk-taking behavior. Women endorsed four symptoms at significantly greater rates than men: stress, irritability, sleep problems, and loss of interest in things you usually enjoy, such as work, hobbies, and personal relationships.

"This is the first study, to our knowledge, to assess the implications of considering alternative, male-type symptoms of depression for sex differences in the prevalence of depression in a nationally representative sample of U.S. adults," the researchers stated.

APA Director of Research Darrel Regier, M.D., M.P.H., who reviewed the report, said the assertion that the alternative "externalizing" symptoms are the equivalent of the depressive disorders requires additional validation.

"Such validators would include the kind of antecedent, concurrent, and predictive validators that were used to

see ***Men*** *on page 32*

APA Election Dates to Note

- **November 1:** The names of candidates in APA's 2014 election will be announced on APA's Web site at www.psychiatry.org.
- **November 15:** Deadline for petition candidates. Those who plan to run by petition should contact Chiharu Tobita at CTobita@psych.org.

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Brain Data May Explain Rare Math Skills in Some With ASD

When high-functioning individuals with autism excel at math, it may be because they break down problems into smaller problems and recruit brain areas typically involved in perception.

BY JOAN AREHART-TREICHEL

In the Academy Award–winning film "Rain Man," actor Dustin Hoffman played a man who had autism and extraordinary math skills. The film was based on anecdotal evidence accumulated over many years suggesting that high-functioning individuals with autism are particularly talented in math.

And now new research seems to add to the evidence that certain individuals with autism have exceptional math skills, and the researchers speculate as to why this might be the case.

The study was headed by Teresa Luculano, Ph.D., a postdoctoral fellow in psychiatry at Stanford University, and the findings were published online August 19 in *Biological Psychiatry*.

The study included 36 children aged 7 to 12. Eighteen had autism spectrum disorder (ASD), but all were within an IQ range considered to be high functioning. The other 18 were typically developing children who were matched with the former on age, gender, and IQ score.

The researchers evaluated all of the children's arithmetic problem-solving abilities. They found that those with ASD excelled significantly more in this area than did their peers without the disorder. Moreover, the children with ASD were significantly more likely than controls to use an analytical technique called decomposition to solve arithmetic problems. Decomposition involves breaking down a problem into smaller problems. Even when typically developing children use decomposition, they tend to be at a more advanced stage of math-skill development than their peers who rely on less-sophisticated strategies such as finger counting.

Subsequently, the researchers used functional MRI imaging to examine the brain activity of all the study subjects while they were attempting to solve arithmetic problems.

The children with ASD engaged the same brain areas as their typically developing peers did. However, those in the ASD group showed different activation patterns in certain regions of the prefrontal cortex, the medial temporal lobe, the posterior parietal cortex, and the ventral temporal-occipital cortex that are known to be involved in numerical problem solving.

But perhaps most interestingly,

see ***Math Skills*** *on page 31*

Life in Substandard Housing Linked to Mental, Physical Illness

Findings from this study are hoped to guide the development of effective health care delivery in marginal housing.

BY VABREN WATTS

Brian Kladko

Those living in marginal housing should be assessed for mental well-being, similar to assessment of individuals in homeless situations, according to William Honer, M.D.

Living in substandard housing is far more than just unpleasant. It appears to be strongly related to substance dependence, mental illness, and infectious disease, according to a study published August 19 in *AJP in Advance*.

Researchers with the Department of Psychiatry at the University of British Columbia conducted a study investigating the multimorbidities associated with people living in substandard dwellings. William Honer, M.D., the lead author and the Jack Bell Chair in Schizophrenia at the University of British Columbia, said in an interview with *Psychiatric News* that the health of individuals living in substandard housing is not well characterized. "Our focus was on the people living in marginal housing, which complements the more extensive evidence base of research concerning frank homelessness."

Honer and colleagues recruited nearly 300 adults living in single-room-occupancy hotels in a low-income neighborhood in Vancouver. The hotels were in need of major repair and plagued with bedbug, cockroach, and rodent infestations. Each floor had a communal toilet and shower facility that was shared by 10 to 15 tenants. The study participants received monthly evaluations for a median of two years to assess incidence of mortality and substance dependence, as well as psychiatric illness other than substance dependence, neurological disorders, and infectious diseases.

At the end of the study, there was a 5 percent death rate that was attributed to consequences of physical illness or drug overdose. No deaths were due to suicide. According to the multiple assessments for diagnoses of *DSM-IV* psychiatric disorders, including substance abuse, nearly 100 percent of the participants reported drug abuse—mainly drug injection—while half of the participants had a mental illness—mostly psychosis.

Neurological disorders, such as those with involuntary movements, were present in 45 percent of patients, and positive serology for the human immunodeficiency virus (HIV) and hepatitis C were detected in 18 percent and 70 percent of patients, respectively.

In addition, participants who received a comorbid diagnosis of psychosis and drug dependency or HIV were less likely to adhere to psychiatric treatment than those with psychosis alone. However, the presence of comorbidity did not negatively influence the frequency of treatment for opioid addiction or HIV disease.

"The reasons [for the discrepancy in treatment] are unclear at present," said Honer. "One possibility is that psychosis is more difficult to diagnose than the other two broad categories of illness, and comorbidity may make diagnosing psychosis more challenging. . . . Another reason could be that psychosis was diagnosed, but participants were unwilling to take medication."

The authors did acknowledge limitations in the study, including the effects of other illnesses that were not diagnosed and the relatively small sample size of female subjects. Honer told *Psychiatric News* that he and his colleagues are working with Vancouver Coastal Health, a regional health agency, to increase study size by 3,000 people to address

see ***Housing*** *on page 33*

Mental Disorders Are Risk Factors For Accidental Death

Psychiatrists should be aware that people with mental illness are more in danger of dying by accident than they are by suicide.

BY JOAN AREHART-TREICHEL

While much attention has been paid to the heightened risk for suicide in people with mental illness, it appears that accidental death is a greater danger to them than suicide is.

This troubling finding has emerged from a large national population study headed by Casey Crump, M.D., Ph.D., a clinical assistant professor of medicine at Stanford University. The results were published online August 22 in the *British Journal of Psychiatry*.

Crump and his colleagues used Swedish national health and other registries to learn about the accidental-death risk among psychiatric patients—a subject about which little has been written.

The study population consisted of all adults living in Sweden in 2001—some 7 million people. The researchers used the Swedish Death Registry to learn which of these individuals died during the subsequent eight years and from what cause. The researchers then used the Swedish Hospital Registry and Swedish Outpatient Registry to determine which people had been diagnosed with a mental illness from 2001 to 2008 and how many of them had died by accident during that period. They then compared those data with cause-of-death data for people without mental illness.

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They found that in the eight-year study period, 26 percent of those who died by accident had received a psychiatric diagnosis, while just 9 percent of those without a psychiatric diagnosis died by accident. In short, people with mental disorders had a substantially increased danger of suffering an accidental death.

The researchers also compared rates of accidental death and suicide among those with a mental illness. They found that the risk of psychiatric patients dying by accident was higher than that of dying by suicide—0.9 percent versus 0.6 percent.

Furthermore, they evaluated which mental illness predisposed people to an

see ***Accidental Death*** *on page 32*

CLINICAL & RESEARCH NEWS

Genes May Determine Drug's Alcohol-Treatment Success

Ondansetron, a nausea medication, may have a role as an effective treatment for alcoholism, depending on a person's genotype.

BY VABREN WATTS

Taking a more personalized approach, several studies are investigating whether patients' genetic makeup can help physicians more effectively treat chronic illnesses, including substance use disorders.

Bankole Johnson, M.D., D.Sc., a professor of psychiatry and neurobehavioral sciences at the University of Virginia, headed a pharmacogenetic study published in the July 2011 *American Journal of Psychiatry* showing that individuals treated for alcohol addiction with ondansetron—a drug that is approved by the Food and Drug Administration to treat nausea in chemotherapy patients—were more likely to abstain from drinking when they expressed both length (LL) and nucleotide (TT) variances in the serotonin transporter gene, SLC6A4, than were those who did not carry the SLC6A4-TT/LL genotype.

Now Johnson and colleagues have reported in the September *American Journal of Psychiatry* that possessing polymorphisms within the HTR3A and HTR3B genes—subunits of serontonin-3 receptors (5-HT3)—may result in even greater benefits for individuals being treating for alcohol dependency with ondansetron.

"The [recently published] paper builds upon earlier work showing that alcohol-dependent individuals vary in genetic profile with respect to the serotonin transporter receptor and 5-HT3 subclasses," Johnson told *Psychiatric News*. He explained that because ondansetron is a selective inhibitor for the A subunit of the 5-HT3 receptor, it was logical to direct attention toward HTR3A—the gene that encodes the A subunit. The HTR3B gene was studied by default because A and B subunits of 5-HT3 receptors form a complex.

Studies conducted by other researchers have shown that genetic deletion of HTR3A in animals is associated with increased alcohol consumption, while human studies have shown that specific variances in the both HTR3A and HTR3B were associated with a higher incidence for combined heroin, cocaine, and alcohol addiction.

In their recent study, Johnson and his team conducted an 11-week double-blind study to assess how allelic variances in the HTR3A and HTR3B genes affect ondansetron efficacy in treating alcoholism.

Using the same 283 alcohol-dependent subjects from their 2011 *AJP* report, the researchers divided the subjects into two groups—ondansetron and placebo. Ondansetron was administered orally twice daily at 4ug/kg of body weight. Participants were tested for 21 polymorphisms for the HTR3A and HTR3B genes, in addition to the SLC6A4-TT/LL genotype from previous studies. The researchers also assessed the effects of drinking outcomes in the presence of multiple variances.

Results showed that individuals possessing one or more genotypes for rs1150226-AG and rs1176713-GG in the HTR3A gene and rs1714942-AC in HTR3B exhibited a reduction of two drinks per drinking day in response to ondansetron as compared with trait carriers who were given placebo.

Ondansetron participants with allelic variances had a 20 percent lower incidence of heavy drinking days and were twice as likely to abstain from alcohol as were those with the same allelic variants taking placebo. In addition, a subpopulation of individuals carrying a combined genotype for SLC6A4-TT/LL and HTR3A/HTR3B polymorphisms were able to reduce drinking days by 34 percent while taking ondansetron, while individuals expressing SLC6A4-TT/LL alone reduced drinking days by 20 percent compared with the control group.

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"The era of personalized medicine by which we can target subpopulations of those with alcohol dependence for optimum treatment effect has arrived," said Johnson, explaining that having variances in both the presynaptic serotonin transporter gene and postsynaptic 5-HT3 suggest a greater response to ondansetron in lowering alcohol consumption.

Ondansetron has yet to be FDA-approved to treat alcoholism, but phase 3 clinical trials for alcoholism are underway, Johnson told *Psychiatric News.*

According to the National Institute on Alcohol Abuse and Alcoholism (NIAAA), millions of U.S. alcohol abusers are not diagnosed and treated until late stages of the disease when there has been much damage—often irreversible.

NIAAA is conducting studies to reproduce the results of Johnson and colleagues. According to Raye Litten, Ph.D., associate director of the Division of Treatment and Recovery Research at NIAAA, the pharmacogenetic aspect of ondansetron "is not ready for primetime just yet" for the field is fairly new. "If we can reproduce Johnson's results it will be very promising for the future of medicine in treating alcohol dependency, which is such a complex disorder" said Litten.

The study was funded by NIAAA. PN

"Determination of Genotype Combinations That Can Predict the Outcome of the Treatment of Alcohol Dependence Using the 5-HT3 Antagonist Ondansetron" is posted at http://ajp.psychiatryonline.org/article.aspx?articleID=1722045.

FDA Warning Highlights Mefloquine's Mental Health Risks

An antimalarial drug with a long history of adverse psychiatric side effects gets a tougher warning label from the Food and Drug Administration.

BY AARON LEVIN

The U.S. Food and Drug Administration (FDA) issued an updated boxed warning in late July about the psychiatric and neurologic side effects of the antimalarial drug mefloquine hydrochloride.

"The neurologic side effects can include dizziness, loss of balance, or ringing in the ears," said the announcement from the agency's Division of Drug Information. "The psychiatric side effects can include feeling anxious, mistrustful, depressed, or having hallucinations."

The label already cautioned against prescribing mefloquine (formerly trade-named Lariam but no longer marketed under that name) to patients with a history of seizures or psychiatric disorders.

The drug was originally developed by scientists at the Walter Reed Army Institute of Research, but military use has declined in recent years, from 17,361 service members in 2008 to 889 in July, according to an August 12 memo from Assistant Secretary of Defense for Health Affairs Jonathan Woodson, M.D., to the surgeons general of the U.S. Army, Navy, and Air Force.

"Mefloquine is the drug of last resort for malaria prophylaxis and should only be used in persons with contraindications to chloroquine, doxycycline, and atovaquone-proguanil," wrote Woodson.

Adverse effects seem to be unpredictable for those without prior risk factors.

Travel medicine specialist Wesley Van Voorhis, M.D., Ph.D., has experienced mefloquine from both sides—treating patients returning from malarial regions and taking the drug himself.

"I had weird dreams but no psychotic effects," he told *Psychiatric News*. His patients, though, have run the gamut, from having no effects at all to those weird dreams to fearfulness to frank paranoia.

"I've prescribed the drug a number of times, and problems have happened only rarely," said Van Voorhis, a professor of medicine and head of the Allergy and Infectious Diseases Division at the University of Washington in Seattle.

The labeling change was primarily motivated by "the possibility of persistent vestibular adverse effects after drug use is discontinued and the possibility of permanent vestibular damage," Stephanie Yao of the FDA's Office of Media Affairs told *Psychiatric News.*

"In our Drug Safety Communication,

see ***FDA Warning*** *on facing page*

LETTERS TO THE EDITOR

Discrepancy Between *DSM-5* and Self-Exam Question

We want to bring to your attention an apparent discrepancy between the text of *DSM-5* and the self-exam questions on trauma and stress-related disorders published in *Psychiatric News* August 15.

The self-exam presents a case "best described as adjustment disorder with prolonged, chronic bereavement." We have two concerns with this. The first is the introduction of new terminology ("prolonged, chronic bereavement") to describe the phenomenon. The second is its placement as an adjustment disorder.

Importantly, in *DSM-5* persistent complex bereavement disorder is not included in the section for "Adjustment Disorders" (Box 19-5, 309.0/2/3/4/9; F43.20-25). Rather it is included in the section "Criteria for Other Specified Trauma- and Stressor-Related Disorders" (Box 19-7, 309.89, F43.8) as an example: 5. Persistent complex bereavement disorder….

Additionally, provisional criteria for this condition are contained in Section 3 as a "condition requiring further research."

We are concerned that the discrepancy between the self-exam question and the *DSM-5* text will be confusing at best and that it may impede the types of research called for in the *DSM*. We ask that this letter be published and attached electronically to the file containing the exam.

M. KATHERINE SHEAR, M.D.
CHARLES REYNOLDS, M.D.
BARRY LEBOWITZ, PH.D.
NAOMI SIMON, M.D.
SIDNEY ZISOOK, M.D
DARREL REGIER, M.D., M.P.H.

Editor's note: The Web version of the* DSM-5 *self-exam question was updated as soon as the error was discovered.

Response from Philip Muskin, M.D., a professor of clinical psychiatry at Columbia University, under whose leadership the* DSM-5 *self-exam questions are developed:

We would like to thank Dr. Shear and her colleagues for pointing out the error in the question on the self-exam. The question and the corrected answer are as follows:

Two years after the death of her husband, a 70-year-old woman is seen for complaints of sadness, anger regarding her husband's unexpected death after a heart attack, a yearning for him to come back, and unsuccessful attempts to move out of her large home because of her inability to remove his belongings. Which diagnosis would best fit this patient?

a) major depressive disorder
b) posttraumatic stress disorder
c) other specified trauma- and stressor-related disorder with the specification of persistent complex bereavement disorder
d) personality disorder
e) normative stress reaction

Correct answer: c) other specified trauma- and stressor-related disorder with the specification of persistent complex bereavement disorder

Rationale: This patient does not fall into any discrete diagnosis within the trauma- and stressor-related disorder category and should be diagnosed with the "other" designation. At least 12 months following the death of a close relative or friend, the individual experiences intense yearning or longing for the deceased, intense sorrow and emotional pain, or preoccupation with the deceased or the circumstances of the death. The person may also display difficulty accepting the death, intense anger over the loss, a diminished sense of self, a feeling that life is empty, or difficulty planning for the future or engaging in activities or relationships. The clinician may choose to communicate the specific reason that the presentation does not meet specific criteria by recording "other" followed by the specific reason. In this case the reason would be persistent complex bereavement disorder. (Provisional criteria for this diagnosis are in the chapter "Conditions for Further Study.") Mourning shows substantial cultural variation; the bereavement reaction must be out of proportion or inconsistent with cultural or religious norms. PN

FDA Warning

continued from facing page

we noted that patients who experienced vestibular symptoms usually had concomitant psychiatric symptoms such as anxiety, confusion, paranoia, and depression," said Yao. "In our decision to add a boxed warning about the vestibular neurologic adverse effects, it made sense to also highlight the existing warning about psychiatric adverse effects."

The FDA warns patients to "contact your health professional right away" if they experience dizziness, vertigo, tinnitus, seizures, or insomnia.

However, the advice to contact one's health professional suggests an implicit contradiction to preventive medicine specialist Remington Nevin, M.D., M.P.H.

"That's like asking a person who's had too many drinks to decide whether or not to drive," said Nevin, a former U.S. Army physician and now a doctoral candidate in the Department of Mental Health at the Johns Hopkins Bloomberg School of Public Health, in an interview. "It is unreasonable to expect someone with symptoms of paranoia, psychosis, or mania to contact a doctor and act appropriately in such a case."

A more reasonable risk-mitigation strategy would be for the FDA to mandate a test prescription of one or two doses of mefloquine before the patient travels to a malarial region, said Nevin, who has studied the drug's effects for more than five years. Medication for the full travel period would be prescribed only after evaluation for neurological or psychiatric reactions.

The more-expensive combination of atovaquone and proguanil (brand name Malarone) is an alternative, said Van Voorhis.

Both Van Voorhis and Nevin noted that whatever causes mefloquine's effects on the brain remains a mystery.

"One hypothesis is that since the drug is a potent inhibitor of intercellular electrical communication, it blocks gap junction channels, especially in inhibitory neurons in the limbic system," said Nevin. "That in turn has downstream effects on dopaminergic tone, with observable behavioral correlates."

Also, while many people who have mild symptoms do not progress to psychosis, those who experience the most serious symptoms appear at greatest risk for chronic symptoms, suggesting potentially direct neurotoxic effects of the drug, he said.

The long-lasting nature of symptoms for some may happen because the drug concentrates in the brain and is eluted slowly, said Van Voorhis. "That may be good for protection against malaria but bad neuropsychiatrically."

However, any explanation is highly speculative at this point, they emphasized.

Nevin raised another point about mefloquine, drawing on his Army experience.

Since the chronic psychiatric side effects can last for years and can include panic, memory problems, and lack of concentration, they could be confused with symptoms of posttraumatic stress disorder (PTSD) or traumatic brain injury (TBI), he noted.

"So maybe many veterans diagnosed with PTSD or TBI may really be suffering from the chronic effects of mefloquine toxicity," he said, backing the change in prescribing priorities. "Mefloquine is an exposure we can safely eliminate to reduce the burden of illness in the military." PN

The FDA announcement about mefloquine is posted at http://www.fda.gov/Drugs/DrugSafety/ucm362227.htm. An abstract of "Psychiatric Side Effects of Mefloquine: Applications to Forensic Psychiatry" by Elspeth Cameron Ritchie, M.D., M.P.H., Jerald Block, M.D., and Remington Nevin, M.D., M.P.H., is posted at http://www.jaapl.org/content/41/2/224.abstract.

Self-Exam

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2. A 19-year-old woman is referred to a psychiatrist by her internist after she admits to him that she repetitively pulls at her eyebrows to the point that she has scarring and has little or no eyebrow hair. She confides that her normal eyebrows look repulsive to her: she sees them as too bushy, saying that she "looks like a caveman." Pictures of her prior to the hair pulling show a normal looking teenager. Which of the following is the most likely diagnosis?

a) hair pulling disorder (trichotillomania)
b) body dysmorphic disorder
c) delusional disorder, somatic type
d) normal age appropriate appearance concerns
e) obsessive-compulsive disorder

3. A 55-year-old retail worker is frequently unavailable at work to the point where he is in danger of losing his job. He explains that he has "chronic halitosis" and fears that his bad breath is "scaring away shoppers." His coworkers regularly reassure him that his breath is fine. He believes they are being polite, and he brings a toothbrush and toothpaste to work and is frequently in the restroom brushing his teeth. In addition he chews mint gum, although his employer has asked him not to. Although he is worried about losing his job, he finds his worries about his breath to be intolerable. He has seen his doctor and dentist; however, both tell him that he is healthy and does not have malodorous breath. Which of the following would be the most appropriate diagnosis?

a) social anxiety disorder
b) obsessive-compulsive disorder
c) body dysmorphic disorder
d) unspecified obsessive-compulsive or related disorder
e) illness anxiety syndrome PN

Kennedy

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Kennedy highlighted APA's leadership role in fighting the stigma, laws, and general medical practices that prevent many Americans from receiving effective care for psychiatric conditions, including substance use disorders.

"Why is it that we don't have screening for depression or addiction or anxiety like we do for high cholesterol, diabetes, or heart disease," he said via satellite on FOX 43 Morning News in Harrisburg, Pa. "We have to make sure that this [mental health] screening is a part of routine medical care."

Having publicly discussed his own struggle with bipolar disorder and substance abuse, Kennedy currently is a spokesperson for APA's new media campaign "A Healthy Minds Minute"—a series of public-service announcements designed to reduce mental illness discrimination and encourage family and friends to help their loved ones get care.

"I've been in recovery for a few years now," Kennedy told Seattle FOX news affiliate, KCPQ. "When I look back, I cannot believe how [sick] I was—but at the time I didn't realize it. If it wasn't for others helping me realize it, then I would not have gotten the treatment that I needed."

Since "A Healthy Minds Minute" was first released in May, it has aired more than 3,000 times on more than 40 stations—reaching an audience of more than 50 million people. The second public-service announcement for "A Healthy Minds Minute" is set for release next month in honor of Veterans Day to support military families who are heavily impacted by suicide and mental illness.

Over the past five years, Kennedy has fought to convince the federal government to enact a final rule that would penalize insurance companies that violate the mental health parity law, which was passed in 2008. Kennedy explained to Andrea Mitchell that implementation of the law was "sidelined" in 2010 by the attention focused on the Affordable Care Act.

"Health care reform is a big win for us, because it eliminates the preexisting condition clause," said Kennedy. He emphasized, however, that advocates must continue to push mental health care to the forefront of health care reform in the cause of eliminating discrimination faced by Americans with mental illness.

At press time Kennedy was scheduled to participate in a "Conversations" event with APA President Jeffrey Lieberman, M.D., at this month's Institute on Psychiatric Services. PN

See "A Healthy Minds Minute" with former Rep. Patrick Kennedy at http://www.psychiatry.org/mental-health/.

From the President

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available on the *Psychiatric News* website (www.psychnews.org) to the topic.

In anticipation of the ACA and the MHPAEA final rule, APA has geared up to prepare and protect psychiatry and mental health care and ensure the best outcome for our patients. Two years ago, then-President John Oldham appointed a Board of Trustees work group on health care reform focusing on integrated care and chaired by current President-Elect Paul Summergrad, who presented the group's report to the Board this past March. Following this, Dilip Jeste and I extended and expanded this work group, appointing one of us (Howard Goldman) as chair and retaining outside consultants including Michael Hogan (former commissioner of mental health in Connecticut, Ohio, and New York), Sherry Glied (dean of the New York University Wagner School of Public Health and former assistant secretary for planning and evaluation in the Department of Health and Human Services in the Obama administration), Tom McGuire (a professor of health economics at Harvard Medical School), and David Satcher (former U.S. surgeon general). These work groups are charged with providing the best advice to the Board and developing an action plan to ensure that the HCR process produces the best outcomes for psychiatrists, mental health care providers, and most importantly, our patients.

In addition, APA has engaged former member of Congress Patrick Kennedy as a consultant and spokesperson on mental health policy and legislation. The work group and consultants work hand in glove with the staff of APA's Division of Advocacy, including Gene Cassel, Sam Muszynski, Nick Meyers, Karen Sanders, and Lizbet Boroughs. In addition, APA has retained the services of a communications company to work with Eve Herold and her staff in the Office of Communications and Public Affairs to develop a communications strategy on HCR topics aimed at our members and stakeholder groups. The activities of these personnel and components will be communicated to APA members on an ongoing basis through *Psychiatric News* and other APA communications formats.

These are indeed interesting and exciting times, but times in which we must "keep our eyes wide" and be ready to address the challenges and take advantage of new opportunities. PN

You can follow Dr. Lieberman on Twitter at @DrJlieberman. To do so, go to https://twitter.com/DrJlieberman, log in or register, and click on "Follow."

From the Experts

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referred for gynecological evaluation to assess her pelvic content. A pelvis ultrasound followed by a CT abdomen/pelvis identified the presence of bilateral ovarian dermoid cysts. She underwent bilateral ovarian cystectomy. Pathology confirmed that the cysts were benign.

Over the course of six months, she slowly improved and was able to go back to work. Her family confirmed her near full recovery. She had no recollection of the period surrounding her initial presentation and hospitalization.

Anti-NMDA receptor encephalitis falls within the broad category of autoimmune limbic encephalitis. These syndromes affect predominantly the medial temporal lobes and orbitofrontal and frontobasal regions of the brain. The nosology of autoimmune limbic encephalitis is still evolving. One classification is based on whether the autoantibodies are directed toward cell-surface membrane or intraneuronal antigens.

Until recently, most autoimmune encephalitides were considered a manifestation of paraneoplastic syndromes. These are rare conditions due to the remote effects of tumors that lie outside the CNS. CNS injury is due to antibody-mediated neuronal damage and specifically excludes injury by tumor invasion, metastasis, or chemotherapy. The damage-inducing antibodies are directed at antigens located in the primary tumor but then cross react with neuronal molecules or related antigens to cause the neurologic disease. For example, anti-Hu antibody is associated with small-cell lung carcinoma, and anti-Ma antibody is associated with testicular carcinoma. These paraneoplastic disorders typically involve intracellular neuronal antigen targets and have cytotoxic T cell pathogenesis.

In the mid 2000s, however, a new type of limbic encephalitis with complex and often bewildering neuropsychiatric presentations was described. The seminal paper by Vitiliani (2005) identified this new form of limbic encephalitis, which was later called anti-NMDA receptor encephalitis and caused by anti-NMDA receptor antibodies. Subsequent confirmatory work was done by Dalmau and his collaborators (Dalmau 2008). In this type of limbic encephalitis, the autoantibodies are directed against neuronal surface membrane antigens and are more amenable to immunotherapy. Other identified neuronal surface antigens that can elicit damage-inducing antibodies and a limbic encephalitis include voltage-gated potassium channels, AMPA-receptors, and GABA receptors. While anti-NMDA receptor encephalitis is not considered a "conventional" paraneoplastic disorder for the above reason, it is associated with ovarian teratomas in about 60% of cases (Dalmau 2008).

Anti-NMDA receptor encephalitis typically occurs in sequential phases. The first phase begins with malaise, headache, and fatigue, followed by florid psychiatric symptoms, including anxiety, mood dysregulation, delirium, agitation, hallucinations, and delusions. In this phase, patients often present to psychiatric services, making limbic encephalitis a quintessential neuropsychiatric disorder. The second phase could be either an unresponsive or hyperactive phase. In the unresponsive phase, patients are often noncommunicative, akinetic, or catatonic; in the hyperactive phase, autonomic instability, hypertension, dyskinesias, or stereotypies predominate.

Prior to the advent of NMDA assays and an increased awareness of this condition, anti-NMDA receptor encephalitis was understandably diagnosed as first-episode psychosis or viral encephalitis. Etiological misattribution was common, since standard blood, CSF, MRI, or EEG investigations may be within normal limits or yield nonspecific abnormalities. Definitive diagnosis is made with anti-NMDA receptor antibody assays in blood and/or CSF. Once diagnosed, the treatment involves immunotherapy—intravenous immunoglobulins, high-dose corticosteroids, plasma exchange, rituximab, azathioprine, and cyclophosphamide deployed sequentially or in parallel.

At the same time, a whole-body search for a tumor is warranted as with conventional paraneoplastic disorders. If a tumor is found, resection leads to better prognosis. The recovery process is slow and may take several months. Residual cognitive-intellectual problems are common. Moreover, in most instances, patients are unable to recall the events of the prodrome and acute illness, consistent with an illness that is centered in the limbic system and disrupts hippocampal function and hence recent memory. PN

References for this article are posted at http://www.psychnews.org/update/experts_3_26.html.

Navy Yard

continued from page 1

Meanwhile, other local and federal agencies quickly organized to help those affected by the shooting. "We are working with the Mayor's Office of Victims Services and other District of Columbia government agencies, the FBI, and the American Red Cross on longer-term services for families," said director of the District of Columbia Department of Mental Health (DCDMH) Steve Baron, L.C.S.W., on the afternoon of the shooting. Those agencies coordinated their efforts with daily telephone conference calls over the next several days.

DCDMH sent children's emergency response teams and school-based mental health clinicians to schools near the Navy Yard and set up an assistance center at the nearby Greenleaf Recreation Center for people in surrounding neighborhoods.

"We are offering counseling provided by our mobile crisis team, which includes social workers and paraprofessionals, supported by a psychiatrist," said psychiatrist Elspeth Cameron Ritchie, M.D., M.P.H., chief medical officer of the DCDMH.

One team was assigned to a school that had been locked down during the shooting. They talked with staff and students, but no clinical work was performed, she said.

The department is planning outreach efforts to city schools over the next few months and will have representatives at memorial services for victims.

Meantime, the U.S. Navy's Fleet and Family Support Program set up an emergency family assistance center (EFAC) at Joint Base Anacostia-Bolling (formerly Bolling Air Force Base), not far from the Navy Yard.

On calmer days, the program provides general support services for the military community at six centers in states around the capital region, said Robert Klebahn, M.A., regional program manager.

"But in emergencies, we grow the EFAC out of the military support center and augment it with additional personnel," he said in an interview. "We plan and train annually, so we knew what was needed."

Because the regional support program is based at Anacostia-Bolling, its personnel could act immediately. The shooting began shortly after 8 a.m., but by 11 that morning, they had opened a center on the base to take calls from affected families and others concerned about Navy Yard employees, he said.

Later that day, a social worker went to the police department in the Navy Yard to work with officers who had engaged the gunman.

AP Photo/Manuel Balce Ceneta

Armed police prepare to enter the Washington Navy Yard as they respond to a shooting last month in which a gunman killed 12 of his coworkers before being killed by police.

The following morning, more social workers from Navy support centers in Maryland arrived to provide crisis counseling to callers. In addition, a Navy Special Psychiatric Rapid Intervention Team (SPRINT) based in Portsmouth, Va., set up shop inside the Navy Yard. Federal Occupational Health Services, a civilian contractor, began offering psychological first aid and crisis counseling, if needed, to civilian employees.

Eventually, Klebahn and his colleagues will determine when they might wind down the EFAC and move its employees back to their regular jobs helping military families.

That transition will be paralleled by one connecting any Navy Yard personnel needing psychosocial services with agencies or clinicians near their homes in Maryland, Virginia, or Washington. In addition, the Fleet and Family Support Centers will still be available to provide counseling to military service members and their families, said Klebahn.

The gunman, Aaron Alexis, 34, was a former Navy Reservist with a troubled personal history who worked as a computer specialist for a government subcontractor at the Navy Yard. PN

APA's Disaster Psychiatry website contains links to information on coping with the mental health aftermath of disasters and tragedies at http://www.psychiatry.org/practice/professional-interests/disaster-psychiatry. Information from the Center for the Study of Traumatic Stress at the Uniformed Services University of the Health Sciences in Bethesda, Md., is posted at http://www.cstsonline.org/tag/disasters and http://www.cstsonline.org/recovery-in-the-aftermath-of-workplace-violence-guidance-for-workers.

Populations

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tems to offer their unique expertise in the care of patients across the medical spectrum.

"One of the clear lessons that came out of work in this area is that policymakers and administrators trust their own data," Druss said. "They are not particularly interested in whether something works in some abstract sense or in a randomized, controlled trial done someplace else. What they are most interested in is looking at their own data and understanding which ones are the high-cost patients—and those are invariably patients with comorbid mental conditions."

And what does the future look like? "One broad theme of what is going on now and is likely to continue is the move to population-based care delivery," Druss told *Psychiatric News*. "That's the common thread through medical homes, accountable care organizations, and other movements today. They are all about improving care across populations." PN

Information on the PCARE study is posted at http://ajp.psychiatryonline.org/data/Journals/AJP/1820/appi.ajp.2009.09050691.pdf. APA's resources on managed can be accessed at http://www.psychiatry.org/practice/professional-interests/integrated-care.

Women

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percent of the physician workforce. As more female physicians become interested in traditionally male-dominated fields, I think we will see further equalization in numbers between male and female physicians in higher-paying specialties."

The study was funded by the National Institute on Aging. PN

An abstract of "Trends in the Earnings of Male and Female Health Care Professionals in the United States, 1987 to 2010" is posted at http://archinte.jamanetwork.com/article.aspx?articleid=1733450.

Math Skills

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the left ventral temporal-occipital cortex was the only brain area where activation patterns predicted numerical problem-solving skills in children with ASD. This brain area, Luculano explained during an interview with *Psychiatric News*, "is normally devoted to face processing, which other researchers have shown to be hypoactivated in children with autism when processing faces." Thus "cortical regions typically involved in perceptual expertise may be utilized in novel ways in autism," Luculano and her team suggested in their report.

The findings "provide new evidence for numerical problem solving as a domain of cognitive strength in children with autism," the researchers said. And as Luculano stressed, "It's vital that not only clinicians, but parents and educators, keep in mind that individuals with autism might be gifted with superior abilities, math being one of them."

The research was funded by the National Institutes of Health, the Stanford Institute for Neuroscience, the Singer Foundation, and University College London. PN

An abstract of "Brain Organization Underlying Superior Mathematical Abilities in Children With Autism" is posted at www.biologicalpsychiatryjournal.com/article/S0006-3223(13)00621-5/abstract.

Accidental Death

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accidental death. The strongest risk factor for death by accident was alcohol abuse—a 14-fold increased risk for women and a nine-fold risk for men—and other substance use disorders—an eight-fold risk for women and a 10-fold risk for men.

Yet several other mental disorders were also strong risk factors for an accidental death among both women and men. Personality disorders were associated with a seven-fold risk among women and a four-fold risk among men. And the risks were two- to four-fold among individuals with anxiety disorders, bipolar disorder, depression, or schizophrenia. Mental disorders overall were linked with more than a five-fold risk of accidental death.

Strong associations were also found between having a mental illness and different types of accidental deaths, especially poisoning and falls. Sociodemographic risk factors for a mental illness-related accidental death included male gender, older age, unmarried status, and low socioeconomic status.

One possible explanation for these findings, Crump and his colleagues suggested, is that common symptoms of psychiatric illness, such as fatigue, poor concentration, and sleep disturbance, may increase the chance of accidents through impaired judgment, coordination, and reaction time. Psychotropic medications may also contribute to these risks as a result of side effects or unintentional overdosing. In addition, some mental disorders are linked with risk-taking or self-destructive behaviors that may occur on a continuum from subintentional to intentional, increasing the chances of either an accidental death or suicide, they noted.

"These findings highlight the need for psychiatrists and other health care providers to be more aware of the risks of accidental death in addition to suicide among psychiatric patients," Crump said during an interview with *Psychiatric News*. "Interventions to reduce early mortality among these patients should address underlying common determinants of accidental death in addition to suicide."

The study was funded by the U.S. National Institute on Drug Abuse and the Swedish Research Council. PN

An abstract of "Mental Disorders and Risk of Accidental Death" is posted at http://bjp.rcpsych.org/content/early/20113/08/10/bjp.bp.112.123992.abstract .

Men

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assess the most appropriate grouping of disorders in *DSM-5*," Regier said. "The *DSM-5* Task Force did not find [depression and these externalizing symptoms] to be equivalent disorders."

He added, "The authors of this paper simply assert that these externalizing symptoms are male equivalents of depression. But there is no evidence provided that they are equivalent—only that they are more prevalent in men than they are in women. An alternative conclusion has been that men have different mental disorder prevalence rates of specific disorders than women—that is, women have higher rates of depression, and men have higher rates of substance use disorders, antisocial personality disorder, and intermittent explosive disorder. It isn't clear why the authors believe that these latter conditions are male equivalents of depression." PN

"The Experience of Depression in Men and Women: An Analysis of the National Comorbidity Study Replication" is posted at http://archpsyc.jamanetwork.com/article.aspx?articleid=1733742.

Residents' Forum

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ties every two months during which challenging cases can be discussed and knowledge exchanged. This can also be a good time to support each other emotionally and intellectually, as proposals for research projects may arise. Advocacy work initiated by the two specialties can have far-reaching effects on patients and their families. Opportunities to streamline care may come to fruition sooner if specialists work together more closely.

A wonderful Web resource that clinicians can recommend to patients who suffer from a mental illness and are at risk for cardiovascular problems is www.nami.org/heartsandminds. The NAMI Hearts & Minds program is an online, interactive educational initiative promoting the idea of wellness in both mind and body. PN

Decision Making

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said the commitment to assess patients' and parents' goals at baseline to increase patience treatment adherence may be ineffective. "We can't solve this problem with a checklist," he told *Psychiatric News*. An avid believer in shared decision making, Benson, who is past speaker of the APA Assembly, stressed that clinicians should provide more information to patients on their disorder and treatment options. "We have to engage parents and children early so that they have a personal investment in their treatment," he explained. Benson also emphasized that psychiatrists should discuss with patients the time frame often involved in effective psychotherapy. "If it's not working, discontinue it," he said.

As for Fiks, he told *Psychiatric News* that future studies will need to address efficacy of medication dose and frequency of behavioral therapy as it relates to achieving patient treatment goals, in addition to accessing the impact of preferences and goals of children and adolescents on treatment initiation and outcomes.

"ADHD causes a lot of stress and wear on parents who are struggling with treatment decisions. I think that our model initiates a much-needed conversation that rarely happens," Fiks said.

This study was supported by the National Institutes of Health. PN

"Parental Preferences and Goals Regarding ADHD Treatment" is posted at http://pediatrics.aappublications.org/content/early/2013/08/28/peds.2013-0152.long.

Maternal

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pressed mothers. (A similar trend was also found for the left amygdala.)

"Our findings suggest that an increased risk for depression may be transmitted from mother to child during fetal life," Qiu said in an interview with *Psychiatric News*. "And together with previous studies of infant behavior, they suggest that screening for antenatal maternal depressive symptoms and intervention programs should begin during the prenatal period."

"This study adds to the growing literature that demonstrates that untreated maternal depression has potentially negative effects on the developing fetus," Jennifer Payne, M.D., an associate professor of psychiatry at Johns Hopkins Medical Institutions and an expert on women's mood disorders, told *Psychiatric News*. "Many people mistakenly think that depression should not be treated during pregnancy. This study shows that untreated depression is an exposure for the child in the same way that taking a medication is an exposure."

The research was funded by the National University of Singapore and the Singapore National Medical Research Council. PN

An abstract of "Prenatal Maternal Depression Associates With Microstructure of Right Amygdala in Neonates at Birth" is posted at www.biologicalpsychiatryjournal.com/article/S0006-3223(13)00622-7/abstract.

Housing

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these and other limitations.

"We just hope the take home message in our current study is that a good assessment for the possibility of mental illness needs to be carried out in those living in marginal housing and presenting with substance use or physical illness," Honer said. "Psychiatric care in this situation may be best delivered in a shared-care model with general medicine and addiction care."

The study was funded by the British Columbia Mental Health and Addictions Services and the Canadian Institutes of Health Research. PN

"The Hotel Study: Multimorbidity in a Community Sample Living in Marginal Housing" is posted at http://ajp.psychiatryonline.org/article.aspx?articleid=1725886.

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Universal Health Services, Inc. (UHS) www.uhsinc.com is the largest facilities based behavioral health provider in the country. Our nearly 200 facilities operate independently and develop programs that satisfy the needs of each community. Our services touch more than 350,000 lives each year – from youth and adult programs to dedicated services for the military.

We are actively currently recruiting General, Child, Geriatric, and Addiction Psychiatrists nationwide. We offer dynamic diverse practice settings and career opportunities with work/life balance. Competitive compensation packages will be offered including bonus opportunity and student loan assistance depending on location. **Some locations are H1/J1 eligible.**

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- **WASHINGTON** – Seattle
- **WEST VIRGINIA – Huntington**

For more information about these and other locations and positions contact: Joy Lankswert, UHS In-house Physician Recruitment @ 866-227-5415 ext: 222 or email joy.lankswert@uhsinc.com. **See all UHS positions and facilities at www.physicianpracticeopportunities.com.**

For information on all advertising products that the American Psychiatric Association has to offer, please visit: www.appi.org/Journals/Pages/AdvertisingInfo.aspx

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ARKANSAS

FAYETTEVILLE: General Psychiatrist. Inpatient & Partial Services. **LITTLE ROCK: Child, General & Geriatric Psychiatrists.** Inpatient & Partial Services. Fulltime positions offering salary, benefits & bonus opportunity. Contact Tiffany Crawford, In-house recruiter @ 866-227-5415; OR email tiffany.crawford@uhsinc.com.

CALIFORNIA

Chair, Program Director
California Pacific Medical Center,
San Francisco, California

The Department of Psychiatry at California Pacific Medical Center is seeking a highly qualified and experienced administrator, clinician and educator to lead our department as both Chair and Program Director of the Residency Program. The two positions are highly interrelated and are currently combined. The CPMC Department of Psychiatry consists of a cohesive, talented group of clinician educators who run the clinical services and are core teachers in the four year residency program.

CPMC is a quaternary care, multi-hospital system within San Francisco that has multiple residency programs and has a primary affiliation with Dartmouth (Geisel) Medical School. It is part of the Sutter Health network. The residency program is mature and very highly regarded and the department also has an excellent Psychology internship and Health Psychology fellowship.

This is a unique and exciting opportunity for a strong, creative, collaborative leader to work with our department and hospital leadership to further evolve psychiatric care and education in San Francisco.

A qualified candidate must have substantial experience as a clinician/educator and in administrative/leadership roles. Experience in complex medical systems and an academic setting is also highly desirable. This position is anticipated to begin July 1, 2014.

CPMC is an equal opportunity employer.

Please send a letter of interest,
along with a C.V. to:
David A. Goldberg, MD
goldber@sutterhealth.org

An Outpatient Adult Psychiatrist is needed for Stanislaus County Behavioral Health & Recovery Services, in the Central Valley less than two hours from San Francisco and Yosemite. Recovery-oriented treatment provided in a multidisciplinary setting. Excellent salary scale with steps starting from 179K to 217K; additional 5% differential for board certification. No call requirements at this time. Full benefit package including medical, vision/dental, vacation, sick time. Excellent retirement package with deferred comp. plan avail.

Fax CV to Uday Mukherjee, MD at
(209) 525-6291 or
Email: umukherjee@stanbhrs.org.

BEAUTIFUL NORTHERN CALIFORNIA POSITION
THERAPEUTIC SOLUTIONS, P.C.
Adult and Adolescent Psychiatrist Needed

- Full-time position, Monday - Friday, 8 a.m.-5 p.m.
- Comprehensive practice with outpatient services, IOP and PHP services, as well as outpatient ECT and TMS.
- Limited office call.
- Very competitive salary with bonus structure included.
- Excellent benefits package.
- Our location offers quality housing prices, little traffic, regional airport, 1½ hour drive to Sacramento, 2 hour drive to Napa Valley, 3 hour drive to San Francisco and the coast.

For further info contact
Pamela Mayhew
Practice Administrator, at:
pmayhew@therapeuticsolutionspc.com.

COLORADO

Denver Health (DH) is seeking a full-time BC/BE psychiatrist for the Psychiatric Emergency Services at DH. Duties include: acute treatment of psychiatric emergencies, consultation with mobile crisis, jails, and Denver CARES.

A 525 licensed bed hospital, DH is the Rocky Mountain Region's Level I academic trauma center and the safety net hospital for the Denver area. The DH system, which integrates acute and emergency care with public and community health, includes the Rocky Mountain Regional Trauma Center, Denver's 911 emergency medical response system, Paramedic Division, eight family health centers, 15 school-based health centers, the Rocky Mountain Poison and Drug Center, NurseLine, Denver CARES, and Denver Public Health.

Interested candidates should send CV to Jeanette.moore@dhha.org

Denver Health is an equal opportunity employer.

Horizon Health seeks an **Attending Psychiatrist** for a new 22-bed Senior Behavioral Health program at our client hospital **Exempla Lutheran Medical Center** in **Wheat Ridge, CO.** Excellent practice opportunity and income. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com. EOE

CLASSIFIEDS

The Denver Health Medical Center department of psychiatry is seeking an academic hospitalist psychiatrist for a full time position. Denver Health is the safety net hospital serving the citizens in the city and county of Denver. The position will include:

- Responsibility for adult inpatients on an acute inpatient unit;
- Working with a multi-disciplinary team;
- Opportunities for medical student and resident education.

The successful candidate will have an academic appointment through the department of psychiatry at the University of Colorado School of Medicine. Applicants must be eligible for a Colorado medical license and be BE/BC in general adult psychiatry. Subspecialty training is a plus.

Interested applicants should send a Curriculum Vitae to

Jeanette Moore at
jeanette.moore@dhha.org
Denver Health is committed to
diversity and equal opportunity.

Chief Medical Officer (CMO)

Behavioral Healthcare, Inc., a local non-profit behavioral health organization located in the Denver metro area, provides Medicaid members with mental health services. BHI is seeking a part-time CMO. For more info or to apply visit BHICares.org.

CONNECTICUT

New private adult residential treatment program in Danbury, CT seeks a CT licensed psychiatrist for 5-8 hrs per week. Must be comfortable in working with dual diagnosis and patients with personality disorders. Email resume: dquinn@blueskybh.com, Fax resume: 203-942-2693.

Yale University School of Medicine, Department of Psychiatry and Yale New Haven Hospital seeks various Psychiatric Physicians (full-time and part-time) to staff a network of Yale New Haven Psychiatry urgent care/IOP/PHP programs in the New Haven Area. Positions may be divided between outpatient and crisis intervention service sectors. Duties include clinical assessment and evaluation of new patients, plus provision of pharmacological treatment and supervision of non-physician staff for established patients. Exciting opportunities are available for developing innovative services and academic activities. Successful candidates would be eligible for a voluntary faculty appointment with Yale School of Medicine, based on qualifications. Candidate must be ABPN certified/eligible, license eligible in Connecticut. Duties include daytime hours with 5-6 weekend coverage requirements over the year. Direct inquires to William H. Sledge, MD at YNHPH, 184 Liberty St, New Haven, CT 06519 or william.sledge@yale.edu. Review of applicants will begin immediately, and continue until positions are filled.

Yale University is an Equal Opportunity/
Affirmative Action Employer.
Qualified women and members of
underrepresented minority groups are
encouraged to apply.

Adult/ Child Psychiatrist
Fairfield, CT

Group Psychiatry practice is seeking a full-time Psychiatrist. Excellent salary and benefits. Email CV to: doctorbeach52@gmail.com or fax to Attn: Evelyn A. 203-255-3126.

Yale University School of Medicine, Department of Psychiatry and Yale New Haven Hospital seeks a General Adult Psychiatrist for full-time, inpatient head of multi-disciplinary team. Experience in dual diagnosis and/or substance abuse is desired. The position available is as an academic psychiatrist with responsibilities for teaching as well as clinical care. Academic rank will be dependent upon review of academic achievements and must meet qualifications to fulfill the Yale University School of Medicine criteria for faculty appointments. Successful candidate must be ABPN certified/eligible, license eligible in Connecticut. Direct inquires to William H. Sledge, MD at YNHPH, 184 Liberty St, New Haven, CT, 06519 or William.sledge@yale.edu. Review of applicants will begin immediately and continue until filled.

Yale University is an Equal Opportunity/
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2 psychiatrists needed: 1st working 1/2 time in general adult outpatient clinic and 1/2 time in peri-natal & post natal mood disorders clinic. 2nd working 3/4 time on 20 bed inpatient unit and 1/4 time in general adult clinic. Award winning community hospital, collegial multidisciplinary staff, reasonable on-call, competitive salary/benefits. Apply in confidence to robert.grillo@midhosp.org or call 860-358-6761.

FLORIDA

PSYCHIATRIST; FULL TIME, FL LICENSE REQUIRED; Aventura, FL; private practice located equidistant between Miami and Ft. Lauderdale; children/adolescent/adult/geriatric pts; email CV to aventuraoffices@bellsouth.net or FAX to Dusty: 305-935-1717.

GEORGIA

PSYCHIATRIST

New Horizons Community Service Board in Columbus, Georgia is seeking an Adult Psychiatrist for its Outpatient/Court Services programs. This growing community offers a pleasing climate and is situated within a short distance to Atlanta and the Gulf Coast. The qualified applicant will possess or be eligible for a valid physician's license from the state of Georgia, have completed a three-year residency in an accredited facility and be board eligible or board certified. Excellent salary with a comprehensive benefits package. Interested parties should send their curriculum vitae to:

Shannon Robertson
srobertson@newhorizonscsb.org
706/317-5001
706/317-5004 (Fax)

Adult Psychiatrist – Metro Atlanta

Cobb-Douglas Community Services Board, a behavioral health organization in metro Atlanta that provides integrated primary care and behavioral healthcare, seeks a BC/BE Adult Psychiatrist 4 days a week for the Assertive Community Treatment (ACT) Team. This position requires meeting with clients both in-clinic and in the community. Please email CV to epfennig@cobbcsb.com.

ILLINOIS

Faculty Teaching Position

The University of Illinois College of Medicine at Peoria Department of Psychiatry invites applications for an assistant professor position. This full-time faculty teaching appointment has been opened to support the growth of our new, fully-accredited, residency training program. Responsibilities include clinical service with adult inpatients and directorship of a Partial Hospitalization program. Resident and medical student education and supervision, program development, and scholarship are other important components. Our state-of-the-art behavioral health facilities provide a wonderful working and educational environment for faculty, residents, and medical students. The teaching position is a perfect opportunity for curriculum development, professional growth, and entry into a successful career in academic medicine.

Applicants should be BE/BC in general psychiatry, have interest and aptitude in academia, and be eligible for an unrestricted Illinois medical license. We offer excellent salary and benefits. We are an AA/EO employer. To learn more, please contact Ryan Finkenbine MD, Chair, at (309) 495-1645 or ryanf@uic.edu. Visit this job posting at: http://jobs.uic.edu/job-board/job-details?jobID=30623

Adult Psychiatrist – Northwest Suburbs of Chicago Outstanding career opportunity for BC/BE psychiatrist to join well established private practice in our Schaumburg and Crystal Lake offices. Flexible hours, outpatient only, no hospital work. On call rotation for practice every 12 weeks. For more information contact Paula Comm, Practice Administrator at 847-240-2211 x224 or Fax resume to: 847-240-2418 or email at pmc@prapsych.com.

KENTUCKY

HOPKINSVILLE (North of Nashville): Staff Psychiatrist for inpatient and partial programs – General Adult services with opportunity to work with military program. **Contact Will DeCuyper, In-house Recruiter @ 866-227-5415 OR email will.decuyper@uhsinc.com.**

Horizon Health seeks a Psychiatrist for our 10-bed Senior Adult, and 10-bed Adult, inpatient Behavioral Health programs our client hospital **St. Claire Regional Medical Center in Morehead, KY.** Experience with geriatric population preferred. Excellent salary, benefits and practice opportunity. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com. EOE.

MAINE

Adult Psychiatrist

MaineGeneral Medical Center in Augusta/Waterville, Maine is seeking a BC/BE adult psychiatrist with interest in substance abuse. You will be joining a staff of five employed physicians and four psychiatric mental health nurse practitioners who provide multidisciplinary inpatient, outpatient and consultative services. Work schedule is five eight-hour days. We will have a 30-bed Inpatient program at our new Augusta Campus in November, five Intensive Outpatient Programs, an ACT Team and an outpatient clinic. We also provide consultative support for our inpatient medical and surgical services. We offer excellent benefits including relocation assistance and competitive salary. MaineGeneral is located in scenic central Maine and is a short drive away from ski resorts, lakes and rivers, award-winning golf courses, abundant hiking trails, and the beautiful Maine coast. We are just an hour north of Portland, Maine's largest city, and three hours from Boston.

Send your CV to Lisa Nutter, Physician Recruiter at lisa.nutter@mainegeneral.org or call 1-800-344-6662. Please visit us at www.mainegeneral.org to learn more about our new 2013 Regional Hospital and expansion plans.

MARYLAND

Incredible Sunsets – Endless Waterviews – Psychiatrist needed on 24-bed adult inpatient psychiatric unit on the beautiful Eastern Shore. Dorchester County—a county of 1,700 miles of shoreline and is an easy drive to Annapolis, Ocean City, and Baltimore. A wonderful laid back quality of life. Also, seeking a Psychiatrist within commuting distance to help with 1 or 2 weekends per month on the unit. Please **call Terry B. Good, Horizon Health, at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

Springfield Hospital Center is seeking Board-certified or Board-eligible **general psychiatrists** for our 350-bed MHA adult inpatient facility. Salary is negotiable, within MHA guidelines. Our rural, tobacco-free campus is 22 miles west of Baltimore, convenient to the Chesapeake Bay, Washington, and a variety of cultural, historic, sports, and recreational venues. Benefits include 27 paid days off in the first year, subsidized health insurance, free parking, a generous retirement program, and a truly pleasant workplace. A Medical Services physician is always on campus to attend to patients' somatic needs. Staff psychiatrists are not expected to work after hours, but some choose to supplement their salary by providing evening and weekend/holiday coverage under contract. In addition, we offer after-hours coverage contracts to psychiatrists who are not full-time staff members. Please send CV to **Paramjit Agrawal, M.D., Clinical Director, SHC, 6655 Sykesville Road, Sykesville, MD 21784. For questions, call (410)970-7006 or e-mail paramjit.agrawal@dhmh.state.md.us.** EOE

CLASSIFIEDS

Faculty Opportunity
Division of Child and Adolescent Psychiatry
University of Maryland, Baltimore

The University of Maryland School of Medicine, Division of Child and Adolescent Psychiatry is seeking a full-time child and adolescent psychiatrist, psychologist, and social worker.
The positions carry faculty appointments at the University and offer exciting opportunities for clinical care, teaching and research. Academic rank and salary are commensurate with experience. Send a letter of introduction and CV to: David B. Pruitt, M.D, Professor of Psychiatry and Pediatrics, Director, Division of Child and Adolescent Psychiatry, 701 W. Pratt Street, #429, Baltimore, Maryland 21201 or email dpruitt@psych.umaryland.edu. The University of Maryland is an AA, EOE, and ADA Employer. Minorities and women are encouraged to apply.

Springfield Hospital Center in Sykesville, MD is accepting applications for a **Forensic Psychiatrist**. Eligible candidates must have board certification including added qualifications in forensic psychiatry (or equivalent). Duties include pretrial evaluations of competency to stand trial and criminal responsibility, competency restoration, and training of residents and students. Please forward a CV and inquiry to Erik Roskes, MD, Director, Forensic Services, Springfield Hospital Center, by fax (410.970.7105) or email (erik.roskes@maryland.gov).

MASSACHUSETTS

WORCESTER, The University of Massachusetts Medical School is seeking a psychiatrist with a career interest in Public Sector Forensic Psychiatry for a position at Worcester Recovery Center and Hospital (WRCH). WRCH, a state-of-art inpatient and rehabilitation facility that opened in October, 2012, is a short walk from the Medical School so research and teaching opportunities are easy to accommodate and actively encouraged. This public psychiatric hospital is unique with person-centered, recovery-foci as fundamental, operative principles in serving civil and forensic patients. The successful candidate must be BE/BC and preferred training/experience in Forensic Psychiatry. Faculty appointment at appropriate rank, competitive salary and excellent benefits. Interested applicants should apply at: www.academicjobsonline.org.

UMass Memorial Medical Center/University of Massachusetts Medical School Department of Psychiatry in Worcester, MA seeks a BC/BE Psychiatrist for its University Hospital Outpatient Clinic. Candidates should have strong academic credentials and sound clinical skills, and interest in pursuing academic opportunities in either training or research. An academic appointment, commensurate with experience, is available. Interested applicants are encouraged to submit CVs and letters of interest to: psychiatryrecruitment@umassmemorial.org

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CAMBRIDGE HEALTH ALLIANCE:
Medical Director, Child/Adolescent Inpatient/Intensive Psychiatric Services

Cambridge Health Alliance, Division of Child and Adolescent Psychiatry, Harvard Medical School. Full-time Medical Director of Child/Adolescent Inpatient and Intensive Psychiatric Services at our Cambridge campus. Oversee care in a dynamic setting with multidisciplinary teams on the child and adolescent inpatient units using a nationally recognized program for restraint reduction. Candidates will be expected to contribute to the academic programs of the department including teaching child psychiatry fellows, general psychiatry residents, medical students, and other trainees. Academic appointment, as determined by the criteria of Harvard Medical School, is anticipated.

Qualifications: BC, demonstrated commitment to public sector populations, strong clinical skills, strong leadership and management skills, team oriented, problem solver. Interest and experience in clinical operations, with proven leadership skills in communication, team building and conflict resolution. Bilingual and/or bicultural abilities are desirable. Interest and experience with dual diagnosis and/or substance use disorders preferred. Competitive compensation, excellent benefit package. Cambridge Health Alliance is an Equal Employment Opportunity employer, and women and minority candidates are strongly encouraged to apply.

CV & letter to Joel Goldstein, MD, Dept. of Psychiatry, 1493 Cambridge Street, Cambridge, MA 02139. Fax 617-665-1204. **Email: JoGoldstein@challiance.org** (email preferred).

Berkshire Health Systems

Psychiatrist Opportunity in the Beautiful Berkshires. Top notch colleagues.

Berkshire Medical Center's Department of Psychiatry and Behavioral Science provides you the opportunity to become part of a stable, highly integrated clinical collaboration among Psychiatry, Primary Care, and Medical Specialty Services. Our Health System has an excellent opportunity for an Adult Psychiatrist to work in a highly integrated clinical collaborative at the interface of Primary Care and Behavioral Health. A clinical background in geriatric psychiatry is preferred. Our psychiatry residency program allows you to contribute to the education of the next generation of mental health specialists. Berkshire Medical Center is nationally recognized by HealthGrades and many other independent organizations for outstanding care.

Please contact Antoinette Lentine in the Physician Recruitment Department at 413-395-7866 or e-mail at mdrecruitment@bhs1.org.

www.psychiatry.org

CAMBRIDGE
Consultation-Liaison Psychiatry and Woman's Health Position

PSYCHIATRISTS: Cambridge Health Alliance is seeking two providers for half- to full-time positions in our Consultation-Liaison Psychiatry and Woman's Mental Health Service. The positions will focus on clinical work and program development in our general hospitals, primary care, specialty medical clinics, and our new, innovative telemedicine program. Clinicians will be co-located and integrated into the medical sites. The Department of Psychiatry at Cambridge Health Alliance is an appointing department at Harvard Medical School. Our public health commitment coupled with a strong academic tradition and existing collaboration with our medical colleagues, make this an ideal opportunity for candidates interested in integrated medical and psychiatric care with underserved and multi-ethnic patient populations. We have strong training programs in Primary Care, Adult and Child Psychiatry, Geriatric, and Psychosomatic Medicine and innovative educational programs for medical students. There are many opportunities for teaching and research. 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 and medical specialists. Fellowship training in Psychosomatic Medicine, as well as bilingual and/or bicultural abilities, is desirable. Interest and experience with 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.**

INPATIENT PSYCHIATRIST
NORTH OF BOSTON

Full-time, salaried psychiatry position available on the 22-bed, general adult inpatient psychiatry unit at Melrose-Wakefield Hospital, a full-service community hospital 8 miles north of Boston. On-call coverage is optional. The adult unit is part of Hallmark Health's comprehensive behavioral health service that includes geriatric inpatient units at Lawrence Memorial Hospital in Medford, ECT, and outpatient services at Community Counseling in Malden and Medford. Voted One of Boston Magazine's Best places to work in Boston, we offer a competitive compensation and benefits package and flexible schedule. Tufts faculty appointment available. Current MA professional license is preferred.

If interested, please forward your CV to Gina Mariona via email: gmariona@hallmarkhealth.org or call 781-338-7517.

WORCESTER, The University of Massachusetts Medical School is seeking a psychiatrist with a career interest in Public Sector Psychiatry for a position at Worcester Recovery Center and Hospital (WRCH). WRCH, a state-of-art inpatient and rehabilitation facility that opened in October, 2012, is a short walk from the Medical School so research and teaching opportunities are easy to accommodate and actively encouraged. This public psychiatric hospital is unique with person-centered, recovery-foci as fundamental, operative principles. The successful candidate must be BE/BC and preferred training/experience in Public Sector Psychiatry. Faculty appointment at appropriate rank, competitive salary and excellent benefits. Interested applicants should apply at: www.academicjobsonline.org.

MICHIGAN

Horizon Health, together with client hospital seeks a Child/Adolescent Psychiatrist to join a behavioral health team of psychiatrists, psychologists, social workers and medical consultants. The program offers 61 licensed inpatient psychiatric beds (47 adult and 14 adolescent) and 7 licensed inpatient chemical dependency beds. Located in Saginaw, a city of Michigan and the seat of Saginaw County, located in the Flint/Tri-Cities region of Michigan. Child/Adolescent Psychiatrist will be employed by hospital. Hospital package will include competitive salary, full benefits, and insurance coverage. Interested candidates please submit CV to Mark Blakeney: mark.blakeney@horizonhealth.com ; Voice: 972-420-7473; Fax 972-420-8233. EOE

MISSISSIPPI

Forrest County General Hospital d/b/a Pine Grove Behavioral Health and Addiction Services located at 2255 Broadway Drive, Hattiesburg, MS 39402 seeks a Psychiatrist to diagnose, treat, and help prevent disorders of the mind at 2255 Broadway Drive, Hattiesburg, MS 39402 and 6051 US Highway 49, Hattiesburg, MS 39402. Applicant must have completed a Psychiatry Residency training program and must be eligible to obtain a Mississippi Medical license. Send resume to Evan S. Dillard, 1 Lincoln Parkway, Suite 202, Hattiesburg, MS 34902.

Horizon Health seeks a **Medical Director** for a 19-bed Adult Inpatient Psychiatric Program in **Northern MS.** Well established, busy program with full complement of support staff and administration. $200K+ Salary, Full Benefits, CME, Relocation and more. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com. EOE

MISSOURI

KANSAS CITY – Child Psychiatrist: Inpatient and Partial programs. **NEVADA – Child Psychiatrist:** Residential and I/P services. **J1 eligible in Nevada and H1 both locations. Top compensation, benefits and bonus opportunity!** Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

CLASSIFIEDS

Make an Income that Matches All the Work You Do - Seeking a Psychiatrist for a very lucrative position with a successful group practice in Festus. Work would be primarily inpatient work on adult & geropsych units in a general hospital. Ideal opportunity for someone who wants the ability to make a very large income based on all your hard work. All billing and scheduling is done for you. Can also employ if in need of H1 or J1 Visa. Please **call Terry B. Good, Horizon Health, at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

MONTANA

Horizon Health seeks a Psychiatrist for a 24-bed (12 adult, 12 geriatric) behavioral health inpatient hospitalization program for short-term behavioral health treatment in beautiful **Helena, MT**. Offering a competitive salary and benefits. Contact: Mark Blakeney, Horizon Health, mark.blakeney@horizonhealth.com or FAX: 972-420-8233. EOE

NEW HAMPSHIRE

Inpatient Psychiatrist:
Child or Adult trained

Hampstead Hospital, Hampstead, NH (www.hampsteadhospital.com)

- Generous compensation and benefits
- Highly skilled psychiatry staff with longevity and collegial relationships
- Rural setting close to seacoast, mountains, Boston

Contact Cindy Gove at
cgove@hampsteadhospital.com or
603-329-5311, x 3226

GEISEL SCHOOL OF MEDICINE at DARTMOUTH Department of Psychiatry is seeking a Neuroscience Researcher with expertise in the neuroscience and neuroimaging of addiction and other psychiatric disorders.

Applicants must have a PhD in neuroscience, psychology, or equivalent and have expertise using multi-modal neuroimaging tools to study drug abuse and psychiatric disorders. A specific focus on tobacco/nicotine is preferred. The successful candidate will provide research-training opportunities for graduate students, residents, and postdoctoral fellows and oversee the day-to-day responsibilities of research assistants. The ability to collaborate with both clinical and preclinical researchers will be necessary to foster translational research objectives. The successful candidate will have opportunities to develop advanced-level seminars in neuroimaging of addiction and other psychiatric disorders.

Applicants should have a consistent record of extramural funding and of independent and high-quality research productivity, demonstrated by publications in top-tier general and specialty journals, or clear evidence of promise toward such a record. The successful candidate must demonstrate knowledge of effective strategies for working with diverse faculty, staff, and students and be able to demonstrate job-related experience with and/or commitment to diversity in the work/academic environment.

Academic rank and salary will be commensurate with experience. A letter of interest, curriculum vitae and three letters of reference should be addressed to Alan Green, MD, Chair for the Department of Psychiatry and e-mailed to psychiatry.jobs@dartmouth.edu. Please reference Neuroscience Researcher in the subject line.

Dartmouth College is an Equal Opportunity/Affirmative Action employer strongly committed to achieving excellence through cultural diversity. The College actively encourages applications and nominations from women, minorities, veterans and persons with disabilities.

NEW JERSEY

Northern NJ – Attractive Compensation Packages with base salary and benefits and RVU based bonus plans that will allow psychiatrists to make well over their base. Inpatient adult and geriatric work; units are all voluntary patients. Please contact **Terry B. Good at 1-804-684-5661,** Fax#: 804-684-5663; Email: terry.good@horizonhealth.com.

Stress Care of New Jersey, LLC a Community Mental Health Center in Matawan, NJ is seeking FT or PT Psychiatrists. Benefits available. Fax CV to (732) 679-4549 or email to Stressmg@optonline.net. To learn more about Stress Care, please visit our website, www.stresscareclinic.com.

NEW YORK CITY & AREA

Rockland Psychiatric Center
Orangeburg, NY
Chief of Psychiatry

Seeking a dynamic, recovery-oriented psychiatrist to lead a department of 70 inpatient and outpatient psychiatrists working in a 7-county area. Rockland Psychiatric Center, now the Lower Hudson Regional Center of Excellence, is the largest state psychiatric hospital system in New York. The Chief sets, communicates, and carries out policy, ensuring that the department continues to improve in quality of care and person-centeredness. The Chief also manages RPC's affiliation with NYU and other academic agreements, and leads the hospital forensic committee.

The main hospital campus is located in Orangeburg, NY, 19 miles north of Manhattan. Please send CV to Mary Barber, MD, Clinical Director, mary.barber@omh.ny.gov.

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.

Project Renewal is a leading non-profit organization known for our comprehensive approach to ending homelessness, renewing lives & reclaiming hope for NYC's homeless. Our mission is to transform the lives of homeless NYC men & women who in addition to being without a home, cope with mental illness and/or addiction to drugs/alcohol. We are seeking FT & PT Psychiatric Nurse Practitioners and BC/BE Psychiatrists to join our multidisciplinary social service team. Psychiatry providers will conduct comprehensive evaluations, medication management and crisis intervention for homeless men and women living in shelters, drop in centers, permanent housing, transitional scattered and congregate housing programs. Providers will collaborate with shelter staff as well as liaison with outside providers as appropriate. Positions offer opportunity for administrative responsibilities. NYS medical license & registration and excellent organizational & interpersonal skills required. Computer efficiency is req'd. Experience working with homeless adults preferred. Buprenorphine waiver a plus. Spanish language a plus. Competitive salaries commensurate w/your exp.

Interested candidates please reach out to us at 200 Varick Street, 9th Floor, NY, NY 10014; Fax: 212-243-4868; e-mail: christine.figaro@projectrenewal.org. NO PHONE CALLS, PLEASE. To learn more about us, please visit www.projectrenewal.org. We are an EOE.

NEW YORK STATE

ELMIRA PSYCHIATRIC CENTER
Adult and Adolescent Psychiatrists
Board Eligible/Board Certified
$168,421 - $256,700*
Limited Permit eligible applicants will also be considered

- All positions **M-F 8-4:30**
- Student loan repayment available
- Excellent NYS benefits package
- Inpatient, Outpatient and Day Treatment services
- Our location offers: quality housing prices; little traffic; regional airport; Cornell University; 4hr drive to NYC, Toronto & Philadelphia; 5-1/2 hr drive to Boston & DC; less than 1hr to Finger Lakes Wine Country; Watkins Glen International Racetrack.

*Includes voluntary low stress on-call at regular pay rate.

For further info contact: Patricia Santulli, Director of Human Resources, Elmira Psychiatric Center, 100 Washington Street, Elmira, NY 14901; e-mail: P.Santulli@omh.ny.gov; call: (607) 737-4726 or fax: (607) 737-4722. An AA/EOE Employer

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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.

St. Lawrence Psychiatric Center
Psychiatrists
NYS Licensed or Limited Permit
(Limited Permit option – see below)**
Salary based on experience
Earn up to an additional $74,000/year through a voluntary on-call program
Fringe Benefits equal to 50.16% of your salary
Monday – Friday, 8:00A – 4:30P

St. Lawrence Psychiatric Center is seeking Licensed Psychiatrists for Adult, Children/Youth, and Sex Offender Treatment Inpatient Services and for Adult and Children/Youth Outpatient Services.

- National Health Services Corps (NHSC) student loan repayment may be available (Up to $60,000 for a 2-year FT commitment; up to $170,000 with a 5-year FT commitment, and possible total debt alleviation with 6 or more years of service)
- Doctors Across New York (DANY) loan repayment or sign-on bonuses may be available (applications are time limited and considered in the order in which they are received).
- Excellent NYS Benefits to include medical/dental/vision insurance, paid vacation, holiday and sick time, an excellent retirement plan, and educational and professional leaves.
- Our location offers quality housing prices, mild traffic, a regional airport, Clarkson University, St. Lawrence University, and 2 SUNY colleges; 1 hr drive to Ottawa; 2 hr drive to Montreal, Lake Placid, and Syracuse.

**Limited Permit Option: If you have finished your residency, but not the USLME, you may be appointed on limited permit, initially for 2 years, renewable for further 2 years.

Applications are available by calling
(315) 541-2179
or send resume to:
Personnel Office
St. Lawrence Psychiatric Center
1 Chimney Point Drive
Ogdensburg, NY 13669-2291
or to Angela Grant at
Angela.Grant@omh.ny.gov.

SLPC is a fully accredited Joint Commission program/AA/EEOE/Self-indemnified.**Affiliated with SUNY Upstate Medical University.**

CLASSIFIEDS

PSYCHIATRIST OPENINGS at CENTRAL NEW YORK PSYCHIATRIC CENTER

A State-operated, Forensic Facility, the first Office of Mental Health Facility to be recognized by the national accrediting body, The Joint Commission, as a Top Performer. Our Facility is seeking full time Psychiatrists for our Inpatient Facility in Marcy, NY, and for our Correction-based programs in various locations throughout the state. These positions are in proximity to Glens Falls, Middletown, Syracuse, Rochester, Batavia, and Utica as well as in Albany and the Bronx. Competitive salary range is $168,421 for NY State License to $181,790 for Board Certification plus additional compensation for some programs. NY State provides a generous and comprehensive benefits package including an outstanding Pension Plan and for NY State Regents Loan Forgiveness. Opportunities may exist for additional compensation.

Dr. Jonathan Kaplan
Clinical Director for
Outpatient Services
(Code 312)
Call at: 845-483-3443
Fax: 845-483-3455
Email: Jonathan.Kaplan@omh.ny.gov

NORTH CAROLINA

Now recruiting for Board Certified or Board Eligible PsychiatristsCoastal Carolina Neuropsychiatric Center, PA has multiple locations in NC. In-patient, out-patient, and a combination of both may be available. Competitive salary and benefits package. H1 & J1 visa applicants may apply. Qualified applicants, please send CV to info@coastalcarolinapsych.com.

HERE WE GROW AGAIN!

Monarch, a non-profit CABHA certified Behavioral Health agency is currently hiring Psychiatrist and PMHNPs in several locations in NC. We provide services through our Open Access Model and always put the people we support first. We currently have full time openings in Raleigh, Greensboro, and Rocky Mount. We also have a few part time positions open as well. Come to a growing organization and help us

Make Dreams take Flight!
If interested please contact:
Brandon Springs
704-816-7524
Brandon.Springs@MonarchNC.org

NORTH DAKOTA

Sanford Clinic North – Fargo, ND has full-time positions available for Adult Psychiatrists in its Behavioral Health Sciences Service. The department is staffed by more than 30 psychiatrists, clinical nurse specialists, doctorate-level psychologists and master's-level psychologists offering a continuum of care, from inpatient hospitalization and partial hospitalization programs, to outpatient individual and group therapy including eating disorders at Sanford's highly regarded Eating Disorders Institute. Responsibilities include teaching psychiatry resident and medical students through the University of North Dakota School of Medicine. Live and work in the progressive communities of Fargo-Moorhead-West Fargo, home to nearly 200,000. This metropolitan community offers excellent schools, a wonderful blend of cultural and sports events, big name entertainment, year-round outdoor recreation and much more. To learn more contact: Jill Gilleshammer, Physician Recruiter, Phone: (701) 417-4852; Email: Jill.Gilleshammer@sanfordhealth.org; Website: careers.sanfordhealth.org

OHIO

OUTPATIENT - SO. OH - Hospital Named 10th in the Top 100 Best Places to Work - Outpatient position with some on-call duties for the geropsych unit. Enjoy small town living; laid-back, wonderful quality of life. An easy drive to Huntington, WV and Cincinnati, OH. Salaried position with attractive bonus plans; medical school loan repayment plan up to $200k. Join our top notch team at this truly impressive hospital and enjoy where you live & work every day. Please **call Terry B. Good, Horizon Health, at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

OREGON

Summit Research Network (Oregon), Inc. is seeking a licensed, board certified Psychiatrist to work with adults in clinical research trials. Must be comfortable working in a team environment as a sub Investigator and/or Principal Investigator in primarily psychiatric pharmaceutical research at our site in **Portland, OR.**

This position is part time with a potential to increase to full time. Summit offers competitive salary based on experience/credentials with an excellent benefit package.

Please send inquires and CV to: James R. Hockley, MBA, Summit Research Network Management, Inc., 2701 NW Vaughn St., Ste.350, Portland, OR 97210 or via email: jhockley@summitnetwork.com.

Summit Research Network (Seattle) LLC is seeking a licensed, board certified Psychiatrist to work with adults in clinical research trials. Must be comfortable working in a team environment as a Sub Investigator and Principal Investigator in primarily psychiatric pharmaceutical research at our site in **Seattle, WA.**

This position is part time with the potential to increase to full time. Summit offers competitive salary based on experience/credentials with an excellent benefit package.

Please send inquiries and CV to:
James R. Hockley, MBA, Summit Research Network Management, Inc., 2701 NW Vaughn St., Ste.350; Portland, OR or via email: jhockley@summitnetwork.com.

PENNSYLVANIA

MEDICAL DIRECTOR & ASSOCIATE POSITIONS – Employment or Contractor Positions (FT or PT) in Lancaster, PA – Close to Hershey - VERY attractive compensation packages available; PT work is also available. Involves inpatient work on adult & geropsych units. Plans to expand services and open outpatient in the works. A beautiful area in eastern PA; strong medical community; an easy drive to several metro areas. Please call **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com

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We have exciting full and part-time positions in our five-hospital system close to Philadelphia and Wilmington. There are immediate openings in our outpatient psychotherapy practice which includes the **Women's Behavioral Health Program, Child/Adolescent, and General Adult.** Psychiatrists provide both psychotherapy and medication management. We also seek psychiatric leadership of our Pain Management Program.

Excellent salaries and benefit package. Send CV to Kevin Caputo, MD, Chairman Department of Psychiatry, Crozer-Keystone Health System, One Medical Center Blvd., Upland, PA 19013 or call 610-874-5257.

LANGHORNE, PA – EXPAND YOUR BUSINESS BY ADDING INPATIENT WORK TO YOUR PRIVATE PRACTICE – Seeking Board Certified Psychiatrist in practice in the area who wishes to incorporate some inpatient geriatric work into their daily schedule to increase revenue and grow their practice. This is a fantastic way to quickly grow one's business, or for a group practice to expand their market to another area/hospital. Please contact **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

Crisis Center Medical Director. Full time position. Either FT Crisis Center @ Mercy Fitzgerald Hospital or half time Crisis and flexible half time practice @ hospital (inpatient/consults) and office. 1:4 weekend rounds on 21 bed adult unit. Paid medical and occurrence malpractice. Compensation is either a competitive salary or a higher salary/ practice draw. Mercy Psychiatry Associates has been practicing for 22 years and provides all psychiatric services to Mercy Fitzgerald Hospital. PA license. Board certified or eligible, if less than five years post residency. Flexibility, productivity, and availability are rewarded. To apply please contact: Jeffrey J. Dekret, M.D.Director of Psychiatry, MFH, 610-237-4123, Fax 610-237-4695.

SOUTH CAROLINA

Adult Inpatient Psychiatrist needed near Coastal South Carolina: McLeod Health Behavioral Health 23 bed Adult Psychiatric Center is located near the Coast; in the beautiful, historic southern town of Darlington, SC close to Myrtle Beach, SC. We are seeking to hire a BC/BE Psychiatrist with an innovative approach to medicine. This is a fully employed inpatient position that offers a Flexible schedule. Schedule can be designed between the physicians and their desired schedule. State of the art facility with a 24 hour Access Center and an experienced staff. Staff includes midlevels who take first call, Certified Counselor in Alcohol & drugs, and 5 Counselors with Masters Degrees. We offer a competitive salary, comprehensive benefits and retirement package, paid professional liability insurance, CME allowance, relocation assistance, and sign on bonus. If interested in joining our Team, please call Angela Stukes at 843-777-7046 or email at astukes@mcleodhelath.org. Check us out at www.mcleodhealth.org

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Medical Director Position - 8-bed inpatient Geropsychiatric Unit; salaried with benefits or practice opportunity for those who prefer independent contract. Weekend call is 1 in 3 or 4. Rounding on weekends is not necessary unless there is an admission on Friday or Saturday. Located in northeast SC, easy drive to Florence, SC and the beach. Please **call Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; Email: terry.good@horizonhealth.com.

TENNESSEE

Telepsychiatry Opportunity!

Horizon Health, in partnership with **Livingston Regional Hospital** in **Livingston, TN,** near beautiful **Dale Hollow Lake,** has an exciting opportunity for a **Medical Director** at our 10-bed Geriatric Inpatient Psychiatric Program. Minimum 2 days onsite coverage **required** with remainder via **Telemedicine.** Excellent income with great quality of life! 2 hours from Nashville and Knoxville and one of the lowest costs of living in the U.S. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

TEXAS

Opening for a boarded/board eligible Adult Psychiatrist, prior research experience preferred, for a well established dedicated clinical trials facility. A minimum of 20 hours/week is required for clinical trial responsibilities, with an opportunity to develop or continue your private practice. Compensation includes a guaranteed stipend, excellent health benefits, and paid vacation. Primary tasks and duties will focus on early drug development for inpatient and outpatient studies. Please send your CV to Douglas Lopez, MBA, Director of Business Operations, dlopez@claghorn-lesem.com.

CLASSIFIEDS

The Department of Psychiatry and Behavioral Sciences of the University of Texas Medical School at Houston has an extraordinary opportunity for psychiatrists seeking to develop and implement new outpatient clinical and research initiatives in community based outpatient clinics within the Houston area with our partner Harris Health. We are also adding faculty to our 250 bed inpatient hospital, the Harris County Psychiatric Center. Our inpatient and outpatient services include unique and robust clinical and research initiatives. The Department is looking to expand clinical and research areas and is seeking general psychiatrists, child and adolescent psychiatrists and geriatric psychiatrists to join a growing academic department dedicated to excellence in training and education, and primacy in research and investigation. The Medical School is part of the University of Texas Health Science Center Houston, located in the Texas Medical Center – the largest medical center in the world. Individuals applying for these positions must be Board Certified in general psychiatry, child & adolescent psychiatry and geriatric psychiatry or have completed an accredited training in these specialty and subspecialty areas in the United States. Additionally, they must be licensed or be eligible for licensing in the State of Texas. Depending upon the applicant's qualification and credentials, faculty appointments at the level of Assistant Professor, Associate Professor or Professor will be offered. Salary levels are very competitive and also carry excellent fringe benefit packages. To find out more information about these unique academically driven positions or to apply for them, please write to Jair C. Soares, M.D., Professor and Chair, and include a copy of your curriculum vitae and a letter of interest to 1941 East Road, Houston, Texas 77054, e-mail: Jair.C.Soares@uth.tmc.edu; phone 713-486-2507; fax 713-486-2553. The University of Texas Health Science Center at Houston is an EO/AA employer. M/F/D/V

AMARILLO: General Psychiatrist – Hospitalist position offering salary, benefits and bonus opportunity. Great schedule and limited call.
EDINBURG/McALLEN: General or Child Psychiatrist – Inpatient and/or Outpatient practice settings. Salary, benefits and bonus opportunity. Great schedule and limited call.
EL PASO: General Psychiatrist – Outpatient Services. Independent contractor with leadership role and stipend offered.
DALLAS: Arlington, DeSoto and Rockwall areas. General and Child Psychiatrists. Independent contractor compensation. Stipend options for leadership roles in inpatient services. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

Do you use social media?

The American Psychiatric Association is on Facebook! Stop by to like our page at **https://www.facebook.com/AmericanPsychiatricAssociation**

VIRGINIA

PSYCHIATRIST or Gero-PSYCHIATRIST
No Call!
Sign-On Bonus!

Catawba Hospital is accepting applications from BE/BC Psychiatrists interested in joining an outstanding medical staff in a 110-bed, Joint Commission accredited, psychiatric hospital. Academic affiliation exists with the local Residency Program. Teaching medical staff have academic faculty appointment. Experience with serving adult and/or geriatric patients with severe mental illness is desired. Applicants must be licensed or eligible for licensure in Virginia. No call required.

Located just minutes from the metropolitan community of Roanoke, VA, the area provides excellent recreational, educational, and cultural opportunities in the Blue Ridge Mountains:

- one of the ten best places to raise a family in the United States (Parenting magazine);
- ranked among the least stressful locations in the United States (Zero Population Growth, Inc.);
- 7th healthiest place to live (Kiplinger's Personal Finance Magazine);
- one of the nation's top 20 cities for quality of life (University of Kentucky study).

Salary up to $175,000/year based on experience and expertise.

In addition, the generous state employee benefits package brings your total compensation to the equivalent of $246,000/year.

- Malpractice covered by the Commonwealth of VA
- Possibility of on grounds housing in a relaxed rural setting
- Financial assistance with moving expenses

No J-I positions available. Position will remain open until filled.

Apply on-line at
https://jobs.agencies.virginia.gov

For telephonic/e-mail inquiries contact:
Gary Hiler, Human Resource Manager
(540) 375-4368
gary.hiler@dbhds.virginia.gov

Submit CV to:

Human Resource Office
CATAWBA HOSPITAL
P.O. Box 200
Catawba, VA 24070-0200
TDD(540)375-4385
FAX(540)375-4359
EOE M/F/H/V

Did you know

APA's advocacy resources include: the Legislative Action Center, where you can get updates on key issues and legislation, plus listings of elected officials and other election news; the APA political action committee; the department of Government Relations; and the APA Congressional Action Network. www.psychiatry.org/advocacy-newsroom

VIRGINIA
Faculty Position
Child & Adolescent Psychiatry

Virginia Tech Carilion School of Medicine and Carilion Clinic a physician-led multispeciality academic healthcare organization with over 600 physicians has a fulltime position for a Child and Adolescent Psychiatrist. The position is associated with the new allopathic medical school and Carilion Roanoke Memorial Hospital, a 700-bed academic tertiary referral center with 12 acute child and adolescent psychiatric beds and community outpatient services. Responsibilities include direct clinical services, teaching medical students, and supervising psychiatry residents and fellows. Child and Adolescent call coverage shared with 5 psychiatrists.

Submit CV and cover letter to Amy Silcox Physician Recruiter, amsilcox@carilionclinic.org or call 540-224-5187.

WEST VIRGINIA

C/A Psychiatrist - 50 Minutes from Pittsburgh – Forbes' Top Ten "Best Places to Live Cheaply" because of the low cost of living, highly rated schools, low unemployment and low crime rate. Impressive general hospital with new Child/Adol. Pavilion; this is an inpatient and outpatient position; salaried with benefits and attractive bonus plan. Top-notch staff; great quality of life—truly a "must see" position when considering a new job in a new place. Contact **Terry B. Good at 1-804-684-5661,** Fax #: 804-684-5663; terry.good@horizonhealth.com. EOE

Excellent private practice opportunity for a adult/ or child-trained psychiatrist in Southern West Virginia to join a well-established practice. In-patient, outpatient, and consultation services. Exceptional salary and benefits. Good place to raise children. Easy drive to several big cities, heaven for outdoor lovers. Can help with visa conversion and sponsorship. Fax cv to (304) 252-1703 or email nafa2 @aol.com.

Fellowships

THE 2014-2016 PAUL JANSSEN FELLOWSHIP IN TRANSLATIONAL NEUROSCIENCE RESEARCH AT COLUMBIA UNIVERSITY

The Paul Janssen Fellowship is awarded to an outstanding young physician-investigator (M.D. or Ph.D. degree) to conduct novel translational research in the field of neuroscience as it relates to psychiatric disease and medicine. The Paul Janssen Fellow will be assigned both a basic scientist mentor and a clinical investigator mentor from the faculty at Columbia University to serve as joint mentors. The fellow will take a basic observation made by the basic science mentor and apply it to the study of disease or treatment with the clinical research mentor. Candidates from the international neuroscience community, holding an M.D. or Ph.D. degree, and preferably having completed initial fellowship research training, are invited to apply.

The award provides a stipend, commensurate with experience. The stipend provided may require supplemental funding by the mentors. The length of the Fellowship can be up to two years. Preliminary/open application period: 9/1/13 to 11/29/13 (by 5 pm).

The following should be provided in 11 point font (Arial or Times New Roman) with a minimum of one-inch margins: 1) Face page letter identifying applicant and a brief description of previous training in medical research, previous research interests, current position and future research interests. 2) NIH biographical sketch (Section A: Personal Statement – not applicable). 3) Letters of support/reference from at least three (3) current or previous mentors (can be PDFs emailed).

Note: A complete project proposal is not required until notified you are a finalist. Preliminary applications should be submitted via e-mail to: Ann Marshak, Administrator, e-mail: am3558@columbia.edu.

Geriatric Psychiatry Fellowship Program: The University of Texas Health Science Center at **San Antonio** is currently accepting applications for 2014-2015. This one-year program offers training in a wide variety of outpatient, inpatient and consultative settings, as well as opportunities for research and teaching. Interested individuals should contact (210)567-5432.

Offering its 37th year of fellowship training in Psychosomatic Medicine, this ACGME-accredited fellowship is currently accepting applications for three PGY-5 positions to start July 1, 2014. Under the guidance of Drs. Thomas Wise and Catherine Crone, the program provides comprehensive training and mentorship in the care and understanding of psychiatric issues in the medically ill. Both inpatient and outpatient consultation-liaison experiences are provided in areas that include collaborative care with internal medicine, oncology, organ transplantation, ob-gyn, and HIV services. Didactic seminars in liaison approaches, administrative issues, neurology, hypnosis, and primary psychosomatic medicine topics help to round out the fellowship training experience. Opportunities in teaching, academic writing, research, and outpatient psychotherapy are encouraged and readily available. The fellowship is based at Inova Fairfax Hospital, an 876-bed tertiary care teaching hospital located in the heart of the DC Metro area.

Interested individuals should contact:

Catherine Crone, M.D., F.A.P.M.
PM Fellowship Program Director
George Washington University
Medical Center c/o Inova Fairfax Hospital
3300 Gallows Road, Falls Church, VA
22042
Phone: 703-776-3626
E-mail: cathy.crone@inova.org