
Schizophrenia can
tear patients apart
Look inside to learn more

Latuda® (lurasidone HCl) tablets

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LATUDA safely and effectively. See full prescribing information (FPI) for LATUDA.

LATUDA (LURASIDONE HCL) tablets for oral administration,
Initial U.S. Approval: 2010

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis. *(5.1)*

INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia *(1)*. Efficacy was established in four 6-week controlled studies of adult patients with schizophrenia *(14.1)*.

DOSAGE AND ADMINISTRATION

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. The maximum recommended dose is 80 mg once daily. LATUDA should be taken with food *(2.2)*.

DOSAGE FORMS AND STRENGTHS

Tablets: 40 mg and 80 mg *(3)*

CONTRAINDICATIONS

Any known hypersensitivity to LATUDA or any components in the formulation *(4)*. Coadministration with a strong CYP3A4 inhibitor (e.g., ketoconazole) and inducer (e.g., rifampin) *(4)*.

WARNINGS AND PRECAUTIONS

- **Cerebrovascular Adverse Reactions:** An increased incidence of cerebrovascular adverse events (e.g., stroke, transient ischemic attack) has been seen in elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs. *(5.2)*.
- **Neuroleptic Malignant Syndrome:** Manage with immediate discontinuation and close monitoring *(5.3)*.
- **Tardive Dyskinesia:** Discontinue if clinically appropriate *(5.4)*.
- **Metabolic Changes:** Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and weight gain *(5.5)*.
- **Hyperglycemia and Diabetes Mellitus:** Monitor patients for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Monitor glucose regularly in patients with diabetes or at risk for diabetes.
- **Dyslipidemia:** Undesirable alterations have been observed in patients treated with atypical antipsychotics.
- **Weight Gain:** Gain in body weight has been observed, clinical monitoring of weight is recommended.
- **Hyperprolactinemia:** Prolactin elevations may occur *(5.6)*.
- **Leukopenia, Neutropenia, and Agranulocytosis** have been reported with antipsychotics. Patients with a pre-existing low white blood cell count (WBC) or a history of 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 *(5.7)*.
- **Orthostatic Hypotension and Syncope:** Dizziness, tachycardia or bradycardia, and syncope may occur, especially early in treatment. Use with caution in patients with known cardiovascular or cerebrovascular disease, and in antipsychotic-naïve patients *(5.8)*.
- **Seizures:** Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold *(5.9)*.
- **Potential for Cognitive and Motor Impairment:** Use caution when operating machinery *(5.10)*.
- **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia. Closely supervise high-risk patients *(5.12)*.
- See Full Prescribing Information for additional **WARNINGS and PRECAUTIONS**

ADVERSE REACTIONS

Commonly observed adverse reactions (incidence > 5% and at least twice the rate for placebo) included somnolence, akathisia, nausea, parkinsonism and agitation *(6.2)*.

To report SUSPECTED ADVERSE REACTIONS, contact: Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- LATUDA is not recommended to be used in combination with strong CYP3A4 inhibitors, e.g., ketoconazole. (*4* and *7.1*)
- Dose adjustment is recommended for moderate CYP3A4 inhibitors (e.g. diltiazem) (*7.1*)
- LATUDA is not recommended to be used in combination with strong CYP3A4 inducers, e.g., rifampin. (*4* and *7.1*)

USE IN SPECIFIC POPULATIONS

- **Geriatric Use:** No dose adjustments required. *(8.5)*
- **Pregnancy:** Use LATUDA during pregnancy only if the potential benefit justifies the potential risk. *(8.1)*
- **Nursing Mothers:** Breast feeding is not recommended. *(8.3)*
- **Pediatric Use:** Safety and effectiveness have not been established. *(8.4)*
- **Renal Impairment:** Dose adjustment is recommended. *(8.6)*
- **Hepatic Impairment:** Dose adjustment is recommended. *(8.7)*

Revised: October 2010

FULL PRESCRIBING INFORMATION: CONTENTS*

***Sections or subsections omitted from the full prescribing information are not listed**

FULL PRESCRIBING INFORMATION

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.
LATUDA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*.

1. INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in four 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)]*.

2. DOSAGE AND ADMINISTRATION

2.1. Schizophrenia

The recommended starting dose of LATUDA is 40 mg once daily. Initial dose titration is not required. LATUDA has been shown to be effective in a dose range of 40 mg/day to 120 mg/day *[see Clinical Studies (14.1)]*. In the 6-week controlled trials, there was no suggestion of added benefit with the 120 mg/day dose, but there was a dose-related increase in certain adverse reactions. Therefore, the maximum recommended dose is 80 mg/day.

2.2. Administration Instructions

LATUDA should be taken with food (at least 350 calories) *[see Clinical Pharmacology (12)]*.

2.3. Dosage in Special Populations

Dosage adjustments are not recommended on the basis of age, gender, and race *[see Use in Specific Populations (8)]*.

Dose adjustment is recommended in moderate and severe renal impairment patients. The dose in these patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

Dose adjustment is recommended in moderate and severe hepatic impairment patients. The dose in these patients should not exceed 40 mg/day *[see Use in Specific Populations (8)]*.

Dosing recommendation for patients taking LATUDA concomitantly with potential CYP3A4 inhibitors: When coadministration of LATUDA with a moderate CYP3A4 inhibitor such as diltiazem is considered, the dose should not exceed 40 mg/day. LATUDA should not be used in combination with a strong CYP3A4 inhibitor (e.g., ketoconazole) *[see Contraindications (4); Drug Interactions (7.1)]*.

Dosing recommendation for patients taking LATUDA concomitantly with potential CYP3A4 inducers: LATUDA should not be used in combination with a strong CYP3A4 inducer (e.g., rifampin) *[see Contraindications (4); Drug Interactions (7.1)]*.

3. DOSAGE FORMS AND STRENGTHS

LATUDA tablets are available in the following shape and color (Table 1) with respective one-sided debossing: 40 mg (white to off-white, round, "L40"), or 80 mg (pale green, oval, "L80").

Table 1: LATUDA Tablet Presentations

Tablet Strength	Tablet Color/Shape	Tablet Markings
40 mg	white to off-white round	"L40"
80 mg	pale green oval	"L80"

4. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone *[see Adverse Reactions (6.6)]*.

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) *[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. LATUDA is not approved for the treatment of dementia-related psychosis *[see Boxed Warning]*.

5.2. 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 *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3. 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 creatinine 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.

5.4. 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.

5.5. 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.

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

Table 2: Change in Fasting Glucose

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
	Mean Change from Baseline (mg/dL)				
	n=438	**n=71**	**n=352**	**n=270**	**n=283**
Serum Glucose	-0.7	-0.6	2.5	-0.9	2.5
	Proportion of Patients with Shifts to ≥ 126 mg/dL				
Serum Glucose (≥126 mg/dL)	8.6% (34/397)	11.7% (7/60)	14.3% (47/328)	10.0% (24/241)	10.0% (26/260)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236) and +1.2 mg/dL at week 52 (n=244).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 3.

Table 3: Change in Fasting Lipids

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
	Mean Change from Baseline (mg/dL)				
	n=418	**n=71**	**n=341**	**n=263**	**n=268**
Total cholesterol	-8.5	-12.3	-9.4	-9.8	-3.8
Triglycerides	-15.7	-29.1	-6.2	-14.2	-3.1
	Proportion of Patients with Shifts				
Total Cholesterol (≥ 240 mg/dL)	6.6% (23/350)	13.8% (8/58)	7.3% (21/287)	6.9% (15/216)	3.8% (9/238)
Triglycerides (≥ 200 mg/dL)	12.5% (39/312)	14.3% (7/49)	14.0% (37/264)	8.7% (17/196)	10.5% (22/209)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n = 238) and -3.5 (n = 238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.

Weight Gain

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

Pooled data from short-term, placebo-controlled studies are presented in Table 4. The mean weight gain was 0.75 kg for LATUDA-treated patients compared to 0.26 kg for placebo-treated patients. In study 3 *[see Clinical Studies (14.1)]* change in weight from baseline for olanzapine was 4.15 kg. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 5.6% for LATUDA-treated patients versus 4.0% for placebo-treated patients.

Table 4: Mean Change in Weight (kg) from Baseline

	Placebo (n = 450)	LATUDA 20 mg/day (n = 71)	LATUDA 40 mg/day (n = 358)	LATUDA 80 mg/day (n = 279)	LATUDA 120 mg/day (n = 291)
All Patients	0.26	-0.15	0.67	1.14	0.68

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.38 kg at week 24 (n = 531), -0.47 kg at week 36 (n = 303) and -0.71 kg at week 52 (n = 244).

5.6. 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)]*.

In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and was - 0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose-dependent (Table 5).

Table 5: Median Change in Prolactin (ng/mL) from Baseline

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
All Patients	-0.6 (n=430)	-1.1 (n=70)	0.3 (n=351)	1.1 (n=259)	3.3 (n=284)
Females	-1.5 (n=102)	-0.7 (n=19)	-0.9 (n=99)	2.0 (n=78)	6.7 (n=70)
Males	-0.5 (n=328)	-1.2 (n=51)	0.5 (n=252)	0.9 (n=181)	3.1 (n=214)

The proportion of patients with prolactin elevations ≥ 5x ULN was 3.6% for LATUDA-treated patients versus 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 8.3% for LATUDA-treated patients versus 1% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5x ULN was 1.9% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n = 188), -5.4 ng/mL at week 36 (n=189) and -3.3 ng/mL at week 52 (n = 243).

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.

5.7. 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/mm³) should discontinue LATUDA and have their WBC followed until recovery.

5.8. Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.4% (4/1004), 0.2 % (1/455)] and syncope [< 0.1% (1/1004), 0%]. Assessment of orthostatic hypotension defined by 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 positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 1.4% with LATUDA 80 mg and 1.7% with LATUDA 120 mg compared to 0.9% with placebo.

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

5.9. 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.

In short-term placebo-controlled trials, seizures/convulsions occurred in < 0.1% (1/1004) of patients treated with LATUDA compared to 0.2% (1/455) placebo-treated patients.

5.10. Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence was reported in 26.5% (77/291) of patients receiving LATUDA 120 mg/day. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

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.

5.11. 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 *[see Patient Counseling Information (17.9)]*.

5.12. 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.

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% (6/1004) for LATUDA treated patients compared to 0.4% (2/455) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13. 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 is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

5.14. Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.6, 8.7)]*. LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies *[see Warnings and Precautions (5.1, 5.8)]*.

6. ADVERSE REACTIONS

6.1. Overall Adverse Reaction Profile

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

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.14)]*

The information below is derived from a clinical study database for LATUDA consisting of over 2096 patients with schizophrenia exposed to one or more doses with a total experience of 624 patient-years. Of these patients, 1004 participated in short-term placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg or 120 mg once daily. A total of 533 LATUDA-treated patients had at least 24 weeks and 238 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.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. Treatment-emergent adverse events were defined as adverse experiences, which started or worsened on or after the date of the first dose through seven days after study medication discontinuation. There was no attempt to use investigator causality assessments; i.e., all events meeting the defined criteria, regardless of investigator causality are included. It is important to emphasize that, although the reactions occurred during treatment with LATUDA, they were not necessarily caused by it. The label should be read in its entirety to gain an understanding of the safety profile of LATUDA.

The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2. Clinical Studies Experience

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 120 mg (n = 1004).

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, nausea, parkinsonism and agitation.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.4% (94/1004) LATUDA-treated patients and 5.9% (27/455) 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 6.

Table 6: Adverse Reaction 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

Body System or Organ Class Dictionary-derived Term	Percentage of Patients Reporting Reaction Placebo (N = 455)	 All LATUDA (N = 1004)
Gastrointestinal Disorders		
Nausea	6	12
Vomiting	6	8
Dyspepsia	6	8
Salivary hypersecretion	<1	2
General Disorders and Administration Site Conditions		
Fatigue	3	4
Musculoskeletal and Connective Tissue Disorders		
Back Pain	3	4
Nervous System Disorders		
Somnolence*	10	22
Akathisia	3	15
Parkinsonism**	5	11
Dystonia***	1	5
Dizziness	3	5
Psychiatric Disorders		
Insomnia	7	8
Agitation	3	6
Anxiety	3	6
Restlessness	2	3

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

6.3. Dose-Related Adverse Reactions

Based on the pooled data from the placebo-controlled, short-term, fixed-dose studies, among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA, the apparent dose-related adverse reactions were akathisia and somnolence (Table 7).

Table 7: Dose-Related Adverse Events

	Percentage of Subjects Reporting Reaction				
Adverse Event Term	Placebo (N = 455) (%)	LATUDA 20 mg/day (N = 71) (%)	LATUDA 40 mg/day (N = 360) (%)	LATUDA 80 mg/day (N = 282) (%)	LATUDA 120 mg/day (N = 291) (%)
Akathisia	3	6	11	15	22
Somnolence*	10	15	19	23	26

Note: Figures rounded to the nearest integer
* Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

6.4. Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% versus 5.1% for placebo-treated patients; and the incidence of akathisia for LATUDA-treated patients was 15.0% versus 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of LATUDA, 120 mg/day (Table 8).

Table 8: Percentage of EPS Compared to Placebo

Adverse Event Term	Placebo (N = 455) (%)	LATUDA 20 mg/day (N = 71) (%)	LATUDA 40 mg/day (N = 360) (%)	LATUDA 80 mg/day (N = 282) (%)	LATUDA 120 mg/day (N = 291) (%)
All EPS events	9	10	24	26	39
All EPS events, excluding Akathisia/Restlessness	5	6	13	11	22
Akathisia	3	6	11	15	22
Dystonia*	1	0	4	5	7
Parkinsonism**	5	6	10	7	17
Restlessness	2	1	4	1	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, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.2; 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, 16.0%; placebo, 7.6%) and the SAS (LATUDA, 5.3%; placebo, 2.5%).

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.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.7% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 4.2% LATUDA 40 mg, 4.6% LATUDA 80 mg and 6.5% LATUDA 120 mg) compared to 0.7% of subjects receiving placebo. Seven subjects (0.7%, 7/1004) discontinued clinical trials due to dystonic events– 4 were receiving LATUDA 80 mg/day and 3 were receiving LATUDA 120 mg/day.

6.5. Laboratory Test Abnormalities and ECG Changes in Clinical Studies

Laboratory Test Abnormalities

In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements; triglycerides or glucose from Baseline to Endpoint *[see Warnings and Precautions (5.5)]*. There were also no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. LATUDA was associated with a dose-related increase in prolactin concentration *[see Warnings and Precautions (5.6)]*

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% (30/977) of LATUDA-treated patients and 1.4% (6/439) on placebo. The threshold for high creatinine value varied from ≥ 1.1 to ≥ 1.3 mg/dL based on the centralized laboratory definition for each study *[see Dosage in Special Population (2.3); Use in Specific Populations (8)]*.

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).

ECG Changes

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

6.6. Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2096 patients. 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 6 are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system 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;* ***Rare:*** *leukopenia, neutropenia*

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, dysphagia*

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

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

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

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

Nervous System Disorders: ***Infrequent:*** *tardive dyskinesia, cerebrovascular accident, dysarthria, syncope;* ***Rare:*** *neuroleptic malignant syndrome, seizure*

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;* ***Rare:*** *suicidal behavior*

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: ***Infrequent:*** *hypertension, orthostatic hypotension*

7. DRUG INTERACTIONS

Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

7.1. Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 9). LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]*.

Table 9: Summary of Effect of Coadministered Drugs on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia

Coadministered drug	Dose schedule		Effect on LATUDA pharmacokinetics		Recommendation
	Coadministered drug	LATUDA	C_{max}	AUC	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 5 days	10 mg single dose	6.9-times LATUDA alone	9-times LATUDA alone	Should not be coadministered with LATUDA
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/ day for 5 days	20 mg single dose	2.1-times LATUDA alone	2.2-times LATUDA alone	LATUDA dose should not exceed 40 mg/day if coadministered
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	1/7th of LATUDA alone	1/5th of LATUDA alone	Should not be coadministered with LATUDA
Lithium	600 mg BID for 8 days	120 mg/ day for 8 days	0.9-times LATUDA alone	1.1-times LATUDA alone	No LATUDA dose adjustment required.

7.2. Potential for LATUDA to Affect Other Drugs

Digoxin (P-gp substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

Midazolam (CYP3A4 substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

Oral Contraceptive (estrogen/progesterone): Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

8. USE IN SPECIFIC POPULATIONS

8.1. Pregnancy

Teratogenic Effects

Pregnancy Category B

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of LATUDA in pregnant women.

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 3 and 12 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area.

No adverse developmental effects were seen 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; this dose is approximately equal to the MRHD based on body surface area.

Non-teratogenic Effects

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.

8.2. Labor and Delivery

The effect of LATUDA on labor and delivery in humans is unknown.

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. Breast feeding in women receiving LATUDA should be considered only if the potential benefit justifies the potential risk to the child.

8.4. Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5. Geriatric Use

Clinical studies of LATUDA in the treatment of schizophrenia 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), lurasidone concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology (12.3)]*. No dose adjustment is necessary in elderly patients.

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. Renal Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe renal impairment (Cl_{cr} ≥ 10 mL/min to < 50 mL/min).

After administration of a single dose of 40 mg LATUDA to patients with mild, moderate and severe renal impairment, mean C_{max} increased by 40%, 92% and 54%, respectively and mean $AUC_{(0-\infty)}$ increased by 53%, 91% and 2- times, respectively compared to healthy matched subjects.

8.7. Hepatic Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of LATUDA 20 mg, lurasidone mean $AUC_{(0-last)}$ was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean C_{max} was 1.3, 1.2 and 1.3-times higher for mild, moderate and severe hepatically impaired patients respectively, compared to the values for healthy matched subjects.

8.8. Gender

Population pharmacokinetic evaluation indicated that the mean AUC of LATUDA was 18% higher in women than in men, and correspondingly, the apparent oral clearance of LATUDA was lower in women. Mean C_{max} of LATUDA was similar between women and men. No dosage adjustment of LATUDA is recommended based on gender.

8.9. Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of LATUDA, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of LATUDA. No dosage adjustment of LATUDA is recommended based on race.

8.10. Smoking Status

Based on in vitro studies utilizing human liver enzymes, LATUDA is not a substrate for CYP1A2; smoking is therefore not expected to have an effect on the pharmacokinetics of LATUDA.

9. DRUG ABUSE AND DEPENDENCE

9.1. Controlled substance

LATUDA is not a controlled substance.

9.2. Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

10. OVERDOSAGE

10.1. Human Experience

In premarketing clinical studies involving more than 2096 patients and/or healthy subjects, 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.

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.

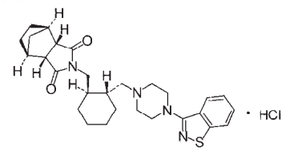
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

11. DESCRIPTION

LATUDA is a psychotropic agent belonging to the chemical class of benzoisothiazol derivatives.

Its chemical name is (3a*R*,4*S*,7*R*,7a*S*)-2-[(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl]hexahydro-4,7-methano-2*H*-isoindole-1,3-dione hydrochloride. Its molecular formula is $C_{28}H_{36}N_4O_2S$·HCl and its molecular weight is 529.14.

The chemical structure is:



Lurasidone hydrochloride is a white to off-white powder. It is very slightly soluble in water, practically insoluble or insoluble in 0.1 N HCl, slightly soluble in ethanol, sparingly soluble in methanol, practically insoluble or insoluble in toluene and very slightly soluble in acetone.
LATUDA tablets are intended for oral administration only. Each tablet contains 40 mg, or 80 mg of lurasidone hydrochloride.
Inactive ingredients are mannitol, pregelatinized starch, croscarmellose sodium, hypromellose, magnesium stearate, Opadry® and carnauba wax. Additionally, the 80 mg tablet contains yellow ferric oxide and FD&C Blue No.2 Aluminum Lake.

12. CLINICAL PHARMACOLOGY

12.1. Mechanism of Action

The mechanism of action of lurasidone, as with other drugs having efficacy in schizophrenia, is unknown. It has been suggested that the efficacy of lurasidone in schizophrenia is mediated through a combination of central dopamine Type 2 (D_2) and serotonin Type 2 ($5HT_{2A}$) receptor antagonism.

12.2. Pharmacodynamics

In vitro receptor binding studies revealed that lurasidone is an antagonist with high affinity at dopamine D_2 receptors (Ki = 0.994 nM) and the 5-hydroxytryptamine (5-HT, serotonin) receptors $5\text{-}HT_{2A}$ (Ki = 0.47 nM) and $5\text{-}HT_7$ (Ki = 0.495 nM), is an antagonist with moderate affinity at human α_{2C} adrenergic receptors (Ki = 10.8 nM), is a partial agonist at serotonin $5\text{-}HT_{1A}$ (Ki = 6.38 nM) receptors, and is an antagonist at α_{2A} adrenergic receptors (Ki = 40.7 nM). Lurasidone exhibits little or no affinity for histamine H_1 and muscarinic M_1 receptors (IC_{50} ≥ 1,000 nM and > 1,000 nM, respectively).

12.3. Pharmacokinetics

The activity of lurasidone is primarily due to the parent drug. The pharmacokinetics of lurasidone is dose-proportional within a total daily dose range of 20 mg to 160 mg. Steady-state concentrations of lurasidone are reached within 7 days of starting LATUDA.

Following administration of 40 mg of LATUDA, the mean (%CV) elimination half-life was 18 (7) hours.

Absorption and Distribution: Lurasidone is absorbed and reaches peak serum concentrations in approximately 1-3 hours. It is estimated that 9-19% of an administered dose is absorbed. Following administration of 40 mg of LATUDA, the mean (%CV) apparent volume of distribution was 6173 (17.2) L. Lurasidone is highly bound (~99%) to serum proteins.

In a food effect study, lurasidone mean C_{max} and AUC were about 3-times and 2-times, respectively, when administered with food compared to the levels observed under fasting conditions. Lurasidone exposure was not affected as meal size was increased from 350 to 1000 calories and was independent of meal fat content *[see Dosage and Administration (2.2)]*.

In clinical studies, establishing the safety and efficacy of LATUDA, patients were instructed to take their daily dose with food *[see Dosage and Administration (2.2)]*.

Metabolism and Elimination: Lurasidone is metabolized mainly via CYP3A4. The major biotransformation pathways are oxidative *N*-dealkylation, hydroxylation of norbornane ring, and *S*-oxidation. Lurasidone is metabolized into two active metabolites (ID-14283 and ID-14326) and two major non-active metabolites (ID-20219 and ID-20220).

Total excretion of radioactivity in urine and feces combined was approximately 89%, with about 80% recovered in feces and 9% recovered in urine, after a single dose of [^{14}C]-labeled lurasidone.

Following administration of 40 mg of LATUDA, the mean (%CV) apparent clearance was 3902 (18.0) mL/min.

13. NONCLINICAL TOXICOLOGY

Carcinogenesis: Lifetime carcinogenicity studies were conducted in ICR mice and Sprague-Dawley rats. Lurasidone was administered orally at doses of 30, 100, 300, or 650 (the high dose was reduced from 1200 in males) mg/kg/day to ICR mice and 3, 12, or 36 (high dose reduced from 50) mg/kg/day to Sprague-Dawley rats.

In the mouse study, there were increased incidences of malignant mammary gland tumors and pituitary gland adenomas in females at all doses; the lowest dose tested produced plasma levels (AUC) 2 times those in humans receiving the maximum recommended human dose (MRHD) of 80 mg/day. No increases in tumors were seen in male mice up to the highest dose tested, which produced plasma levels (AUC) 15-25 times those in humans receiving the MRHD.

In rats, an increased incidence of mammary gland carcinomas was seen in females at the two higher doses; the no-effect dose of 3 mg/kg produced plasma levels (AUC) 0.7 times those in humans receiving the MRHD. No increases in tumors were seen in male rats up to highest dose tested, which produced plasma levels (AUC) 10 times those in humans receiving the MRHD.

Proliferative and/or neoplastic changes in the mammary and pituitary glands of rodents have been observed following chronic administration of antipsychotic drugs and are considered to be prolactin mediated. The relevance of this increased incidence of prolactin-mediated pituitary or mammary gland tumors in rodents in terms of human risk is unknown *[see Warnings and Precautions (5.6)]*.

Mutagenesis: Lurasidone was not genotoxic in the Ames test, the *in vitro* chromosomal aberration test in Chinese Hamster Lung (CHL) cells, or the *in vivo* mouse bone marrow micronucleus test.

Impairment of Fertility: Lurasidone was administered orally to female rats at doses of 0.1, 1.5, 15, or 150 mg/kg/day for 15 consecutive days prior to mating, during the mating period, and through day 7 of gestation. Estrus cycle irregularities were seen at 1.5 mg/kg and above; the no-effect dose of 0.1 mg/kg is approximately 0.01 times the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area. Fertility was reduced only at the highest dose and this was shown to be reversible after a 14 day drug-free period. The no-effect dose for reduced fertility was 15 mg/kg, which is 1.8 times the MRHD based on body surface area.

Fertility was not affected in male rats treated orally with lurasidone for 64 consecutive days prior to mating and during the mating period at doses up to 150 mg/kg/day (12 times the MRHD based on body surface area).

14. CLINICAL STUDIES

14.1. Schizophrenia

The efficacy of LATUDA for the treatment of schizophrenia was established in four short-term (6-week), placebo-controlled studies in adult patients (mean age of 38.8 years, range 18-72) who met DSM-IV criteria for schizophrenia. One study included an active-control arm (olanzapine) to assess assay sensitivity.

Several instruments were used for assessing psychiatric signs and symptoms in these studies:

1. Positive and Negative Syndrome Scale (PANSS), is a multi-item inventory of general psychopathology used to evaluate the effects of drug treatment in schizophrenia. PANSS total scores may range from 30 to 210.
2. Brief Psychiatric Rating Scale derived (BPRSd), derived from the PANSS, is a multi-item inventory primarily focusing on positive symptoms of schizophrenia, whereas the PANSS includes a wider range of positive, negative and other symptoms of schizophrenia. BPRSd scores may range from 18 to 126.
3. The Clinical Global Impression severity scale (CGI-S) is a validated clinician-rated scale that measures the subject's current illness state on a 1 to 7-point scale.

The endpoint associated with each instrument is change from baseline in the total score to the end of week 6. These changes are then compared to placebo changes for the drug and control groups.

The results of the studies follow:

1. In a 6-week, placebo-controlled trial (N=145) involving two fixed doses of LATUDA (40 or 120 mg/day), both doses of LATUDA at Endpoint were superior to placebo on the BPRSd total score, and the CGI-S.
2. In a 6-week, placebo-controlled trial (N=180) involving a fixed dose of LATUDA (80 mg/day), LATUDA at Endpoint was superior to placebo on the BPRSd total score, and the CGI-S.
3. In a 6-week, placebo and active-controlled trial (N=473) involving two fixed doses of LATUDA (40 or 120 mg/day) and an active control (olanzapine), both LATUDA doses and the active control at Endpoint were superior to placebo on the PANSS total score, and the CGI-S.
4. In a 6-week, placebo-controlled trial (N=489) involving three fixed doses of LATUDA (40, 80 or 120 mg/day), only the 80 mg/day dose of LATUDA at Endpoint was superior to placebo on the PANSS total score, and the CGI-S.

Thus, the efficacy of LATUDA at doses of 40, 80 and 120 mg/day was established in two studies for each dose. However, the 120 mg dose did not appear to add additional benefit over the 40 mg dose (Table 10).

Table 10: Summary of Results for Primary Efficacy Endpoints

		LS Mean (SE)[a] Difference from Placebo in Change from Baseline			
Study Number	Primary Endpoint	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day	Olanzapine 15 mg/day
1	$BPRS_d$	-5.6* (2.1)	–	-6.7* (2.2)	–
2	$BPRS_d$	–	-4.7* (1.8)	–	–
3	PANSS	-9.7* (2.9)	–	-7.5* (3.0)	-12.6* (2.8)
4	PANSS	-2.1 (2.5)	-6.4* (2.5)	-3.5 (2.5)	–

* adjusted p-value <0.05 (except for olanzapine)
[a] Least Squares Mean (Standard Error)

Examination of population subgroups based on age (there were few patients over 65), gender and race did not reveal any clear evidence of differential responsiveness.

16. HOW SUPPLIED/STORAGE AND HANDLING

LATUDA tablets are white to off-white, round (40 mg), or pale green, oval (80 mg) and identified with strength specific one-sided debossing , "L40" (40 mg), or "L80" (80 mg). Tablets are supplied in the following strengths and package configurations (Table 11):

Table 11: Package Configuration for LATUDA Tablets

Tablet Strength	Package Configuration	NDC Code
40 mg	Bottles of 30	63402-304-30
	Bottles of 90	63402-304-90
	Bottles of 500	63402-304-50
	Box of 28 4 blister cards, 7 tablets each	63402-304-04 Carton 63402-304-07 Blister
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-304-10 Carton 63402-304-01 Blister
80 mg	Bottles of 30	63402-308-30
	Bottles of 90	63402-308-90
	Bottles of 500	63402-308-50
	Box of 28 4 blister cards, 7 tablets each	63402-308-04 Carton 63402-308-07 Blister
	Box of 100 (Hospital Unit Dose) 10 blister cards, 10 tablets each	63402-308-10 Carton 63402-308-01 Blister

Storage

Store LATUDA tablets at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F) *[See USP Controlled Room Temperature]*.

17. PATIENT COUNSELING INFORMATION

Physicians are advised to discuss with patients for whom they prescribe LATUDA all relevant safety information including, but not limited to, the following:

17.1 Increased Mortality in Elderly Patients with Dementia-Related Psychosis

Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. LATUDA is not approved for elderly patients with dementia-related psychosis *[see Boxed Warning; Warnings and Precautions (5.1)]*.

17.2 Neuroleptic Malignant Syndrome

Patients and caregivers should be counseled that a potentially fatal symptom complex sometimes referred to as NMS has been reported in association with administration of antipsychotic drugs. Signs and symptoms of NMS include hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia) *[see Warnings and Precautions (5.3)]*.

17.3 Hyperglycemia and Diabetes Mellitus

Patients should be aware of the symptoms of hyperglycemia (high blood sugar) and diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should have their blood glucose monitored at the beginning of and periodically during treatment *[see Warnings and Precautions (5.5)]*.

17.4 Orthostatic Hypotension

Patients should be advised of the risk of orthostatic hypotension, particularly at the time of initiating treatment, re-initiating treatment, or increasing the dose *[see Warnings and Precautions (5.8)]*.

17.5 Leukopenia/Neutropenia

Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking LATUDA *[see Warnings and Precautions (5.7)]*.

17.6 Interference with Cognitive and Motor Performance

Patients should be cautioned about performing activities requiring mental alertness, such as operating hazardous machinery or operating a motor vehicle, until they are reasonably certain that LATUDA therapy does not affect them adversely *[see Warnings and Precautions (5.10)]*.

17.7 Pregnancy and Nursing

Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy with LATUDA *[see Use in Specific Populations (8.1)]*.

17.8 Concomitant Medication and Alcohol

Patients should be advised to inform their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs, since there is a potential for interactions. Patients should be advised to avoid alcohol while taking LATUDA *[see Drug Interactions (7)]*.

17.9 Heat Exposure and Dehydration

Patients should be advised regarding appropriate care in avoiding overheating and dehydration *[see Warnings and Precautions (5.11)]*.

SUNOVION

Manufactured for:
Sunovion Pharmaceuticals Inc.
Marlborough, MA 01752,

For Customer Service, call 1-888-394-7377.
For Medical Information, call 1-800-739-0565.
To report suspected adverse reactions, call 1-877-737-7226.

Revised: October 2010
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INDICATION AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in four 6-week controlled studies of adult patients with schizophrenia. 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.

IMPORTANT SAFETY INFORMATION FOR LATUDA

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Please see full Prescribing Information enclosed.

Latuda®
(lurasidone HCl) tablets
40mg and 80mg

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Psychiatric
Association

PSYCHIATRIC NEWS

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inside

PERIODICALS:
TIME-SENSITIVE MATERIALS

Credit: Karen Layser (k-photographs)

Washington insider and reporter Stuart Rothenberg talks about the intricacies of electoral politics to participants at APA's 2011 Advocacy Day. See story on page 14.

Leading Ladies Work to Improve Military Families' Mental Health

Military families get a boost in several crucial aspects of their lives, including mental health, education, and employment, from Michelle Obama and Jill Biden.

BY AARON LEVIN

Supporting military families is becoming the new watchword in Washington, and leading that effort are the nation's first and second ladies, Michelle Obama and Jill Biden.

On April 12, the two women—introduced by their husbands (who have significant jobs in their own right)—discussed further steps that they hope will enhance resilience among the families of military service members through a project called Joining Forces.

Their work is part of a White House program announced in January to enhance the well-being of military families, improve education for their children, increase child-care availability, and develop educational and career opportunities for military spouses.

"[W]e're going to focus on the specific things our military families have told us they care most about and things that I think that all of us can make a unique contribution to—the areas of employment, education, and wellness, and that includes mental health," said Michelle Obama. "We're going to remind this nation that, just as our troops deserve the best support when dealing with the stresses of war and long deployments, so do military spouses and children."

APA and other professional organizations are also bringing their expertise to bear on the effort. Two segments of the "Healthy Minds" TV series, hosted by psychiatrist Jeffrey Borenstein, M.D., and shown on PBS stations nationwide, will deal with veterans' mental health. The American Psychiatric Foundation (APF) and APA provide support for the program and advice on its contents, said Linda Bueno, director of industry relations for the APF.

APA has also developed an algorithm for psychiatrists to help them follow up on the patient screening question, "Have you been in military service?"

please see ***Leading Ladies*** *on page 10*

Physicians Key to Strategy For Reducing Opioid Abuse

Under a new White House plan to curtail prescription drug abuse, physicians would receive training in the prescribing of long-acting and extended-release opioids. APA has voiced its support for the plan.

BY RICHARD FAUST

APA has praised a new White House plan to curtail prescription drug abuse that would, for the first time, require physicians to receive specialized training in prescribing long-acting and extended-release opioids.

On April 19 the Obama administration brought together the heads of several government agencies to mark the release of a coordinated federal plan to deal with the nation's growing prescription drug abuse epidemic. APA, the American Academy of Addiction Psychiatry (AAAP), and the American Osteopathic Academy of Addiction Medicine (AOAAM) released a joint press release on April 21 applauding the administration's efforts.

White House Director of National Drug Control Policy Gil Kerlikowske was joined by Assistant Secretary for Health and Human Services Howard Koh, M.D., Food and Drugs (FDA) Commissioner Margaret Hamburg, M.D., and Drug Enforcement Agency Administrator Michele Leonhart in releasing "Epidemic: Responding to America's Prescription Drug Abuse Crisis," which details the new expansion of the National Drug Control Strategy.

Under the plan the FDA would require drug manufacturers to develop education programs for prescribers to help them identify, treat, and end dependence on prescription drugs. The plan notes that while there are a number of classes of prescription drugs that are abused, it "primarily focuses on the growing and often deadly problem of prescription opioid abuse."

The document stresses that "prescription drug abuse is the nation's fastest-growing drug problem." While the abuse of illegal street drugs, such as cocaine, has declined, the number of prescription drug abusers has risen markedly. "Data from the National Survey on Drug Use and Health (NSDUH) show that nearly one-third of people aged 12 and over who used drugs for the first time in 2009 began by using a prescription drug nonmedically."

In an interview with *Psychiatric News*, John Renner, M.D., chair of APA's Council on Addiction Psychiatry, said that the plan reflects a shift in emphasis for federal drug policy. He noted that illicit-drug distribution has moved from dealers to friends and relatives, and ultimately the

please see ***Opioid Abuse*** *on page 34*

IMPORTANT SAFETY INFORMATION FOR LATUDA

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in the drug-treated patients of between 1.6 to 1.7 times that seen in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5% compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone. LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS

Cerebrovascular Adverse Reactions, Including Stroke: 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. 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.

Tardive Dyskinesia (TD): The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic 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.

LATUDA, a once-daily, oral atypical antipsychotic[1]

- The efficacy of LATUDA was established in 2 studies for each dose
- The safety and tolerability of LATUDA were evaluated in multiple studies
- The recommended starting dose is 40 mg/day taken with food (at least 350 calories) with no initial dose titration required. The maximum recommended dose is 80 mg/day
  - For patients with moderate and severe renal or hepatic impairment, the dose of LATUDA should not exceed 40 mg/day
  - When coadministered with a moderate CYP3A4 inhibitor such as diltiazem, the dose of LATUDA should not exceed 40 mg/day
  - LATUDA should not be administered with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin

NEW

Latuda®

(lurasidone HCl) tablets 40mg and 80mg

INDICATION AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in four 6-week controlled studies of adult patients with schizophrenia. 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.

Please see Important Safety Information below, including **Boxed Warning**, and accompanying Brief Summary.

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 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. LATUDA should be used with caution in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), cerebrovascular disease, or conditions that predispose the patient to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications). Monitoring of orthostatic vital signs should be considered in all patients who are vulnerable to hypotension.

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: In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose. 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 is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

DRUG INTERACTIONS

Drug Interactions: Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

ADVERSE REACTIONS

Commonly Observed Adverse Reactions (≥5% and at least twice that for placebo): The most commonly observed adverse reactions in patients treated with LATUDA in short-term clinical studies were somnolence, akathisia, nausea, parkinsonism, and agitation.

Reference: 1. LATUDA prescribing information. Sunovion Pharmaceuticals Inc. October 2010.

FOR MORE INFORMATION, PLEASE CALL 1-888-394-7377 OR VISIT **www.LatudaHCP.com**.

SUNOVION

LATUDA® (lurasidone HCl) Tablets

Brief Summary (for full prescribing information, see package insert)

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

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6 to 1.7 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature.

Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear.

LATUDA is not approved for the treatment of patients with dementia-related psychosis. *[see Warnings and Precautions (5.1)]*

1. INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

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

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]*.

4. CONTRAINDICATIONS

LATUDA is contraindicated in any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone [*see Adverse Reactions (6.6)*].

LATUDA is contraindicated with strong CYP3A4 inhibitors (e.g., ketoconazole) and strong CYP3A4 inducers (e.g., rifampin) [*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. LATUDA is not approved for the treatment of dementia-related psychosis [*see Boxed Warning*].

5.2 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 *[see also Boxed Warning and Warnings and Precautions (5.1)]*.

5.3 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 creatinine 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.

5.4 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.

5.5 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.

Pooled data from short-term, placebo-controlled studies are presented in Table 1.

Table 1: Change in Fasting Glucose

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
Mean Change from Baseline (mg/dL)					
	n=438	**n=71**	**n=352**	**n=270**	**n=283**
Serum Glucose	-0.7	-0.6	2.5	-0.9	2.5
Proportion of Patients with Shifts to ≥ 126 mg/dL					
Serum Glucose (≥ 126 mg/dL)	8.6% (34/397)	11.7% (7/60)	14.3% (47/328)	10.0% (24/241)	10.0% (26/260)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.6 mg/dL at week 24 (n=186), +0.3 mg/dL at week 36 (n=236) and +1.2 mg/dL at week 52 (n=244).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 2.

Table 2: Change in Fasting Lipids

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
Mean Change from Baseline (mg/dL)					
	n=418	**n=71**	**n=341**	**n=263**	**n=268**
Total cholesterol	-8.5	-12.3	-9.4	-9.8	-3.8
Triglycerides	-15.7	-29.1	-6.2	-14.2	-3.1
Proportion of Patients with Shifts					
Total Cholesterol (≥ 240 mg/dL)	6.6% (23/350)	13.8% (8/58)	7.3% (21/287)	6.9% (15/216)	3.8% (9/238)
Triglycerides (≥ 200 mg/dL)	12.5% (39/312)	14.3% (7/49)	14.0% (37/264)	8.7% (17/196)	10.5% (22/209)

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -4.2 (n=186) and -13.6 (n=187) mg/dL at week 24, -1.9 (n=238) and -3.5 (n=238) mg/dL at week 36 and -3.6 (n=243) and -6.5 (n=243) mg/dL at week 52, respectively.

Weight Gain

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

Pooled data from short-term, placebo-controlled studies are presented in Table 3. The mean weight gain was 0.75 kg for LATUDA-treated patients compared to 0.26 kg for placebo-treated patients. In study 3 [*see Clinical Studies (14.1)*] change in weight from baseline for olanzapine was 4.15 kg. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 5.6% for LATUDA-treated patients versus 4.0% for placebo-treated patients.

Table 3: Mean Change in Weight (kg) from Baseline

	Placebo (n=450)	LATUDA 20 mg/day (n=71)	LATUDA 40 mg/day (n=358)	LATUDA 80 mg/day (n=279)	LATUDA 120 mg/day (n=291)
All Patients	0.26	-0.15	0.67	1.14	0.68

In the uncontrolled, longer-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.38 kg at week 24 (n=531), -0.47 kg at week 36 (n=303) and -0.71 kg at week 52 (n=244).

5.6 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)]*.

In short-term placebo-controlled studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was 1.1 ng/mL and was -0.6 ng/mL in the placebo-treated patients. The increase in prolactin was greater in female patients; the median change from baseline to endpoint for females was 1.5 ng/mL and was 1.1 ng/mL in males. The increase in prolactin concentrations was dose-dependent (Table 4).

Table 4: Median Change in Prolactin (ng/mL) from Baseline

	Placebo	LATUDA 20 mg/day	LATUDA 40 mg/day	LATUDA 80 mg/day	LATUDA 120 mg/day
All Patients	-0.6 (n=430)	-1.1 (n=70)	0.3 (n=351)	1.1 (n=259)	3.3 (n=284)
Females	-1.5 (n=102)	-0.7 (n=19)	-0.9 (n=99)	2.0 (n=78)	6.7 (n=70)
Males	-0.5 (n=328)	-1.2 (n=51)	0.5 (n=252)	0.9 (n=181)	3.1 (n=214)

The proportion of patients with prolactin elevations ≥ 5x ULN was 3.6% for LATUDA-treated patients versus 0.7% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5x ULN was 8.3% for LATUDA-treated patients versus 1% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥ 5x ULN was 1.9% versus 0.6% for placebo-treated male patients.

In the uncontrolled longer-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of -1.9 ng/mL at week 24 (n=188), -5.4 ng/mL at week 36 (n=189) and -3.3 ng/mL at week 52 (n=243).

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]*. 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.

5.7 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.

5.8 Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonism. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.4% (4/1004), 0.2% (1/455)] and syncope [< 0.1% (1/1004), 0%]. Assessment of orthostatic hypotension defined by 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 positions). In short-term clinical trials orthostatic hypotension occurred with a frequency of 0.8% with LATUDA 40 mg, 1.4% with LATUDA 80 mg and 1.7% with LATUDA 120 mg compared to 0.9% with placebo.

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

5.9 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.

In short-term placebo-controlled trials, seizures/convulsions occurred in < 0.1% (1/1004) of patients treated with LATUDA compared to 0.2% (1/455) placebo-treated patients.

5.10 Potential for Cognitive and Motor Impairment

LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, somnolence was reported in 22.3% (224/1004) of patients treated with LATUDA compared to 9.9% (45/455) of placebo patients, respectively. The frequency of somnolence increases with dose; somnolence was reported in 26.5% (77/291) of patients receiving LATUDA 120 mg/day. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

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.

5.11 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 *[see Patient Counseling Information (17.9)]*.

5.12 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.

In short-term, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.6% (6/1004) for LATUDA treated patients compared to 0.4% (2/455) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13 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 is not indicated for the treatment of dementia-related psychosis, and should not be used in patients at risk for aspiration pneumonia.

5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant systemic illnesses is limited *[see Use in Specific Populations (8.7, 8.8)]*. LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies *[see Warnings and Precautions (5.1, 5.8)]*.

6 ADVERSE REACTIONS

6.1 Overall Adverse Reaction Profile

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

- Use in Elderly Patients with Dementia-Related Psychosis *[see Boxed Warning and Warnings and Precautions (5.1)]*
- Cerebrovascular Adverse Reactions, Including Stroke *[see Warnings and Precautions (5.2)]*
- Neuroleptic Malignant Syndrome *[see Warnings and Precautions (5.3)]*
- Tardive Dyskinesia *[see Warnings and Precautions (5.4)]*
- Hyperglycemia and Diabetes Mellitus *[see Warnings and Precautions (5.5)]*
- Hyperprolactinemia *[see Warnings and Precautions (5.6)]*
- Leukopenia, Neutropenia, and Agranulocytosis *[see Warnings and Precautions (5.7)]*
- Orthostatic Hypotension and Syncope *[see Warnings and Precautions (5.8)]*
- Seizures *[see Warnings and Precautions (5.9)]*
- Potential for Cognitive and Motor Impairment *[see Warnings and Precautions (5.10)]*
- Body Temperature Regulation *[see Warnings and Precautions (5.11)]*
- Suicide *[see Warnings and Precautions (5.12)]*
- Dysphagia *[see Warnings and Precautions (5.13)]*
- Use in Patients with Concomitant Illness *[see Warnings and Precautions (5.14)]*

The information below is derived from a clinical study database for LATUDA consisting of over 2096 patients with schizophrenia exposed to one or more doses with a total experience of 624 patient-years. Of these patients, 1004 participated in short-term placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg or 120 mg once daily. A total of 533 LATUDA-treated patients had at least 24 weeks and 238 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.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. Treatment-emergent adverse events were defined as adverse experiences, which started or worsened on or after the date of the first dose through seven days after study medication discontinuation. There was no attempt to use investigator causality assessments; i.e., all events meeting the defined criteria, regardless of investigator causality are included. It is important to emphasize that, although the reactions occurred during treatment with LATUDA, they were not necessarily caused by it. The label should be read in its entirety to gain an understanding of the safety profile of LATUDA.

The figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical studies. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses and investigators. The cited figures, however, do provide the prescriber with some basis for estimating the relative contribution of drug and nondrug factors to the adverse reaction incidence in the population studied.

6.2 Clinical Studies Experience

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 120 mg (n=1004).

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, nausea, parkinsonism and agitation.

Adverse Reactions Associated with Discontinuation of Treatment: A total of 9.4% (94/1004) LATUDA-treated patients and 5.9% (27/455) 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 5.

Table 5: Adverse Reaction 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	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=455)**	**All LATUDA (N=1004)**
Gastrointestinal Disorders		
Nausea	6	12
Vomiting	6	8
Dyspepsia	6	8
Salivary hypersecretion	<1	2
General Disorders and Administration Site Conditions		
Fatigue	3	4
Musculoskeletal and Connective Tissue Disorders		
Back Pain	3	4
Nervous System Disorders		
Somnolence*	10	22
Akathisia	3	15
Parkinsonism**	5	11
Dystonia***	1	5
Dizziness	3	5
Psychiatric Disorders		
Insomnia	7	8
Agitation	3	6
Anxiety	3	6
Restlessness	2	3

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

6.3 Dose-Related Adverse Reactions

Based on the pooled data from the placebo-controlled, short-term, fixed-dose studies, among the adverse reactions that occurred with a greater than 5% incidence in the patients treated with LATUDA, the apparent dose-related adverse reactions were akathisia and somnolence (Table 6).

Table 6: Dose-Related Adverse Events

	Percentage of Subjects Reporting Reaction				
Adverse Event Term	**Placebo (N=455) (%)**	**LATUDA 20 mg/day (N=71) (%)**	**LATUDA 40 mg/day (N=360) (%)**	**LATUDA 80 mg/day (N=282) (%)**	**LATUDA 120 mg/day (N=291) (%)**
Akathisia	3	6	11	15	22
Somnolence*	10	15	19	23	26

Note: Figures rounded to the nearest integer
*Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence

6.4 Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported EPS-related events, excluding akathisia and restlessness, was 14.7% versus 5.1% for placebo-treated patients; and the incidence of akathisia for LATUDA-treated patients was 15.0% versus 3.3% for placebo-treated patients. Akathisia appeared to be dose-related and the greatest frequency of parkinsonism and dystonia occurred with the highest dose of LATUDA, 120 mg/day (Table 7).

Table 7: Percentage of EPS Compared to Placebo

Adverse Event Term	**Placebo (N=455) (%)**	**LATUDA 20 mg/day (N=71) (%)**	**LATUDA 40 mg/day (N=360) (%)**	**LATUDA 80 mg/day (N=282) (%)**	**LATUDA 120 mg/day (N=291) (%)**
All EPS events	9	10	24	26	39
All EPS events, excluding Akathisia/ Restlessness	5	6	13	11	22
Akathisia	3	6	11	15	22
Dystonia*	1	0	4	5	7
Parkinsonism**	5	6	10	7	17
Restlessness	2	1	4	1	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, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.2; 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, 16.0%; placebo, 7.6%) and the SAS (LATUDA, 5.3%; placebo, 2.5%).

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.

In the short-term, placebo-controlled clinical trials, dystonia occurred in 4.7% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 4.2% LATUDA 40 mg, 4.6% LATUDA 80 mg and 6.5% LATUDA 120 mg) compared to 0.7% of subjects receiving placebo. Seven subjects (0.7%, 7/1004) discontinued clinical trials due to dystonic events – 4 were receiving LATUDA 80 mg/day and 3 were receiving LATUDA 120 mg/day.

6.5 Laboratory Test Abnormalities and ECG Changes in Clinical Studies

Laboratory Test Abnormalities

In a between-group comparison of the pooled data from short-term, placebo-controlled studies, there were no clinically important changes in total cholesterol measurements; triglycerides or glucose from Baseline to Endpoint [*see Warnings and Precautions (5.5)*]. There were also no clinically important differences between LATUDA and placebo in mean change from baseline to endpoint in routine hematology, urinalysis, or serum chemistry. LATUDA was associated with a dose-related increase in prolactin concentration [*see Warnings and Precautions (5.6)*]

Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in creatinine was 0.06 mg/dL for LATUDA-treated patients compared to 0.03 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.1% (30/977) of LATUDA-treated patients and 1.4% (6/439) on placebo. The threshold for high creatinine value varied from ≥ 1.1 to ≥ 1.3 mg/dL based on the centralized laboratory definition for each study [*see Dosage in Special Population; Use in Specific Populations*].

Transaminases: The mean changes in AST and ALT for LATUDA- and placebo-treated patients were similar. The proportion of patients with transaminases (AST and ALT) elevations ≥ 3 times ULN was similar for all LATUDA-treated patients (0.8% and 0.8%, respectively) to placebo-treated patients (0.9% and 1.1%, respectively).

ECG Changes

Electrocardiogram (ECG) measurements were taken at various time points during the LATUDA clinical trial program. No post-baseline QT prolongations exceeding 500 msec were reported in patients treated with LATUDA. Within a subset of patients defined as having an increased cardiac risk, no potentially important changes in ECG parameters were observed. No cases of torsade de pointes or other severe cardiac arrhythmias were observed in the pre-marketing clinical program.

The effects of LATUDA on the QT/QTc interval were evaluated in a dedicated QT study involving 87 clinically stable patients with schizophrenia or schizoaffective disorder, who were treated with LATUDA doses of 120 mg daily, 600 mg daily, or ziprasidone 160 mg daily. Holter monitor-derived electrocardiographic assessments were obtained over an eight hour period at baseline and steady state. No patients treated with LATUDA experienced QTc increases > 60 msec from baseline, nor did any patient experience a QTc of > 500 msec.

6.6 Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of MedDRA terms that reflect adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2096 patients. 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 5 are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by MedDRA system 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;* ***Rare:*** *leukopenia, neutropenia*
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, dysphagia*
General Disorders and Administrative Site Conditions: ***Rare:*** *Sudden death*
Investigations: ***Frequent:*** *CPK increased*
Metabolic and Nutritional System Disorders: ***Frequent:*** *decreased appetite*
Musculoskeletal and Connective Tissue Disorders: ***Rare:*** *rhabdomyolysis*
Nervous System Disorders: ***Infrequent:*** *tardive dyskinesia, cerebrovascular accident, dysarthria, syncope;* ***Rare:*** *neuroleptic malignant syndrome, seizure*
Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorder;* ***Rare:*** *suicidal behavior*
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: ***Infrequent:*** *hypertension, orthostatic hypotension*

7 DRUG INTERACTIONS

Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP4A11, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 or CYP2E1 enzymes. This suggests that an interaction of LATUDA with drugs that are inhibitors or inducers of these enzymes is unlikely.

LATUDA is predominantly metabolized by CYP3A4; interaction of LATUDA with strong and moderate inhibitors or inducers of this enzyme has been observed (Table 8). LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]*.

Table 8: Summary of Effect of Coadministered Drugs on Exposure to LATUDA in Healthy Subjects or Patients with Schizophrenia

Coadministered drug	**Dose schedule**		**Effect on LATUDA pharmacokinetics**		**Recommendation**
	Coadministered drug	**LATUDA**	**C_{max}**	**AUC**	
Ketoconazole (strong CYP3A4 inhibitor)	400 mg/day for 5 days	10 mg single dose	6.9-times LATUDA alone	9-times LATUDA alone	Should not be coadministered with LATUDA
Diltiazem (moderate CYP3A4 inhibitor)	240 mg/day for 5 days	20 mg single dose	2.1-times LATUDA alone	2.2-times LATUDA alone	LATUDA dose should not exceed 40 mg/day if coadministered
Rifampin (strong CYP3A4 inducer)	600 mg/day for 8 days	40 mg single dose	1/7th of LATUDA alone	1/5th of LATUDA alone	Should not be coadministered with LATUDA
Lithium	600 mg BID for 8 days	120 mg/day for 8 days	0.9-times LATUDA alone	1.1- times LATUDA alone	No LATUDA dose adjustment required.

7.2 Potential for LATUDA to Affect Other Drugs

Digoxin (P-gp substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of digoxin (0.25 mg) increased C_{max} and $AUC_{(0-24)}$ for digoxin by approximately 9% and 13%, respectively relative to digoxin alone. Digoxin dose adjustment is not required when coadministered with LATUDA.

Midazolam (CYP3A4 substrate): Coadministration of LATUDA (120 mg/day) at steady state with a single dose of 5 mg midazolam increased midazolam C_{max} and $AUC_{(0-24)}$ by approximately 21% and 44%, respectively relative to midazolam alone. Midazolam dose adjustment is not required when coadministered with LATUDA.

Oral Contraceptive (estrogen/progesterone): Coadministration of LATUDA (40 mg/day) at steady state with an oral contraceptive (OC) containing ethinyl estradiol and norelgestimate resulted in equivalent $AUC_{(0-24)}$ and C_{max} of ethinyl estradiol and norelgestromin relative to OC administration alone. Also, sex hormone binding globulin levels were not meaningfully affected by coadministration of LATUDA and OC. Dose adjustment of OC dose is not required when coadministered with LATUDA.

8. USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

Lurasidone was not teratogenic in rats and rabbits. There are no adequate and well-controlled studies of LATUDA in pregnant women.

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 3 and 12 times, in rats and rabbits respectively, the maximum recommended human dose (MRHD) of 80 mg/day based on body surface area.

No adverse developmental effects were seen 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; this dose is approximately equal to the MRHD based on body surface area.

Non-teratogenic Effects

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.

8.3 Labor and Delivery

The effect of LATUDA on labor and delivery in humans is unknown.

8.4 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. Breast feeding in women receiving LATUDA should be considered only if the potential benefit justifies the potential risk to the child.

8.5 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.6 Geriatric Use

Clinical studies of LATUDA in the treatment of schizophrenia 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), lurasidone concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology]*. No dose adjustment is necessary in elderly patients.

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]*.

8.7 Renal Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe renal impairment (Cl_{cr} ≥ 10 mL/min to < 50 mL/min).

After administration of a single dose of 40 mg LATUDA to patients with mild, moderate and severe renal impairment, mean C_{max} increased by 40%, 92% and 54%, respectively and mean $AUC_{(0-\infty)}$ increased by 53%, 91% and 2- times, respectively compared to healthy matched subjects.

8.8 Hepatic Impairment

It is recommended that LATUDA dose should not exceed 40 mg/day in patients with moderate and severe hepatic impairment (Child-Pugh Class B and C). In a single-dose study of LATUDA 20 mg, lurasidone mean $AUC_{(0-last)}$ was 1.5-times higher in subjects with mild hepatic impairment (Child-Pugh Class A), 1.7-times higher in subjects with moderate hepatic impairment (Child-Pugh Class B) and 3-times higher in subjects with severe hepatic impairment (Child-Pugh Class C) compared to the values for healthy matched subjects. Mean C_{max} was 1.3, 1.2 and 1.3-times higher for mild, moderate and severe hepatically impaired patients respectively, compared to the values for healthy matched subjects.

8.9 Gender

Population pharmacokinetic evaluation indicated that the mean AUC of LATUDA was 18% higher in women than in men, and correspondingly, the apparent oral clearance of LATUDA was lower in women. Mean C_{max} of LATUDA was similar between women and men. No dosage adjustment of LATUDA is recommended based on gender.

8.10 Race

Although no specific pharmacokinetic study was conducted to investigate the effects of race on the disposition of LATUDA, population pharmacokinetic evaluation revealed no evidence of clinically significant race-related differences in the pharmacokinetics of LATUDA. No dosage adjustment of LATUDA is recommended based on race.

8.11 Smoking Status

Based on in vitro studies utilizing human liver enzymes, LATUDA is not a substrate for CYP1A2; smoking is therefore not expected to have an effect on the pharmacokinetics of LATUDA.

10. OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies involving more than 2096 patients and/or healthy subjects, 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.

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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Psychiatrists Disagree Over Choice Of Tutu as Convocation Speaker

Carol Bernstein, M.D., says she hopes controversy about the choice of this year's Convocation speaker at the annual meeting will be a "teachable moment" about disagreeing without being disagreeable.

BY MARK MORAN

In an open letter to APA, the Black Psychiatrists of America (BPA) registered support for the choice of Archbishop Desmond Tutu as this year's Convocation speaker at APA's 2011 annual meeting, which was occurring at press time.

Moreover, the BPA denounced some accusations leveled against Tutu by a group of psychiatrists angry over comments Tutu made about the Israeli-Arab conflict in the Middle East.

"Archbishop Tutu was not invited to speak about his personal political stance on the Israeli-Palestinian conflict," the BPA stated. "He was invited to share his story of facing a great societal evil at a time when most of the Western world gave only lip service and passive support to the cause. . . . Like other great people throughout history who have held unpopular views on the important issues of their day, . . . he is an important part of the historical record of speaking truth to power, and his views or alleged views on one issue must not diminish his great accomplishments in other areas."

The April 7 letter from the BPA was in response to a paid advertisement in the February *Psychiatric Times* by 27 APA members protesting the choice of Tutu. The ad drew attention to what the group called Tutu's "persistent vituperative stance regarding the State of Israel and those who support it," as well as the archbishop's support for divestment and boycott of certain Israeli institutions.

The ad noted that some of the 27 would not be attending the meeting because of the choice of Tutu, others would be planning various forms of protest, and a few were "seriously considering whether [they] want to continue to belong" to APA. Also, they urged APA to rescind the invitation to Tutu.

In its letter, the BPA urged APA President Carol Bernstein, M.D., not to rescind the offer and said it hoped APA would resolve differences of opinion among its membership through "civil discourse."

"[The] BPA in the spirit of 'truth and reconciliation' seeks to encourage the APA and its membership to listen to 'better angels' in order to resolve any differences that may exist within its membership and utilize the skills of conflict resolution and address this issue through civil discourse. When the dust settles, what would have been accomplished by this entire process if it fails to seek understanding and resolution in a healthy and productive way?"

In an interview with *Psychiatric News* before the meeting, Bernstein said Tutu would indeed be speaking at the annual meeting in Honolulu. She said that charismatic leaders and social reformers, however revered they may be by history or in their own time by some of their contemporaries, have typically been despised, at least by some.

please see ***Tutu*** *on page 36*

DSM-5 Web Site: Check It Out

The *DSM-5* Web site at <www.DSM5.org>was relaunched earlier this month in response to the numerous revisions that have been made since the initial launch in February 2010. They include a revised chapter structure for *DSM-5,* revisions to diagnostic criteria, the addition of new disorders, and the addition of severity measures. A detailed listing of these changes is posted on the site.

The last comment period was extremely successful, and input from visitors was used to inform revisions to draft proposals. The updated site is again open for a six-week comment period (ending June 15), and viewers are encouraged to submit questions and comments about the current draft proposals. All comments will be reviewed by the work groups.

Following completion of the field trials in the fall, work groups will use feedback from the site, as well as results from field tests, to make a third round of revisions. Afterward, the revised criteria will be posted, and the site will be open for a third comment period.

Eligible viewers are also asked to use the site to register as volunteer clinicians for the field trials taking place in routine clinical practice settings. Visitors can read the "Field Trials" section of the site at <www.dsm5.org/pages/registration.aspx> to learn more about eligibility and the application process.

An update and further details on **DSM-5** ***appear on page 21.***

APA RESOURCES

- ***Psychiatric News*** **Web Site:** psychnews.org
- **APA and the APA Answer Center:** (888) 35-PSYCH in the U.S. and Canada; in other countries: (703) 907-7300. The Answer Center is open Monday through Friday, 8:30 a.m. to 6 p.m. Eastern time. All APA departments and staff may be reached through the Answer Center.
  Fax: (703) 907-1085
  E-Mail: apa@psych.org
- **APA Web Site:** www.psych.org
- **APA Job Bank:** www.psych.org/jobbank
- **Managed Care Help Line:** (800) 343-4671
- **Member2Member List Serve (M2M):** www.psych.org/apa_members/list serves.cfm
- **American Psychiatric Publishing Inc.**
  Phone Order Line: (800) 368-5777
  Fax: (703) 907-1091
  Web Site: www.appi.org
- **APA Member Update:** To subscribe, send an e-mail to update@psych.org.
- **APA Advocacy News:** To subscribe, send an e-mail to advocacy@psych.org.
- **American Psychiatric Foundation**
  Phone: (703) 907-8512
  Web Site: www.PsychFoundation.org
- **Mental Health Parity Watch**
  Phone: (866) 882-6227
  Web Site: www.Mentalhealthparitywatch.org

Autism Prevalence Findings Surprise Researchers

Evaluating children for autism where they live, instead of just their through their medical records, reveals a surprisingly higher prevalence of autism spectrum disorder.

BY LESLIE SINCLAIR

The often-quoted and most widely accepted statistic regarding the prevalence of autism spectrum disorder (ASD) in children is 1 in 110. It is based on a 2006 retrospective review of evaluation records in multiple sites participating in the Autism and Developmental Disabilities Monitoring (ADDM) Network.

The CDC collected data from existing records in 11 ADDM Network sites in 2006 and published results in the *Morbidity and Mortality Weekly Report* in 2009. The CDC report indicated ASD prevalence ranging from 4.2 to 12.1, with most states identifying a prevalence of 7.5 to 10.4 cases (the average was 9 cases) per 1,000 8-year-old children, slightly less than 1 percent.

But could there be children—undiagnosed, untreated—who are unaccounted for in those numbers? It's a question Richard Grinker, Ph.D., a professor of anthropology, international affairs, and human sciences at the Elliott School of International Affairs at George Washington University, has been asking himself for years. Grinker's 19-year-old daughter has been diagnosed with ASD and was mainstreamed in school with the help of special-education classes. "It has always struck me that there were kids in mainstream schools who had undiagnosed autism. And I suspected the numbers were higher than thought, because determination of those numbers was made by evaluating medical records, not children themselves," said Grinker in an interview with *Psychiatric News*.

Photo courtesy of Young Shin Kim, M.D., Ph.D.

Credit: Grinker, George Washington University

Richard Grinker, Ph.D., and fellow researcher Young Shin Kim, M.D., Ph.D. (inset), who was the lead author/investigator, just two of the team of international researchers involved in this study of ASD in Korean schoolchildren.

Recently, Grinker collaborated with a like-minded and multicultural group of researchers that included Young Shin Kim, M.D., Ph.D., and Bennett Leventhal, M.D., both associated with the Nathan S. Kline Institute for Psychiatric Research, and Yun-Joo Koh, Ph.D., of the Korea Institute for Children's Social Development and Rudolph Child Research Center.

Along with seven other co-researchers, the group asked "what if you went into a community and looked not only at the records, but also at every child?

And they did just that, in a study conducted from 2005 to 2009 in the Ilsan district of Goyang City, South Korea, a stable residential community near Seoul, representative of the general Korean population.

They estimated ASD prevalence and described ASD clinical characteristics in a population-based sample of 55,266 children aged 7 to 12. The population of children included a low-probability sample from regular education schools and a high-probability group from special-education schools and a disability registry.

The results were unprecedented: an ASD prevalence of 2.64 percent, with only 0.75 percent in the high-probability group (in the lower range of prior ASD prevalence estimates) but 1.89 percent in the general population sample. The study method may have identified an entire population of children with ASD that has not yet been characterized.

"The majority of the previously undiagnosed children uncovered by this study were in mainstream schools, with average or above average intelligence. They had impairments, but not enough to qualify for supportive services. Many of them were identified by their parents, but not by their teachers, because their teachers did not find them to be a burden. It's a compelling example of how a condition can be common in a population, even if it is not commonly diagnosed," said Grinker.

"More than it suggests a number, this study suggests that the method used to determine numbers, when it comes to autism, will profoundly influence the outcome," he added.

Kim and Leventhal told *Psychiatric News* that the participation of Koh, a developmental psychologist, was a critical element of the study. "Many people try to do international studies," said Kim, "but one of the difficulties is that you must have local people you can trust and work with."

In the report, the researchers described their methods for avoiding cultural bias and indicators they used to evaluate whether any cultural bias had occurred.

Kim intends to continue working with the Ilsan population to look at environmental and genetic factors and to determine a rate of incidence of ASD.

The research was funded by an Autism Speaks Pilot Research Grant, a Children's

please see ***Autism*** *on page 17*

Psychiatrists Vie for AMA Positions

Psychiatry Major Player At AMA

Within the AMA "House of Medicine," psychiatry flexes a lot of muscle.

One psychiatrist serves as an elected officer of the House of Delegates and several others occupy elected and appointed leadership positions on AMA councils.

Officers of the AMA and members of the Board of Trustees and four councils are elected by the House of Delegates at the AMA's Annual Meeting. The four councils are the Council on Constitution and Bylaws, Council on Medical Education, Council on Medical Service, and Council on Science and Public Health.

Nominations for these offices are widely solicited throughout the AMA's federation of state and specialty medical societies. The elections are held on site by secret ballot under the Committee on Rules and Credentials and the chief teller, who are appointed by the speaker and vice speaker.

The AMA Board of Trustees consists of 21 members—including designated positions for a public member, young physician, resident physician, and a medical student—who serve a four-year term. Seven individuals, one of whom is an incumbent, are running this year for four open seats on the board.

This year three psychiatrists and prominent APA members are candidates for AMA office. Jeremy Lazarus, M.D., currently speaker of the House of Delegates, is running unopposed as a candidate for president-elect of the AMA. If elected, Lazarus will be only the second psychiatrist to be president of the AMA. (The first, Rock Sleyster, M.D., was installed as the 93rd president of the organization in 1939.) In addition to being speaker of the House, Lazarus has served on the AMA Board of Trustees; he is also a past speaker of the APA Assembly.

Also running for office are Patrice Harris, M.D., a candidate for one of the four open seats on the Board of Trustees, and John McIntyre, M.D., a candidate for a second term on the Council on Medical Service. (Five other candidates are running for election to three open seats on the council.)

Carolyn Robinowitz, M.D., chair of the Section Council on Psychiatry, told *Psychiataric News,* "We owe our success at the AMA over the past decade to the effective leadership of Drs. Joseph English and Jack McIntyre, who chaired the section council, as well as to the immense contributions of the delegation chairs from the American Academy of Child and Adolescent Psychiatry and the American Academy of Psychiatry and the Law: Drs. Louis Kraus, David Fassler, Robert Phillips, and Howard Zonana."

At right is information on Harris and McIntyre. More information is posted on their Web sites: Patrice Harris, M.D., at <www.patricefortrustee.com> and John McIntyre, M.D., at <www.jackmcintyremd.com>.

***Information on Lazarus will appear in the next issue of* Psychiatric News.**

Harris Seeks Board Of Trustees Seat

Harris says her experience as a lobbyist in Georgia and as chair of the AMA Council on Legislation has taught her the value of unity in advocating for physicians and patients.

BY MARK MORAN

Psychiatrist Patrice Harris, M.D., is a candidate for the Board of Trustees of the AMA.

Harris, who is chair of the AMA Council on Legislation and serves as a delegate from APA to the AMA, is supported in her candidacy for the board by the Section Council on Psychiatry (which includes APA, the American Academy of Child and Adolescent Psychiatry, and the American Academy of Psychiatry and the Law), the Medical Association of Georgia, and the Southeastern Delegation to the AMA House of Delegates.

The election will be held at next month's meeting of the AMA House of Delegates in Chicago.

In an interview with *Psychiatric News*, Harris said that the AMA Board of Trustees will be involved in the coming year in a range of issues affecting every physician in America. These include the physician response to the ever-evolving health care landscape, access to care, efforts to replace the flawed Medicare physician payment formula, mechanisms for funding graduate medical education, looming physician workforce shortages, and strategies for reducing the costs of defensive medicine and malpractice liability.

Additionally, the board will need to address how to increase AMA membership.

As a private-practice physician, public health administrator, patient advocate, and medical society lobbyist, Harris said that she brings the skills and the experience necessary to contribute as an effective board member on all of these issues.

"My experience has given me a keen understanding of what is needed to ensure that physicians are in the lead in discussions and debate about an evolving health care system," she said. "My work as chair of the Council on Legislation and as a lobbyist in Georgia has taught me the perils of division and the importance of unity. As physicians, we need to speak with one voice."

Credit: Jolene Butts Freeman

Patrice Harris, M.D.

In addition to the private practice of general and child and adolescent psychiatry, Harris is director of health services for Fulton County, Ga., which includes Atlanta. She directs all county health services, including health partnerships that deliver a wide range of public safety, behavioral health, and primary care treatment and prevention services.

Harris told *Psychiatric News* that psychiatry is an integral and valued member of the house of medicine at the AMA and that physicians of every specialty have come to

please see ***Harris*** *on page 35*

McIntyre Would Guide Key Policy Issues

McIntyre has a track record of leadership within APA and the AMA and a longtime interest in the socioeconomic issues that affect the practice of medicine in general and psychiatry in particular.

BY MARK MORAN

Psychiatrist and past APA President John McIntyre, M.D., is a candidate for a second term on the AMA's Council on Medical Service.

The election will be held at next month's meeting of the AMA House of Delegates in Chicago. McIntyre is one of six candidates, including two incumbents for three open seats on the council. He was elected to a first term in 2007.

The Council on Medical Service formulates policy around socioeconomic issues that affect the practice of medicine and makes recommendations to the House of Delegates.

McIntyre brings to his candidacy for the council an extensive background in organized medicine and psychiatry and rich experience working on the issues that will be commanding the council's attention in the coming year. In addition to being a past APA president, he was speaker of the APA Assembly, and he has been senior delegate from the APA to the AMA House of Delegates. (McIntyre continues to serve as a delegate with Carolyn Robinowitz, M.D., now senior delegate and chair of the Section Council on Psychiatry.)

John McIntyre, M.D.

Health care reform will continue to be front and center for the council. In an interview with *Psychiatric News*, McIntyre said the council has been developing AMA policy around expanding access to care while addressing cost issues for decades.

In some cases, the AMA has anticipated events on the national stage. McIntyre noted that five years ago the council recommended—and the House of Delegates adopted—a policy endorsing an "individual responsibility" to purchase insurance for catastrophic costs and preventive care for anyone earning more than 500 percent of the federal income poverty level.

Now, the Patient Protection and Affordable Care Act includes an "individual mandate" to purchase more comprehensive insurance and carries penalties for failure to do so.

The mandate has become a hot-button issue politically, and McIntyre said a resolution to reaffirm the existing AMA policy on individual responsibility was referred back to the council at last year's Interim Meeting and will be debated again next month in Chicago.

Very prominent also on the house agenda next month will be the subject of accountable care organizations (ACOs). Delegates at the meeting will be debating a report by the council titled "Implementing Alternative Healthcare Delivery and Physician Payment Models," which will have recommendations on the structure and function of ACOs and the use of payment methodologies such as "bundling services."

Other issues the council will be addressing at next month's meeting include denial of Medicare payments to hospitals on the basis of volume of services provided; financing of interpretative services, which are currently borne by physicians in the Medicare program; and the longstanding exclusion of "institutions of mental diseases" from federal matching funds under the Medicaid program.

"I'm looking forward to continuing work on the council and on core issues for the practice of medicine and psychiatry," McIntyre said. ■

Prison Culture, Rules Make Providing MH Care Difficult

University of Maryland psychiatry residents introduce fellow clinicians to a hidden culture—the world inside America's jails and prisons.

BY AARON LEVIN

Psychiatric clinicians must understand the cultural gap between prison and the world in which the rest of us live if they are to treat current or former prisoners, said participants in a daylong workshop presented by psychiatry residents at the University of Maryland School of Medicine in Baltimore in March.

The event was part of an annual series of programs presented by psychiatry residents exploring different cultures.

About 2.5 million people now are incarcerated in American jails and prisons, and as many as 10 million have cycled through those systems in recent years. Half are African American. Most—80 percent—are believed to have been physically or sexually abused at some time in their lives. A similar percentage have abused substances.

Credit: Aaron Levin

Terry Kupers, M.D.: "Correctional psychiatry offers opportunities to devise new and creative interventions to treat patients who would not be treatable in other settings."

Many had mental disorders before they were imprisoned, and others developed them behind bars, said psychiatrist Terry Kupers, M.D., of the Alta Bates Summit Medical Center in Oakland, Calif., at the Maryland workshop.

"Many people who should be receiving psychiatric services are put into prisons," where services are less than optimal, noted Kupers.

There are two cultures in prison, the official and unofficial, he said. As expected, the official culture is nominally under the control of the warden and the correctional officers (who, said Kupers, hate to be called "guards").

"In prison, there are 10 rules for every one rule in the outside world, and they are stringently enforced," he said. Even minor exceptions can't be made at the line level and are passed up the chain of command. Once, on his way to interview a prisoner, Kupers asked the officer at the gate if he could bring his computer in. The officer couldn't answer and had to ask his superior, who passed the question up to his commander.

The unofficial culture is the world of the inmates. It places a premium on toughness and vengeance against informing to officers. Officers have their own "no-snitch" rule, too, one that discourages anyone from reporting misbehavior by officers.

The unofficial culture is also ruled by a code that reflects a dominance hierarchy, said Kupers. "You have to be the top dog or you get used as a sexual object." Mentally ill prisoners have real problems navigating between the unofficial and official cultures.

In prison, friends count, said Kupers. "You don't hit, rape, steal from people with friends," he said. "People with severe mental illness don't have friends. They're loners, so they become targets. If they report assault or mistreatment, they only invite retaliation."

In addition, use of isolation cells is becoming more common today, which leads only to more anxiety, more anger, and more paranoia. About 56 percent of prisoners held in isolation units (formerly called solitary confinement) endorse symptoms of mental illness, according to Kupers.

Furthermore, staff and prisoners are more and more isolated from each other, he said. Prisoners are frequently locked into their cells and kept in isolation. They avoid even the most innocuous conversations with officers, fearing that such interactions might be misconstrued from across the yard as snitching. The two groups don't know how to talk to each other, further decreasing understanding between them and leading to more anger, confrontations, and violence.

Prisoners Shortchanged on MH Care

Mental health care is generally poor in the American prison system because society has decided not to provide much of it, and conditions within prisons make the work of mental health professionals difficult, said Kupers.

For one thing, the prison staff is concerned about malingering by prisoners. For another, in some prisons, security issues or staff shortages preclude moving prisoners held in isolation units to an office for confidential interviews.

"That means that the psychiatrist talks to the patient through the bars or through the food port in a solid cell door, within earshot of prisoners in neighboring cells or staff passing by," Kupers explained in an interview. "When prisoners with mental illness are stigmatized as 'dings' or worse, the clinician must ask in a voice loud enough to be overheard, 'Are you still hearing voices?,' 'How is that new medication working?,' 'Are you feeling suicidal?' More often than not, the prisoner refuses to respond, so the information gleaned from the cell-door interview is not even reliable."

Refuse Cell-Door Interviews

For that reason, mental health personnel should refuse to do cell-door interviews, said Kupers.

Mental health staff members are also pressed from the opposite direction by the "blue code," he said. If they observe an inappropriate use of force by officers, they must decide whether to keep silent or turn in the offending officer and risk retaliation.

Retaliation may take several forms, said Kupers. Officers can refuse to escort mental health staff on rounds, they can stall and keep mental health staff waiting to see prisoners, or, in more extreme situations, they can delay responding when a member of the mental health staff is assaulted by prisoners.

"I am certainly not claiming that all prison staff are unethical and unprofessional in this way," he said. "However, mental health staff sometimes overidentify with the officer culture and the blue code, and then they, like the nonabusive officers who fail to report, become complicit in the abuses of the minority of 'bad apples' among officers even though, if asked, they do not really condone maltreatment."

In general, said Kupers, providing mental health care in prisons is difficult for a number of reasons. Funding often fails to cover services urgently needed for the many individuals with serious mental illness in prison. There is a very high sui-

please see ***Prison*** *on page 35*

Primary Care Expansion Could Improve Minorities' Access to MH Care

Ten years after the U.S. surgeon general's report recommended integrating primary and psychiatric care to increase access for racial and ethnic minorities, there is still much work to be done.

BY AARON LEVIN

The humble neck—whether perceived anatomically or philosophically—may be enjoying a resurgence, said Ruth Shim, M.D., M.P.H., at the national conference of the 2011 Substance Abuse and Mental Health Services Administration (SAMHSA) Minority Fellows Program in March in Rockville, Md.

The conference brought together fellows in psychiatry, nursing, psychology, social work, and family therapy to learn more about how to improve mental health in diverse populations. Eight APA/SAMHSA Minority Fellows attended, as did three APA Diversity Leadership Fellows (partly supported by AstraZeneca).

Shim was referring both to the physiological interactions between the brain and the postcervical body and, metaphorically, to the integration of psychiatric and primary care.

"Half of all mental disorders are treated in general medical settings," she reminded her listeners.

Primary care physicians prescribe the majority of psychotropic medications to children and adults, said Shim, an assistant professor of psychiatry and behavioral health at Morehouse School of Medicine in Atlanta. She also serves as associate director of behavioral health at the National Center for Primary Care at Morehouse.

Primary care settings are also the first place that most patients—especially members of minority groups—are likely to go when they are experiencing mental health problems, she said. That makes those clinics a good place to address deficiencies and disparities in access to care.

"Given some of the lingering stigma around mental illness in racially and ethnically diverse populations, it is essential to expand capacity within primary care settings, or those mental health needs will go unaddressed," said Annelle Primm, M.D., M.P.H., an APA deputy medical director and head of its Office of Minority and National Affairs, who attended the conference.

Racial and ethnic disparities in mental health were documented in the landmark 2001 "Surgeon General's Report on Mental Health: Culture, Race, and Ethnicity." According to the report, minorities had less access to mental health services and were less likely to receive care and more likely to get poor quality care than non-Hispanic whites.

Racism, poverty, discrimination, and violence all affect the incidence and treatment of mental illness, said Shim; thus, it's not surprising that minority groups still underutilize mental health services. In areas where many minority patients are treated, there is often a lack of resources, she said. Also, clinicians serving those populations can easily get burned out.

For these and other reasons, progress in ending disparities in mental health care has been slow, she said. For instance, among African Americans, schizophrenia is overdiagnosed, while typical antipsychotics are overprescribed, compared with whites. Among Latinos, schizophrenia is underdiagnosed, but there are too few studies on prescribing antipsychotics to tell whether there are significant differences in prescribing patterns between Latinos and whites, said Shim in an interview afterward.

Integrating primary and mental health care might help overcome some of those anomalies, she said, echoing recommendations in the surgeon general's supplementary report. The majority of people treated in these settings have good clinical outcomes that are also achieved cost-effectively. Primary care has far to go as a locus of mental health care, however.

"Most mental disorders go undiagnosed there, so patients are poorly treated," she said. Or primary care clinicians may refer patients to mental health specialists but often do not participate in follow-up care.

please see ***Minorities*** *on page 10*

NIDA 'Warmline' Connects M.D.s With Addiction Experts

A government agency teams up with addiction medicine specialists to sponsor an innovative avenue for informing primary care physicians about caring for patients who have a substance abuse problem or disorder.

BY AARON LEVIN

The National Institute on Drug Abuse (NIDA) wants primary care clinicians to be just a phone call or an e-mail away from expert advice and support when managing patients with substance abuse problems.

In April the Physician Clinical Support System for Primary Care (PCSS-P) began connecting primary care physicians with online information and resources, as well as experienced mentors for more specific advice about screening, intervening, treating, or referring patients who abuse drugs or alcohol. A NIDA grant funds the project, which is administered by the American Society of Addiction Medicine.

The PCSS-P service is a "warmline" system. It provides a response within 24 hours—but not immediately as with a true hotline.

When primary care clinicians need help in managing an individual patient, they can call PCSS-P. That begins a triage process that routes calls or e-mails to one of seven clinical advisors (called mentors) or to one of the two medical directors—David Fiellin, M.D., a professor of medicine and public health at Yale University, and Louis Baxter Sr., M.D., president of the American Society of Addiction Medicine and medical director of New Jersey's professional assistance program.

Each mentor's specialty or practice experience can be matched as closely as possible with the caller's background and inquiry, said Fiellin in an interview with *Psychiatric News*.

"We have mentors who are specialists in family medicine, internal medicine, emergency medicine, as well as some who work in federally qualified health centers," said Fiellin. "We wanted mentors who had broad training in addiction medicine and were also good teachers who could work with primary care doctors with varying knowledge of the subject."

Each mentor can advise 50 to 100 primary care physicians, he said. The highest use for each primary care doctor who accesses the system will likely occur in the first two or three weeks after that physician's first contact, but should become less intense as he or she gains knowledge and experience, Fiellin noted.

How well the system will work may depend on the preferences of individual practitioners and patients, said Virginia Hood, M.B.B.S., M.P.H., a professor of medicine at the University of Vermont and president of the American College of Physicians.

"The issue of substance abuse is a large and serious problem for our patients, so any initiative is always welcome," said Hood in an interview. "We support efforts to help educate our members to recognize, treat, and counsel patients about alcohol and drug abuse."

The PCSS-P represents a good first step, although many primary care clinicians could use an immediate consultation at the point of care to help them start some type of intervention before the patient leaves the office, said Hood, who is not connected with PCSS-P.

Much of the clinicians' education will come not only from direct contact with the PCSS-P experts but from the project's Web site, which provides links to resource material for physicians and patients. This information includes a brief initial screening tool produced by NIDA that can be completed either by the patient, the physician, or a staff person. If that indicates actual or potential abuse of drugs or alcohol, a more detailed screening tool is available to define the nature and severity of the patient's problem.

"We hope to get feedback from participating primary care physicians about the value of these resources and use that information to make the NIDA and PCSS-P Web sites more user friendly," said Fiellin.

The PCSS-P system is a modified version of similar programs that provide specialized expertise to help primary care physicians who are using methadone and buprenorphine treatments in their practices. Many of those physicians had taken required courses in the use of these medications, but needed additional advice when confronted with real-world problems that arose in the course of their practice, said Fiellin.

A study of the buprenorphine project published online on May 11, 2010, in the *Journal of General Internal Medicine* reported that from July 2005 to July 2009, 632 primary care participants in 48 states had 1,455 contacts with 67 mentors and four other clinical experts.

The Physician Clinical Support System for Primary Care (PCSS-P) Web site is <www.pcssprimarycare.org>. NIDA's "Resources for Medical and Health Professionals," including a basic screening tool, is posted at <www.drugabuse.gov/nidamed>. ■

Leading Ladies

continued from page 1

In her remarks, Obama noted that some large corporations have agreed to reserve job vacancies for employees who are the spouses of military personnel and are transferred to new locations where the businesses also operate.

Credit: The White House

At the White House on April 12, President Obama introduces First Lady Michelle Obama and Jill Biden, wife of Vice President Joe Biden. The two women are leading Joining Forces, a program to support military families and enhance their well-being.

"Companies like Sears, Kmart, and Sam's Club are telling military spouses who work at their stores that if they move to a new duty station, they'll do their best to have a job waiting for those spouses," said Obama. Walmart and Target have also signed up. The large electronics firm Siemens is setting aside 10 percent of its open positions for veterans, she added.

Such initiatives are critical for the families of enlisted personnel, because military salaries are low and often must be supplemented by a spouse's outside income. Frequent moves make it hard for the spouse to hold a job or find one in a new location, so stabilizing a spouse's employment can go a long way toward strengthening families already facing high levels of stress.

Rotary and Lions clubs, which are strong in rural areas and small cities, also have been enlisted in the Joining Forces initiative. They are starting outreach efforts to find and help families living near military bases in their regions.

Veterinarians have stepped up to donate some types of care for military families' pets.

In addition, APA members organized several sessions at this month's annual meeting in Honolulu at which leading military and VA psychiatrists discussed combat trauma and readjustment problems, including one session focusing on the effects of the extended period of war on soldiers and their families. (Coverage of the annual meeting will begin in the next issue.)

More on Michelle Obama's and Jill Biden's work to help military families is posted at <www.whitehouse.gov/blog/2011/04/13/president-vice-president-first-lady-and-dr-jill-biden-launch-joining-forces>. ■

Minorities

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At the same time, people with mental illnesses often have increased levels of physical illnesses. "Mental illness exacerbates disabilities caused by cardiovascular disease, pulmonary disease, diabetes, arthritis, and others," said Shim. "This leads to higher medical utilization and costs."

Yet specialist mental health care providers either may not be trained to provide general medical care for patients with co-existing conditions or, in the case of psychiatrists, may be so busy at their specialty that it does not seem a good use of resources for them to work as general medical doctors. Many do not practice at locations where patients can also get such care, she said. Many primary care physicians have had only minimal training in psychiatry, as well.

Better integration of mental health care with other types of medical care might ease some of the problems facing patients, clinicians, and health systems. Strong evidence from several randomized trials on anxiety and depression shows that those conditions can be effectively treated in primary care, given careful advance planning.

For instance, in the IMPACT trial, University of Washington researchers demonstrated the value of stepped care for late-life depression. Based in a primary care clinic, the IMPACT plan used a care manager (usually a nurse, social worker, or psychologist) to educate, counsel, and monitor patients and to support antidepressant therapy prescribed by the primary care physician. A psychiatrist consulted to the care manager and the primary care clinician on difficult cases and recommended additional treatment or referral for patients who did not improve as expected.

IMPACT is now available for other health systems to place into regular use.

A second approach, RESPECT-D, is also being implemented. It used phone-based support and consulting psychiatrists to monitor patients and add interventions as needed. About 16 percent of patients were members of "ethnic minorities."

The NIMH-funded Prevention of Suicide in Primary Care Elderly: Collaborative Trial (PROSPECT), published in 2009, reduced depression in older patients as part of a program to prevent suicide in this population. After two years, patients were more likely to achieve remission than were those in usual care. About 68 percent of the patients were listed as "white," while the rest were of "unspecified" race or ethnicity, so the results need to be replicated in minority populations.

"More and better research is needed on minority populations," said Shim. "It is incorrect to assume that the research findings that apply to one specific population (like white males) can uniformly apply to people from all different populations."

Myriad studies show that health differences in racial and ethnic populations exist, but there is not enough research on those populations to characterize those differences, she said.

She urged the fellows in the audience to pursue research on health disparities as part of their careers.

"Research data are the currency for making population-based change," she said.

"There will be more and more opportunities to practice in primary care," said Primm. "So I hope discussions like these will raise the fellows' interest in that setting as a career path." ■

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Viibryd™

vilazodone HCl

10 mg, 20 mg, 40 mg tablets

for the treatment of adults with Major Depressive Disorder (MDD)

Important Safety Information

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD 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. VIIBRYD is not approved for use in pediatric patients.

Please also see additional Important Safety Information and Brief Summary of Prescribing Information on the following pages.

Indication

- VIIBRYD (vilazodone) is indicated for the treatment of major depressive disorder (MDD) in adults. The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD.

Important Safety Information (continued)

Contraindications

- VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. Allow at least 14 days after stopping VIIBRYD before starting an MAOI.

Warnings and Precautions

- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients daily.** Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.
- The development of potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (eg, agitation, hallucinations, coma), autonomic instability (eg, tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (eg, hyperreflexia, incoordination) and/or gastrointestinal symptoms (eg, nausea, vomiting, diarrhea). Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms while treated with VIIBRYD.
- Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder.
- The use of drugs that interfere with serotonin reuptake, including VIIBRYD, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation or bleeding.
- Symptoms of mania/hypomania were noted in 0.1% of patients treated with VIIBRYD in clinical studies. As with all antidepressants, VIIBRYD should be used cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania.
- 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. VIIBRYD is not approved for use in treating bipolar depression.
- Discontinuation symptoms have been reported with discontinuation of serotonergic drugs such as VIIBRYD. Gradual dose reduction is recommended, instead of abrupt discontinuation, whenever possible. Monitor patients when discontinuing VIIBRYD. If intolerable symptoms occur following a dose decrease or upon discontinuation of treatment, consider resuming the previously prescribed dose and decreasing the dose at a more gradual rate.
- Advise patients that if they are treated with diuretics, or are otherwise volume depleted, or are elderly, they may be at greater risk of developing hyponatremia while taking VIIBRYD. Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Adverse Reactions

- The most commonly observed adverse reactions in MDD patients treated with VIIBRYD in placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were: diarrhea (28% vs 9%), nausea (23% vs 5%), insomnia (6% vs 2%), and vomiting (5% vs 1%).

Please also see Brief Summary of Prescribing Information on the following pages and full Prescribing Information at www.viibryd.com.

Viibryd™
vilazodone HCl
10 mg, 20 mg, 40 mg tablets

Forest Pharmaceuticals, Inc.
Subsidiary of Forest Laboratories, Inc.
St. Louis, Missouri 63045

47-1020730T 5/11

VIIBRYD (vilazodone HCl) **Rx Only**
Tablets for oral administration
Brief Summary of Full Prescribing Information
Initial U.S. Approval: 2011

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of VIIBRYD 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. VIIBRYD is not approved for use in pediatric patients [*see Warnings and Precautions, Use in Specific Populations, and Patient Counseling Information*]

INDICATIONS AND USAGE: VIIBRYD is indicated for the treatment of major depressive disorder (MDD). The efficacy of VIIBRYD was established in two 8-week, randomized, double-blind, placebo-controlled trials in adult patients with a diagnosis of MDD *[see Clinical Studies]*. Major depressive disorder consists of one or more major depressive episodes. A major depressive episode (DSM-IV-TR) implies a prominent and relatively persistent (nearly every day for at least 2 weeks) depressed or dysphoric mood that usually interferes with daily functioning, and includes at least 5 of the following 9 symptoms: depressed mood, loss of interest in usual activities, significant change in weight and/or appetite, insomnia or hypersomnia, psychomotor agitation or retardation, increased fatigue, feelings of guilt or worthlessness, slowed thinking or impaired concentration, or a suicide attempt or suicidal ideation.

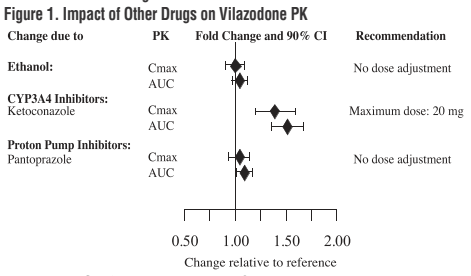
CONTRAINDICATIONS: Monoamine Oxidase Inhibitors - VIIBRYD must not be used concomitantly in patients taking MAOIs or in patients who have taken MAOIs within the preceding 14 days due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions have been associated with symptoms that include tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, rigidity, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Allow at least 14 days after stopping VIIBRYD before starting an MAOI *[see Drug Interactions]*.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk - Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment. Pooled analyses of short-term placebo-controlled studies of antidepressant drugs (selective serotonin reuptake inhibitors [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 MDD and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older. The pooled analyses of placebo-controlled studies in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term studies of 9 antidepressant drugs in over 4,400 patients. The pooled analyses of placebo-controlled studies in adults with MDD or other psychiatric disorders included a total of 295 short-term studies (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk differences (drug vs. placebo), however, were relatively stable within age strata and across indications. These risk differences (drug-placebo difference in the number of cases of suicidality per 1000 patients treated) are provided in Table 1. There were 14 additional cases reported in patients under the age of 18, while 5 additional cases were reported in patients between 18 and 24 years of age. Patients between 25 and 64 years of age reported 1 fewer case of suicidality, while patients 65 years of age and over reported 6 fewer cases. No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and nonpsychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that abrupt discontinuation can be associated with certain symptoms [*see Warnings and Precautions and Dosage and Administration*]. Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for VIIBRYD should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose *[see also Patient Counseling Information]*. **Screening patients for bipolar disorder -** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled studies) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that VIIBRYD is not approved for use in treating bipolar depression. **Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions -** The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions has been reported with antidepressants alone, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs that impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Symptoms of serotonin syndrome were noted in 0.1% of patients treated with VIIBRYD. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble NMS, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. The concomitant use of VIIBRYD with MAOIs intended to treat depression is contraindicated *[see Contraindications]*. If concomitant treatment of VIIBRYD with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*. The concomitant use of VIIBRYD with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*. Treatment with VIIBRYD and any concomitant serotonergic (SSRI, serotonin–norepinephrine reuptake inhibitor [SNRI], triptan, buspirone, tramadol, etc.) or antidopaminergic drugs, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated. **Seizures -** VIIBRYD has not been systematically evaluated in patients with a seizure disorder. Patients with a history of seizures were excluded from clinical studies. Like other antidepressants, VIIBRYD should be prescribed with caution in patients with a seizure disorder. **Abnormal Bleeding -** The use of drugs that interfere with serotonin reuptake inhibition, including VIIBRYD, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs (NSAIDS), warfarin, and other anticoagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of VIIBRYD and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Activation of Mania/Hypomania -** Symptoms of mania/hypomania were reported in 0.1% of patients treated with VIIBRYD in clinical studies. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other antidepressants. As with all antidepressants, use VIIBRYD cautiously in patients with a history or family history of bipolar disorder, mania, or hypomania. **Discontinuation of Treatment with VIIBRYD -** There have been reports of adverse events occurring upon discontinuation of serotonergic antidepressants, particularly when discontinuation is abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Monitor patients for these symptoms when discontinuing VIIBRYD. Reduce the dose gradually whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, consider resuming the previously prescribed dose. Subsequently, the dose may be decreased, but at a more gradual rate *[see Dosage and Administration]*. **Hyponatremia -** Although no cases of hyponatremia resulting from VIIBRYD treatment were reported in the clinical studies, hyponatremia has occurred as a result of treatment with SSRIs and SNRIs. In many cases, hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported. Elderly patients may be at greater risk of developing hyponatremia with SSRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk. Discontinuation of VIIBRYD in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which can lead to falls. Signs and symptoms associated with more severe and/or acute cases have included hallucination, syncope, seizure, coma, respiratory arrest, and death.

ADVERSE REACTIONS: Clinical Studies Experience - The most commonly observed adverse reactions in VIIBRYD-treated MDD patients in placebo-controlled studies (incidence ≥5% and at least twice the rate of placebo) were: diarrhea, nausea, vomiting, and insomnia. **Patient Exposure -** The safety of VIIBRYD was evaluated in 2,177 patients (18-70 years of age) diagnosed with MDD who participated in clinical studies, representing 552 patient-years of exposure. In an open-label 52 week study at 40 mg daily, 599 patients were exposed to VIIBRYD for a total of 348 patient-years. The information presented in these sections was derived from studies of VIIBRYD 40 mg daily in major depressive disorder including: 1) 2 placebo-controlled 8-week studies in 861 patients, including 436 receiving vilazodone; and 2) an open-label 52-week study of 599 patients. These studies included a titration period of 10 mg daily for 7 days followed by 20 mg daily for 7 days. In these clinical trials, VIIBRYD was administered with food. Because clinical trials are conducted under widely varying conditions and varying lengths of time, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect rates observed in practice. **Adverse reactions reported as reasons for discontinuation of treatment -** In the placebo-controlled studies of MDD there was no single adverse reaction leading to discontinuation in > 1% of the patients. Overall, 7.1% of the patients who received VIIBRYD discontinued treatment due to an adverse reaction, compared with 3.2% of placebo-treated patients in these studies. **Common adverse reactions in placebo-controlled MDD studies -** Table 2 shows the incidence of common adverse reactions that occurred in ≥2% of VIIBRYD-treated MDD patients (and greater than in placebo-treated patients) in the placebo-controlled studies. The first value displays the number of patients exhibiting the adverse reaction while receiving VIIBRYD 40 mg/day (N = 436) and the second value is the number of patients exhibiting the adverse reaction while receiving Placebo (N = 433). **Gastrointestinal disorders:** Diarrhea (28, 9); Nausea (23, 5); Dry mouth (8, 5); Vomiting (5, 1); Dyspepsia (3, 2); Flatulence (3, 2); Gastroenteritis (3, <1); **Nervous system disorders:** Dizziness (9, 5); Somnolence (3, 2); Paresthesia (3, 1); Tremor (2, 0); **Psychiatric disorders:** Insomnia (6, 2); Abnormal dreams (4, 1); Libido decreased (4, <1); Restlessness* (3, <1); Orgasm abnormal** (3, 0); **General disorders:** Fatigue (4, 3); Feeling jittery (2, <1); **Cardiac disorders:** Palpitations (2, <1); **Musculoskeletal and connective tissue disorders:** Arthralgia (3, 2); **Reproductive system and breast disorders:** Delayed ejaculation*** (2, 0); Erectile dysfunction*** (2, 1); **Metabolism and nutrition disorders:** Increased appetite (2, 1). *Includes restlessness, akathisia, and restless legs syndrome; **Includes orgasm abnormal and anorgasmia; ***Male patients only (Placebo n=182; VIIBRYD n=170). Table 3 shows the percentages of Sexual Adverse Reactions in the Placebo-Controlled Studies. The first grouping shows the percentages in Males with VIIBRYD (N=170) and Placebo (N=182). The second grouping shows the percentages in Females with VIIBRYD (N=266) and Placebo (N = 251). Decreased libido (5,0)/(3,<1); Abnormal orgasm* (4,0)/(2,0); Delayed ejaculation (2,0)/(–,–); Erectile dysfunction (2,1)/(–,–); Sexual dysfunction (2,0)/(<1,<1). – Not applicable; *Includes anorgasmia. **Laboratory Tests** - VIIBRYD has not been associated with any clinically important changes in laboratory test parameters in serum chemistry (including liver function tests), hematology and urinalysis, as measured in placebo-controlled studies. These studies include analysis of (1) mean change from baseline and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies. **ECG** - VIIBRYD has not been associated with any clinically significant effect on ECG parameters, including QT, QTc, PR and QRS intervals, or with any arrhythmogenic potential. ECGs were evaluated in a thorough QTc study at doses up to 80 mg daily with food and in the placebo-controlled studies *[see Clinical Pharmacology]*. **Vital Signs** - VIIBRYD has not been associated with any clinically significant effect on vital signs, including systolic and diastolic blood pressure and heart rate, as measured in placebo-controlled studies. These studies included analyses of (1) change from baseline, and (2) the proportion of patients meeting criteria for potentially clinically significant changes from baseline. Results from a 52-week open-label study were consistent with the findings from the placebo-controlled studies. **Weight -** VIIBRYD had no effect on body weight as measured by the mean change from baseline in the 8-week, placebo-controlled studies. The mean changes in weight were +0.16 kg in the VIIBRYD group and +0.18 kg in the placebo group. The proportions of patients with a weight gain ≥7% were 0.9% in the VIIBRYD group and 1.2% in the placebo group.The proportions of patients with a weight decrease ≥7% were 1.4% in the VIIBRYD group and 1.4% in the placebo group. **Other adverse reactions observed in clinical studies** - The following listing does not include reactions: 1) already listed in previous tables or elsewhere in labeling, 2) for which a drug cause was remote, 3) which were so general as to be uninformative, 4) which were not considered to have significant clinical implications, or 5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: *frequent* adverse reactions are those occurring in at least 1/100 patients; *infrequent* adverse reactions are those occurring in 1/100 to 1/1000 patients; *rare* reactions are those occurring in fewer than 1/1000 patients; Cardiac disorders: *infrequent*: ventricular extrasystoles; Eye disorders: *frequent:* vision blurred, dry eye; *infrequent:* cataracts; General disorders: *infrequent*: feeling abnormal; Metabolism and nutrition disorders: *frequent*: decreased appetite; Nervous System: *frequent*: sedation, migraine; *infrequent*: dysgeusia; Psychiatric disorders: *infrequent*: panic attack, mania; Renal and Urinary disorder: *infrequent*: pollakiuria; Skin and subcutaneous tissue disorders: *frequent*: hyperhidrosis, night sweats

DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents - The risk of using VIIBRYD in combination with other CNS-active drugs has not been systematically evaluated. Consequently, use caution when VIIBRYD is prescribed in combination with other CNS-active drugs. **Monoamine Oxidase Inhibitors (MAOI) -** Adverse reactions, some of which are serious or fatal, can develop in patients who use MAOIs or who have recently been discontinued from an MAOI and started on antidepressant(s) with pharmacological properties similar to VIIBRYD (e.g. SSRIs), or who have recently had SSRI therapy discontinued prior to initiation of an MAOI. Do not prescribe VIIBRYD concomitantly with an MAOI or within 14 days of discontinuing or starting an MAOI *[see Contraindications]*. **Serotonergic Drugs -** Based on the mechanism of action of VIIBRYD and the potential for serotonin toxicity, also known as serotonin syndrome, caution is advised when VIIBRYD is coadministered with other drugs that may affect the serotonergic neurotransmitter systems (e.g., MAOI, SSRIs, SNRIs, triptans, buspirone, tramadol, and tryptophan products etc.) *[see Warnings and Precautions]*. **Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin) -** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when VIIBRYD is initiated or discontinued *[see Warnings and Precautions]*.
Potential for Other Drugs to Affect Vilazodone

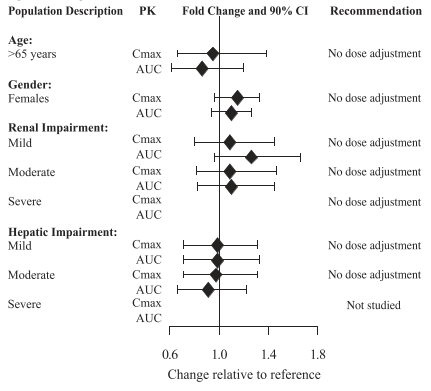
Figure 1. Impact of Other Drugs on Vilazodone PK



Inhibitors of CYP3A4 - Metabolism by CYP3A4 is a major elimination pathway for vilazodone. Concomitant use of VIIBRYD and strong inhibitors of CYP3A4 (e.g., ketoconazole) can increase vilazodone plasma concentrations by approximately 50% (see Figure 1). The VIIBRYD dose should be reduced to 20 mg if co-administered with a strong inhibitor of CYP3A4. During co-administration with moderate inhibitors of CYP3A4 (e.g., erythromycin), the VIIBRYD dose should be reduced to 20 mg for patients with intolerable adverse events. No dose adjustment is recommended when VIIBRYD is co-administered with mild inhibitors of CYP3A4 (e.g., cimetidine). **Inducers of CYP3A4 -** Concomitant use of VIIBRYD with inducers of CYP3A4 has the potential to reduce vilazodone systemic exposure. However, the effect of CYP3A4 inducers on vilazodone plasma concentrations has not been evaluated. **Inhibitors of other CYP enzymes -** Concomitant administration of VIIBRYD with inhibitors of CYP2C19 and CYP2D6 is not expected to alter plasma concentrations of vilazodone. These isoforms are minor elimination pathways in the metabolism of vilazodone. *In vitro* studies have shown that CYP1A2, CYP2A6, CYP2C9 and CYP2E1 have minimal contribution to the metabolism of vilazodone. **Potential for Vilazodone to Affect Other Drugs - Drugs metabolized by CYP1A2, CYP2C9, CYP2D6, CYP3A4 or CYP2C19.** Coadministration of VIIBRYD with substrates for CYP1A2, CYP2C9, CYP3A4, or CYP2D6 is unlikely to result in clinically significant changes in the concentrations of the CYP substrates. A study in healthy subjects found that VIIBRYD (20 mg/day for 8-10 days) had no effect on the pharmacokinetics of caffeine, flurbiprofen, nifedipine or debrisoquine, probes for CYP1A2, CYP2C9, CYP3A4, and CYP2D6, respectively. VIIBRYD coadministration with mephenytoin to healthy subjects resulted in a small (11%) increase in mephenytoin biotransformation, suggestive of a minor induction of CYP2C19. *In vitro* studies have shown that VIIBRYD is a moderate inhibitor of CYP2C19 and CYP2D6. **Drugs metabolized by CYP2C8 -** Coadministration of VIIBRYD with a CYP2C8 substrate may lead to an increase in concentration of the other drug. *In vitro* studies suggest that VIIBRYD may inhibit the biotransformation of substrates of CYP2C8. The effect of VIIBRYD on CYP2C8 activity has not been tested *in vivo*. **Induction of CYP isoforms -** VIIBRYD did not induce CYP1A1, 1A2, 2A6, 2B6, 2C9, 2C19, 2D6, 2E1, 3A4 or 3A5 in an *in vitro* study in cultured human hepatocytes. Chronic administration of vilazodone is unlikely to induce the metabolism of drugs metabolized by these major CYP isoforms. **Drugs Highly Bound to Plasma Protein -** The interaction between vilazodone and other highly protein-bound drugs has not been evaluated. Because vilazodone is highly bound to plasma protein, administration of VIIBRYD to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug.

USE IN SPECIFIC POPULATIONS: Pregnancy, Teratogenic Effects - Pregnancy Category C - Vilazodone caused some developmental toxicity in rats, but was not teratogenic in rats or rabbits. There are no adequate and well-controlled studies of VIIBRYD in pregnant women. When treating pregnant women with VIIBRYD, carefully consider whether the potential benefits outweigh the potential risks of treatment. No teratogenic effects were observed when vilazodone was given to pregnant rats or rabbits during the period of organogenesis at oral doses up to 200 and 36 mg/kg/day, respectively. These doses are 48 and 17 times, in rats and rabbits, respectively, the maximum recommended human dose (MRHD) of 40 mg on a mg/m^2 basis. Fetal body weight gain was reduced, and skeletal ossification was delayed in both rats and rabbits at these doses; these effects were not observed at doses up to 10 times the MRHD in rats or 4 times the MRHD in rabbits. When vilazodone was administered to pregnant rats at an oral dose of 30 times the MRHD during the period of organogenesis and throughout pregnancy and lactation, the number of live born pups was decreased. There was an increase in early postnatal pup mortality, and among surviving pups there was decreased body weight, delayed maturation, and decreased fertility in adulthood. There was some maternal toxicity at this dose. These effects were not seen at 6 times the MRHD. **Nonteratogenic Effects -** Neonates exposed to serotonergic antidepressants late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of serotonergic antidepressants or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions]*. **Labor and Delivery -** The effect of VIIBRYD on labor and delivery in humans is unknown. VIIBRYD should be used during labor and delivery only if the potential benefit outweighs the potential risk. **Nursing Mothers -** Vilazodone is excreted into the milk of lactating rats. The effect of VIIBRYD on lactation and nursing in humans is unknown. Breast feeding in women treated with VIIBRYD should be considered only if the potential benefit outweighs the potential risk to the child. **Pediatric Use -** Clinical studies on the use of VIIBRYD in pediatric patients have not been conducted; therefore, the safety and effectiveness of VIIBRYD in the pediatric population have not been established. VIIBRYD is not approved for use in pediatric patients *[see Boxed Warning and Warnings and Precautions]*. **Geriatric Use -** No dose adjustment is recommended on the basis of age (see Figure 2). Results from a single-dose (20 mg) pharmacokinetic study in elderly (> 65 years-old) vs. young (24-55 years-old) subjects demonstrated that the pharmacokinetics were generally similar between the two age groups. Of the 2177 patients in clinical studies with VIIBRYD, 37 (1.7%) were 65 years of age or older, and 272 (12.5%) were 55 to 64 years of age. Greater sensitivity of some older individuals cannot be ruled out *[see Dosage and Administration]*. Serotonergic antidepressants have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*. **Hepatic Impairment -** Vilazodone is eliminated primarily by hepatic metabolism. In mild and moderate hepatic impairment, no dose adjustment is necessary (see Figure 2). VIIBRYD has not been studied in patients with severe hepatic impairment *[see Dosage and Administration]*. **Renal Impairment -** In mild, moderate, and severe renal impairment, no dose adjustment is necessary (see Figure 2 below) *[see Dosage and Administration]*. **Gender Effect -** After adjustment for body weight, the systemic exposures between males and females are similar (see Figure 2) *[see Dosage and Administration]*.

Figure 2. Impact of Intrinsic Factors on Vilazodone PK



The data shown for elderly subjects (>65 years) are relative to younger subjects (24-55 years).
The data shown for female subjects are relative to male subjects.
The data shown for renal and hepatic impairment are relative to subjects with normal renal and hepatic function, respectively.

OVERDOSAGE: Human Experience - There is limited clinical experience regarding human overdosage with VIIBRYD. Four patients and 1 patient's child experienced an overdose of VIIBRYD; all recovered. The adverse reactions associated with overdose of VIIBRYD at doses of 200-280 mg as observed in clinical trials included serotonin syndrome, lethargy, restlessness, hallucinations, and disorientation. **Management of Overdose -** Consult a Certified Poison Control Center for up-to-date guidance and advice. Telephone numbers for certified poison control centers are listed in the Physicians' Desk Reference® (PDR). No specific antidotes for vilazodone are known. In case of an overdose, provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdose. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be considered. Removal of vilazodone by dialysis has not been studied; however, the high volume of distribution of vilazodone suggests that dialysis will not be effective in reducing vilazodone plasma concentrations.

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Congress Hears From Psychiatrist Constituents

Advocacy Day 2011 provided 70 APA members with the opportunity to learn lobbying skills and to ply those skills in the halls of Congress.

BY RICHARD FAUST

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Photos: Karen Layser (k-photographs)

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1 Bruce Hershfield, M.D., Congressman and physician Phil Gingrey, M.D., and APA*PAC* Chair John Wernert, M.D., enjoy some casual face time at the Advocacy Day evening reception.
2 APA Advocacy Day participant Melinda Young, M.D., and incoming President-elect Dilip Jeste, M.D., get down to work stuffing Advocacy Day information packets.
3 Congressman and physician Bill Cassidy, M.D., stresses to APA members the importance of doctors being involved in the political process.
4 John Oldham, M.D., APA president-elect, recognizes Colibri Jenkins, M.D., the 2010 Spurlock Fellow, for her service to individuals with mental illness and their families and her outstanding advocacy efforts on their behalf.

Advocacy Day brought 70 psychiatrists last month from 42 states to Washington, D.C., to learn advocacy skills and the intricacies of policies and legislation about key mental health issues. Also part of the schedule were meetings with their congressional representatives and opportunities to interact with their fellow psychiatrists. Participants conducted almost 250 Capitol Hill visits in one day, covering nearly half of Congress's 535 members.

Breakout sessions for participants focused on topics such as mental health parity, Medicare scope of practice, posttraumatic stress disorder, public health funding, workforce issues, and Medicare physician payment (SGR formula). Attendees were also given talking-point handouts on several mental health policy topics, as well as a draft letter to Health and Human Services Secretary Kathleen Sebelius on implementation of the mental health parity law.

Matthew Sturm, an associate director in APA's Department of Government Relations, told *Psychiatric News* that the sessions and handouts served as good preparation for the APA members' Capitol Hill visits.

APA Area 5 Trustee Mary Helen Davis, M.D., served as a moderator for some of the breakout sessions, including ones devoted to the parity law and to accountable care organizations. Davis told *Psychiatric News* that "having been a participant in advocacy days over the past 15 years, I think that the current environment is the most exciting. We are in the midst of major health care transformation including changing policy in the mental health care arena. We have to build on the parity legislation, keep ourselves and our members knowledgeable of the changing face of health care delivery models, as well as advocate for our patients, ensuring that mental health needs are understood by the decision makers who will be developing health care policy over the next couple of decades." Davis added, "Although this is a time of great opportunity, there is also monumental uncertainty, with no guarantees of the success or failure of any of the new programs that are emerging."

An APA Advocacy Day evening reception provided the opportunity for continued interaction in a more relaxed setting. It was well attended by members of Congress, including Reps. Phil Gingrey (R-Ga.), Laura Richardson (D-Calif.), Jason Altmire (D-Pa.), and Loretta Sanchez (D-Calif.), as well as dozens of congressional staff.

Altmire told *Psychiatric News*, "I always value having the opportunity to talk to constituents about the topics they feel most strongly about. Hearing the insights and concerns of the American Psychiatric Association members will help me make more informed decisions on the issues affecting Americans who struggle with mental illness and those who treat them."

A sense of the magnitude of the possibilities for advances in health care policy and the need for vigilance in trying to shape policy was echoed by attendees. In a sort of running diary of Advocacy Day events for *Psychiatric News*, New Jersey psychiatrist Steve Resnick, M.D., noted that the current state of psychiatry and health care policy offers exciting opportunities for advances to occur, but there are also concerns stemming from budget cuts and threats to confidentiality.

Resnick said he was enthralled by the opportunity to talk with colleagues and then policymakers on the Hill about these issues. "As I listen to the state of affairs, there is a concern about the future, but also an excitement about the input I can personally have in shaping the future." He went on to say that the changes being made in health care policy are "a crucial turning point for medicine in general and psychiatry specifically, and we can have a great impact on the outcome of these changes."

In another Advocacy Day event, psychiatrist Don Harr, M.D., of Montana was presented with the Advocacy Leadership Award. Charles Price M.D., a member of APA's Council on Advocacy and Government Relations, cited Harr's more than 40 years of championing mental health causes to the Montana legislature. In speaking with *Psychiatric News*, Harr said his hope for the award is that "to those in attendance it will be some added incentive to stay with the advocacy program and develop it to be even more successful than it already is."

Two keynote speakers addressed Advocacy Day participants. Stuart Rothenberg, editor and publisher of the *Rothenberg Political Report* and columnist for *Roll Call*, kicked off the event, offering colorful commentary on the current state of U.S. politics. Rothenberg talked electoral politics and the impossibility of knowing what is in store for the next election cycle. He praised APA for its efforts at shaping policy through an event such as Advocacy Day.

Rep. Bill Cassidy (R-La.) opened day two, stressing to attendees the importance of physicians being advocates. Cassidy is a physician and an associate professor of medicine at Louisiana State University and wanted the audience to know that he considers himself a doctor first and a politician much further down the list of descriptors he would apply to himself. He said that doctors need to remember that they cannot afford to think that politics is beneath them. If doctors don't advocate on behalf of health care and patients, the results may be a system that fails to represent these interests.

In a statement to *Psychiatric News*, Cassidy's office summed up Advocacy Day, saying that "Congressman Cassidy was honored to address the American Psychiatric Association Advocacy Day. As a physician himself, Dr. Cassidy truly understands the vital importance of APA and greatly appreciates its advocacy work. Dr. Cassidy was excited to discuss the importance of physician political action. It is critical that physicians' values have a voice in the political process; their values are not the values of lawyers or business interests—they are unique and need to be represented. If not, a vacuum will be created, which will be filled with voices not focused on patient care."

Advocacy Day handouts are posted at <www.psych.org/MainMenu/AdvocacyGovernmentRelations/GovernmentRelations/Current-Legislative-Fact-Sheets-112th-Congress.aspx>. ■

M.D.s Won't Face Prison Under Revised Gun Bill

Language providing for civil and criminal penalties against physicians for asking patients about gun ownership has been removed from a Florida bill, but physicians can still be brought before the state medical board for sanctions.

BY RICHARD FAUST

The Florida legislature has passed what is being called a compromise bill restricting physicians from inquiring about or recording information concerning patient firearms ownership.

Civil and criminal penalties contained in the original version of the bill have been removed; however, physicians can still be referred to the Florida Board of Medicine for possible sanctions. The current language in House Bill 155 also allows an exception for physicians asking about gun ownership for "relevance of the information to the patient's medical care or safety or the safety of others." The governor has stated his intention to sign the bill.

The original language of the bill would have allowed doctors to be fined up to $5 million and would have subjected them to up to five years in prison for simply asking a patient about gun possession (*Psychiatric News*, March 4).

The bill's sponsor, State Rep. Jason Brodeur, cited concerns that under provisions of the federal Patient Protection and Affordable Care Act—the 2010 health care reform law—information about gun ownership could end up in the hands of the government or insurance companies and be used against patients. However, a search of the Affordable Care Act finds a clause specifically prohibiting the government from collecting information on gun ownership or insurance companies from charging higher rates based on gun ownership.

The Florida Medical Association originally opposed the bill, but now has expressed satisfaction with the compromise language. In March, Asher Gorelik, M.D., president of the Florida Psychiatric Society (FPS), expressed to *Psychiatric News* his membership's opposition to the bill, particularly "a great deal of concern about how this law would interfere with the ability of the psychiatrist to properly assess a patient." But in a recent follow-up interview, Gorelik stated that the new language in the bill "no longer interferes with the ability of a psychiatrist to perform a risk assessment."

Gorelik's statement should not, however, be confused with support for the bill by the FPS. Debra Barnett, M.D., the president-elect of the FPS, told *Psychiatric News* that the district branch's best efforts went into defeating the bill. She said the bill still leaves open questions about who will define harassment. A patient complaint to the medical board concerning a physician asking about gun ownership would put the burden of proof on the physician to show medical relevancy.

Barnett went on to say, however, that the new language in the bill is an improvement. "While we don't support the bill, we support the amended language to mitigate the effects of the bill and how it affects the psychiatric community."

Barnett believes that there are lessons psychiatrists around the country can take from the Florida battle over this bill. She said psychiatrists need to know that similar bills may be coming up in their states, and they may not be able to stop them from passing. It is possible, though, "to work with legislators and plant seeds on issues that affect psychiatrists and mitigate the language to the benefit of both doctors and the patients."

Florida House of Representatives bill 155 is posted at <www.myfloridahouse.gov/Sections/Bills/billsdetail.aspx?BillId=44993&SessionId=66>. The Patient Protection and Affordable Care Act is posted at <www.gpo.gov/fdsys/pkg/BILLS-111hr3590enr/pdf/BILLS-111hr3590enr.pdf>. ■

Become an APA Fellow

Being an APA fellow is an earned, honorary designation. While yearly dues rates for general members and fellows are the same, fellowship carries several benefits:

- Fellows may use the FAPA designation on all of their professional documentation.
- New fellows will be recognized at the Convocation of Distinguished Fellows at APA's 2012 annual meeting in Philadelphia.
- Fellows receive a lapel pin and an embossed certificate as a symbol of their status.

The major requirements are five years of general membership and Board certification.

A fellowship application form is posted at <www.psych.org/Resources/Membership/EnrollmentFormsApplications/FellowshipGuidelinesandNominationForm.aspx>. More information is available by calling (888) 357-7924 and asking for a Membership Department staff person. ■

Jockey Rides to Victory In Bipolar Disorder Stakes

Sylvia Harris is only the second African-American female jockey in U.S. history to win a major thoroughbred race, and she notched that achievement despite having one of the most challenging mental illnesses—bipolar disorder.

BY JOAN AREHART-TREICHEL

There is probably nothing that people love more than a success story that unfurls against great odds. This is one of those stories, and it's about a 44-year-old woman in Wilmington, Del., named Sylvia Harris. She managed to become a professional jockey in spite of being female and African American and having bipolar disorder. And in spite of being such a "long shot," she has won 16 races.

Harris was born in 1967 to U.S. Army parents in Frankfurt, Germany, and grew up in northern California. She had her first bout with bipolar disorder at age 19. Her life spiraled downhill after that in myriad ways. There were a few hospitalizations because of her bipolar disorder. She lost custody of her children in 1995 because of problems related to her bipolar disorder. One of her sons was diagnosed with attention-deficit/hyperactivity disorder in 1998. She had only sporadic access to psychiatric care and psychotropic medications because of a lack of health insurance and money. She was even homeless for a while.

But her life was studded with some positives as well—family members who helped her, such as her brother sending her money; her three children, whom she deeply loved; and her devotion to Buddhism, whose chanting rituals calmed and uplifted her. And then there were the horses!

In 2000, when she was 33 years old and homeless in Orlando, Fla., "someone kind of scooped me up and set me in the middle of horse country—Ocala, Florida—and it was like, yeah, this is what I really wanted to do as a child, be around horses," Harris said in a recent interview. "It was like a second chance—a rebirth kind of situation."

Ocala is one of the most important centers for thoroughbred horse breeding and training in the world. Only two counties in Kentucky top Ocala in revenue from the sale of thoroughbred horses.

Harris found work in Ocala mucking out stalls and feeding and grooming horses. She progressed to walking and exercising horses and halter-breaking colts and fillies. She said that she was quite content with what she was doing. "This was a good time in my life, when everyone liked being around Sylvia, including me," she noted.

But then, one day, a jockey approached her and said, "You ought to become a jockey because you are petite and good with horses." She replied that she was "too old to get up on a racehorse." He then retorted with a chuckle, "Who says you're too old? I didn't start riding until I was 37, and I didn't win my first race until I was 42."

"Suddenly it was clear to me," said Harris. "I wanted to ride, and I wanted to be a jockey."

Getting a Break From Racing Pioneer

So she saved money for a riding helmet and vest. In 2001, a kindly, elderly horse-farm owner, who turned out to be one of the pioneers in the Florida horse-racing industry, began training her to become a jockey. "He inspired and motivated me to search for something higher than myself," she recalled.

In 2004, she moved to Chicago and managed to ride in her first professional race, and then another—which qualified her for a jockey's license. She was now, at age 37, an official player in a physically brutal sport where, as she noted, women, African Americans, and mentally ill individuals are generally shunned.

"Countless times I have seen jockeys launched from their thousand-pound steeds, then trampled by oncoming horses, [but] I had done what I wanted to do!" she exclaimed. "If it was the last moment of my life, I knew that I would be able to pass away with a smile on my face."

"I would love to race in the Kentucky Derby, but the therapeutic aspects of horses and helping other people are even more important to me."

Credit: Amy Nichole Harris/Shutterstock.com

But more achievements were to come—her first win in Chicago in December 2007, when she was 40 years old and with her family present and cheering her on. And 15 more wins since then "in spite of a terrible riding accident in May 2009, where I broke my neck in four places and crushed part of my skull."

Bipolar Turns Out to Be Two-Sided Coin

As for her bipolar disorder, it has been both a blessing and a curse for her work as a jockey. For example, she has sometimes been in a manic phase while riding, and it was a "definite advantage because you feel as if you can overcome anything and accomplish anything." But she also has to be careful not to ride when her manic phases take her "over the top" and rob her of good judgment. Fortunately she is now more adept at sensing when she is heading in that direction than when she was younger, she said. And as far as her depressive episodes are concerned, they are a drawback in her work; she can't ride at all until they lift.

Today Harris works as a jockey at Delaware Park in Wilmington. Her three children are in college, and her father is still living. "I want to make sure that they have what they need to be as secure as they can be," she said, adding that although jockey pay isn't great, the money isn't bad either.

As for the future, she contemplates getting certified to do equine-assisted therapy with inner-city children or people with mental disabilities. "Sure, I would love to race in the Kentucky Derby, but the therapeutic aspects of horses and helping other people are even more important to me."

Her advice to other people, especially those with bipolar disorder? "We all have setbacks and obstacles. But don't give up on your dreams and goals. Maybe you can't accomplish all that you would like to, but you can surely accomplish some of it. And that will put a smile not just on your face, but in your heart and soul!"

More information about Sylvia Harris's life can be found in her autobiography,* "Long Shot—My Bipolar Life and the Horses Who Saved Me,"** ***published by HarperCollins in 2011. ■

MH Professionals Helped On Her Successful Ride

Credit: Four Footed Fotos

Jockey Sylvia Harris: "We all have setbacks and obstacles. But don't give up on your dreams and goals."

Although Sylvia Harris gets the credit for her remarkable successes as a professional jockey (see article at left), some people in the mental health field helped Harris achieve the recovery that allowed her to ride to victory.

For example, there is the staff of the Backstretch Employee Assistance Program at Delaware Park, where she has worked as a jockey since June 2010. Most racetracks have some kind of employee assistance program, but Delaware Park's is really exceptional, Harris said. As soon as she joined the program, she was connected with a community mental health program and was able to use it "without paying a dime."

The program staff also told her that if she wanted to work at Delaware Park, she would have to take psychotropic medications for her bipolar disorder on a regular basis and attend their one-on-one counseling sessions as well as group-therapy sessions to address her alcohol, substance abuse, and anger-management issues. She did so. "I will always appreciate the backbone that the program's psychologist, Wesley Jones, and his colleagues have given me, as well as the boundaries they taught me to set," she said.

Moreover, the program provides Harris with excellent health insurance. It covers her visits to a psychiatrist of her choice and her psychotropic medications.

While Harris said that she has had some unpleasant experiences with mental health professionals over the years, there is one psychiatrist she particularly liked. It is Anita Everett, M.D., who treated Harris at a community mental health clinic near Staunton, Va., in 1996.

"She was the most compassionate doctor I have ever been around," Harris recalled. "She listened and included my younger son in sessions and healing. And when I was doing pretty well on a particular medication, yet it was burning my stomach, she said, 'Why don't we back off a bit and change the dosage and see if that helps?' She cared. I know she cared for everybody else the same way she cared for me. She made a difference in my life. That is when I started trusting the mental health system."

In 1999, Everett was appointed inspector general of Virginia's public mental health system. Today she is director of community and general psychiatry at the Johns Hopkins Bayview campus in Baltimore *(Psychiatric News,* November 19, 2010) and chair of the APA Council on Healthcare Systems and Financing.

Nominations Invited

APA is inviting nominations for its Jack Weinberg Memorial Award for Geriatric Psychiatry. The award, established in 1983 in memory of Jack Weinberg, M.D., honors a psychiatrist who has demonstrated special leadership or who has done outstanding work in clinical practice, training, or research in geriatric psychiatry.

Candidates for the award must be psychiatrists who are nominated by an APA member. The award winner will receive a $500 honorarium and a plaque at APA's 2012 annual meeting in Philadelphia.

Submissions must include six copies of a letter summarizing the accomplishments of the nominee, two letters of endorsement from APA members, a current curriculum vitae, and bibliography.

The deadline for nominations is July 31. Submissions should be sent to Diane Pennessi, Staff Liaison, Council on Psychosomatic Medicine and Geriatric Psychiatry, APA, 1000 Wilson Boulevard, Suite 1825, Arlington, Va. 22209-3901. More information is available by contacting Pennessi at (703) 907-8668 or dpennessi@psych.org. ■

Court Rejects Fast Track For Health Reform Challenge

The Supreme Court denies Virginia Attorney General Ken Cuccinelli's motion to move the state's case against the Patient Protection and Affordable Care Act—the health care reform law—directly to the high court, bypassing appeals courts.

BY RICHARD FAUST

On April 25 the Supreme Court denied certiorari to Virginia Attorney General Ken Cuccinelli's challenge to the Obama administration's Patient Protection and Affordable Care Act. Certiorari is a petition to the court to bypass the normal appeals process and move a case straight to the high court.

The denial of fast-track treatment for the lawsuit was not unexpected. The court rarely grants certiorari, particularly when the government argues against it, as was the case here. The Department of Justice strongly opposed the motion.

The primary provision of the law that is in dispute is the so-called individual mandate, which would require people to buy health insurance or face a tax penalty. Two courts have ruled that the mandate is unconstitutional, while two have upheld the provision. Courts with Republican-appointed judges have ruled against the mandate, and those with Democratic appointees have voted to uphold it.

In December 2010, Judge Henry Hudson of the Richmond, Va., Federal District Court struck down the individual insurance mandate, but allowed the rest of the law to stand (*Psychiatric News*, January 7). This decision was followed by a decision in a case brought in Florida by 26 state attorneys general. On January 31, Judge Roger Vinson of Federal District Court in Pensacola, Fla., struck down the individual mandate and ruled that the mandate was not severable from the rest of the law; thus, the entire health care law was deemed unconstitutional. A different federal district court in Virginia and one in Michigan have upheld the individual mandate.

Supporters of Virginia's request for expedited Supreme Court review pointed to the contradictory lower-court decisions and argued that they created uncertainty for the states regarding implementation of the health reform law. The Obama administration argued that many aspects of the law, including the disputed mandate, do not take effect until 2014. Thus the court had an obligation to allow the appeals process to run its course. Completed appeals would also provide the Supreme Court with the greatest number of decisions and opinions to consider should the justices decide to hear the case.

The fate of the health care law is currently on the dockets in three federal appeals courts. The two Virginia cases were scheduled to have oral arguments heard together by the U.S Court of Appeals for the Fourth Circuit in Richmond at press time. The Michigan case, which upheld the mandate, is scheduled for arguments before the U.S. Court of Appeals for the Sixth Circuit in Cincinnati on June 1. The Florida ruling is likely to reach the Court of Appeals for the 11th Circuit later this summer.

Despite the setback to the Virginia case, given the calendar, it is in that case that the first appeals court decision is likely to be handed down, perhaps as early as the end of the year. Assuming then, as expected, that the Supreme Court takes up the case, it could hear arguments in the case during its fall 2012 term, just in time for the next presidential election.

The Florida case is posted at <http://graphics8.nytimes.com/packages/pdf/national/20110131VINSON_HEALTH.pdf>. The Virginia case is posted at <http://documents.nytimes.com/health-care-law-ruled-unconstitutional?ref=policy>. The Virginia case upholding the health care reform law is posted at <http://graphics8.nytimes.com/packages/pdf/us/20101201-lawsuit.pdf>. The Michigan Case is posted at <www.mied.uscourts.gov/News/Docs/09714485866.pdf>. ■

Family's Autism Experience Leads to Poignant TV Series

PBS aired a six-part series on autism spectrum disorder during April, which was Autism Awareness Month. It was created and anchored by Robert MacNeil, who provided an intimate look at the life of his young grandson, who has autism.

BY LESLIE SINCLAIR

Credit: PBS Newshour

Robert MacNeil

Retired veteran journalist Robert MacNeil, who paired with Jim Lehrer to create the acclaimed "MacNeil/Lehrer Report" from 1975 until MacNeil's retirement in 1995, returned to PBS in April with a broad and thoughtful look at a psychiatric disorder that hits close to home for him.

In the first installment of a six-part series titled "Autism Now," MacNeil introduces viewers to his 6-year-old grandson, Nick, diagnosed with autism spectrum disorder (ASD) at age 15 months. For context, he also interviewed his daughter (Nick's mother, Alison MacNeil) and Nick's 10-year-old sister, Neely. It's an intimate picture of a family struggling to cope with a child's special needs.

MacNeil spent over a year researching and preparing the stories for the series, along with his producer, Caren Zucker, whose teenage son has autism.

The series continued with segments that individually address the prevalence, causes, available services (primarily educational), and adult support options (or the lack thereof) for those with ASD. The final segment is a roundtable discussion focusing on ways in which "this deepening national health emergency" can be addressed.

Perhaps the most disturbing segment is the fifth, in which MacNeil describes what he calls "a freight train about to run into the social-services system," the population of children with ASD who will soon outgrow the special services guaranteed to them by the public-education system. "For hundreds of thousands of adolescents with autism about to become adults, there are very few programs available. For those desperate to find a solution, it is a public-health crisis," said MacNeil in the segment.

One concern that has been voiced about the series is the lack of focus on the lives of adults with ASD. The Autistic Self Advocacy Network (ASAN), an organization that calls itself "the nation's leading advocacy organization run entirely by and for autistic adults and youth," released a statement expressing concern over the failure of the series to interview representatives of organizations run by autistic adults: "To pretend that any comprehensive account of autism is meaningful without substantively engaging with autistic people ourselves is disgraceful and offensive," said ASAN.

Credit: PBS Newshour

Robert MacNeil and his 6-year-old grandson, Nick, look for ducks in a waterway near Nick's home in Cambridge, Mass., on a winter day. Nick, diagnosed with ASD, is the inspiration for MacNeil's six-part series.

Zucker responded to those concerns in an interview with *Psychiatric News*: "There are hundreds of stories that I would love to start producing tomorrow, ranging from issues surrounding autism insurance laws, the scary fact that individuals with autism are being incarcerated rather than being evaluated and treated, to taking an in-depth look at the neurodiversity movement. We had a finite number of stories we could do for this series and tried to pick what we believed were the most comprehensive issues surrounding 'what we know about autism today.' We knew we would not have the airtime or financial resources to do everything."

"The response has been overwhelmingly positive, about 85 percent or so," added MacNeil. "The most common message is one of gratitude for such an extended and comprehensive look at so many autism issues and for making the diversity of autism behaviors so visible."

In an interview with Hari Sreenivasan after the series aired, MacNeil emphasized, "I don't pretend to be an expert; I'm a journalist," and he described his desire to chronicle "the growing impact of autism as seen through the eyes of families, children, educators, and clinicians."

The entire PBS series, along with extended interviews with some of MacNeil's guests, is posted at <www.pbs.org/newshour/news/autism/>. ■

Autism

continued from page 7

Brain Research Foundation Research Grant, NIMH Career Awards, and the George Washington University Institute for Ethnographic Research. Additional funding was provided by the Jean Young and Walden W. Shaw Foundation, Daniel X. and Mary Freedman Foundation, and Dukyoung Foundation.

"Prevalence of Autism Spectrum Disorder in a Total Population Sample" is posted at <http://ajp.psychiatryonline.org/cgi/content/abstract/appi.ajp.2011.10101532v1>. ■

Psychosis Nonconverters Present Clinical, Research Dilemma

Better understanding of the characteristics and longitudinal course of nonconverters may help improve criteria for predicting who is and is not at very high risk for psychosis.

BY MARK MORAN

Individuals identified as at risk for psychosis but who did not convert to psychosis within two and a half years showed improvement in symptoms and functioning from baseline, but continued to perform significantly more poorly compared with normal controls.

At-risk adolescents and young adults enrolled in the North American Prodrome Longitudinal Study 1 (NAPLS 1) who did not convert to psychosis within 30 months ("nonconverters") showed significant improvement in attenuated positive symptoms and negative symptoms as measured by the Scale of Prodromal Symptoms and in social and role functioning as measured by the Global Assessment of Functioning.

The results were presented by Jean Addington, Ph.D., one of the principal investigators of NAPLS at the University of Calgary, in an adddress at the International Congress on Schizophrenia Research (ICOSR) in April in Colorado Springs, Colo.

NAPLS 1 is an eight-site study directed by the National Institute of Mental Health that has followed more than 300 individuals classified as "high risk" according to the Structured Interview for Prodromal Symptoms (SIPS). Criteria for prodromal psychosis include a family history of psychosis accompanied by deterioration in functioning and/or the presence of attenuated positive symptoms of psychosis; the latter include unusual thought content, delusional ideas, suspiciousness or persecutory ideas, grandiose ideas, perceptual abnormalities or hallucinations, and disorganized communication.

Addington reviewed published data on rates of conversion to psychosis in prevention studies, but also presented new information on 76 subjects who had met criteria for entry into the NAPLS study, had never taken antipsychotic medication, and had not converted to psychosis by two years.

The improvement over baseline in symptoms and functioning among these nonconverters largely occurred in the first year of follow-up, Addington said. "Over a two-year period, from the first year to the second year of follow-up, there was some slight improvement in scores, but most of the really significant improvement occurred in the first year," she said

But in a comparison with 111 healthy controls, Addington reported that the nonconverters continued to perform significantly more poorly. "So even though there was an improvement in symptoms and functioning, they are still not back to normal levels," she said.

The subject of psychosis risk has become a major focus among schizophrenia researchers, a fact reflected in the number of presentations, symposia, and workshops on the subject at this year's congress and in the existence of a satellite International Prodromal Research Network that meets concurrently with the congress.

Several large-scale studies around the world have yielded data on conversion rates of individuals identified as at risk for psychosis. In NAPLS, 35 percent of the more than 300 subjects who met criteria for prodromal psychosis had converted to a full-blown psychosis within two years—data that were originally reported in the January 2008 *Archives of General Psychiatry*.

That rate was matched by the Prevention Through Risk Identification, Management, and Education (PRIME) study, which also reported a 35 percent conversion rate at 12 months.

As debate has grown around the possible inclusion of a diagnostic category in *DSM-5* for psychosis risk, along with concern voiced in some quarters about "false positives" and possible stigmatization of adolescents, researchers have turned their attention to those individuals who *do not* convert to psychosis. Better insight into the demographics, baseline characteristics, and longitudinal course of individuals who originally meet at-risk criteria but who do not convert to active psychosis may help advance understanding of the prospective course of at-risk individuals and improve predictive rates.

Conversion Rates Falling

Intriguingly, Addington and others at the congress reported that conversion rates among at-risk samples appear to be falling somewhat. When research on the prodrome began, most studies were replicating the 35 percent conversion rates found in NAPLS, but some other studies are now showing conversion rates of 15 percent to 27 percent, she said.

Why this is happening is unclear; it may represent the success of early detection and prevention efforts that involve various forms of treatment, or it may represent a "dilution effect" from the inclusion in samples of a growing number of individuals with less-severe symptoms.

Addington said that among nonconverters in the NAPLS sample, just 5.4 percent still met the criteria for prodromal psychosis at two years, but that 31 percent (40.5) had at least one positive symptom at the attenuated level. "So what appears to be happening is that some people were still experiencing symptoms, but had a decrease in symptoms so that they no longer met criteria," she said. "In fact, nobody had positive symptoms at any point in the follow-up greater than the symptoms they had at baseline."

Thirty-two percent of the nonconverters had an anxiety disorder at two years, and 14 percent had depression. Twenty-nine percent had a range of Axis II disorders.

Treatment protocols across the eight sites in NAPLS 1 varied and may have included case management and close monitoring of symptoms or treatment with antidepressant or antipsychotic medications. (However, the data Addington presented at the ICOSR on nonconverters excluded any who had ever had an antipsychotic.)

A fuller description of NAPLS 1 methods and protocols appeared online in the January 25, 2007, *Schizophrenia Bulletin*.

New Category for Psychosis Risk?

The ongoing debate about inclusion of a category in the *DSM-5* for psychosis risk was an undercurrent throughout the congress and emerged in a question-and-answer period following Addington's presentation.

She concluded her remarks by saying that the data on nonconverters—and the fact that conversion rates appear to be falling in prevention studies—challenges researchers to think about issues of diagnostic boundaries and the specificity of measures used to categorize individuals as "at risk." And she expressed skepticism about the inclusion of a diagnostic category for psychosis risk in *DSM-5*.

In remarks to *Psychiatric News* after the congress, Addington said that better predictive criteria are needed, as is a better understanding of the clinical course of people who remain below the threshold of active psychosis. She added that NAPLS 2, a sequel to the first study now enrolling 360 at-risk subjects and 180 normal controls, will have more rigorous data about both converters and nonconverters.

But at ICOSR, Addington was challenged after her presentation by William Carpenter, M.D., chair of the psychosis work group for *DSM-5*. He noted that the issue of a category in *DSM-5* for psychosis risk is very controversial and that opinions within the work group itself are not uniform.

But in response to Addington's concern about the danger of creating a classification for people, some of whom will not convert to psychosis, Carpenter pointed out that the nonconverters in NAPLS 1 were among a help-seeking population that continued to require psychiatric treatment, as evidenced by the persistence of Axis I and II diagnoses. "Where is the harm?" he asked.

In the May *American Journal of Psychiatry*, Carpenter coauthored an editorial exploring all of the aspects of the "at-risk" controversy with Jim van Os, M.D., a leading researcher who has opposed the inclusion of a psychosis risk category (see box).

Also responding to Addington at the congress, Thomas McGlashan, M.D., a pioneer in research on psychosis risk and

please see ***Nonconverters*** *on page 36*

'Attenuated Psychosis Syndrome' Subject of *AJP* Editorial

In an editorial in this month's *American Journal of Psychiatry,* William Carpenter, M.D., and Jim van Os, M.D., outlined the still-to-be-resolved questions surrounding the inclusion in *DSM-5* of a category for psychosis risk to be called "attenuated psychosis syndrome." The inclusion of that category to diagnose individuals—invariably adolescents—with attenuated psychotic symptoms that have not progressed to full-blown psychosis is controversial and by no means a certainty. In comments to *Psychiatric News,* Carpenter—who is chair of the *DSM-5* Work Group for Psychotic Disorders—said that field trials are under way to determine whether the diagnosis can be made reliably over time by different clinicians on the same patient and in agreement with those who have conducted the initial research.

If the diagnosis proves reliable, the work group will need to weigh the following questions outlined by Carpenter and van Os:

- Will the diagnosis promote helpful treatment for these individuals?
- Will the diagnosis stimulate research to prevent psychotic disorders?
- Will the diagnosis unnecessarily stigmatize individuals, or will it actually promote their acceptance?

In separate introductory statements to the editorial, the two authors—who approach the questions from opposite sides of the controversy—summarized their own views.

Van Os, who opposes the creation of a new diagnostic category, said that the best hope for early intervention in psychotic disorders resides in public health measures for the population as a whole rather than in attempts to diagnose risk in individuals for what will be a low incidence of future psychosis. "Creating a diagnostic class that does not unambiguously define a specific group, treatment, or outcome does not add value for patients and their families," van Os wrote.

Carpenter, who has generally supported the inclusion of the new category, said that the evidence for attenuated psychosis syndrome as a clinical entity with predictive validity has been established and that early detection and intervention can positively alter the long-term outcome.

"There is much that clinicians can and should do for care-seeking individuals with distress and dysfunction who manifest early psychotic-like psychopathology," he wrote. "A new *DSM-5* diagnosis can focus attention on this syndrome and stimulate the creative acquisition of new knowledge that may be life altering for afflicted persons."

In comments to *Psychiatric News,* Carpenter said that the newly proposed term—"attenuated psychosis syndrome"—reflects the idea that a disorder, as opposed to a risk for a disorder, already exists, and that it is not specific to the development of schizophrenia.

He added that he believes some of the mistrust for the proposal may stem from early use of the term "risk syndrome," implying primary prevention rather than the existence of a disorder with implications for treatment and secondary prevention. "Rather than a parallel with hyperlipidemia marking risk for cardiovascular disease, it is more appropriate to compare [attenuated psychosis syndrome] with angina, indicating a disorder and the hope that treatment reduces risk for a more severe outcome," he said.

"Should Attenuated Psychosis Syndrome Be a* DSM-5 *Diagnosis?" is posted at <http://ajp.psychiatryonline.org/cgi/content/full/168/5/460>.

Form of CBT Can Improve Stubborn Psychosis Symptoms

Developed by Aaron Beck, M.D., goal-directed therapy aims to help patients identify achievable goals and treats negative symptoms—manifest in negative attitudes and beliefs—as barriers to achieving the goals.

BY MARK MORAN

Patients with schizophrenia having the most severe negative symptoms appear to endorse certain defeatist and asocial beliefs, as well as have low expectations of success or pleasure, characteristics that may be amenable to a form of cognitive-behavioral therapy.

That's important because the severe negative symptoms of "deficit-syndrome" patients have been presumed by some to be the result of neurobiological deficits that often do not respond either to antipsychotic medication or to standard psychosocial treatments. The "deficit syndrome" is thought to characterize a pathophysiologically distinct subgroup of patients with schizophrenia whose negative symptoms—blunted affect, anhedonia, avolition, and asociality—are enduring features that do not appear to be secondary to other aspects of schizophrenia.

But in an address titled "Defeatist Beliefs, Asocial Beliefs, and Low Expectations: The Emerging Cognitive Behavioral Science of Negative Symptoms and the Deficit Syndrome" at the International Congress of Schizophrenia Research (ICOSR). Paul Grant, Ph.D., described preliminary research showing that these chronic patients appear to endorse negative beliefs that may respond to goal-directed cognitive therapy.

That intervention is a form of therapy developed especially for schizophrenia patients by Aaron Beck, M.D., the renowned founder of cognitive therapy.

In comments to *Psychiatric News* following the presentation, Grant explained that the theory behind goal-directed cognitive therapy is that there may be "some psychological factors associated with the negative symptoms of these deficit-syndrome patients that are rarely targeted for treatment with antipsychotic medications and existing psychosocial treatments."

Grant said these deficit-syndrome patients are liable to comprise a large percentage—a quarter or a third—of the typical clinical population of patients with chronic schizophrenia.

"Our hypothesis was that some of these patients may have untapped potential and that there might be a level of negative attitudes and beliefs that were contributing to their low functioning," he told *Psychiatric News*.

To test the hypothesis, Grant and colleagues at the University of Pennsylvania used the Proxy for the Deficit Syndrome—a measurement tool described by Brian Kirkpatrick, M.D., and colleagues at the Maryland Psychiatric Research Center in the early 1990s—to identify 22 deficit-syndrome patients and 72 nondeficit schizophrenia patients. (The instrument uses the Brief Psychiatric Rating Scale to identify patients who have blunted affect but who do not have depressed mood, anxiety, hostility, or guilt feelings.)

Grant then compared the two groups for how frequently subjects endorsed a series of negative statements about the meaning of engaging in constructive activity and socializing, and their chances for future enjoyment. "We found that the deficit-syndrome patients actually endorse these attitudes more than the nondeficit patients who have negative symptoms," he reported.

For instance, deficit-syndrome patients were significantly more likely than nondeficit-syndrome patients to agree with statements such as: "If I fail partly, it is as bad as being a complete failure."

Similarly, the deficit-syndrome patients were significantly more likely to agree with statements about their willingness to engage socially with other patients, such as: "People sometimes think I am shy, when I really just want to be left alone."

Grant said both statements may represent reactions to past failures and social rejections. "If you come to believe these statements, you are not going to want to try to take even relatively minor risks," he said. "You might perceive that even a small risk could turn out to be a disaster."

A similar comparison was undertaken to test the groups' likelihood of endorsing a statement reflecting low expectation of pleasure from physical sensations, social activities, and recreational pursuits. Grant explained that the hypothesis behind this comparison is that the feature of anhedonia in deficit-syndrome patients may reflect not so much the inability to experience pleasure, but the fact that they do not expect to, and for that reason do not undertake pleasurable activities.

In this comparison, the deficit-syndrome group again scored higher than the control group—reflecting low expectations of pleasure—though the difference was not statistically significant.

Grant told *Psychiatric News* that some preliminary clinical research using goal-directed cognitive therapy has shown its efficacy in treating negative symptoms.

"The therapy is on a continuum with everything that Beck has done with developing cognitive-behavioral therapies," Grant said. "The critical idea is that even these deficit-syndrome patients may very well have goals if you can get them to articulate them."

Common goals that are articulated—to get a job, finish school, or have a girlfriend or a house or a car—are broken down into small, stepped tasks. Grant described one patient who expressed the belief that she couldn't read—in fact she could—and the therapy began by having her read a short paragraph out loud and longer texts later.

"In the framework of goal-directed therapy, you are not talking to patients about psychosis but about their functioning and their quality of life and working with them at a level they might be interested," he told *Psychiatric News*. "You treat the negative and positive symptoms as barriers to the goals."

He added that much of the emphasis of treatment research in schizophrenia has turned to adolescents and the prodrome—reflected in the number of sessions on these topics at the ICOSR—but goal-directed cognitive therapy targets a population of severely and chronically ill patients who have in some ways been left behind. "We think the things that are holding these patients back are these negative beliefs, so we look to identify them and help patients take actions to achieve what goals they can." ■

Device Helps Reduce Suicide Risk In Schizophrenia Patients

The intervention was designed as an adjunctive psychosocial approach to target patients who have problems getting to the hospital because of transportation barriers.

BY MARK MORAN

A telehealth monitoring system, utilizing a home-based telephone device that serves as an interface between patients and hospital staff, appears to help reduce suicidal symptoms in patients with schizophrenia recently discharged from the hospital.

In a poster presented at the April meeting of the International Congress on Schizophrenia Research in Colorado Springs, Colo., John Kasckow, M.D., Ph.D., said the main finding from the small pilot study was that the group that used the telehealth device had a higher probability of improvement in suicidal symptoms compared with a control group of patients who received intensive case management but not the telehealth intervention.

Kasckow is staff psychiatrist with the VA Pittsburgh Healthcare System Mental Illness Research, Education, and Clinical Center (MIRECC), VA Behavioral Health Service, and Western Psychiatric Institute and Clinic.

The monitoring system is called Health Buddy, a device that patients take home with them and prompts them with daily questions about symptoms of suicide and depression using scripted dialogues. Responses are downloaded daily to the hospital staff and read every four hours, seven days a week; when patients' responses indicate an increase in suicidal symptoms, they are contacted by clinical staff.

Kasckow and Gretchen Haas, Ph.D., the director of VA Pittsburgh's MIRECC, developed the system in collaboration with the nursing staff at VA Pittsburgh Healthcare System. They have had a longstanding research interest in managing suicidal behavior in patients with schizophrenia—a leading cause of premature death in patients with psychosis—using an integrated psychosocial and pharmacological approach.

"We were interested in creating a psychosocial intervention using telehealth as a strategy to target high-risk patients who have a hard time getting to the hospital because of barriers like transportation," Kasckow told *Psychiatric News*.

In the study, 19 patients were randomized to receive the Health Buddy home telehealth intervention, and 19 were randomized to a control group. Patients in both groups received intensive case management over six months with twice weekly phone calls using the Suicide Symptom Inventory and Personal Health Questionnaire scales, and weekly face-to-face assessments with the Calgary Depression Rating Scale and the Clinical Global Impressions scale.

At three months, the group that received the Health Buddy intervention had significantly reduced suicidal symptoms compared with the control group, which received only the intensive case management.

Kasckow told *Psychiatric News* that the pilot study is not adequately powered to examine exactly how the system is producing effects. But he said that the improved monitoring and expedited clinical attention to patients with worsening symptoms, plus the psychoeducation and support provided by the device itself are likely factors.

"It allows us to monitor suicidal ideation in a more in-depth manner and to monitor depression, a risk factor for suicide," he said. "In this way we think we are able to capture someone before their symptoms escalate. In addition, it addresses another risk factor—social isolation—by facilitating communication.

"But the dialogues used with the device probably also contribute by offering support to patients," Kasckow said. "If their symptoms get worse, it tells patients to contact their physician. And if patients are having suicidal ideation, it will instruct them to call a 1-800 suicide hotline and to contact their physician.

"Our goal now is to improve the system," Kasckow continued. "We would like to optimize the dialogue scripts and add something to detect early warning signs of psychosis. And we want to test the dialogues in the same population of patients to optimize acceptability and usability, then perform an additional field test for making final improvements prior to launching a large-scale intervention study.

"We are optimistic about expanding this, since our preliminary studies indicate it reduces suicidal behavior and possibly has important impacts on other behaviors associated with patients with schizophrenia." ■

What Do White-Matter Changes Have To Do With Anxiety?

Disruptions in white matter in the amygdala and other anxiety-processing brain areas is linked with the personality trait of anxiety. Whether the defective white matter actually contributes to anxiety and depressive disorders is still a question.

BY JOAN AREHART-TREICHEL

When people are anxious by nature, could it be due to a major disruption in white matter—that is, in the bundles of nerve axons wiring the brain? It's a possibility, a new study suggests.

Subjects who scored high on the temperament trait of anxiety had fewer white-matter connections in the amygdala and other anxiety-processing brain areas than did subjects who scored low on this trait.

The study was headed by Lars Westlye, Ph.D., a postdoctoral fellow in the Center for the Study of Human Cognition at Norway's University of Oslo. Results were published in the April *Archives of General Psychiatry*.

"Decreased white matter integrity has been found in many neurodegenerative and psychiatric disorders, including Alzheimer's disease and schizophrenia."

In recent years, considerable evidence has emerged that anxiety-related personality traits are important predisposing factors to anxiety and depressive disorders. Emotional processing is known to rely on the structural and functional integrity of distributed neuronal circuits in the brain. Therefore Westlye and his colleagues wondered whether anxiety-related personality traits and an associated increased risk of anxiety and depressive disorders might be rooted in aberrations in white matter in areas of the brain crucial for anxiety processing, such as the amygdala, hippocampus, thalamus, subgenual cingulate, and orbitofrontal cortices.

The study sample consisted of 263 volunteers with no evidence of psychiatric disease ranging in age from 20 to 85. Subjects' tendency to be anxious was evaluated with the "harm avoidance" subscale of the Temperament and Character Inventory. Individuals who score high in harm avoidance are characterized as fearful, tense, worried, cautious, shy, and easily fatigued. Individuals who score low on harm avoidance are characterized as optimistic, confident, carefree, outgoing, uninhibited, and energetic.

New Neuroimaging Method Used

The scientists then used a relatively new neuroimaging method called diffusion tensor imaging (DTI) on the subjects. DTI makes it possible to map the organization and strength of white matter—that is, its integrity—in the human brain. Finally they assessed whether there were any significant differences in white-matter integrity between subjects who scored high on anxiety and those who did not, while taking possibly confounding factors—age, gender, years of education, alcohol consumption, IQ, and Mini-Mental State Examination results—into consideration.

The researchers found that subjects who scored high on anxiety had decreased white-matter integrity in precisely those brain areas anticipated—the amygdala, hippocampus, thalamus, subgenual cingulate, and orbitofrontal cortices—as well as in the areas connecting them.

Whether decreased white-matter integrity actually contributes to anxiety and depressive disorders remains to be seen. But if it does, there might be clinical implications for such a finding.

Future Research Implications Cited

"I doubt that a drug targeting the mechanisms for the decreased white-matter integrity observed in our study alone would suffice to treat symptoms of anxiety and depression, but it could perhaps be used successfully in conjunction with psychological therapeutic interventions and other pharmacological substances," Westlye told *Psychiatric News*. "I am not aware of any scientists looking for such a drug, but since decreased white-matter integrity has been found in many neurodegenerative and psychiatric disorders, including Alzheimer's disease and schizophrenia, I would not be surprised if this is an active area of research in the pharmaceutical industry."

Credit: Lars Westlye, Ph.D.

Lars Westlye, Ph.D.: "I doubt that a drug targeting the exact mechanisms for the decreased white matter integrity observed in our study alone would suffice to treat symptoms of anxiety and depression. But it could perhaps be used successfully in conjunction with. . . other pharmacological substances."

Westlye also pointed out that while the specific gene variants coding for the harm-avoidance personality trait have not yet been identified, "it is very likely that some of these variants have their impact on harm avoidance via defects in the brain's white matter." Indeed, he and his team are collecting genetic data from their subjects in this study to see whether they can "detect gene variants involved in both anxiety-related personality traits and white-matter integrity."

"This study has been thoughtfully designed and has dealt with most of my criticisms about much research into personality characteristics such as harm avoidance," Anne Farmer, M.D., a professor of psychiatric nosology at the Institute of Psychiatry in London, England, told *Psychiatric News*. Farmer published a study on a related subject—the personality trait of harm avoidance as a predisposing factor to major depression—in the May 2003 *Archives of General Psychiatry*. "The results. . . point to disruption in the architecture of [nerve axons], which certainly makes sense in terms of current theories about the etiology of depression and anxiety."

The study was funded by the Research Council of Norway and the University of Oslo.

An abstract of "Linking an Anxiety-Related Personality Trait to Brain White Matter Microstructure" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/68/4/369>. ■

Suicide-Related Gene Could Point Way to Drug Target

Another gene that contributes to suicidal behavior may have been identified. It may lead to development of a novel medication that could interrupt biological processes that prompt people to engage in suicidal behavior.

BY JOAN AREHART-TREICHEL

There is a reason to believe that suicidal behavior has a genetic component independent of the risk imposed by psychiatric disorders such as alcoholism, bipolar disorder, and depression. Some candidate genes in this domain have also been identified—for example, the serotonin transporter gene, the tryptophan hydroxylase genes, and hypothalamus-pituitary-adrenal axis genes such as BDNF, NTRK2, and SSAT.

Now another gene that may make an independent contribution to suicidal behavior has been identified. It is called the ACP1 gene and is located on chromosome 2 in a region known as 2p25.

The lead investigator of the study that identified this gene was Virginia Willour, Ph.D., an assistant professor of psychiatry at Johns Hopkins University. The senior investigator was James Potash, M.D., an associate professor of psychiatry there. The results were published online March 22 in *Molecular Psychiatry*.

Willour and her colleagues compared genetic material from some 1,200 subjects with bipolar disorder and a history of suicide attempts with genetic material from about 1,500 subjects with bipolar disorder but without a history of suicide attempts. Their hope was to identify snips of genetic material that distinguished the former from the latter and thus would constitute genetic risk material for suicidal behavior independently of any risk imposed by having bipolar disorder.

They found one snip that possibly distinguished those who attempted suicide from those who did not. It was located on the short arm of chromosome 2 at a position called 2p25.

Furthermore, this snip of genetic material contained four genes, one of which was called ACP1. The researchers then went on to examine the expression of the ACP1 gene in the brains of 14 subjects with bipolar disorder who had died from suicide and in the brains of 20 subjects with bipolar disorder who had died by other means. They found that expression of the ACP1 gene was significantly elevated in the prefrontal cortex of the former group. As a result, they believe that the ACP1 gene might contribute independently to suicidal behavior.

Another reason they think that such a link might exist is that the protein made by the ACP1 gene influences a biological pathway that is regulated by lithium, and lithium's ability to counter suicidal behavior is well established.

How might the ACP1 gene increase suicide risk? Possibly by contributing to impulsive aggression, Willour told *Psychiatric News*, "with individuals having both a psychiatric disorder and a tendency toward impulsive aggression having the greatest risk for suicidal behavior."

When asked whether their findings have any clinical implications at this point, Willour noted, "My colleague James Potash has a number of ongoing clinical and genetic research projects focused on the role of lithium in the treatment of bipolar disorder. We are hoping that our findings that relate to ACP1 and its potential role in attempted suicide might complement that work. Our results could inform the development of novel treatments that, like lithium, have antisuicidal properties."

Potash agreed: "This paper will not itself change clinical practice. But the goals of this kind of work are to make a difference for patients. There are several ways that this could happen. The most important would be that finding a gene takes us into a pathway, and then studying the pathway points us to new 'druggable' targets—places in the pathway where novel medications might interrupt the process that leads people toward suicidal behavior."

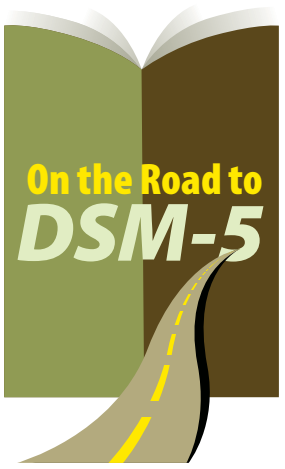
Willour also pointed out that the Psychiatric Genomewide Association Study Consortium—which was launched in 2007

please see ***Suicide*** *on page 33*

Updated *DSM-5* Web Site Has New Comment Period

This article is the fourth in a series of commentaries by the chair of the *DSM-5* Task Force overseeing the manual's development. The series will continue until the release of *DSM-5* in May 2013.

BY DAVID J. KUPFER, M.D.



In February 2010, APA and the *DSM-5* leadership gave the public a first look at potential changes for the upcoming fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders (DSM-5).* With the launching of the <www.dsm5.org> Web site, visitors learned about proposed draft diagnostic criteria, how those proposed changes compared with current criteria in *DSM-IV,* and the rationale for these suggested changes. The site is also home to a wide variety of relevant background information about the development of *DSM-5*, such as its task force and work group members and updates on concurrent development activities, such as recent *DSM-5*-related publications and presentations.

This month, we launched a revised *DSM-5* Web site that represents some important changes from the original site posted more than a year ago. Visitors to the new site may immediately notice a change in the organizational structure of how disorders are grouped. Rather than being organized to parallel the chapter structure of *DSM-IV,* the new site reflects the proposed organizational structure for *DSM-5*. While the two are largely similar, there are some noteworthy differences. For instance, rather than collectively grouping all childhood and adolescent disorders into one chapter, these diagnoses are distributed throughout *DSM-5* into the relevant diagnostic sections. Visitors can now read about pica under the category "Eating and Feeding Disorders," for example. Similarly, trauma- and stress-related disorders, such as posttraumatic stress disorder and adjustment disorders, are now a distinct category rather than being housed under anxiety disorders, as in *DSM-IV.*

The revised organizational structure of diagnoses is not the only change. Nearly all of the disorder proposals have been refined in one way or another since last February. While many contain only minor changes to wording, others include more significant changes to criteria. For instance, the Sleep-Wake Disorders Work Group revised the criteria for primary insomnia to better address variations in symptomatology across the lifespan. Readers may notice that the newly proposed mild and major neurocognitive disorders each now include criteria for a subtype to account for traumatic brain injury as an etiology. And autism spectrum disorder has been revised to include severity measures and has improved clarity by including examples among the criteria.

The new *DSM-5* Web site also includes a detailed section on field trials that was not present on the original site. Within the content posted here is information about the purpose and design of the field trials, detailed protocols from each of the two main types of field trials being conducted, and descriptions of where field testing is taking place. Throughout the past 14 months, we have also continued to update media content, the *DSM-5* timeline, relevant lists of *DSM* publications and presentations, and more. A detailed listing of all changes that have occurred to the site over the past year is provided.

As with the February 2010 release, this second release of the Web site features a comment period in which we welcome professionals and the public to submit feedback about our proposals. In the first six weeks following release of the new site, which was launched May 4, visitors can once again send the work groups questions and considerations about draft changes until June 15. Work group members will review all comments and determine whether additional changes in proposals are needed.

Although we initially planned two commenting periods—the first in 2010 and another following the completion of the field trials—we believe the changes represented on the new *DSM-5* Web site are sufficient enough to warrant public comment. Alterations in diagnostic criteria, dimensional assessments, and the organizational structure may potentially impact how clinicians and researchers use *DSM-5*, which means patients and their family members may be equally likely to feel the effects of these proposals.

A third period of public posting will take place after the field trials have concluded. At that time, draft criteria will be revised based on both submissions to the Web site during this comment period and findings from field tests. In fact, visitors to the site should be aware that the diagnostic criteria as currently posted will not change until after the field trials are completed. In short, this commenting period does not represent the final opportunity for those individuals who are interested to voice their opinions on proposed *DSM-5* revisions.

Our previous period of public feedback yielded more than 8,000 questions and suggestions from patients, family members, advocates, clinicians, and researchers, and while we do not expect the same volume of responses during this comment period, we are optimistic that the public will once again share with us their invaluable perspective on *DSM-5.* We look forward to hearing from you during this time. ■

David J. Kupfer, M.D., is chair of the *DSM-5* Task Force and a professor of psychiatry at University of Pittsburgh Medical Center and Western Psychiatric Institute and Clinic.

Colorado Site Tackling Challenges of Field Trials For Children, Adolescents

The University of Colorado and the Children's Hospital of Denver have combined forces to provide *DSM-5* field trial assessments of 275 pediatric patients. APA is moving forward with the *DSM-5* field trial project and has been able to open four sites for assessment of pediatric patients as of March. Given the late start but the still-clear final deadline, sites have had to be creative and hard working to come close to the target number of patients they agreed to assess.

The Colorado site has taken on this challenge by recruiting a large number of clinicians, who include child psychiatrists, psychologists, and clinical social workers, as well as child psychiatry residents and psychology postdoctoral students, to perform the three required assessments of each child and the primary caregiver. According to Marianne Wamboldt, M.D., the site's principal investigator and division head of child psychiatry and chair of the Children's Hospital Department of Psychiatry and Behavioral Sciences, this field trial has been an opportunity to bring a research mind set to a large clinical department. It is too early to discuss the merits of the proposed changes to the diagnostic system, but already trainees and clinical staff have benefitted from learning a more standardized approach to assessment, as well as the potential uses of patient/caregiver computerized input. This site has added on its own assessment of the caregiver-child relationship problem as a test of whether more specific criteria for this V code diagnosis will provide a more reliable assessment. They will also assess whether mental health professionals who work with children see the value of a standardized assessment of the caregiver-child relationship to be as clinically useful as assessment of Axis I diagnoses.

Here are the *DSM-5* field trial participants at the University of Colorado and Children's Hospital of Denver. First row from left to right: Claire Dean-Sinclair, M.A., Isabelle Guillemet, M.D., Scot McKay, M.D., Laurie Burnside, M.S.M., C.C.R.C., Marisa Murgolo, L.C.S.W., Sarah Tlustos-Carter, M.A., Deniece Vanessa Waruinge, and Darci Anderson. Second row, left to right: Adam Burstein, D.O., Ashley Smith, L.C.S.W., Debbie Carter, M.D., Jamie Blume, M.A., Meredith Chapman, M.D., Audrey Dumas, M.D., Marianne Wamboldt, M.D., Kimberly Kelsay, M.D., Heather Kennedy, M.P.H., Paulette Christian, A.P.N. Third row, left to right: Charles Harrison, Ph.D., Michael Rollin, M.D., Jason Williams, Psy.D., Helen Thilly, L.C.S.W., Tammy Herckner, L.C.S.W., Idalia Massa, M.A., Megan Klabunde, M.A., Kelly Caywood, Ph.D., Marlena Romero, L.C.S.W.. Not pictured are Galia Abadi, M.D., Amy Becker, M.D., Steven Behling, Ph.D., Carol Beresford, M.D., Kelly Bhatnager, Ph.D., Mary Cook, M.D., Anthony Cordaro, M.D., Dena Dunn, Psy.D., Jennifer Eichberg, L.C.S.W., Guido Frank, M.D., Karen Frankel, Ph.D., Jennifer Hagman, M.D., Darci Harvey, L.C.S.W., Katherine Keeton, D.O., Jamielyn Kost, L.C.S.W., Harrison Levine, M.D., Charolette Lippolis, D.O., Raven Lipmanson, M.D., Susan Lurie, M.D., Asa Marokus, M.D., James Masterson, L.C.S.W., Christine McDunn, Ph.D., Alyssa Oland, Ph.D., Lina Patel, Ph.D., Diane Reichmuth, Psy.D., Tami Roblek, Ph.D., Michelle Roy, Ph.D., Elise Sannar, M.D., Daniel Savin, M.D., Mindy Solomon, Ph.D., Celeste St. John-Larkin, M.D., Jessica Stern, M.D., Sally Tarbell, Ph.D., Holly Vause, A.P.N., Elizabeth Wallace, Angela Ward, M.S.W., David Williams, M.D., and Brennan Young, M.A.

Cymbalta is indicated in adults for:

- The treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in 4 short-term trials and 1 maintenance trial.
- The treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in 3 short-term trials and 1 maintenance trial.
- The management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic pain due to osteoarthritis (OA).
- The management of diabetic peripheral neuropathic pain (DPNP).
- The management of fibromyalgia (FM).

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I will support your goal of doing what's best for your patients.

We provide information and educational resources designed to help appropriate patients at the start of and throughout their treatment plan with Cymbalta. To find out more, speak with your Cymbalta sales representative or call 1-877-CYMBALTA.

Important Safety Information About Cymbalta

Warning: Suicidality and Antidepressant Drugs—Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta 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. Cymbalta is not approved for use in pediatric patients.

(cont.)

See Important Safety Information, including Boxed Warning, above and on next page, and Brief Summary of Prescribing Information on following pages.

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Important Safety Information About Cymbalta *(Cont.)*

Contraindications

- Concomitant use in patients taking Monoamine Oxidase Inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome.

  At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI.

- Cymbalta was associated with an increased risk of mydriasis; therefore, it should not be used in patients with uncontrolled narrow-angle glaucoma and used cautiously in patients with controlled narrow-angle glaucoma.

Warnings and Precautions

- **Clinical Worsening and Suicide Risk**

  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 within the first few months of treatment and when changing the dose. Consider changing the therapeutic regimen, including possibly discontinuing the medication in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. If discontinuing treatment, the medication should be tapered. **Families and caregivers of patients being treated with antidepressants for any indication should be alerted about the need to monitor patients. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management, in order to reduce the risk of overdose.**

- Hepatic failure, sometimes fatal, has been reported in patients treated with Cymbalta. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

- Because it is possible that Cymbalta and alcohol may interact to cause liver injury or that Cymbalta may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

- Orthostatic hypotension and syncope have been reported with therapeutic doses of Cymbalta. This tends to occur within the first week of therapy but can occur at any time during Cymbalta treatment, particularly after dose increases. Consideration should be given to discontinuing Cymbalta in patients who experience symptomatic orthostatic hypotension and/or syncope.

- The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms. Concomitant use with serotonin precursors (e.g., tryptophan) is not recommended. Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

(cont.)

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Important Safety Information About Cymbalta *(Cont.)*

Warnings and Precautions *(Cont.)*

- SSRIs and SNRIs, including Cymbalta, may increase the risk of bleeding events. Patients should be cautioned about the risk of bleeding associated with concomitant use of Cymbalta and NSAIDs, aspirin, warfarin, or other drugs that affect coagulation.
- On abrupt or tapered discontinuation, spontaneous reports of adverse events, some of which may be serious, have been reported during the marketing of SSRIs and SNRIs. A gradual reduction in dose rather than abrupt cessation is recommended when possible.
- Cymbalta should be used cautiously in patients with a history of mania or with a history of a seizure disorder.
- In clinical trials across indications relative to placebo, treatment with Cymbalta was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment.
- Co-administration of Cymbalta with potent CYP1A2 inhibitors or thioridazine should be avoided.
- SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia that appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs.
- The effect that alterations in gastric motility may have on the stability of the enteric coating of Cymbalta is unknown. As duloxetine is rapidly hydrolyzed in acidic media to naphthol, caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).
- Cymbalta should ordinarily not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (creatinine clearance <30 mL/min).
- As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In the extension phases (up to 52 weeks) of the DPNP studies, an increase in HbA_{1c} in both the Cymbalta (0.5%) and the routine care groups (0.2%) was noted.
- Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during Cymbalta treatment, this effect may be drug-related. In postmarketing experience, urinary retention has been observed.

Use in Specific Populations

- Pregnancy and Nursing Mothers: Use only if the potential benefit justifies the potential risk to the fetus or child.

Most Common Adverse Events

- The most commonly reported adverse events (≥5% and at least twice placebo) for Cymbalta vs placebo in controlled clinical trials (N=6020 vs 3962) were: nausea (24% vs 8%), dry mouth (13% vs 5%), somnolence* (10% vs 3%), fatigue (10% vs 5%), constipation* (10% vs 4%), dizziness (10% vs 5%), decreased appetite* (8% vs 2%), and increased sweating (7% vs 2%).

  * Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies that did not have a placebo lead-in period or dose titration.

- In placebo-controlled clinical trials, the overall discontinuation rates due to adverse events were: **MDD:** 9% vs 5%; **GAD:** 15% vs 4%; **DPNP:** 13% vs 5%; **FM:** 20% vs 12%; **OA:** 16% vs 6%; **CLBP:** 17% vs 6%.

  The common adverse events reported as a reason for discontinuation and considered to be drug related were: **MDD:** nausea (1.3% vs 0.5%). **GAD:** nausea (3.7% vs 0.2%), vomiting (1.3% vs 0%), dizziness (1.0% vs 0.2%). **DPNP:** nausea (3.5% vs 0.7%), dizziness (1.2% vs 0.4%), somnolence (1.1% vs 0%). **FM:** nausea (1.9% vs 0.7%), somnolence (1.5% vs 0%), fatigue (1.3% vs 0.2%). **OA:** nausea (2.9% vs 0.8%), asthenia (1.3% vs 0%). **CLBP:** nausea (3.0% vs 0.7%), somnolence (1.0% vs 0%).

For more safety information, please see Brief Summary of Prescribing Information, including Boxed Warning, on following pages.

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A commitment to help support your patients.

Cymbalta® duloxetine HCl DELAYED RELEASE CAPSULES Promise PROGRAM™

The Cymbalta Promise Program provides resources to help appropriate patients at the start of and throughout their treatment plan with Cymbalta.

Your patients can sign up to receive ongoing information and educational materials and tools during treatment. If eligible, they can also enroll in the 60-day money-back offer. If you and your patients new to Cymbalta aren't satisfied, patients may be reimbursed up to 100% of their out-of-pocket prescription costs for the first 60 days on Cymbalta.*

To get your patients started in the Cymbalta Promise Program, have them visit **cymbalta.com/promiseprogram**, call **1-877-CYMBALTA**, or complete and return the enrollment reply card in the *Getting Started With Cymbalta* brochure.

* Restrictions apply. See full Terms and Conditions. The 60-day money-back offer is not a guarantee of efficacy. It provides a trial period that may help you and your patients assess the efficacy, safety, and tolerability of Cymbalta.

Terms and Conditions

Reimbursement offered for up to 60 days of Cymbalta therapy to a maximum of $700. Prescriptions for more than 2 capsules per day are not eligible for reimbursement. Limit one reimbursement per person.

Offer void where prohibited by law. Valid only in the United States for US residents. Offer not valid for patients whose prescription claims for Cymbalta are reimbursed, in whole or in part, by (1) any governmental program, including, without limitation, Medicaid, Medicare, or any other federal or state program, such as Champus, the VA, TRICARE, or a state pharmaceutical assistance program, or (2) any third-party payer in the state of Massachusetts. By accepting this offer, patient agrees to notify his/her insurance carrier of reimbursement if required to do so by law or under the terms of coverage.

Additional exclusions may apply and this offer may be terminated, rescinded, revoked, or amended by Lilly USA, LLC, at any time without notice. Cymbalta® and the Cymbalta logo are registered trademarks of Eli Lilly and Company.

Select Important Safety Information About Cymbalta

- **Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children, adolescents, and young adults with major depressive disorder (MDD) and other psychiatric disorders.**
- **Patients of all ages started on therapy should be monitored appropriately and observed closely for clinical worsening, suicidality, or unusual changes in behavior.**
- **Cymbalta is not approved for use in pediatric patients.**

See Important Safety Information, including Boxed Warning, on previous pages, and Brief Summary of Prescribing Information on following pages.

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CYMBALTA

(duloxetine hydrochloride) Delayed-Release Capsules

Brief Summary: Consult the package insert for complete prescribing information.

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of major depressive disorder (MDD) and other psychiatric disorders. Anyone considering the use of Cymbalta 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. Cymbalta is not approved for use in pediatric patients. *[See Warnings and Precautions and Use in Specific Populations.]*

INDICATIONS AND USAGE: Major Depressive Disorder—Cymbalta is indicated for the acute and maintenance treatment of major depressive disorder (MDD). The efficacy of Cymbalta was established in four short-term trials and one maintenance trial in adults.

Generalized Anxiety Disorder—Cymbalta is indicated for the treatment of generalized anxiety disorder (GAD). The efficacy of Cymbalta was established in three short-term trials and one maintenance trial in adults.

Diabetic Peripheral Neuropathic Pain—Cymbalta is indicated for the management of neuropathic pain (DPNP) associated with diabetic peripheral neuropathy.

Fibromyalgia—Cymbalta is indicated for the management of fibromyalgia (FM).

Chronic Musculoskeletal Pain—Cymbalta is indicated for the management of chronic musculoskeletal pain. This has been established in studies in patients with chronic low back pain (CLBP) and chronic pain due to osteoarthritis.

CONTRAINDICATIONS: Monoamine Oxidase Inhibitors—Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated due to the risk of serious, sometimes fatal, drug interactions with serotonergic drugs. These interactions may include hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued serotonin reuptake inhibitors and are then started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome *[see Warnings and Precautions]*.

Uncontrolled Narrow-Angle Glaucoma—In clinical trials, Cymbalta use was associated with an increased risk of mydriasis; therefore, its use should be avoided in patients with uncontrolled narrow-angle glaucoma *[see Warnings and Precautions]*.

WARNINGS AND PRECAUTIONS: Clinical Worsening and Suicide Risk—Patients with major depressive disorder (MDD), both adult and pediatric, may experience worsening of their depression and/or the emergence of suicidal ideation and behavior (suicidality) or unusual changes in behavior, whether or not they are taking antidepressant medications, and this risk may persist until significant remission occurs. Suicide is a known risk of depression and certain other psychiatric disorders, and these disorders themselves are the strongest predictors of suicide. There has been a long-standing concern, however, that antidepressants may have a role in inducing worsening of depression and the emergence of suicidality in certain patients during the early phases of treatment.

Pooled analyses of short-term, placebo-controlled trials of antidepressant drugs (SSRIs and others) showed that these drugs increase the risk of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults (ages 18-24) with major depressive disorder (MDD) and other psychiatric disorders. Short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24; there was a reduction with antidepressants compared to placebo in adults aged 65 and older.

The pooled analyses of placebo-controlled trials in children and adolescents with MDD, obsessive compulsive disorder (OCD), or other psychiatric disorders included a total of 24 short-term trials of 9 antidepressant drugs in over 4400 patients. The pooled analyses of placebo-controlled trials in adults with MDD or other psychiatric disorders included a total of 295 short-term trials (median duration of 2 months) of 11 antidepressant drugs in over 77,000 patients. There was considerable variation in risk of suicidality among drugs, but a tendency toward an increase in the younger patients for almost all drugs studied. There were differences in absolute risk of suicidality across the different indications, with the highest incidence in MDD. The risk 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.

If the decision has been made to discontinue treatment, medication should be tapered, as rapidly as is feasible, but with recognition that discontinuation can be associated with certain symptoms *[see Warnings and Precautions for descriptions of the risks of discontinuation of Cymbalta]*.

Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and nonpsychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to healthcare providers. Such monitoring should include daily observation by families and caregivers. Prescriptions for Cymbalta should be written for the smallest quantity of capsules consistent with good patient management in order to reduce the risk of overdose.

Screening Patients for Bipolar Disorder—A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that Cymbalta (duloxetine) is not approved for use in treating bipolar depression.

Hepatotoxicity—There have been reports of hepatic failure, sometimes fatal, in patients treated with Cymbalta. These cases have presented as hepatitis with abdominal pain, hepatomegaly, and elevation of transaminase levels to more than twenty times the upper limit of normal with or without jaundice, reflecting a mixed or hepatocellular pattern of liver injury. Cymbalta should be discontinued in patients who develop jaundice or other evidence of clinically significant liver dysfunction and should not be resumed unless another cause can be established.

Cases of cholestatic jaundice with minimal elevation of transaminase levels have also been reported. Other postmarketing reports indicate that elevated transaminases, bilirubin, and alkaline phosphatase have occurred in patients with chronic liver disease or cirrhosis.

Cymbalta increased the risk of elevation of serum transaminase levels in development program clinical trials. Liver transaminase elevations resulted in the discontinuation of 0.3% (89/29,435) of Cymbalta-treated patients. In most patients, the median time to detection of the transaminase elevation was about two months. In placebo-controlled trials in any indication, for patients with normal and abnormal baseline ALT values, elevation of ALT >3 times the upper limit of normal occurred in 1.37% (132/9611) of Cymbalta-treated patients compared to 0.49% (35/7182) of placebo-treated patients. In placebo-controlled studies using a fixed-dose design, there was evidence of a dose response relationship for ALT and AST elevation of >3 times the upper limit of normal and >5 times the upper limit of normal, respectively.

Because it is possible that duloxetine and alcohol may interact to cause liver injury or that duloxetine may aggravate pre-existing liver disease, Cymbalta should not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Orthostatic Hypotension and Syncope—Orthostatic hypotension and syncope have been reported with therapeutic doses of duloxetine. Syncope and orthostatic hypotension tend to occur within the first week of therapy but can occur at any time during duloxetine treatment, particularly after dose increases. The risk of blood pressure decreases may be greater in patients taking concomitant medications that induce orthostatic hypotension (such as antihypertensives) or are potent CYP1A2 inhibitors *[see Warnings and Precautions and Drug Interactions]* and in patients taking duloxetine at doses above 60 mg daily. Consideration should be given to discontinuing duloxetine in patients who experience symptomatic orthostatic hypotension and/or syncope during duloxetine therapy.

Serotonin Syndrome or Neuroleptic Malignant Syndrome (NMS)-like Reactions—The development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome (NMS)-like reactions have been reported with SNRIs and SSRIs alone, including Cymbalta treatment, but particularly with concomitant use of serotonergic drugs (including triptans) with drugs which impair metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. Serotonin syndrome symptoms may include mental status changes (e.g., agitation, hallucinations, coma), autonomic instability (e.g., tachycardia, labile blood pressure, hyperthermia), neuromuscular aberrations (e.g., hyperreflexia, incoordination), and/or gastrointestinal symptoms (e.g., nausea, vomiting, diarrhea). Serotonin syndrome, in its most severe form, can resemble neuroleptic malignant syndrome, which includes hyperthermia, muscle rigidity, autonomic instability with possible rapid fluctuation of vital signs, and mental status changes. Patients should be monitored for the emergence of serotonin syndrome or NMS-like signs and symptoms.

The concomitant use of Cymbalta with MAOIs intended to treat depression is contraindicated *[see Contraindications]*.

If concomitant treatment of Cymbalta with a 5-hydroxytryptamine receptor agonist (triptan) is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Drug Interactions]*.

The concomitant use of Cymbalta with serotonin precursors (such as tryptophan) is not recommended *[see Drug Interactions]*.

Treatment with duloxetine and any concomitant serotonergic or antidopaminergic agents, including antipsychotics, should be discontinued immediately if the above events occur and supportive symptomatic treatment should be initiated.

Abnormal Bleeding—SSRIs and SNRIs, including duloxetine, may increase the risk of bleeding events. Concomitant use of aspirin, nonsteroidal anti-inflammatory drugs, warfarin, and other anti-coagulants may add to this risk. Case reports and epidemiological studies (case-control and cohort design) have demonstrated an association between use of drugs that interfere with serotonin reuptake and the occurrence of gastrointestinal bleeding. Bleeding events related to SSRI and SNRI use have ranged from ecchymoses, hematomas, epistaxis, and petechiae to life-threatening hemorrhages.

Patients should be cautioned about the risk of bleeding associated with the concomitant use of duloxetine and NSAIDs, aspirin, or other drugs that affect coagulation.

Discontinuation of Treatment with Cymbalta—Discontinuation symptoms have been systematically evaluated in patients taking duloxetine. Following abrupt or tapered discontinuation in placebo-controlled clinical trials, the following symptoms occurred at 1% or greater and at a significantly higher rate in duloxetine-treated patients compared to those discontinuing from placebo: dizziness, nausea, headache, paresthesia, fatigue, vomiting, irritability, insomnia, diarrhea, anxiety, and hyperhidrosis.

During marketing of other SSRIs and SNRIs (serotonin and norepinephrine reuptake inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (e.g., paresthesias such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. Although these events are generally self-limiting, some have been reported to be severe.

Patients should be monitored for these symptoms when discontinuing treatment with Cymbalta. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose but at a more gradual rate *[see Dosage and Administration]*.

Activation of Mania/Hypomania—In placebo-controlled trials in patients with major depressive disorder, activation of mania or hypomania was reported in 0.1% (2/2489) of duloxetine-treated patients and 0.1% (1/1625) of placebo-treated patients. No activation of mania or hypomania was reported in GAD, fibromyalgia, or chronic musculoskeletal pain placebo-controlled trials. Activation of mania or hypomania has been reported in a small proportion of patients with mood disorders who were treated with other marketed drugs effective in the treatment of major depressive disorder. As with these other agents, Cymbalta should be used cautiously in patients with a history of mania.

Seizures—Duloxetine has not been systematically evaluated in patients with a seizure disorder, and such patients were excluded from clinical studies. In placebo-controlled clinical trials, seizures/convulsions occurred in 0.03% (3/10,524) of patients treated with duloxetine and 0.01% (1/7699) of patients treated with placebo. Cymbalta should be prescribed with care in patients with a history of a seizure disorder.

Effect on Blood Pressure—In placebo-controlled clinical trials across indications from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.5 mm Hg in systolic blood pressure and 0.8 mm Hg in diastolic blood pressure compared to mean decreases of 0.6 mm Hg systolic and 0.4 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure. In a clinical pharmacology study designed to evaluate the effects of duloxetine on various parameters, including blood pressure at supratherapeutic doses with an accelerated dose titration, there was evidence of increases in supine blood pressure at doses up to 200 mg twice daily. At the highest 200 mg twice daily dose, the increase in mean pulse rate was 5.0 to 6.8 beats and increases in mean blood pressure were 4.7 to 6.8 mm Hg (systolic) and 4.5 to 7 mm Hg (diastolic) up to 12 hours after dosing.

Blood pressure should be measured prior to initiating treatment and periodically measured throughout treatment *[see Adverse Reactions]*.

Clinically Important Drug Interactions—Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Potential for Other Drugs to Affect Cymbalta

CYP1A2 Inhibitors—Co-administration of Cymbalta with potent CYP1A2 inhibitors should be avoided *[see Drug Interactions]*.

CYP2D6 Inhibitors—Because CYP2D6 is involved in duloxetine metabolism, concomitant use of duloxetine with potent inhibitors of CYP2D6 would be expected to, and does, result in higher concentrations (on average of 60%) of duloxetine *[see Drug Interactions]*.

Potential for Cymbalta to Affect Other Drugs

Drugs Metabolized by CYP2D6—Co-administration of Cymbalta with drugs that are extensively metabolized by CYP2D6 and that have a narrow therapeutic index, including certain antidepressants (tricyclic antidepressants [TCAs], such as nortriptyline, amitriptyline, and imipramine), phenothiazines, and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution. Plasma TCA concentrations may need to be monitored and the dose of the TCA may need to be reduced if a TCA is co-administered with Cymbalta. Because of the risk of serious ventricular arrhythmias and sudden death potentially associated with elevated plasma levels of thioridazine, Cymbalta and thioridazine should not be co-administered *[see Drug Interactions]*.

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Other Clinically Important Drug Interactions

Alcohol—Use of Cymbalta concomitantly with heavy alcohol intake may be associated with severe liver injury. For this reason, Cymbalta should not be prescribed for patients with substantial alcohol use *[see Warnings and Precautions and Drug Interactions]*.

CNS Acting Drugs—Given the primary CNS effects of Cymbalta, it should be used with caution when it is taken in combination with or substituted for other centrally acting drugs, including those with a similar mechanism of action *[see Warnings and Precautions and Drug Interactions]*.

Hyponatremia—Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including Cymbalta. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Cases with serum sodium lower than 110 mmol/L have been reported and appeared to be reversible when Cymbalta was discontinued. Elderly patients may be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted may be at greater risk *[see Use in Specific Populations]*. Discontinuation of Cymbalta should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted.

Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls. More severe and/or acute cases have been associated with hallucination, syncope, seizure, coma, respiratory arrest, and death.

Use in Patients with Concomitant Illness—Clinical experience with Cymbalta in patients with concomitant systemic illnesses is limited. There is no information on the effect that alterations in gastric motility may have on the stability of Cymbalta's enteric coating. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics).

Cymbalta has not been systematically evaluated in patients with a recent history of myocardial infarction or unstable coronary artery disease. Patients with these diagnoses were generally excluded from clinical studies during the product's premarketing testing.

Hepatic Insufficiency—Cymbalta should ordinarily not be used in patients with hepatic insufficiency *[see Warnings and Precautions and Use in Specific Populations]*.

Severe Renal Impairment—Cymbalta should ordinarily not be used in patients with end-stage renal disease or severe renal impairment (creatinine clearance <30 mL/min). Increased plasma concentration of duloxetine, and especially of its metabolites, occur in patients with end-stage renal disease (requiring dialysis) *[see Use in Specific Populations]*.

Controlled Narrow-Angle Glaucoma—In clinical trials, Cymbalta was associated with an increased risk of mydriasis; therefore, it should be used cautiously in patients with controlled narrow-angle glaucoma *[see Contraindications]*.

Glycemic Control in Patients with Diabetes—As observed in DPNP trials, Cymbalta treatment worsens glycemic control in some patients with diabetes. In three clinical trials of Cymbalta for the management of neuropathic pain associated with diabetic peripheral neuropathy, the mean duration of diabetes was approximately 12 years, the mean baseline fasting blood glucose was 176 mg/dL, and the mean baseline hemoglobin A_{1c} (HbA_{1c}) was 7.8%. In the 12-week acute treatment phase of these studies, Cymbalta was associated with a small increase in mean fasting blood glucose as compared to placebo. In the extension phase of these studies, which lasted up to 52 weeks, mean fasting blood glucose increased by 12 mg/dL in the Cymbalta group and decreased by 11.5 mg/dL in the routine care group. HbA_{1c} increased by 0.5% in the Cymbalta group and by 0.2% in the routine care groups.

Urinary Hesitation and Retention—Cymbalta is in a class of drugs known to affect urethral resistance. If symptoms of urinary hesitation develop during treatment with Cymbalta, consideration should be given to the possibility that they might be drug-related.

In postmarketing experience, cases of urinary retention have been observed. In some instances of urinary retention associated with duloxetine use, hospitalization and/or catheterization has been needed.

Laboratory Tests—No specific laboratory tests are recommended.

ADVERSE REACTIONS: Clinical Trial Data Sources—The data described below reflect exposure to duloxetine in placebo-controlled trials for MDD (N=2489), GAD (N=910), OA (N=239), CLBP (N=600), DPNP (N=906), and FM (N=876). The population studied was 17 to 91 years of age; 65.5%, 62.5%, 61.5%, 42.9%, and 94.9% female; and 86.5%, 81.2%, 86.2%, 74.0%, and 88% Caucasian for MDD, GAD, OA and CLBP, DPNP, and FM, respectively. Most patients received doses of a total of 60 to 120 mg per day *[see Clinical Studies (14)]*.

The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse reaction of the type listed. A reaction was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. Reactions reported during the studies were not necessarily caused by the therapy, and the frequencies do not reflect investigator impression (assessment) of causality.

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 practice.

Adverse Reactions Reported as Reasons for Discontinuation of Treatment in Placebo-Controlled Trials—Major Depressive Disorder—Approximately 9% (209/2327) of the patients who received duloxetine in placebo-controlled trials for MDD discontinued treatment due to an adverse reaction, compared with 4.7% (68/1460) of the patients receiving placebo. Nausea (duloxetine 1.3%, placebo 0.5%) was the only common adverse reaction reported as a reason for discontinuation and considered to be drug-related (i.e., discontinuation occurring in at least 1% of the duloxetine-treated patients and at a rate of at least twice that of placebo).

Generalized Anxiety Disorder—Approximately 15.3% (102/668) of the patients who received duloxetine in placebo-controlled trials for GAD discontinued treatment due to an adverse reaction, compared with 4.0% (20/495) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.7%, placebo 0.2%), and vomiting (duloxetine 1.3%, placebo 0.0%), and dizziness (duloxetine 1.0%, placebo 0.2%).

Diabetic Peripheral Neuropathic Pain—Approximately 12.9% (117/906) of the patients who received duloxetine in placebo-controlled trials for DPNP discontinued treatment due to an adverse reaction, compared with 5.1% (23/448) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.5%, placebo 0.7%), dizziness (duloxetine 1.2%, placebo 0.4%), and somnolence (duloxetine 1.1%, placebo 0.0%).

Fibromyalgia—Approximately 19.6% (172/876) of the patients who received duloxetine in 3- to 6-month placebo-controlled trials for FM discontinued treatment due to an adverse reaction, compared with 11.8% (63/535) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 1.9%, placebo 0.7%), somnolence (duloxetine 1.5%, placebo 0.0%), and fatigue (duloxetine 1.3%, placebo 0.2%).

Chronic Pain due to Osteoarthritis—Approximately 16.3% (39/239) of the patients who received duloxetine in 13-week, placebo-controlled trials for chronic pain due to OA discontinued treatment due to an adverse reaction, compared with 5.6% (14/248) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 2.9%, placebo 0.8%) and asthenia (duloxetine 1.3%, placebo 0.0%).

Chronic Low Back Pain—Approximately 16.5% (99/600) of the patients who received duloxetine in 13-week, placebo-controlled trials for CLBP discontinued treatment due to an adverse reaction, compared with 6.3% (28/441) for placebo. Common adverse reactions reported as a reason for discontinuation and considered to be drug-related (as defined above) included nausea (duloxetine 3.0%, placebo 0.7%), and somnolence (duloxetine 1.0%, placebo 0.0%).

Most Common Adverse Reactions—Pooled Trials for all Approved Indications—The most commonly observed adverse reactions in Cymbalta-treated patients (incidence of at least 5% and at least twice the incidence in placebo patients) were nausea, dry mouth, somnolence, fatigue, constipation, decreased appetite, and hyperhidrosis.

Diabetic Peripheral Neuropathic Pain—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, somnolence, decreased appetite, constipation, hyperhidrosis, and dry mouth.

Fibromyalgia—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, dry mouth, constipation, somnolence, decreased appetite, hyperhidrosis, and agitation.

Chronic Pain due to Osteoarthritis—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, fatigue, and constipation.

Chronic Low Back Pain—The most commonly observed adverse reactions in Cymbalta-treated patients (as defined above) were nausea, dry mouth, insomnia, somnolence, constipation, dizziness, and fatigue.

Adverse Reactions Occurring at an Incidence of 5% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Table 2 in full PI gives the incidence of treatment-emergent adverse reactions in placebo-controlled trials (N=6020 Cymbalta; N=3962 placebo) for approved indications that occurred in 5% or more of patients treated with duloxetine and with an incidence greater than placebo. These adverse events were: nausea, headache, dry mouth, fatigue (includes asthenia), somnolence* (includes hypersomnia and sedation), insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), dizziness, constipation*, diarrhea, decreased appetite* (includes anorexia), and hyperhidrosis.

*Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

Adverse Reactions Occurring at an Incidence of 2% or More Among Duloxetine-Treated Patients in Placebo-Controlled Trials—Pooled MDD and GAD Trials—Table 3 in full PI gives the incidence of treatment-emergent adverse reactions in MDD and GAD placebo-controlled trials (N=2995 Cymbalta; N=1955 placebo) for approved indications that occurred in 2% or more of patients treated with duloxetine and with an incidence greater than placebo. These adverse events were: Cardiac Disorders—palpitations; Eye Disorders—vision blurred; Gastrointestinal Disorders—nausea, dry mouth, diarrhea, constipation*, abdominal pain (includes abdominal pain upper, abdominal pain lower, abdominal tenderness, abdominal discomfort, and gastrointestinal pain), vomiting; General Disorders and Administration Site Conditions—fatigue (includes asthenia); Investigations—weight decreased*; Metabolism and Nutrition Disorders—decreased appetite (includes anorexia); Nervous System Disorders—dizziness, somnolence (includes hypersomnia and sedation), tremor; Psychiatric Disorders—insomnia (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor agitation), anxiety, libido decreased (includes loss of libido), orgasm abnormal (includes anorgasmia), abnormal dreams (includes nightmare); Reproductive System and Breast Disorders—erectile dysfunction, ejaculation delayed*, ejaculation disorder (includes ejaculation failure and ejaculation dysfunction); Respiratory, Thoracic, and Mediastinal Disorders—yawning; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—hot flush.

*Events for which there was a significant dose-dependent relationship in fixed-dose studies, excluding three MDD studies which did not have a placebo lead-in period or dose titration.

DPNP, FM, OA, and CLBP—Table 4 in full PI gives the incidence of treatment-emergent adverse events that occurred in 2% or more of patients treated with Cymbalta (determined prior to rounding) in the premarketing acute phase of DPNP, FM, OA, and CLBP placebo-controlled trials (N=2621 Cymbalta; N=1672 placebo) and with an incidence greater than placebo. These adverse events were: Gastrointestinal Disorders—nausea, dry mouth*, constipation*, diarrhea, abdominal pain (includes abdominal discomfort, abdominal pain lower, abdominal pain upper, abdominal tenderness, and gastrointestinal pain), vomiting, dyspepsia (includes stomach discomfort); General Disorders and Administration Site Conditions—fatigue (includes asthenia); Infections and Infestations—nasopharyngitis, upper respiratory tract infection, influenza; Metabolism and Nutrition Disorders—decreased appetite* (includes anorexia); Musculoskeletal and Connective Tissue Disorders—musculoskeletal pain* (includes myalgia and neck pain), muscle spasm; Nervous System Disorders—headache, somnolence* (includes hypersomnia and sedation), dizziness, paraesthesia (includes hypoaesthesia, hypoaesthesia facial, and paraethesia oral), tremor*; Psychiatric Disorders—insomnia* (includes middle insomnia, early morning awakening, and initial insomnia), agitation (includes feeling jittery, nervousness, restlessness, tension, and psychomotor hyperactivity); Reproductive System and Breast Disorders—erectile dysfunction*, ejaculation disorder; Respiratory, Thoracic, and Mediastinal Disorders—cough, oropharyngeal pain*; Skin and Subcutaneous Tissue Disorders—hyperhidrosis; Vascular Disorders—flushing (includes hot flush).

*Incidence of 120 mg/day is significantly greater than the incidence for 60 mg/day.

Effects on Male and Female Sexual Function—Changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of psychiatric disorders or diabetes, but they may also be a consequence of pharmacologic treatment. Because adverse sexual reactions are presumed to be voluntarily underreported, the Arizona Sexual Experience Scale (ASEX), a validated measure designed to identify sexual side effects, was used prospectively in 4 MDD placebo-controlled trials. In these trials, patients treated with Cymbalta experienced significantly more sexual dysfunction, as measured by the total score on the ASEX, than did patients treated with placebo. Gender analysis showed that this difference occurred only in males. Males treated with Cymbalta experienced more difficulty with ability to reach orgasm (ASEX Item 4) than males treated with placebo. Females did not experience more sexual dysfunction on Cymbalta than on placebo as measured by ASEX total score. Physicians should routinely inquire about possible sexual side effects. (See *Table 5* in full PI for specific ASEX results.)

Vital Sign Changes—In placebo-controlled clinical trials across approved indications for change from baseline to endpoint, duloxetine treatment was associated with mean increases of 0.07 mm Hg in systolic blood pressure and 0.62 mm Hg in diastolic blood pressure compared to mean decreases of 1.31 mm Hg systolic and 0.73 mm Hg diastolic in placebo-treated patients. There was no significant difference in the frequency of sustained (3 consecutive visits) elevated blood pressure *[see Warnings and Precautions]*.

Duloxetine treatment, for up to 26 weeks in placebo-controlled trials across approved indications, typically caused a small increase in heart rate for change from baseline to endpoint compared to placebo of up to 1.40 beats per minute.

Weight Changes—In placebo-controlled clinical trials, MDD and GAD patients treated with Cymbalta for up to 10 weeks experienced a mean weight loss of approximately 0.5 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In studies of DPNP, FM, OA, and CLBP, patients treated with Cymbalta for up to 26 weeks experienced a mean weight loss of approximately 0.6 kg compared with a mean weight gain of approximately 0.2 kg in placebo-treated patients. In one long-term fibromyalgia 60-week uncontrolled study, duloxetine patients had a mean weight increase of 0.7 kg. In one long-term CLBP 54-week study (13-week, placebo-controlled acute phase and 41-week, uncontrolled extension phase), duloxetine patients had a mean weight decrease of 0.6 kg in 13 weeks of acute phase compared to study entry, then a mean weight increase of 1.4 kg in 41 weeks of extension phase compared to end of acute phase.

Laboratory Changes—Cymbalta treatment in placebo-controlled clinical trials across approved indications, was associated with small mean increases from baseline to endpoint in ALT, AST, CPK, and alkaline phosphatase; infrequent, modest, transient, abnormal values were observed for these analytes in Cymbalta-treated patients when compared with placebo-treated patients *[see Warnings and Precautions]*.

Electrocardiogram Changes—Electrocardiograms were obtained from duloxetine-treated patients and placebo-treated patients in clinical trials lasting up to 13 weeks. No clinically significant differences were observed for QTc, QT, PR, and QRS intervals between duloxetine-treated and placebo-treated patients. There were no differences in clinically meaningful QTcF elevations between duloxetine and placebo. In a positive-controlled study in healthy volunteers using duloxetine up to 200 mg twice daily, no prolongation of the corrected QT interval was observed.

Other Adverse Reactions Observed During the Premarketing and Postmarketing Clinical Trial Evaluation of Duloxetine—Following is a list of treatment-emergent adverse reactions reported by patients treated with duloxetine in clinical trials. In clinical trials of all indications, 29,435 patients were treated with duloxetine. Of these, 30.4% (8953) took duloxetine for at least 6 months, and 14.7% (4317) for at least one year. The following listing is not intended to include reactions (1) already listed in previous tables or elsewhere in labeling, (2) for which a drug cause was remote, (3) which were so general as to be uninformative, (4) which were not considered to have significant clinical implications, or (5) which occurred at a rate equal to or less than placebo. Reactions are categorized by body system according to the following definitions: frequent adverse reactions are those occurring in at least 1/100 patients; infrequent adverse reactions are those occurring in 1/100 to 1/1000 patients; rare reactions are those occurring in fewer than 1/1000 patients. **Cardiac Disorders**—*Frequent:* palpitations; *Infrequent:* myocardial infarction and tachycardia. **Ear and Labyrinth Disorders**—*Frequent:* vertigo; *Infrequent:* ear pain and tinnitus. **Endocrine Disorders**—*Infrequent:* hypothyroidism. **Eye Disorders**—*Frequent:* vision blurred; *Infrequent:* diplopia and visual disturbance. **Gastrointestinal Disorders**—*Frequent:* flatulence; *Infrequent:* eructation, gastritis, halitosis, and stomatitis; *Rare:* gastric ulcer, hematochezia, and melena. **General Disorders and Administration Site Conditions**—*Frequent:* chills/rigors; *Infrequent:* feeling abnormal, feeling hot and/or cold, malaise, and thirst; *Rare:* gait disturbance. **Infections and Infestations**—*Infrequent:* gastroenteritis and laryngitis. **Investigations**—*Frequent:* weight increased; *Infrequent:* blood cholesterol increased. **Metabolism and Nutrition Disorders**—*Infrequent:* dehydration and hyperlipidemia; *Rare:* dyslipidemia. **Musculoskeletal and Connective Tissue Disorders**—*Frequent:* musculoskeletal pain; *Infrequent:* muscle tightness and muscle twitching. **Nervous System Disorders**—*Frequent:* dysgeusia, lethargy, and paraesthesia/hypoesthesia; *Infrequent:* disturbance in attention, dyskinesia, myoclonus, and poor quality sleep; *Rare:* dysarthria. **Psychiatric Disorders**—*Frequent:* abnormal dreams and sleep disorder; *Infrequent:* apathy, bruxism, disorientation/confusional state, irritability, mood swings, and suicide attempt; *Rare:* completed suicide. **Renal and Urinary Disorders**—*Infrequent:* dysuria, micturition urgency, nocturia, polyuria, and urine odor abnormal. **Reproductive System and Breast Disorders**—*Frequent:* anorgasmia/orgasm abnormal; *Infrequent:* menopausal symptoms, and sexual dysfunction. **Respiratory, Thoracic and Mediastinal Disorders**—*Frequent:* yawning; *Infrequent:* throat tightness. **Skin and Subcutaneous Tissue Disorders**—*Infrequent:*

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cold sweat, dermatitis contact, erythema, increased tendency to bruise, night sweats, and photosensitivity reaction; *Rare:* ecchymosis. **Vascular Disorders**—*Frequent:* hot flush; *Infrequent:* flushing, orthostatic hypotension, and peripheral coldness.

Postmarketing Spontaneous Reports—The following adverse reactions have been identified during postapproval use of Cymbalta. 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.

Adverse reactions reported since market introduction that were temporally related to duloxetine therapy and not mentioned elsewhere in labeling include: anaphylactic reaction, aggression and anger (particularly early in treatment or after treatment discontinuation), angioneurotic edema, erythema multiforme, extrapyramidal disorder, galactorrhea, glaucoma, gynecological bleeding, hallucinations, hyperglycemia, hyperprolactinemia, hypersensitivity, hypertensive crisis, muscle spasm, rash, restless legs syndrome, seizures upon treatment discontinuation, supraventricular arrhythmia, tinnitus (upon treatment discontinuation), trismus, and urticaria.

Serious skin reactions including Stevens-Johnson Syndrome that have required drug discontinuation and/or hospitalization have been reported with duloxetine.

DRUG INTERACTIONS: Both CYP1A2 and CYP2D6 are responsible for duloxetine metabolism.

Inhibitors of CYP1A2—When duloxetine 60 mg was co-administered with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to male subjects (n=14) duloxetine AUC was increased approximately 6-fold, the C_{max} was increased about 2.5-fold, and duloxetine $t_{1/2}$ was increased approximately 3-fold. Other drugs that inhibit CYP1A2 metabolism include cimetidine and quinolone antimicrobials such as ciprofloxacin and enoxacin *[see Warnings and Precautions]*.

Inhibitors of CYP2D6—Concomitant use of duloxetine (40 mg once daily) with paroxetine (20 mg once daily) increased the concentration of duloxetine AUC by about 60%, and greater degrees of inhibition are expected with higher doses of paroxetine. Similar effects would be expected with other potent CYP2D6 inhibitors (e.g., fluoxetine, quinidine) *[see Warnings and Precautions]*.

Dual Inhibition of CYP1A2 and CYP2D6—Concomitant administration of duloxetine 40 mg twice daily with fluvoxamine 100 mg, a potent CYP1A2 inhibitor, to CYP2D6 poor metabolizer subjects (n=14) resulted in a 6-fold increase in duloxetine AUC and C_{max}.

Drugs that Interfere with Hemostasis (e.g., NSAIDs, Aspirin, and Warfarin)—Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of the case-control and cohort design that have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs or SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when duloxetine is initiated or discontinued *[see Warnings and Precautions]*.

Lorazepam—Under steady-state conditions for duloxetine (60 mg Q 12 hours) and lorazepam (2 mg Q 12 hours), the pharmacokinetics of duloxetine were not affected by co-administration.

Temazepam—Under steady-state conditions for duloxetine (20 mg qhs) and temazepam (30 mg qhs), the pharmacokinetics of duloxetine were not affected by co-administration.

Drugs that Affect Gastric Acidity—Cymbalta has an enteric coating that resists dissolution until reaching a segment of the gastrointestinal tract where the pH exceeds 5.5. In extremely acidic conditions, Cymbalta, unprotected by the enteric coating, may undergo hydrolysis to form naphthol. Caution is advised in using Cymbalta in patients with conditions that may slow gastric emptying (e.g., some diabetics). Drugs that raise the gastrointestinal pH may lead to an earlier release of duloxetine. However, co-administration of Cymbalta with aluminum- and magnesium-containing antacids (51 mEq), or Cymbalta, with famotidine, had no significant effect on the rate or extent of duloxetine absorption after administration of a 40 mg oral dose. It is unknown whether the concomitant administration of proton pump inhibitors affects duloxetine absorption *[see Warnings and Precautions]*.

Drugs Metabolized by CYP1A2—*In vitro* drug interaction studies demonstrate that duloxetine does not induce CYP1A2 activity. Therefore, an increase in the metabolism of CYP1A2 substrates (e.g., theophylline, caffeine) resulting from induction is not anticipated, although clinical studies of induction have not been performed. Duloxetine is an inhibitor of the CYP1A2 isoform in *in vitro* studies, and in two clinical studies the average (90% confidence interval) increase in theophylline AUC was 7% (1%-15%) and 20% (13%-27%) when co-administered with duloxetine (60 mg twice daily).

Drugs Metabolized by CYP2D6—Duloxetine is a moderate inhibitor of CYP2D6. When duloxetine was administered (at a dose of 60 mg twice daily) in conjunction with a single 50-mg dose of desipramine, a CYP2D6 substrate, the AUC of desipramine increased 3-fold *[see Warnings and Precautions]*.

Drugs Metabolized by CYP2C9—Duloxetine does not inhibit the *in vitro* enzyme activity of CYP2C9. Inhibition of the metabolism of CYP2C9 substrates is therefore not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP3A—Results of *in vitro* studies demonstrate that duloxetine does not inhibit or induce CYP3A activity. Therefore, an increase or decrease in the metabolism of CYP3A substrates (e.g., oral contraceptives and other steroidal agents) resulting from induction or inhibition is not anticipated, although clinical studies have not been performed.

Drugs Metabolized by CYP2C19—Results of *in vitro* studies demonstrate that duloxetine does not inhibit CYP2C19 activity at therapeutic concentrations. Inhibition of the metabolism of CYP2C19 substrates is therefore not anticipated, although clinical studies have not been performed.

Monoamine Oxidase Inhibitors—*[See Contraindications and Warnings and Precautions.]* **Switching Patients to or from a Monoamine Oxidase Inhibitor**—At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Cymbalta. In addition, at least 5 days should be allowed after stopping Cymbalta before starting an MAOI *[see Contraindications and Warnings and Precautions]*.

Serotonergic Drugs—Based on the mechanism of action of SNRIs and SSRIs, including Cymbalta, and the potential for serotonin syndrome, caution is advised when Cymbalta is co-administered with other drugs that may affect the serotonergic neurotransmitter systems, such as triptans, linezolid (an antibiotic which is a reversible non-selective MAOI), lithium, tramadol, or St. John's Wort. The concomitant use of Cymbalta with other SSRIs, SNRIs, or tryptophan is not recommended *[see Warnings and Precautions]*.

Triptans—There have been rare postmarketing reports of serotonin syndrome with use of an SSRI and a triptan. If concomitant treatment of Cymbalta with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases *[see Warnings and Precautions]*.

Alcohol—When Cymbalta and ethanol were administered several hours apart so that peak concentrations of each would coincide, Cymbalta did not increase the impairment of mental and motor skills caused by alcohol. In the Cymbalta clinical trials database, three Cymbalta-treated patients had liver injury as manifested by ALT and total bilirubin elevations, with evidence of obstruction. Substantial intercurrent ethanol use was present in each of these cases, and this may have contributed to the abnormalities seen *[see Warnings and Precautions]*.

CNS Drugs—*[See Warnings and Precautions.]*

Drugs Highly Bound to Plasma Protein—Because duloxetine is highly bound to plasma protein, administration of Cymbalta to a patient taking another drug that is highly protein bound may cause increased free concentrations of the other drug, potentially resulting in adverse reactions.

USE IN SPECIFIC POPULATIONS: Pregnancy—Teratogenic Effects, Pregnancy Category C—In animal reproduction studies, duloxetine has been shown to have adverse effects on embryo/fetal and postnatal development.

When duloxetine was administered orally to pregnant rats and rabbits during the period of organogenesis, there was no evidence of teratogenicity at doses up to 45 mg/kg/day (7 times the maximum recommended human dose [MRHD, 60 mg/day] and 4 times the human dose of 120 mg/day on a mg/m^2 basis, in rat; 15 times the MRHD and 7 times the human dose of 120 mg/day on a mg/m^2 basis in rabbit). However, fetal weights were decreased at this dose, with a no-effect dose of 10 mg/kg/day (2 times the MRHD and ≈1 times the human dose of 120 mg/day on a mg/m^2 basis in rats; 3 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis in rabbits).

When duloxetine was administered orally to pregnant rats throughout gestation and lactation, the survival of pups to 1 day postpartum and pup body weights at birth and during the lactation period were decreased at a dose of 30 mg/kg/day (5 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis); the no-effect dose was 10 mg/kg/day. Furthermore, behaviors consistent with increased reactivity, such as increased startle response to noise and decreased habituation of locomotor activity, were observed in pups following maternal exposure to 30 mg/kg/day. Post-weaning growth and reproductive performance of the progeny were not affected adversely by maternal duloxetine treatment.

There are no adequate and well-controlled studies in pregnant women; therefore, duloxetine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nonteratogenic Effects—Neonates exposed to SSRIs or serotonin and norepinephrine reuptake inhibitors (SNRIs), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome *[see Warnings and Precautions]*.

When treating pregnant women with Cymbalta during the third trimester, the physician should carefully consider the potential risks and benefits of treatment. The physician may consider tapering Cymbalta in the third trimester.

Lilly maintains a pregnancy registry to monitor the pregnancy outcomes of women exposed to Cymbalta while pregnant. Healthcare providers are encouraged to register any patient who is exposed to Cymbalta during pregnancy by calling the Cymbalta Pregnancy Registry at 1-866-814-6975 or by visiting www.cymbaltapregnancyregistry.com.

Labor and Delivery—The effect of duloxetine on labor and delivery in humans is unknown. Duloxetine should be used during labor and delivery only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers—Duloxetine is excreted into the milk of lactating women. The estimated daily infant dose on a mg/kg basis is approximately 0.14% of the maternal dose. Because the safety of duloxetine in infants is not known, nursing while on Cymbalta is not recommended. However, if the physician determines that the benefit of duloxetine therapy for the mother outweighs any potential risk to the infant, no dosage adjustment is required as lactation did not influence duloxetine pharmacokinetics. (See *Nursing Mothers* section in full PI for additional information.)

Pediatric Use—Safety and effectiveness in the pediatric population have not been established *[see Boxed Warning and Warnings and Precautions]*. Anyone considering the use of Cymbalta in a child or adolescent must balance the potential risks with the clinical need.

Geriatric Use—Of the 2418 patients in premarketing clinical studies of Cymbalta for MDD, 5.9% (143) were 65 years of age or over. Of the 1041 patients in CLBP premarketing studies, 21.2% (221) were 65 years of age or over. Of the 487 patients in OA premarketing studies, 40.5% (197) were 65 years of age or over. Of the 1074 patients in the DPNP premarketing studies, 33% (357) were 65 years of age or over. Of the 1761 patients in FM premarketing studies, 7.9% (140) were 65 years of age or over. Premarketing clinical studies of GAD did not include sufficient numbers of subjects age 65 or over to determine whether they respond differently from younger subjects. In the MDD, DPNP, FM, OA, and CLBP studies, no overall differences in safety or effectiveness were observed between these subjects and younger subjects, and other reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. SSRIs and SNRIs, including Cymbalta, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event *[see Warnings and Precautions]*. (See *Geriatric Use* section in full PI for additional information.)

Gender—Duloxetine's half-life is similar in men and women. Dosage adjustment based on gender is not necessary.

Smoking Status—Duloxetine bioavailability (AUC) appears to be reduced by about one-third in smokers. Dosage modifications are not recommended for smokers.

Race—No specific pharmacokinetic study was conducted to investigate the effects of race.

Hepatic Insufficiency—*[See Warnings and Precautions-Use in Patients with Concomitant Illness.]* (See *Use in Patients with Concomitant Illness-Hepatic Insufficiency* section in full PI for additional information.)

Severe Renal Impairment—*[See Warnings and Precautions-Use in Patients with Concomitant Illness.]* (See *Use in Patients with Concomitant Illness-Severe Renal Impairment* section in full PI for additional information.)

DRUG ABUSE AND DEPENDENCE: Abuse—In animal studies, duloxetine did not demonstrate barbiturate-like (depressant) abuse potential. While Cymbalta has not been systematically studied in humans for its potential for abuse, there was no indication of drug-seeking behavior in the clinical trials. However, it is not possible to predict on the basis of premarketing experience the extent to which a CNS active drug will be misused, diverted, and/or abused once marketed. Consequently, physicians should carefully evaluate patients for a history of drug abuse and follow such patients closely, observing them for signs of misuse or abuse of Cymbalta (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).

Dependence—In drug dependence studies, duloxetine did not demonstrate dependence-producing potential in rats.

OVERDOSAGE: Signs and Symptoms—In postmarketing experience, fatal outcomes have been reported for acute overdoses, primarily with mixed overdoses, but also with duloxetine only, at doses as low as 1000 mg. Signs and symptoms of overdose (duloxetine alone or with mixed drugs) included somnolence, coma, serotonin syndrome, seizures, syncope, tachycardia, hypotension, hypertension, and vomiting.

Management of Overdose—There is no specific antidote to Cymbalta, but if serotonin syndrome ensues, specific treatment (such as with cyproheptadine and/or temperature control) may be considered. In case of acute overdose, treatment should consist of those general measures employed in the management of overdose with any drug. (See *Management of Overdose* section in full PI for additional information.)

NONCLINICAL TOXICOLOGY: Carcinogenesis, Mutagenesis, and Impairment of Fertility—Carcinogenesis—Duloxetine was administered in the diet to mice and rats for 2 years. In female mice receiving duloxetine at 140 mg/kg/day (11 times the maximum recommended human dose [MRHD, 60 mg/day] and 6 times the human dose of 120 mg/day on a mg/m^2 basis), there was an increased incidence of hepatocellular adenomas and carcinomas. The no-effect dose was 50 mg/kg/day (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis). Tumor incidence was not increased in male mice receiving duloxetine at doses up to 100 mg/kg/day (8 times the MRHD and 4 times the human dose of 120 mg/day on a mg/m^2 basis).

In rats, dietary doses of duloxetine up to 27 mg/kg/day in females (4 times the MRHD and 2 times the human dose of 120 mg/day on a mg/m^2 basis) and up to 36 mg/kg/day in males (6 times the MRHD and 3 times the human dose of 120 mg/day on a mg/m^2 basis) did not increase the incidence of tumors.

Mutagenesis—Duloxetine was not mutagenic in the *in vitro* bacterial reverse mutation assay (Ames test) and was not clastogenic in an *in vivo* chromosomal aberration test in mouse bone marrow cells. Additionally, duloxetine was not genotoxic in an *in vitro* mammalian forward gene mutation assay in mouse lymphoma cells or in an *in vitro* unscheduled DNA synthesis (UDS) assay in primary rat hepatocytes, and did not induce sister chromatid exchange in Chinese hamster bone marrow *in vivo*.

Impairment of Fertility—Duloxetine administered orally to either male or female rats prior to and throughout mating at doses up to 45 mg/kg/day (7 times the maximum recommended human dose of 60 mg/day and 4 times the human dose of 120 mg/day on a mg/m^2 basis) did not alter mating or fertility.

PATIENT COUNSELING INFORMATION: See FDA-approved Medication Guide and Patient Counseling Information section of full PI.

Additional information can be found at www.Cymbalta.com.

Literature revised: November 8, 2010

Lilly

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Favorable Long-Term Results Found for DBS in Depression

A group of Canadian physicians reports success in the long-term control of treatment-resistant depression by using deep brain stimulation, but they acknowledge that longer and larger trials are still needed.

BY LESLIE SINCLAIR

They are among the most hopeless of the hopeless, those patients with deep and lasting depression that cannot seem to be conquered despite aggressive treatment. Estimates of the number of patients suffering from major depressive disorder who do not respond to antidepressants and other therapies vary, since studies used various definitions of treatment resistance, and misdiagnosis or inadequate treatment may play a part.

Nevertheless, treatment-resistant depression comprises a significant realm of psychiatric illness and one that is ripe for application of neurological devices, such as those for vagus nerve stimulation and repetitive transcranial magnetic stimulation, both of which are approved by the Food and Drug Administration (FDA) for treatment of major depression.

Deep brain stimulation (DBS) is another such intervention, a targeted therapeutic alternative for treatment-resistant depression that involves the bilateral placement of electrodes at specific neuroanatomical sites to deliver continuous stimulation from a subcutaneously implanted pulse generator.

The FDA has already approved DBS as a treatment for neurologic disorders, including essential tremor, Parkinson's disease, dystonia, and severe obsessive-compulsive disorder. In the March 2005 *Neuron*, researchers Helen Mayberg, M.D., and colleagues initially reported six-month outcomes for six patients who received DBS to the subcallosal cingulate gyrus (Brodmann's area 25) for treatment-resistant depression. They subsequently reported, in the September 2008 *Biological Psychiatry*, on 12-month outcomes in an expanded sample of 20 patients (*Psychiatric News*, September 5, 2008).

In the February *American Journal of Psychiatry*, they presented data on the extended follow-up of these 20 patients, with data from three to six years after DBS implantation. "Given the invasive and experimental nature of DBS for [treatment-resistant depression], it is particularly important to obtain long-term effectiveness and safety data," said the researchers.

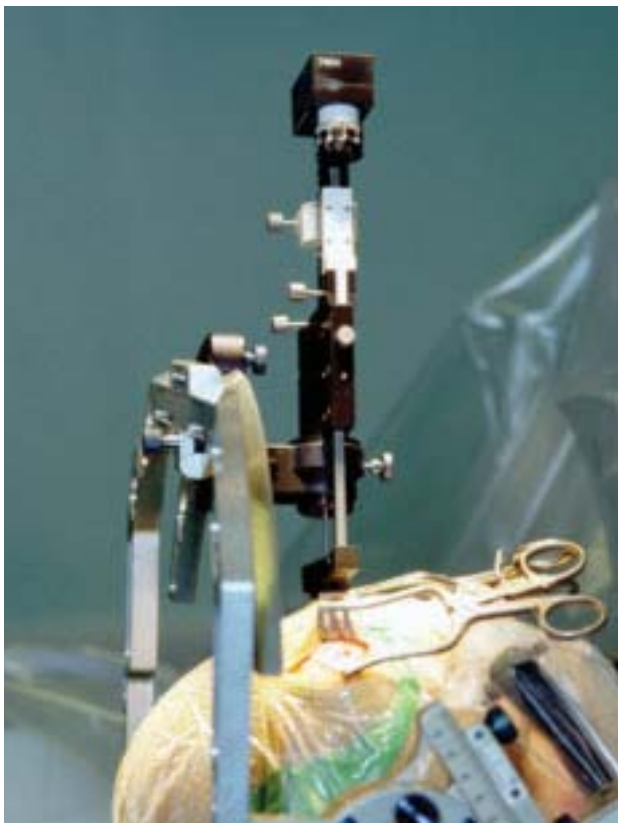
Inclusion criteria for participants were a *DSM-IV-TR* diagnosis of major depressive disorder, with a current major depressive episode of longer than one year and documented nonresponse to at least four adequate treatment trials (which could include pharmacotherapy, ECT, and evidence-based psychotherapy). The 17-item Hamilton Rating Scale for Depression (HAM-D) was also used, with inclusion criteria of a HAM-D score of 20 or higher.

After an initial 12 months of DBS, patients were seen annually and then at a last follow-up visit between September 1, 2009, and December 30, 2009, to assess depression severity, functional outcomes, and adverse events. At baseline, 12 months, and the last follow-up visit, the 36-item Short-Form Health Survey Questionnaire (SF-36) was completed in addition to the HAM-D.

Overall results of the study were favorable: The percentage of patients who responded with improved HAM-D scores was 62.5 percent after one year, 46.2 percent after two years, 75 percent after three years, and 64.3 percent at last follow-up visit. Patients who responded positively to DBS required less medication after DBS implantation, either in dosage or in number of medications. The rate of employment at the time of DBS surgery was 10 percent, and that rate increased to 50 percent by the end of the first year and onward. Three patients also began doing volunteer work, resulting in 65 percent of patients being engaged in work-related activities by the end of the study.

The authors acknowledged the possibility that the symptom improvements were due to placebo effect of the nonspecific aspects of psychiatric care, but countered that "sustained antidepressant response for longer than three years in a cohort of patients with [treatment-resistant depression] is inconsistent with a placebo response, particularly when battery failure [as occurred in some patients] was associated with return of symptoms."

The results are encouraging, but caveats are required. Three of the original cohort of 20 patients died during the study, one from unrelated and previously undiagnosed colon cancer. Despite achieving remission for extended periods during the study, suicide was a likely cause of death for the other two patients, although an accidental overdose could not be ruled out in one of the patients. Both patients were being actively monitored by their psychiatrists.



Deep brain stimulation requires placement of electrodes at specific neuroanatomical sites.

"The death of two patients by suspected suicide suggests use of caution and reinforces the need for long-term psychiatric management, including psychosocial and pharmacologic therapies, in combination with DBS," the researchers pointed out. "These data suggest that in the long term, DBS remains a safe and effective treatment for [treatment-resistant depression], but additional trials with larger samples are needed to confirm these findings."

"Deep Brain Stimulation for Treatment-Resistant Depression: Follow-up After 3 to 6 Years" is posted at <http://ajp.psychiatryonline.org/cgi/reprint/appi.ajp.2010.10081187v1>. ■

Close Depression Monitoring Urged During Menopause, Postmenopause

Clinicians should view the menopausal transition and the early postmenopausal period as times in which women are at increased risk for development of major depression.

BY JOAN AREHART-TREICHEL

Although menopause is infamous for triggering turbulent hormonal and mood swings, can it actually put women at risk for a major depression?

The answer has been murky based on the cross-sectional studies that have been conducted to answer this question. However, a new 10-year prospective study suggests that the answer is yes.

The study's lead investigator was Joyce Bromberger, Ph.D., an associate professor of epidemiology and psychiatry at the University of Pittsburgh, and findings were published online on February 9 in *Psychological Medicine*.

The study included 221 women aged 42 to 52 who were premenopausal at study entry. The Structured Clinical Interview for *DSM-IV* Axis I Disorders (SCID) was used to determine whether the subjects had ever experienced a major depression prior to the start of the study or whether they were experiencing a major depression at the time the study started. The SCID was also deployed during the subjects' annual follow-up assessments to determine whether they were experiencing a major depression.

Subjects were likewise evaluated annually to determine if they had experienced psychologically stressful events in the prior 12 months, and blood samples were taken annually to assay for reproductive hormone levels. If a subject was on hormone therapy at the time of an annual visit, data from that visit were not included in the study analyses.

Bromberger and her colleagues then examined whether subjects were significantly more likely to experience a major depressive disorder when they were perimenopausal or postmenopausal than when they were premenopausal. In evaluating this question, they considered possibly confounding factors such as a history of major depression, current psychologically stressful events, reproductive hormone levels, psychotropic medication use, body mass index, and hot flashes or night sweats.

It turned out that the risk of major depression was significantly greater not only during menopause, but within two years after the last menstrual period—that is, early postmenopause—than it was premenopausally.

"I was somewhat surprised that the risk for major depression in our sample was significantly higher during postmenopause than premenopause," Bromberger told *Psychiatric News*.

Why the menopause and postmenopause might increase women's risk of having a major depression, however, is not clear from this study. The researchers could find no significant associations between any reproductive hormone and major depressive episodes. Nonetheless, reproductive hormones could be the culprits, the researchers noted, since "single annual hormone samples have limited ability to provide information about the underlying hormonal dynamics that occur during the menopausal transition."

As for clinical implications of these findings, "it is important for health care providers to recognize that the risk for clinical depression, not just depressive symptoms, is greater during the menopausal transition and possibly early postmenopause," Bromberger said. "Women who present with depressive symptoms may benefit from close monitoring of mood and functioning and assessment of their situational and environmental circumstances. Such monitoring could lead to earlier interventions designed to interrupt the progression from depressive mood to major depression."

"This [was a] carefully done, long-term, prospective, cohort study," Deborah Cowley, M.D., a professor of psychiatry at the University of Washington, commented in the March 21 *Journal Watch Psychiatry*.

Please see ***Menopause*** *on page 33*

med check

COMPILED BY LESLIE SINCLAIR

Regulatory Brief

• On April 6, the FDA approved *Horizant extended release tablets (gabapentin enacarbil)*, a once-daily treatment for moderate-to-severe restless legs syndrome. Gabapentin enacarbil is a precursor of gabapentin that is efficiently absorbed and rapidly converted to gabapentin after oral dosing. Like all drugs used to treat to treat seizures in people with epilepsy, gabapentin carries warnings that it may cause suicidal thoughts and actions in a small number of people. Horizant will have the same warning and be dispensed with an FDA-approved medication guide that explains the drug's uses and risks. Horizant was developed by GlaxoSmithKline and Xenoport.

Legal Brief

• A South Carolina jury decided in March that a Johnson & Johnson unit violated consumer protection laws by sending doctors a misleading letter in 2003 about the safety and effectiveness of the antipsychotic ***Risperdal (risperidone).*** The jurors also determined that the warning-label information was deceptive. Jurors in state court in Spartanburg, S.C., found that the company's Ortho-McNeil-Janssen Pharmaceuticals unit engaged in "unfair and deceptive acts" by claiming in the letter that Risperdal was better than competing drugs. The letter was sent to some 700,000 doctors nationwide, including 7,200 in South Carolina. The FDA issued the company a warning letter about false and misleading claims that minimized risks such as diabetes and overstated the drug's benefits. South Carolina's unfair trade practices law allows a judge to decide whether the company can be fined as much as $5,000 for each Risperdal letter sent to South Carolina doctors. That decision was expected in April, but a decision has been deferred by the judge in the case.

Industry Briefs

• On March 24, Targacept Inc. announced in a press release top-line results from a phase 2 proof-of-concept trial of ***TC-5619*** as a treatment for adults with attention-deficit/hyperactivity disorder (ADHD). In the trial, conducted in nonsmokers, TC-5619 did not meet the primary efficacy outcome measure—a change from baseline on the Conners' Adult ADHD Rating Scale–Investigator Rated Total ADHD Symptoms (CAARS-INV) score after four, eight, and 12 weeks of dosing. TC-5619 is a highly selective alpha7 neuronal nicotinic receptor modulator, subject to license by Targacept's strategic collaborator AstraZeneca.

Analysis of the full dataset from the ADHD trial is ongoing, and Targacept plans to present more detailed results at a scientific meeting. In addition to its complete phase 2 trials in ADHD, Targacept is conducting clinical and nonclinical studies designed to support potential phase 2 development of TC-5619 for Alzheimer's disease.

• On March 30, Dainippon Sumitomo Pharma Ltd. (DSP) and Takeda Pharmaceutical Company Ltd., both of Osaka, Japan, announced that they have entered into a licensing agreement for the joint development and exclusive marketing of the oral formulation of ***lurasidone*** for treatment of schizophrenia and bipolar disorder in 26 member countries of the European Union, excluding the United Kingdom. Lurasidone, an atypical antipsychotic agent originally developed by DSP, was approved by the FDA for treatment of schizophrenia in adult patients in the United States in October 2010 and is marketed as Latuda.

• On March 28, Greenstone announced a voluntary recall of medicines with lot number FI050058-A on the label. Bottles labeled as ***citalopram*** contain ***finasteride*** (used to treat benign prostatic hyperplasia). Women who are or who may become pregnant should not take or handle finasteride due to the risk of abnormalities to the external genitalia of a developing male fetus.

Patients who discontinue citalopram abruptly by inadvertently taking the mislabeled product may experience discontinuation symptoms and/or worsening of depression. The recall includes citalopram 10 mg tablets (100-count bottle) and finasteride 5 mg tablets (90-count bottle), both distributed in the U.S. market. The recall is due to the possibility that incorrect labels have been placed on the bottles by a third-party manufacturer..

• On March 22, Japan-based Takeda Pharmaceutical Company announced the launch of ***Reminyl (galantamine hydrobromide)*** for the treatment of patients in Japan with dementia of the Alzheimer's type. Reminyl was developed jointly by Johnson and Johnson Pharmaceutical Research and Development and Shire PLC, under a licensing agreement between Janssen Pharmaceutica and Synaptec Inc.

Since its approval for clinical use in Sweden in 2000, it has been used clinically in more than 70 countries and regions around the world to treat patients with mild to moderate dementia of the Alzheimer's type. Galantamine controls the progress of various symptoms of progressive Alzheimer's-type dementia. It enhances the functions of nicotinic acetylcholine receptors in addition to inhibiting acetylcholinesterase. The dual mechanism of action increases the concentration of acetylcholine in the brain, accelerates the release of the neurotransmitter, increases receptor sensitivity, and protects nerve cells.

• At the American Academy of Neurology annual meeting last month in Honolulu, Quanterix Corporation announced in a company release the finding of elevated amyloid beta 42 (Abeta42) in the blood of 26 patients recovering from cardiac arrest at Uppsala University Hospital, Uppsala, Sweden. Abeta42 is a 42 amino acid peptide that is better known as a component of the plaques that are a hallmark of Alzheimer's disease (AD).

All 26 patients exhibited a significant elevation of their blood level of Abeta42 ranging from approximately 50 percent to more than 30-fold. The discovery indicates the possibility of a direct link between brain injury caused by hypoxia and increased serum Abeta42 levels. The finding is the result of the availability of Single Molecule Array (SiMoA) assay, a proprietary technology used by Quanterix to measure clinically important proteins in blood.

"A theory of what causes the elevation and buildup of these plaques in patients with AD is that hypoxic conditions (lack of proper levels of oxygen) trigger the release of Abeta42, which accumulates over time," explained David Wilson, Ph.D., senior director of product development at Quanterix. "If this is the case, then cardiac arrest patients, whose brains have been exposed to acute oxygen deprivation, might show signs of elevated Abeta42 in their blood. We were surprised to see clear elevations of Abeta42 in the blood of every patient we tested."

The results suggest the prognostic value of Abeta42 determination: "We believe the Abeta42 elevations reflect the extent of oxygen deprivation to the brain during the cardiac arrest, and thus correlate with cognitive impairment from the oxygen deprivation," said Wilson. ■

journal digest

COMPILED BY LESLIE SINCLAIR

Secondhand Smoke Affects Children's Mental Health

Exposure to secondhand smoke can lead to symptoms of major depressive disorder, generalized anxiety disorder, attention-deficit/hyperactivity disorder, and conduct disorder in children and adolescents, according to a report in the April *Archives of Pediatric and Adolescent Medicine*. The results were gleaned from the National Health and Nutrition Examination Survey (NHANES), a program of studies designed to assess the health and nutritional status of adults and children in the United States. The survey is unique in that it combines interviews and physical examinations. NHANES is a major program of the National Center for Health Statistics, part of the Centers for Disease Control and Prevention.

Frank Bandiera, M.P.H., of the Department of Epidemiology and Public Health at the University of Miami Miller School of Medicine, and his colleagues looked at children and adolescents aged 8 to 15 who participated in the NHANES from 2001 to 2004. Serum levels of cotinine, a metabolite of nicotine that serves as a biomarker for exposure to tobacco smoke, were determined to confirm secondhand smoke exposure among nonsmokers. Information on mental disorders in the study participants was derived from the National Institute of Mental Health's Diagnostic Interview Schedule for Children Version IV.

The association of serum cotinine levels with symptoms of mental health disorders remained even after adjusting for survey design, age, sex, race/ethnicity, poverty, migraine, asthma, hay fever, maternal smoking during pregnancy, and allostatic load. These associations were more apparent for boys and for subjects of non-Hispanic white race/ethnicity.

"Future research is warranted to establish the biological or psychological mechanisms of association," said Bandiera and colleagues.

Bandiera FC, Kalaydjian Richardson A, Lee DJ, et al.: Secondhand Smoke Exposure and Mental Health Among Children and Adolescents. Arch Pediatr Adolesc Med. 2011; 165 (4): 332-338. An abstract is posted at <http://archpedi.ama-assn.org/cgi/content/abstract/165/4/332>.

Genes May Influence Obesity of Women Using Antipsychotics

For many patients, weight gain poses a serious threat to successful treatment for psychosis. Especially in women, it can lead to other morbidities, including type II diabetes mellitus, hypertension, and other cardiovascular diseases. It may also contribute to reduced treatment compliance. While the atypical antipsychotics olanzapine and clozapine are the more well-known culprits in weight gain, almost none of the atypical and typical antipsychotics are free of this side effect. The idea that certain genetic risk factors may be important to produce weight gain and therefore enable individualized treatment in patients receiving antipsychotics is supported by the substantial interindividual and interracial differences in antipsychotic-induced weight gain.

One gene possibly involved in the multifaceted development of antipsychotic-induced obesity is the roundabout axon guidance receptor, homolog 1 (ROBO1) gene. In a recently published cross-sectional study of a pooled sample of Dutch Caucasian psychiatric patients, 435 patients—335 of whom had a diagnosis in the schizophrenia spectrum, 77 of whom had schizoaffective disorder, two of whom had schizophreniform disorder, and 21 of whom had a psychotic disorder not otherwise specified—were evaluated for a single nucleotide polymorphism (rs1455832) of ROBO1. Investigators then investigated the association between body mass index (BMI) of the subjects and the presence of rs1455832.

The results were gender specific: The rs1455832 polymorphism studied was significantly associated with BMI and obesity in female patients and therefore may play a role in inducing obesity in female patients using antipsychotics.

please see ***Journal Digest*** *on facing page*

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This association was not exhibited in male patients.

The study was conducted by Jelle Vehof, M.D., of the departments of Psychiatry and Epidemiology of the University Medical Center Groningen, Groningen, the Netherlands, and colleagues.

Vehof J, Al Hadithy, AFY, Burger H, et al.: Association Between the ROBO1 Gene and Body Mass Index in Patients Using Antipsychotics. Psych Gen. 2011; [Epub ahead of print March 15]. An abstract is posted at <http://journals.lww.com/psychgenetics/Abstract/publishahead/Association_between_the_ROBO1_gene_and_body_mass.99862.aspx>.

Mexican Migrants Prone to Depression, Anxiety

A new study has determined that migrants from Mexico to the United States are more prone to depressive or anxiety disorders than are the nonmigrant family members they left behind. Researchers in California and Mexico performed a population survey of 554 Mexican migrants to the United States and 2,519 nonmigrant family members in Mexico, looking for the first onset of any depressive or anxiety disorder.

Results indicated that, after arrival in the United States, migrants had a significantly higher risk for first onset of any depressive or anxiety disorder than did nonmigrant family members of migrants in Mexico. The associations between migration and disorder varied with age, but the elevated risk was restricted to those aged 18 to 35, with particularly strong association in the youngest migrants, aged 18 to 25.

"The findings are consistent with the hypothesized adverse effect of migration from Mexico to the United States on the mental health of migrants, but only among migrants in recent birth cohorts," said Joshua Breslau, Ph.D., of the Department of Internal Medicine at the University of California, Davis, School of Medicine and colleagues.

Breslau J, Borges G, Tancredi D, et al.: Migration from Mexico to the United States and Subsequent Risk for Depressive and Anxiety Disorders. Arch Gen Psych. 2011; 68(4):428-433. An abstract is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/68/4/428>.

Does Ibuprofen Mediate Parkinson's Development?

A study published in the March 8 *Neurology* examined the use of ibuprofen in relation to the risk for Parkinson's disease (PD). The study, conducted in Boston, sought to determine whether the use of nonsteroidal anti-inflammatory drugs (NSAIDs) in general, and ibuprofen in particular, might mediate the neuroinflammation that contributes to the pathogenesis of PD. Researchers prospectively examined whether use of ibuprofen or other NSAIDs was associated with lower risk for PD among 136,197 participants in the Nurses' Health Study (NHS) and the Health Professionals Follow-Up Study (HPFS) free of PD at baseline (1998 for NHS, and 2000 for HPFS). During six years of follow-up, 291 incident PD cases were identified. Users of ibuprofen had a significantly lower risk than nonusers after adjustment for age, smoking, caffeine intake, and other covariates. Use of other types of analgesics was not associated with lower risk. "The association between use of ibuprofen and lower PD risks, not shared by other NSAIDS or acetaminophen, suggests ibuprofen should be further investigated as a potential neuroprotective agent against PD," concluded the researchers.

Gao X, Chen H, Schwarzschild MA J, et al.: Use of Ibuprofen and Risk of Parkinson Disease. Neurology. 2011; 76(10):863-869. An abstract is posted at <www.neurology.org/content/early/2011/03/01/WNL.0b013e31820f2d79>. ■

Suicide

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and today includes more than 100 scientists from 11 countries— is not just attempting to identify genetic risk factors for bipolar disorder, major depression, schizophrenia, and some other psychiatric disorders, but to identify genetic risk factors for suicidal behavior. "We are eager to see whether [their results] will provide further evidence for the 2p25 candidate region and for ACP1 in particular," she said.

The study was funded by the National Institute of Mental Health and the American Foundation for Suicide Prevention.

An abstract of "A Genome-wide Association Study of Attempted Suicide" is posted at <www.nature.com/mp/journal/vaop/ncurrent/abs/mp20114a.html>. ■

Menopause

continued from page 31

"Clinicians should view the menopausal transition and early postmenopause as a high-risk time for major depressive episodes and consider antidepressants and/or psychotherapy, which remain the mainstay of treatment, given conflicting data about the benefit of hormonal inventions."

The study was funded by the National Institutes of Health and the Department of Health and Human Services.

An abstract of "Major Depression During and After the Menopausal Transition: Study of Women's Health Across the Nation (SWAN)" is posted at <http://journals.cambridge.org/action/displayAbstract?fromPage=online&aid=8059759&ful..>. ■

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Pain Control Advances Leave Troublesome Legacy

A stunning increase in the diversion and abuse of opioid medications may be an unintended measure of the success of efforts to provide patients with better control of their pain.

BY LESLIE SINCLAIR

The beginning of the new millennium brought unprecedented focus to the issue of pain control.

In 1997, the American Academy of Pain Medicine and the American Pain Society teamed up to promulgate guidelines on the use of opioids for the treatment of chronic pain; the American Society of Anesthesiologists introduced their guidelines for chronic pain management that year as well. In late 2000, Congress passed and President Clinton signed into law a measure that declared the period that began January 1, 2001, as the Decade of Pain Control and Research. Also in January 2001, the Joint Commission presented pain-management standards for ambulatory care facilities, behavioral health care organizations, hospitals, and other medical care settings. In 2004, the Federation of State Medical Boards published its model policy for the use of controlled substances for pain treatment.

Advocates of pain control hailed the results of these events, saying they've led to heightened awareness, improved treatment, and more funding for pain-control efforts and research. But as the "Decade" ended, it left behind a less desirable legacy of unintended consequences: that of a spectacular rise in the diversion and abuse of opioid pain-control medications.

Nowhere has that been more evident than in West Virginia, where the nation's most substantial increase in drug overdose mortality rates—a 550 percent jump—occurred from 1999 to 2004. In 2006, 295 West Virginia residents suffered unintentional overdose with prescription pharmaceuticals, the majority of which were due to nonmedical use and diversion of opioid analgesics, according to a report in the December 10, 2008, *Journal of the American Medical Association (JAMA)*.

And West Virginia is by no means alone. Statistics from the Centers for Disease Control and Prevention (CDC) and the Substance Abuse and Mental Health Services Administration are equally alarming:

- Drug treatment admissions related to pharmaceutical opioid use from 1998 to 2008 increased five-fold.
- Emergency department visits related to pharmaceutical opioid use increased from 144,644 in 2004 to 305,885 in 2008.
- Unintentional opioid-related overdose deaths increased from 3,000 in 1999 to 12,000 in 2007.
- In 2007 the number of deaths involving opioid analgesics was 1.93 times the number involving cocaine and 5.38 times the number involving heroin.
- Opioid overdose is now the second-leading cause of unintentional death in the United States, second only to motor-vehicle crashes, prompting the CDC to label pharmaceutical opioid overdose a national epidemic.

In the April 6 *JAMA*, Amy Bohnert, Ph.D., of the Department of Veterans Affairs Health Services Research and Development Center of Excellence, and the Serious Mental Illness Treatment Resource and Evaluation Center in Ann Arbor, Mich., and colleagues described their efforts to see if there is an association between the maximum prescribed daily opioid dose and dosing schedule ("as needed," regularly scheduled, or both) and the risk of opioid overdose death. "Among patients receiving opioid prescriptions for pain, higher opioid doses—those equivalent to 50 mg/day or more of morphine—were associated with increased risk of opioid overdose death," the researchers found.

Physicians Not Barriers to Abuse

Indeed, physicians appear to be a failed first line of defense against this pharmacoepidemic. In the online February 24 *Journal of General Internal Medicine*, Joanna Starrels, M.D., M.S., of the Division of General Internal Medicine at Albert Einstein College of Medicine and Montefiore Medical Center, and colleagues found that primary care physicians' adoption of opioid risk-reduction strategies is limited, even among patients at increased risk of misuse.

"Well-meaning, thoughtful primary care physicians face many obstacles to implementing monitoring strategies for these patients," said Starrels in an interview with *Psychiatric News*. "Primary care physicians lack the tools that could help to make this easier, such as written agreements or policies that can help them provide routine, structured care." Starrels and her colleagues also said in their report that lack of time with each patient plays a part: "This lack of face-to-face encounters represents missed opportunities for physicians to examine responses to treatment, propose alternative treatments when the response is inadequate, detect side effects, and assess for misuse."

Nora Volkow, M.D., director of the National Institute on Drug Abuse, and A. Thomas McLellan, Ph.D., director of the Center for Substance Abuse Solutions of the University of Pennsylvania School of Medicine, and colleagues further characterized the problem in a research letter in the April 6 *JAMA*. Overall, they pointed out, the main prescribers of opioid analgesics were primary care physicians, followed by internists, dentists, and orthopedic surgeons. For patients aged 10 to 19, dentists were the main prescribers followed by primary care and emergency medicine physicians.

Physician Education Needs Bolstering

Expressing her concern, Volkow told *Psychiatric News*, "Education for health professionals about pain management has not kept pace; thus physicians may not be properly trained on best prescribing practices for opioids, their potential for abuse and addiction, and other adverse consequences. To balance benefits while mitigating risk is a key challenge to physicians and other prescribers and calls for targeted education and training to improve the screening and management of pain and the use of opioid medications" (see page 1).

NIDA has developed information for practicing physicians and physicians in training. "We hope this information will result, for physicians, in their greater engagement in drug-abuse screening and help guide thoughtful and informed prescribing practices without depriving patients of needed pain relief," said Volkow.

NIDA's information for physicians about prescription opioid medication is posted at <www.drugabuse.gov/coe>. ■

Opioid Abuse

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prescribers.

In the joint press release Joseph Liberto, M.D., AAAP president, said, "The administration's action plan to address the growing problem of prescription drug abuse in our nation, especially among our youth, is an unprecedented step forward in helping to reduce the morbidity and mortality associated with addiction. Essential elements of the plan include a call to require training of our health care workforce on the appropriate use of opioid medications and the call to strongly recommend provider education on early identification and treatment of substance use disorders. This is consistent with the educational missions of AAAP, APA, and AOAAM."

Renner noted that "this is the first time that there is recognition that physician prescribing is part of the problem and that the need for better education of doctors is paramount."

At the heart of the plan is the requirement that drug manufacturers provide educational programs to those licensed to prescribe long-acting and extended-release opioids. In addition, manufacturers would be required to provide materials to assist physicians in counseling patients in the proper use and risks of these drugs.

In support of the plan, the FDA moved forward with requirements and guidelines for risk evaluation and mitigation strategies (REMS). The FDA has the authority to require manufacturers to develop REMS under the Food and Drug Administration Amendments Act of 2007. According to the plan, the REMS would require manufacturers "to develop effective educational materials and initiatives to train practitioners on the appropriate use of opioid pain relievers" and require them "to develop effective materials for patients on the appropriate use and disposal of opioid pain relievers." At this point physician training is not mandatory; however, companies have 120 days to issue draft REMS with the goal of putting them into effect in early 2012.

Another component of the plan is better tracking of where and how patients are obtaining their drugs. The plan calls for an improved national system to track prescribing habits of physicians and the habits of patients in seeking these prescriptions.

In addition, the plan also takes note of the great benefits these drugs provide and seeks to strike a balance between controlling abuse and ensuring adequate access for those in legitimate need. The plan states that the "potent medications science has developed have great potential for relieving suffering, as well great potential for abuse. There are many examples: acute medical pain treatment and humane hospice care for cancer patients would be impossible without prescription opioids; benzodiazepines are the bridge for many people with serious anxiety disorders to begin the process of overcoming their fears; and stimulants have a range of valuable uses across medical fields."

"Epidemic: Responding to America's Prescription Drug Abuse Crisis" is posted at <www.whitehousedrugpolicy.gov/publications/pdf/rx_abuse_plan.pdf>. The joint press release is posted at <www.psych.org/MainMenu/Newsroom/NewsReleases/2011-News-Releases_1/Combating-Prescription-Drug-Abuse-.aspx?FT=.pdf>. ■

2011 World Congress To Be Held in Buenos Aires

The World Congress of Psychiatry, organized by the World Psychiatric Association every three years, is the main international scientific event in the field of psychiatry. The next congress on the schedule—the 15th—will be held from September 18 to 22 at the Sheraton Buenos Aires Hotel and Convention Center.

Under the theme "Our Heritage and Our Future," the congress aims to provide a comprehensive overview of those achievements that have stood the test of time and of the most promising current trends in psychiatric research and practice, with the contribution of the most prominent experts of the various topics.

An outstanding scientific program is being put together, according to Mario Maj, M.D., the president of the World Congress. The list of the keynote lectures and core symposia is posted on the Web site of the congress, <www.wpa-argentina2011.com.ar>.

More than 4,500 individuals have registered for the congress, and more than 10,000 are expected. The official language of the Congress will be English, but simultaneous translation into Spanish and Portuguese will be available for many sessions.

To help attendees get the most out of their trip to Buenos Aries, guided tours are also being offered. Descriptions can be found at <www.wpa-argentina2011.com.ar/local_tours.htm>.

Attendees may earn up to 32 Category 1 credits.

Registration and other information about the World Congress are posted at <www.wpa-argentina2011.com.ar/>. ■

Prison

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cide rate in jails and prisons. Security concerns can hamper providing adequate care. Finally, a relatively small number of very disturbed prisoners are prone to act out and need a lot of clinical attention.

"Still, correctional psychiatry offers opportunities to devise new and creative interventions to treat patients who would not be treatable in other settings," said Kupers.

Credit: Aaron Levin

Merrill Rotter, M.D.: "Incarceration is a form of cultural adaption. The psychological environment is full of danger and the threat of violence."

Prison Culture Lingers

Treating prisoners is a major challenge, agreed Merrill Rotter, M.D., a forensic psychiatrist and an associate clinical professor of psychiatry and director of the Division of Law and Psychiatry at Albert Einstein College of Medicine in New York City.

To succeed in therapeutic engagement, clinicians must understand the impact of "doing time" and then take a culturally competent approach in engaging people who are or have been in prison.

"Incarceration is a form of cultural adaption," said Rotter. "The psychological environment is full of danger and the threat of violence. The social environment is rife with rules, codes, gangs, and race."

Shedding that world view isn't easy, said Rotter. Distrust of staff and peers is normal inside, but distrusting everyone after release is dysfunctional.

In fact, life inside prison distorts the prisoner's value system and makes it hard to function in the outside world after release. Lifesaving adaptations to prison life and correctional codes tend to be seen as "resistance" to therapy, inside or outside prison.

Minding one's own business, trusting no one, not sharing information, or manipulating others are unhelpful traits in a therapeutic milieu, the job market, or relationships, said Rotter.

Thus, to help ex-prisoners adjust to the outside world, mental health clinicians must understand the cultural environment inside prisons, he said. Simply knowing that the patient has been incarcerated is not enough. "That's just the tip of the iceberg."

For instance, psychotropic medications carry different meaning inside and outside prison. Inside, being strong and self-reliant are behavioral assets, so accepting medications (an external support) is seen as weakness. Where hypervigilance is a necessity, some side effects (like sedation) may prove deadly when danger lies around any corner.

So, clinicians working with prisoners or ex-prisoners must learn more about this population to overcome their own resistance to it and to minimize stigma, just as they would with any other subculture, Rotter believes. Then they must help patients decrease resistance engendered by immersion in prison culture.

"Be willing to listen and learn about patients' experiences behind bars," he said. "Ask what the experience was like and how they got by and if those patterns are helpful when not in prison. Be aware of the differences and similarities between the cultures of prison and therapy."

Finally, Rotter advocates using cognitive-behavioral therapy variants to lessen the effects of cultural behaviors learned in prison and develop the skills to create new lives on the outside.

***More information is available in* Psychiatric Services *in a study by Rotter and colleagues, "Best Practices: The Impact of the 'Incarceration Culture' on Reentry for Adults With Mental Illness: A Training and Group Treatment Model," posted at <http://ps.psychiatryonline.org/cgi/content/full/56/3/265>.** ■

Harris

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recognize mental health as an essential part of general medical health. She noted that AMA support was crucial to the passage of parity legislation and that the organization continues to be a leader on issues of vital importance to psychiatry—especially scope-of-practice issues.

"The AMA Scope of Practice Partnership has been enormously helpful to APA district branches in responding to efforts to grant psychologists and other nonphysicians the right to practice medicine by legislative fiat," she said.

She added that the "medical home," with which many states are experimenting as a model for delivery system reform, must have room for psychiatrists. "It is vital that we are at the table as these new care models are piloted to ensure that psychiatrists are considered as integral leaders of health teams." she said.

APA members who wish to aid in Harris's candidacy should contact physicians active in their state medical societies and request that the state's AMA delegates vote for her in June. ■

Need Help With Parity Law?

The Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equity Act has been in effect since January 1, 2010, and the law and the regulations implementing it are complicated. To help APA members and patients better understand the law and its impact on benefits, APA's Office of Healthcare Systems and Financing has created <www.mentalhealthparitywatch.org>. Also, the federal agencies monitoring the law have asked APA and its members to identify insurance plans not in compliance with the act. APA members can help by visiting the site to learn more and report any concerns.

Isaac Ray Award

The American Psychiatric Association and the American Academy of Psychiatry and the Law invites nominations for the Isaac Ray Award for 2012. This Award honors Dr. Isaac Ray, one of the original founders and the fourth President of the American Psychiatric Association, and is presented to a person who has made outstanding contributions to forensic psychiatry or to the psychiatric aspects of jurisprudence. The Award, which will be presented at the Convocation of Fellows at the Annual Meeting of the American Psychiatric Association in Philadelphia, PA, in May 2012, includes an honorarium of $l,500. The recipient obligates him or herself to deliver a lecture or series of lectures on these subjects and to present the manuscript for publication.

Nominations are requested as follows: (1) a primary nominating letter (sent with the consent of the candidate), which includes a curriculum vitae and specific details regarding the candidate's qualifications for the Award, and (2) a supplemental letter from a second nominator in support of the candidate. Additional letters related to any particular candidate will not be accepted or reviewed by the Award Committee. Nominators should not submit letters on behalf of more than one candidate. The deadline for receipt of nominations is **July 1, 2011**. Nominations will be kept in the pool of applicants for two years.

Nominations, as outlined above, should be submitted to:

Renee L. Binder, M.D., Chairperson
c/o Lori Klinedinst, Staff Liaison
Isaac Ray Award Committee
American Psychiatric Association
1000 Wilson Boulevard, Suite 1825
Arlington, VA 22209
E-mail: advocacy@psych.org

Tutu

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And Tutu is among those, she said. At the meeting, Tutu will be speaking about his human-rights work in South Africa—work that earned him enemies among the white establishment there—and the activities of the Truth and Reconciliation Commission in South Africa, which has helped to heal the wounds of apartheid.

Bernstein commented that Tutu has also spoken out about issues and conflicts outside South Africa, including human rights abuses in other parts of Africa; the treatment of detainees at Guantanamo; gay rights and women's rights within the Episcopal Church and in society in general; and about poverty and HIV disease. And since the end of apartheid, Tutu has not hesitated to be critical of corruption within the black leadership of South Africa.

Tutu also has spoken out periodically about the conflict between Israelis and Palestinians. For instance, a speech by Tutu in Boston almost 10 years ago in which the archbishop angrily denounced Israeli policies toward Palestinian Arabs and American support for those policies, especially angered the 27 psychiatrists who placed the ad in *Psychiatric Times;* that speech, which took place during the second intifada (or uprising, in which some 1,400 Israelis and 3,400 Palestinians were killed) drew analogies to the policies of Hitler, Mussolini, and Milosovich.

In more recent comments, Tutu has drawn on the legacy of Old Testament teachings in urging reconciliation between Israelis and Palestinians. And he has stated his support for Israel's security and has denounced suicide bombings against Israelis.

Bernstein, who invited Tutu to speak, said that in e-mails and phone calls she has been personally vilified and excoriated by some, which, she said, has caused her both shock and hurt. But she reports that she has also spoken to at least a few of the 27 signers and found them to be conciliatory and reasonable, and she has received much support from many other APA members.

Bernstein said she hopes the controversy—which has engaged a relatively small portion of the membership—will be a "teachable moment" for both sides about being willing to disagree without being disagreeable.

"The more important conversation we should be having as a psychiatric organization is how to listen to and interact with each other even when we have very strong emotional opinions about issues that are divisive," Bernstein said.

She added that she chose to invite Tutu after hearing him speak at last year's meeting of the American College of Psychiatrists—a deeply inspiring address, Bernstein said, which merited no protests whatsoever despite the fact that the great majority of the college membership is also among APA's membership.

"I hope ultimately that this is an opportunity for us all to think about how to be respectful of each other even when we have extremely strong, divergent opinions," she said. "It's easy for things to spiral out of control, but we have to maintain our decency and civil dialogue, even when we disagree."

The BPA's open letter to APA is posted at <www.blackpsych.org/sitebuildercontent/sitebuilderfiles/bpatutu.pdf>. ■

clinical & research news

Nonconverters

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prevention, said that nonconverters continue to require the close monitoring of mental health professionals.

"What these young people need is to be watched very closely," he said. "They need a clinician to be with them, and that requires an investment of time and effort on the part of the clinician. And in order to be paid for that time and effort, you need to have a diagnosis."

"Prediction of Psychosis in Youth at High Clinical Risk: A Multi-Site Longitudinal Study in North America" is posted at http://archpsyc.ama-assn.org/cgi/content/full/65/1/28. ■

Nominations Invited

APA invites applications for the Blanche F. Ittleson Research Award, Agnes Purcell McGavin Award for Prevention, and Agnes Purcell McGavin Award for Distinguished Career Achievement in Child and Adolescent Psychiatry. These awards are given to psychiatrists who have made significant contributions to child and adolescent psychiatry. They will be presented at APA's 2012 annual meeting in Philadelphia.

The Blanche F. Ittleson Research Award recognizes research that promises to foster important advances in promoting the mental health of children and adolescents. A psychiatrist or a group of psychiatric investigators must have published this research within five years or have it officially accepted for publication in the near future.

The Agnes Purcell McGavin Award for Prevention recognizes a psychiatrist who has been successful in research or policy that is recognized as contributing to primary prevention of mental illness among children and adolescents.

The Agnes Purcell McGavin Award for Distinguished Career Achievement in Child and Adolescent Psychiatry recognizes a psychiatrist whose career demonstrates success in research, teaching, publications, clinical care, or policy.

The deadline for nominations is August 1. Detailed information about the materials required for nomination and the address for submission can be accessed at <www.psych.org/Share/OMNA/AwardsandFellowships.aspx> or obtained from Alison Bondurant at abondurant@psych.org or (703) 907-8639. ■

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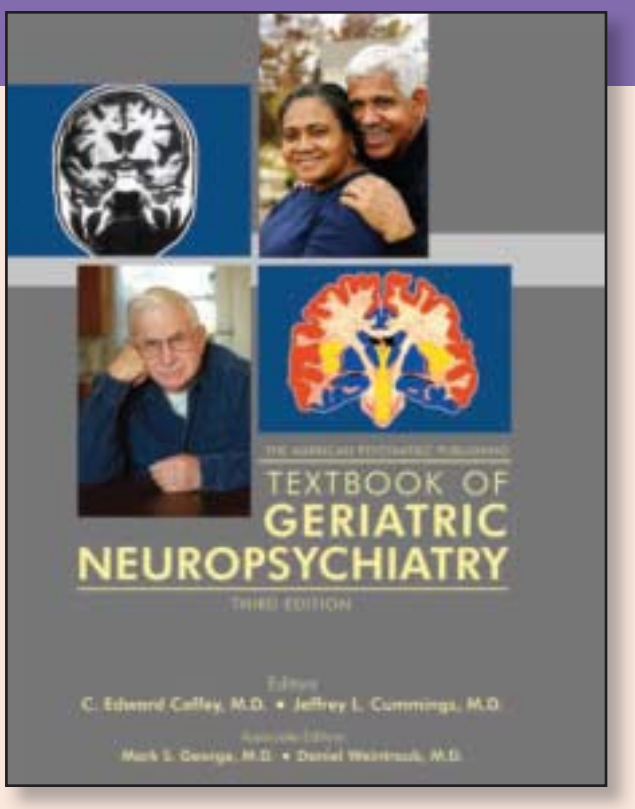

The American Psychiatric Publishing **Textbook of Geriatric Neuropsychiatry, Third Edition**

Edited by C. Edward Coffey, M.D., and Jeffrey L. Cummings, M.D.
Associate Editors: Mark S. George, M.D., and Daniel Weintraub, M.D.

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Issue	Deadline (Friday, 5 p.m. E.T.)
June 17	June 3
July 1	June 17

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Psychiatry Opportunities -

Competitive salary and sign-on bonus

The Columbus Organization is expanding its team of psychiatrists at a mental health facility in **Georgia**, a facility in **Central Pennsylvania**, and an agency in **Southern California**.

Immediate openings. Interviews now being scheduled. Competitive salary, sign-on bonus, and comprehensive benefits. NO WEEKENDS AND NO ON-CALL. We invite you to explore the difference Columbus can make for you!

Columbus offers industry leading compensation and benefits (medical insurance, with prescription and vision plan, dental, life, and disability insurance, 401k plan with employer contribution, full malpractice insurance, $1500 CME allowance, and reimbursement for licensure/certification, relocation assistance up to $3,500 and additional compensation for minimal call schedule.

If interested in hearing more about this opportunity send CV to recruit@columbusorg.com. For additional information, call 800-229-5116. EOE.

Forefront TeleCare: Are YOU ready to join the Telehealth Revolution?

Forefront is building a nationwide network of psychiatrists to serve patients in rural SNFs and small town health care facilities through our Telehealth Network. Work from home or office for as few as 8 hrs per week or full time, we have patients in need of your care. We will train you, set you up with needed equipment, and introduce you to un-served facilities. NO Travel; No Special Technical Skills; No Investment needed. Look for us @ APA Booth #604. For more info call Merritt at 916-419-5900 or email your CV to merritt@forefronttelecare.com.

Anthem Blue Cross and Blue Shield is a proud member of the WellPoint family of companies. At Anthem, we are dedicated to our mission of improving the health of the people we serve. We believe the best health care coverage can actually help people stay healthy.

Bring your expertise to our innovative, performance-focused culture, and you will discover lasting rewards and the opportunity to take your career further than you can imagine.

This position may be located in any **St. Louis, MO; Mason, OH; or Indianapolis, IN, preferably St. Louis MO**.

Responsible for the administration of medical services for company health plans in the Central Zone and ensures clinical integrity of broad and significant clinical programs, including the overall medical policies of the business unit. Primary duties may include, but are not limited to: Interprets existing policies and develops new policies based on changes in the healthcare or medical arena. Leads, develops, directs and implements clinical and non-clinical activities that impact health care quality cost and outcomes. Supports the Medical Management staff ensuring timely and consistent responses to members and providers. Identifies and develops opportunities for innovation to increase effectiveness and quality. Serves as a resource and consultant to other areas of the company. May chair or serve on company committees. May be required to represent WellPoint to external entities and/or serve on external committees.

Requires MD licensure in some of the Anthem states, and 10 years of post residency experience in addition to extensive managed behavioral care or Medicare knowledge. Requires board certification. Prior Medical Director experience with expertise in Behavioral Health Utilization Management required. Requires in-depth knowledge of Behavioral Health medical & quality operations in the commercial sector; In-depth knowledge of Behavioral Health Accreditation and regulatory requirements; Ability to provide medical operational support to multi-site operations requiring travel as needed; Proven track record of success managing Behavioral Health cost of care in the Commercial Sector.

WellPoint is ranked as one of America's Most Admired Companies among health insurers by Fortune magazine and is a 2008 DiversityInc magazine Top 50 Company for Diversity. To learn more about our company please visit us at www.wellpoint.com/careers.

Psychiatry Networks is looking for general adult psychiatrists to deliver 3 to 40 hours a week of telepsychiatry consultations. Candidates must be licensed in any of the following states: **AK, AR, AZ, CA, CO, FL, ID, LA, MO, MN, MS, MT, ND, NM, NV, OK, OR, UT, VA, TX, WA, WY**. Psychiatry Networks offers the ability to work from home or office while filling in openings in your clinical schedule with as few as three consultations per week.

If you are interested please contact **Psychiatry Networks** at 1-866-220-3434 or at **contactus@psychiatrynetworks.com**.

Universal Health Services, Inc. (UHS) is one of the nation's largest and most respected hospital management companies. Through our subsidiaries we operate over 150 behavioral health treatment facilities nationwide. We are currently recruiting Psychiatrists for diverse practice positions at our facility locations below as well as in other areas.

For more detailed information about all locations and positions contact: Joy Lankswert, In-house Physician Recruiter @ 866-227-5415 ext: 222 or email joy.lankswert@uhsinc.com

- **ALASKA-** Anchorage- Outpatient OR Inpatient
- **COLORADO-** Denver and Boulder
- **DELAWARE-**
- **FLORIDA-** Panama City-Ocala-Orlando
- **GEORGIA-** Atlanta
- **IDAHO-** Boise
- **ILLINOIS-** Chicago and Springfield (Academic Affiliation)
- **INDIANA**- Bloomington-Outpatient only
- **KENTUCKY-** Louisville area
- **LOUISIANA-** Shreveport
- **MASSACHUSETTS-** BOSTON city & suburbs
- **MICHIGAN-** Detroit and Grand Rapids
- **MISSISSIPPI-** Meridian
- **NEW MEXICO-** Las Cruces- Medical Director
- **OHIO-** Cleveland
- **OKLAHOMA-** Oklahoma City
- **PENNSYLVANIA-** Philadelphia-State College-Shippensburg
- **SOUTH CAROLINA-**Aiken
- **TEXAS-** Austin, Dallas, San Angelo-Salaried Employment
- **VIRGINIA-** Leesburg AND Portsmouth/Norfolk
- **WEST VIRGINIA-** Huntington

Competitive comprehensive compensation packages offered including bonus opportunity and student loan assistance depending on location. See the UHS website: www.uhsinc.com for full list of our facility locations.

ARIZONA

The University of Arizona **Department of Psychiatry** is recruiting for several professional positions to join a progressive and growing academic department located in the beautiful Southwest, with over 300 days of sunshine every year! These positions will support residency and fellowship expansion and new facilities opening in 2011. Candidates must have current credentials to practice medicine in the United States and be Board-certified or Board-eligible in Psychiatry.

Assistant/Associate Professor, Psychiatry (NTE) - Inpatient/Outpatient Psychiatrist -Job #46987
Successful candidates will join our psychiatrists providing inpatient services at the brand new 62 bed behavioral health pavilion on the Kino campus. Position is affiliated with our adult residency program offering direct supervision of psychiatry residents, interns and other trainees. Other duties may include participation in committees and department services as directed by the Department Head. Opportunities may also exist for work in a new ambulatory Crisis Response Center. Salary: $185-200K+ (DOE)

Assistant/Associate Professor, Psychiatry (NTE) — Child Psychiatrist-Job #43272

We are seeking a dynamic, academically-oriented psychiatrist to join our expanding child and adolescent program! Responsibilities include providing clinical services in an academic outpatient setting, offering consultation/liaison support to the University hospitals, and contributing to the didactic and supervisory component of residency and fellowship programs. Opportunities may exist for community-based contract work. Individuals must be Board-Certified or Board-Eligible in Child & Adolescent Psychiatry. Salary: DOE

For additional information and/or to apply visit www.uacareertrack.com and reference specific title from above. If you have questions, please contact:

Jessica Bodzioch
Human Resources Representative
Dept. of Psychiatry
1501 N. Campbell Avenue, P.O. Box 245002
Tucson, AZ 85724-5002
(520) 626-3819 or bodzioch@email.arizona.edu.

Review of applications is ongoing until positions are filled. **The University of Arizona** is an EEO/AA Employer- M/W/D/V.

CALIFORNIA

Outpatient Adult Psychiatrist needed for a progressive county mental health system, 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 call 209-525-6119; e-mail at umukherjee@stanbhrs.org.

BE/BC Psychiatry: DMH ASH $187-$192 per hour. DMH Coalinga $190 per hour. CDCR $171-$173 an hour and $45 an hour on call. (805) 703-3729. www.intuitivehealthservices.com.; intuitivehealthservices@intuitivehealthservices.com.

Atascadero & Coalinga state hospitals and CA Prisons looking for BE/BC Psychiatrists. $160-185/hr. Up to $44k/mo. 8-12hr/day. Wknds $42/on call. Alameda Co. up to 270k/yr. H1/J1 Welcome. Tel. (707)694-6890/(707)226-2426/(707)694-3805; Fax(415)814-5764. bayareadoctors@gmail.com

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MEDICAL DIRECTOR

The San Diego County Psychiatric Hospital is a free-standing adult facility located in the heart of the County and is a key component in the County Behavioral Health Division's continuum of care. The Medical Director can play a leading role in the development of the overall County safety net health system, and is a key medical leader in the dynamic, innovative Health & Human Services Agency. Teaching opportunities available. Requires proven leadership and supervisory skills. Interest in primary care integration helpful. Salary competitive.

CV and letter of interest can be submitted online at www.sdcounty.ca.gov/hr. For questions about the application process, please contact Gloria Brown, Human Resources Analyst at (619) 531-5117 or **Gloria.Brown@sdcounty.ca.gov**. Questions about the position may be directed to Marshall Lewis, MD, Behavioral Health Clinical Director, HHSA at **Marshall.Lewis@sdcounty.ca.gov**

Now Hiring outpatient adult or child psychiatrists at 125/ hr, up to $260,000 per year. Malpractice coverage negotiable. Please contact Tina Cavalli, tcavalli@buttecounty.net or Will Anand, M.D., wanand@buttecounty.net. 530-891-2850. J1/H1 visa applicants welcome.

Coalinga & Napa state hospitals need full time contract psychiatrists. No call. No weekends. $180/hr + malpractice. Call 661-274-9674. Fax CV to 800-758-7013 or **e-mail decy@hahacorp.com.**

CONNECTICUT

BEAUTIFUL SUBURBAN CT/ 1 1/4 HRS FROM NYC

CT licensed BC/BE Psychiatrist to join a 30 year well established multi-disciplinary practice providing adult psychiatric services. Excellent Compensation. Send CV/cover letter by fax 203-797-0877 or email: afrymd@yahoo.com.

FLORIDA

PSYCHIATRIST DELRAY BEACH, FLORIDA

South County Mental Health Center offers an exciting opportunity for a full time psychiatrist.

South County Mental Health Center is an outpatient community based mental health center located in beautiful southeast Florida. We offer a competitive salary and excellent benefits package.

CV/Resume may be faxed to:
(561)637-1005 or submitted to:
Human Resources
Email: SCMHCHR@scmhcinc.org

Psychiatrist for CSU and Detox Facility

Punta Gorda is an attractive waterfront community on Charlotte Harbor leading to the Gulf of Mexico. CBHC is the local community mental health and substance abuse provider.

CBHC is seeking a full-time FL Licensed Psychiatrist to provide psychiatric services to consumers in an 18-bed crisis stabilization unit (adults and adolescents) and a 15-bed adult detox/res facility, as well as providing some outpatient services. Work schedule is full time Monday through Friday, with some flexibility in scheduling; typically on call M-TH nights. Responsibilities include working as part of a team and documenting to an electronic medical record. Prefer exp treating co-occurring disorders; exp. in inpatient setting is also preferred. CBHC prefers that candidates be bc ~ adults and children. Competitive pay and good benefits. Must have or obtain certification to prescribe Suboxone.

For consideration, please email, mail or FAX your CV. For more information, call Dr. Matthews-Ferrari @ (941) 347-6408.

Charlotte Behavioral Health Care, Inc.
1700 Education Avenue; Punta Gorda, FL 33950
Phone: (941) 639-8300; Fax: (941) 347-6493
Email: jvanderweele@cbhcfl.org; www.cbhcfl.org
An Equal Opportunity Employer.

DAYTONA - MELBOURNE - ORLANDO - OCALA-
Psychiatrists needed for rapidly expanding Nursing Home Service. Great support. No call. Average Salary 210K + benefits. Part-time available. Some travel required. Must have FL Medicare & FL Medicaid individual provider #s. No Restrictions (H1B Candidates Considered). Call our Clinical Coordinator, Linda at 866-936-5250.

Wellington Retreat, Inc., a residential and outpatient addiction and psychiatric treatment facility, seeks a board-certified addiction psychiatrist for administrative and clinical duties. Small, private, upscale, state-of-the-art, evidence-based program with opportunity for local academic affiliation. Excellent salary and benefits. Florida licensure required. ASAM certification preferred. Please email CV to DrRobertAMoran@aol.com."

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

Atlanta Psych Consultants, an established multidisciplinary private practice strategically located in Atlanta, has an immediate need for a Child/Adolescent or Adult Psychiatrist to affiliate with 1 psychiatrist and 5 psychologists. Full service practice is located in class 'A' medical building near 3 major hospitals. Collegial atmosphere with great potential for a clinical practice through medication management for current patients, referral sharing, and joint marketing.

Please email CV to
apc@Atlantapsych.net, Attn:
Kim Oppenheimer, Ph.D.

Adult Mental Health & Forensic BE/BC Psychiatrists needed to join our interdisciplinary, inpatient facilities at Southwestern Regional Hospital in Thomasville, GA and Central State Regional Hospital in Milledgeville, GA. Adult Mental Health psychiatrist needed in Atlanta, GA! Great schedules, complete benefit package including malpractice. CBS News singled out Thomasville as top city with "outstanding in climate, housing prices and entertainment opportunities." Milledgeville has wonderful lakefront communities with plenty of water recreation and beautiful historic homes. Please email CV to ctwormley@dbhdd.ga.gov Indicate PN-jobs.

Augusta, Georgia
Growing Department Seeks General Psychiatrists for New Academic Partnership

With expanding programs and financial stability, the Department of Psychiatry and Health Behavior at Georgia Health Sciences University (GHSU) now seeks BC/BE psychiatrists to lead the expansion of a new public psychiatry partnership with the Georgia Department of Behavioral Health and Developmental Disabilities. Position will manage medical and clinical care at East Central Regional Hospital-Augusta (located only five miles from the medical school campus), a GHSU teaching facility with a 150 bed psychiatric facility, 71 forensic beds and a developmental disabilities facility caring for 300 individuals. Position will enhance teaching throughout the department by expanding the GHSU presence and enhancing core didactic and residency practical instruction in psychiatry.

Teaching components include oversight of medical and nursing students, psychiatry residents, forensic and psychotic disorders fellows, psychology interns and post-doctoral candidates. Additional educational and clinical research opportunities constitute a significant portion of the position's time. The candidate will also be expected to contribute to activities related to public policy and the regulation of psychiatry in the state of Georgia. A detailed description of the department structure, programs, research and education is provided on the departmental website. The desired candidate will have ABPN certification, be eligible for a Georgia license and possess medical management experience. The successful candidate will be appointed to the academic faculty at GHSU at a rank commensurate with experience and previous academic achievements.

Augusta, home of the Master's golf tournament and a charming Southern city, is a superb place to live! Low cost of living, close to Georgia/Carolina mountains and Georgia/Florida coast. Salary and fringe benefits package are highly competitive. GHSU is an equal employment, equal access and equal educational opportunity and affirmative action institution. It is the policy of the university to recruit, hire, train, promote and educate persons without regard to age, disability, gender, national origin, race, religion, sexual orientation or veteran status. See http://www.mcg.edu/som/psychiatry/ for more information. Contact: Stewart Shevitz, M.D., MSHA, Professor and Interim Chair, sshevitz@georgiahealth.edu (706) 721-6719.

Georgia Health Sciences University (formerly Medical College of Georgia) Augusta, GA
Growing Department Seeks New Faculty in Adult Psychiatry Program

With expanding programs and financial stability, the Department of Psychiatry and Health Behavior at Georgia Health Sciences University (GHSU) now seeks BE/BC adult psychiatrists to provide medical and clinical services in acute care areas. Positions are needed to fill clinical needs in the delivery of outpatient services, contract care with the state and local correctional facilities and to assist in the organization of emergency psychiatry services. Clinician-educator positions are available. The department, which has sustained growth and financial stability, has strong, nationally recognized training programs in general, child and adolescent, and forensic psychiatry, an internship program in health psychology, and competitively funded clinical and preclinical research. The department has inpatient adult geriatric and child units and outpatient programs of child and adolescent, schizophrenia and mood disorders, and health behavior programs. The Department of Psychiatry has a prominent role in the community, with GHSU being the only academic medical center for the region. Multiple collaborative opportunities exist. Our new public psychiatry partnership with the Georgia Department of Behavioral Health and Developmental Disabilities to manage and provide clinical care to the regional state hospital (located only five miles from the medical school campus), expands our faculty recruitment, educational and clinical research opportunities. GHSU has a strong research infrastructure including core laboratories, statistical consultation and core genetics facilities. Extensive research training program for junior faculty includes a master's program in clinical translational research and internal grant programs with generous career development awards.

Augusta, home of the Master's golf tournament and a charming Southern city, is a superb place to live! Low cost of living, close to Georgia/Carolina mountains and Georgia/Florida coast. Salary and fringe benefits are highly competitive. GHSU is an equal employment, equal access and equal educational opportunity and affirmative action institution. It is the policy of the university to recruit, hire, train, promote and educate persons without regard to age, disability, gender, national origin, race, religion, sexual orientation. Contact: Stewart Shevitz, MD, MSHA, Professor and Interim Chair, sshevitz@georgiahealth.edu; (706) 721-6719.

IDAHO

Twin Falls, Idaho
Psychiatry Opportunities

Are you currently practicing psychiatry in an unparalleled environment? Are you working with a collegial group of physicians in an area with little to no managed care and great income potential? Do you and your family have a quality of life including time and access to limitless outdoor recreation including skiing, biking, fishing, golfing, and white water rafting?

If you answered no to any of the questions above and are looking for an outstanding psychiatry opportunity, then St. Luke's Magic Valley Regional Medical Center and Canyon View Psychiatric and Addiction Services in Twin Falls, Idaho is the place for you!!

Below are a few key points about this practice opportunity that make it stand out from all other Psychiatry positions:

- Highly Competitive First Year Salary and Employment Benefits
- Future Income Potential $175K-$225K
- Little to no managed care
- 1:5 Call Schedule(with additional income potential for extra call coverage, plans to move to a 1:6 rotation)

For details on this exceptional opportunity please call:

Caryn Grossman
St. Lukes Health System
Physician Recruitment
1-800-723-4852 or email drcareers@slhs.org
stlukesonline.org

ILLINOIS

Seeking a board certified psychiatrist for the Medical Director position at **McFarland Mental Health Center, Springfield, Illinois**, a Joint Commission accredited state psychiatric inpatient hospital serving forensic and civil adults. Candidate must possess strong clinical and administrative skills and experience. Compensation is competitive with comprehensive benefit package.

Interested candidates contact Karen Schweighart, Hospital Administrator, at 217-786-6994 or E-mail: Karen. Schweighart@illinois.gov.

SPRINGFIELD - Medical Director - Child Psychiatric Hospital. Academic affiliation & training site. Salary, benefits and bonus opportunity. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

KANSAS

Psychiatrist for Kansas Outpatient Community Mental Health Center. No on-call. Integrated model with primary care. NHSC loan repayment eligible. Benefits package with KPERS retirement. KS licensure preferred and Board eligible. EOE. Contact Blair at 620-332-1996. See us at **www.fourcounty.com**.

KENTUCKY

ADULT PSYCHIATRIST

Full-Time position available immediately for Adult and Child Psychiatric outpatient services**@ Blanchfield Army Community Hospital, FT Campbell, KY, home of the legendary 101st Screaming Eagle (Air Assault) Division**.

Psychiatrists will have the opportunity to provide a critical service to Soldiers and their families during this pivotal time in United States History. Substantial benefit package is available, which includes 10 paid holidays, time off during all federal holidays, opportunities for paid trainings, annual & sick leave, Thrift Savings (401K), retirement, health & life insurance. Recruitment Incentive also available.

Contact:
Pam Elston at Human Resources Division
@ 270-798-8009/8031Fax: 270-956-0035.

Child and Adolescent Psychiatrist - Fort Campbell, Kentucky

Work as a civilian Child and Adolescent Psychiatrist at **Blanchfield Army Community Hospital** and help serve those who serve our country! We are seeking a BC/BE Child and Adolescent Psychiatrist for an immediate full-time opportunity at **Fort Campbell, KY** located one hour from Nashville, TN.

As a psychiatrist for our School Based Mental Health Services, you will have the unique opportunity to care for Children and Families of Active Duty members within the school and clinic settings. Expect a 40 hour work week with infrequent on-call duty. Salary is commensurate with experience at the GP-15 level and a full package of Federal benefits is available including retirement, health and life insurance, long term care insurance, leave and savings plan (401 K equivalent).

Contact:
Pam Elston at Human Resources Division
@ 270-798-8009/8031; Fax: 270-956-0035.

LOUISIANA

CHILD PSYCHIATRISTS

THE DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for BE/BC child psychiatrists at the instructor or assistant professor level, salary commensurate with experience. Clinical responsibilities available in the areas of consultation liaison psychiatry, community based child and adolescent psychiatry, and early childhood mental health. Teaching responsibilities include the supervision of residents, clinical psychology fellows and interns, and medical students rotating through the clinical facilities serviced by this position as well as the presentation of grand rounds and participation in the didactic series in child psychiatry. Clinical research is strongly encouraged. The persons selected must be professionally competent and be board eligible/certified in general psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at TulaneUniversity Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until a suitable qualified candidate is found.

Send CV and list of professional/academic references to Charley Zeanah, Jr, MD, Professor and Vice Chair, Child and Adolescent Psychiatry, Tulane University School of Medicine, Department of Psychiatry and Behavioral Sciences, 1440 Canal Street TB52, New Orleans, LA 70112 (czeanah@tulane.edu).

Tulane is strongly committed to policies of nondiscrimination and affirmative action in student admission and in employment.

View the classifieds online at pn.psychiatryonline.org

DEPARTMENT OF PSYCHIATRY AND BEHAVIORAL SCIENCES, TULANE UNIVERSITY SCHOOL OF MEDICINE in New Orleans, LA, is recruiting for several general and forensic psychiatrists (clinical track) for our growing department, at the Assistant/Associate Professor level, salary commensurate with experience. Candidates must have completed an approved general psychiatry residency and be board certified/eligible in general psychiatry and forensic psychiatry, respectively. Responsibilities will include direct patient care, teaching of medical students and house officers, and research (clinical and basic science) at various state hospitals, state correctional institutions, and at Tulane University Health Sciences Center. Time allocations will be based upon individual situations. Applicants must be eligible to obtain a Louisiana medical license. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Applications will be accepted until suitable qualified candidates are found.

Email (winstead@tulane.edu) or send CV and list of references to Daniel K. Winstead, MD, Heath Professor and Chair, Department of Psychiatry and Behavioral Sciences, Tulane University School of Medicine, 1440 Canal Street TB48, New Orleans, LA 70112. For further information, you may contact Dr. Winstead, at 504-988-5246 or winstead@tulane.edu.

Tulane is strongly committed to policies of nondiscrimination and affirmative action in student admission and in employment.

ADULT PSYCHIATRIST
Full Time Faculty Position LSUHSC School of Medicine

The Department of Psychiatry of the Louisiana State University Health Sciences Center (LSUHSC) School of Medicine at New Orleans is seeking candidates for a full-time, clinical track assistant professor to support our expanding residency program and our clinical programs. Successful candidate must be BC/BE in Psychiatry and eligible for or licensed to practice in Louisiana. This is an excellent opportunity to be an integral part of evolving programs in Public/Community Psychiatry Systems of Care within the Department of Psychiatry. This position includes involvement in undergraduate medical education, as well as resident and fellowship training. There are also excellent opportunities available for clinical research, including clinical trials; collaborative efforts with the Department of Neurology and with the Neuroscience Center of Excellence and the Alcohol Research Center are encouraged.

Interested applicants should forward a CV and cover letter electronically to ctorre@lsuhsc.edu. LSUHSC is an equal opportunity, affirmative action employer.

FORENSIC PSYCHIATRY FELLOWSHIP DIRECTOR

The Department of Psychiatry and Behavioral Sciences at Tulane University School of Medicine is recruiting a forensic psychiatry fellowship training director for a full-time faculty position. The candidate selected for this position will assume the responsibilities for the Directorship of the fully accredited Forensic Fellowship Program. He/she will lead the forensic team responsible for supervision of residents, forensic fellows, and medical students during their rotations at Feliciana Forensic Facility and in various state mental health facilities where they will provide clinical services. He/she must be professionally competent and be board certified in general psychiatry and in forensic psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Salary will be competitive and commensurate with the level of the candidate's academic appointment. We will continue to accept applications for this position until a suitable qualified candidate is identified.

Qualified applicants should send email of interest, updated CV and list of references to John W. Thompson, Jr, MD, Professor and Vice Chair for Adult Psychiatry, Director of the Division of Forensic Neuropsychiatry at jthomps3@tulane.edu.

Tulane is strongly committed to policies of nondiscrimination and affirmative action in student admissions and in employment.

MAINE

BE/BC Adult and Child Psychiatrists
Acadia Hospital, the nation's first Psychiatric Magnet Hospital, is a 74 bed community-based, full service psychiatric hospital located in Bangor, Maine. We are currently recruiting for BE/BC adult and child psychiatrists to cover our inpatient and outpatient units. We offer acute psychiatric care for adults and children, as well as substance abuse programs, and have recently opened a 10 bed psychiatric observation unit. Acadia Hospital is a teaching site for Tufts and University of New England medical schools. Positions are tailored to specialty interest. Acadia Hospital offers a competitive salary, full benefits, moving expenses and a loan repayment program. The area offers an international airport, symphony, and the University of Maine flagship campus. Four season outdoor activities include boating, hiking, biking, skiing and golfing. The area includes excellent school systems, affordable housing and a safe living environment. Bangor is located less than one hour from Acadia National Park and two hours New England's largest ski resorts. Acadia accepts and supports candidates working toward/on a J-1 Visa Process. Contact: Nancy Barrows at nbarrows@emh.org or apply on line at www.acadiahospital.org - careers.

MAINE COAST - OUTPATIENT PSYCHIATRY. Pen Bay Medical Center seeks a full-time BC/BE adult psychiatrist with qualifications and/or interest in addiction medicine to for our hospital-employed, community-based integrated behavioral health network. Join a collegial team to serve a diverse client base. Competitive salary and comprehensive benefit package, including loan repayment program. Enjoy Maine's spectacular natural beauty, four-season outdoor recreation, rich cultural opportunities, great schools & safe communities.

Contact John Bragg at jbragg@penbayhealthcare.org or (207) 596-8214.

MARYLAND

Eastern Shore Hospital Center, Cambridge, Maryland is seeking both a Clinical Director and a Board-certified psychiatrist for this 76-bed, state-of-the-art Joint Commission accredited state psychiatric facility located on Maryland's Eastern Shore. ESHC provides outstanding care to those with chronic/severe mental illness, including many who are court committed for evaluation/treatment. Live near the Chesapeake Bay where you can enjoy sailing, crabs, beaches, quaint towns, and the best of country living, all within 90 minutes of the academic and cultural resources of Baltimore and Washington, D.C. Clinical Director is responsible for the development, maintenance, and supervision of all clinical service operations, including recruitment, training, supervision, and evaluation of medical staff and clinical department heads; overseeing the process of credentialing and privileging; providing leadership in performance improvement activities; establishing policies and procedures; and ensuring that patient care is delivered in accordance with Joint Commission standards. Board-certified psychiatrist provides direct patient care on a 20-bed inpatient unit and leads a multidisciplinary team to provide patient-centered, recovery-based case. Clinical Director - minimum 3-5 years of administrative or supervisory experience. State benefits and leave package. EOE. Facility is located in designated Health Professional Shortage Area.

Please send CV to Cassandra Stanley, Personnel Administrator, Eastern Shore Hospital Center, P. O. Box 800, Cambridge, MD 21613. For questions call 410-221-2330 or e-mail cstanley@dhmh.state.md.us.

Psychopharmacology/Clinical Trials Psychiatrist

WASHINGTON DC AREA, 15 minutes from National Institutes of Health. Busy, expanding outpatient practice, clinic + psychopharmacology trials, long-established. Opportunity for substantial practice, with excellent financial profile. No hospital obligations. Fluency in Spanish a plus. Possibilities for university connections. Send your CV via fax: 703-907-1093 or email: lfox@psych.org. Attn: Job #225284.

PSYCHIATRIST

BE/BC Child/Adolescent Psychiatrist/Medical Director needed 20-40 hours a week for outpatient community mental health facility on Maryland's Eastern Shore, approximately one hour fifteen minutes from the Balto-Wash. Area.

Send resume/vitae with cover letter to Michael Campbell, LCSW-C, Director, Caroline Co. Mental Health Clinc, P.O. Box 10 Denton, Md. 21629, phone 410-479-3800 ext 117, fax 410-479-0052 or e-mail mikecampbell@dhmh.state.md.us EOE.

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

Full time outpatient psychiatric position at The Univ of Md., College Park Health Center. Primarily responsible for prevention, diagnosis and treatment of mental health disorders in college students. Apply online: https://jobs.umd.edu/applicants/Central?quickfind=53934; posting #100375.

MASSACHUSETTS

Boston area—Northeast Hospital Corp, a local nonprofit medical and psychiatric system on Boston's North Shore, has openings for full time and part time inpatient attending psychiatrists and night/weekend on call psychiatrists at Bay-Ridge Hospital and Beverly Hospital. The Hospitals are teaching sites for Boston University School of Medicine, and for the inpatient psychiatrist positions, there is no required night call, a competitive salary, and a full benefit package including generous time off as well as reimbursement for malpractice insurance and CME expenses. The lucrative night/weekend on-call opportunities can be scheduled to fit your needs, and both on-site and call from home options are available.

Contact Barry Ginsberg, M.D., Chief and Administrative Director, NHC Dept. of Psychiatry, 60 Granite Street, Lynn MA 01904. Phone (781) 477-6964, Fax (781) 477-6967, email bginsber@nhs-healthlink.org.

WORCESTER, DIRECTOR OF CLINICAL AND PROFESSIONAL SERVICES, The University of Massachusetts Medical School, Division of Public Sector Psychiatry is seeking an experienced, board certified psychiatrist to serve as CLINICAL LEADER at the closely affiliated Worcester State Hospital (WSH). Worcester State Hospital is a JACHO accredited Department of Mental Health hospital, providing inpatient services to patients who require intermediate and long term care for severe and persistent mental illness and/or acute forensic evaluations. WSH is a short walk from the medical school and the Brudnick Neuropsychiatric Research Institute is contiguous with the hospital. The Director of Clinical and Professional Services serves as a member of the hospital leadership, provides supervision to other

psychiatrists, and performs clinical consultations and other patient services as needed. Candidates should have a career interest in Public Sector Psychiatry. Research interest and experience would be an added qualification. Faculty appointment and teaching at the medical school and at WSH (rotation site for 3rd year medical students and PGY 2 residents) is part of the job.

Send letter of interest and C.V. to Jeffrey Geller, MD, MPH, Director, Public Sector Psychiatry, UMMS, 55 Lake Avenue North, Worcester, MA 01655 or to jeffrey.geller@umassmed.edu. AA/EOE.

WORCESTER, The University of Massachusetts Medical School, Division of Public Sector Psychiatry is seeking a psychiatrist with a career interest in Public Sector Psychiatry for a position at Worcester State Hospital. Worcester State Hospital is a short walk from the Medical School so research and teaching opportunities are easy to accommodate and actively encouraged. Faculty appointment at appropriate rank, competitive salary and excellent benefits.

Send letter of interest and C.V. to Jeffrey Geller, MD, MPH, Director, Public Sector Psychiatry, UMMS, 55 Lake Avenue North, Worcester, MA 01655, email Jeffrey.Geller@umassmed.edu, or fax 508-856-3270. UMMS is an affirmative action, equal opportunity employer.

Starr Psychiatric Center seeks a 20-40 hr psychiatrist for dynamic established psychiatric practice On Boston's South Shore. Medical model, multi-disciplinary staff. Stimulating environment, good pay. Clinic has a reputation for successful care, where others have failed. Email davidzstarr@juno.com or call 508.580.2211.

CAMBRIDGE: Consultation Liaison Psychiatry Position

PSYCHIATRIST: Cambridge Health Alliance is seeking a half- to full-time psychiatrist to join our Consultation-Liaison Psychiatry Service serving a multi-ethnic and diverse patient population. The position will include some inpatient work but will be focused on outpatient work and program development within Women's Health, Medical Specialty, and Primary Care Clinics. 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 medicine, make this an ideal opportunity for candidates interested in integrated medical and psychiatric care with underserved populations. We have strong training programs in Primary Care, Adult and Child Psychiatry, and Psychosomatic Medicine and innovative educational programs for medical students. These programs provide 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.

Unique Career / Financial Opportunity

The Figman Psychiatric Group is a multidiscipline, for profit, out patient clinic in the Raynham Woods Medical Center (near Boston and Providence) with over 2,000 active patients and, on average, fifteen to twenty new referrals each week. I seek a highly qualified, energetic psychiatrist with entrepreneurial skills and a long term vision to become partner and within ten years, as I retire, owner of the practice.

Contact **Robert Figman, M.D.** at nfigman@gmail.com or 617-201-8935 to learn of a very lucrative, creative financing plan resulting in ownership. This is not an offer to sell the practice.

MISSISSIPPI

MERIDIAN: Adult Psych & Addiction Services- Private Inpatient and Outpatient Treatment Facility. Directorship opportunity with top range salary, benefits and bonus potential. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com

MISSOURI

Child and Adolescent Psychiatrist - The Department of Psychiatry, University of Missouri-Columbia, is seeking 2 full-time, board certified or board eligible Child and Adolescent Psychiatrists:

- A full-time person to work in **The Thompson Center for Autism**. The position will include clinical care, participation in research (particularly psychopharmacological and neuroimaging studies) as well as supervision of child and adolescent psychiatry fellows. Candidates should have a strong interest in autism and neurodevelopmental disorders and welcome the opportunity to work collaboratively with a multidisciplinary group of clinicians and investigators in an academic setting.

- A full-time person to work in **The Missouri Psychiatric Center**. Providing services as the primary inpatient attending for the 12 bed Child and Adolescent unit.

Both positions will be on the clinical track with a title of Assistant, Associate, or Professor of Clinical Psychiatry. Salary range will be $165,000-$185,000, depending on qualifications, plus employee benefit plan. Send inquiries to Laine Young-Walker, M.D., Director of Child and Adolescent Division, Department of Psychiatry, University of Missouri Hospital and Clinics, One Hospital Drive, DCO67.00, Columbia, MO 65211 by July 30, 2011 or until filled. The University of Missouri-Columbia is committed to cultural diversity and it is expected that successful candidate(s) will share in this commitment. MU is an equal opportunity/AA institution and encourages applications from women and minority candidates. The University of Missouri-Columbia complies with the Americans with Disabilities Act of 1990. If you have a disability and need accommodations in the job application process, please contact Richard Erwin, by phone at (573) 882-6277 or by E-mail at Erwinrw@health.missouri.edu.

NEVADA

Horizon Health, in partnership with **Northeastern Nevada Regional Hospital in Elko, NV**, has an exciting opportunity for a **Medical Director** for a **16-bed** Geriatric Inpatient Psychiatric Program. Excellent income and quality of life! State-of-the-Art facilities, and complete program support with full complement of staffing to include: Nursing, Social Work, Therapy, and Marketing. For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

Las Vegas: General Psychiatry. Well established private practice with high patient volume seeking additional Psychiatrist. Candidate would have immediate case-load and unlimited growth potential with nursing home consults. Excellent income potential and office sharing agreement. Contact Kelly Morgan, In-house recruiter, 866-227-5415 x225, fax 866-758-3649, kellyj.morgan@uhsinc.com.

NEW JERSEY

CATHOLIC CHARITIES
DIOCESE OF TRENTON

- **Child Psychiatrist-PT (Burlington, NJ)**
- **Adult Psychiatrist-PT (Trenton, NJ)**

Seeking **part-time** Board Certified / Board Eligible Psychiatrists to perform work in a warm, collegial environment. The Psychiatrists will provide psychiatric evaluations and medication management. Will also be responsible to collaborate with therapists and other staff. Must be licensed in NJ and maintain individual malpractice insurance.**Competetive rate and flexible schedule.**

Please email your resume to: HR@cctrenton.org. To learn more about the organization, please visit our website at: **www.catholiccharitiestrenton.org**. EOE/AA.

OPPORTUNITY to start private practice @ no cost, Summit NJ. Office with a great view in a prestigious medical center adjacent to Overlook Hospital. Psychiatrist in pre retirement phase needs easy transition for patients. TURN KEY. 908/522-3099, tedshah@gmail.com.

NEW MEXICO

LAS CRUCES: Medical Director -Private behavioral health hospital with I/P, RTC and O/P services. Highly competitive salary, benefits and bonus opportunity package. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

NEW YORK CITY & AREA

Child and Adolescent Psychiatrist
P/T - 10-15 hours per week (evenings and/or weekends) in a Child and Family Mental Health Center in Brooklyn. Excellent compensation. No call. Fax resume to (718) 553-6769, or email to clinicaldirector@nypcc.org

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Exceptional Career Opportunity!
Long Island College Hospital
Department of Psychiatry
97 Amity Street, Brooklyn, NY. 11201

Long Island College Hospital, a 500 bed general hospital located in Brooklyn Heights, seeks BC/BE psychiatrists for the following:

- Moonlighting Positions Available: Weekdays, Nights, and Weekends!

We seek highly motivated and committed physicians; and offer a competitive salary/benefits package. Please email your resume to: cluther@chpnet.org, or fax to: (718) 780-1827; Attn: Charles Luther, M.D.

We are committed to diversity and equal opportunity.

PHS

Work for the national leader in correctional healthcare services.
PRISON HEALTH SERVICES...

The largest correctional healthcare provider in the U.S. provides healthcare services for inmates at **Rikers Island in Queens, NY.**

Correctional medicine offers work independence, diversity of duties, continuity of care and an opportunity to provide care to the underserved and in need of help.

Make a Difference...
- Looking for new challenges?
- Want to make a real difference?
- Have questions about this unique environment?

PSYCHIATRISTS
FULL TIME/PART TIME/PER DIEM. FLEXIBLE SHIFTS

Prison Health Services Medical P.C. invites you to join its substantial, comprehensive, multidisciplined M.H. team at Riker's Island.

Tours: 8am-4pm; 4pm-12am; 12am-8am with some flexibility. Salaries and benefits are competitive.

For more info please contact: David Rosenberg MD, Supervising Psychiatrist, Tel: 646 717 4061, or email us your resume: PHSNYC@riepf.com.

PRISON HEALTH
MEDICAL SERVICES, PC
49-04 19th Ave., Astoria, NY 11105
PHS is an Equal Opportunity Employer
M/F/D/V

ALBERT EINSTEIN COLLEGE OF MEDICINE
Of Yeshiva University
Department of Psychiatry and Behavioral Sciences

The Sound View Throgs Neck Community Mental Health Center

PSYCHIATRISTS - Two Full-Time - Adult Outpatient Program. This Program seeks psychiatrists experienced in diagnostic evaluation and psychopharmacology to provide clinical care, supervise a team and teach medical students, psychiatry residents and clinical fellows. New York State License, Board Certified/Board Eligible in Psychiatry. DEA Registration. These positions carry a faculty appointment. Knowledge of Spanish a plus.

In return for your expertise, we offer a competitive salary, outstanding benefits package and a professional work environment offering career growth potential.

For consideration, please submit your CV with salary history to: Thomas F. Betzler, M.D., Executive Director, Sound View Throgs Neck Community Mental Health Center, 2527 Glebe Avenue, Room 304, Bronx, NY 10461; Fax: (718) 931-7307; Email: thomas.betzler@einstein.yu.edu. Equal Opportunity Employer.

PSYCHIATRISTS

Mercy Medical Center, located in **Rockville Centre, LI**, has excellent full time opportunities available for our Inpatient Psych Unit. Private practice opportunities also available. Must be a BC/BE Psychiatrist.

Excellent salary and benefits. Please apply online at: www.mercymedicalcenter.info or fax to: (516) 705-2584, Attn: HR. EOE.

NEW YORK STATE

Practice In the Perfect Place: Saratoga Springs, NY

Saratoga Hospital seeks BE/BC, NYS-licensed psychiatrists for a full time inpatient position. This is an opportunity to work with a close-knit, experienced, multi-disciplinary care team on a 16-bed adult inpatient unit and with emergency department and hospital staff for consultation liaison service. Participate in reasonable hospital inpatient call schedule, 1:6, with plans to expand call pool. The compensation and benefit package is competitive.

Our Location is a destination, just a half hour from Albany, three hours from New York City, Montreal and Boston. Saratoga Springs is a family-oriented community known for its restaurants and local shops, neighborhoods, and excellent schools. World-class entertainment, culture, and recreational opportunities are abundant in and around Saratoga Springs!

Contact: Denise Romand, Saratoga Hospital (518) 583-8465, email: docfind@saratogacare.org. Visit us at www.saratogahospital.org or our community at www.saratoga.org.

Western New York-Chautauqua Region: Jamestown Psychiatric PC is seeking a Psychiatrist to join our rapidly growing Adult and Child Psychiatric team. Competitive salary and flexible growth opportunities are offered. We will offer a starting bonus to eligible candidates. Loan repayment, J1 or H1 assistance available. Please contact Mrs. Linda Jones, office manager @ lj@psychwebmd.com or Phone 716-483-2603. Fax CV and qualifications to 716-483-2828.

NORTH CAROLINA

Adult Staff Psychiatrists

Charlotte, NC

Carolinas HealthCare System has unique opportunities for Adult Staff Psychiatrists at its Behavioral Health Center. The center is part of a 874- bed regional teaching facility nestled in the heart of Charlotte. Join an outstanding team of psychiatrists in a very collegial working environment.
Adult Staff Positions - Inpatient and outpatient work.
Excellent benefits package which includes:
- **Two weeks CME**
- **Paid vacation**
- **Short and long-term disability**
- **401K, 457B and pension plan**

Opportunity for extra income by seeing private patients or by taking shifts in the ER
Interested applicants should email their CV to Elaine Haskell at: elaine.haskell@carolinashealthcare.org for more information.

EOE/AA

FirstHealth OF THE CAROLINAS

PSYCHIATRIST
Behavioral Services

FirstHealth of the Carolinas is a leading healthcare system that puts patients first. We are seeking a Psychiatrist at Moore Regional Hospital in **Pinehurst, NC**.

Position responsible for performing general adult psychiatry in our hospital based outpatient program and will also provide backupcoverage for psychiatry group and inpatient units.

To qualify you must be a graduate from an accredited school of medicine and residency program in Psychiatry. Must be able to successfully complete medical staffcredentialing at Moore Regional Hospital. Active NC Medical License required.

For more information and to apply online, please visit www.firsthealth.jobs. An equal opportunity employer.

CARF accredited, fast growing, private psychiatric practice is seeking a psychiatrist to join six other psychiatrists, five nurse practitioners, one physician assistant, five doctorate level psychologists, and sixteen master level therapists. Candidate must be a MD or equivalent and have North Carolina Medical License; completed residency in an accredited psychiatry program and be Board eligible or (maintained) Board certified with the American Board of Neurology and Psychiatry. All psychiatry specialists or subspecialists are welcome - adult, child or adolescent. J-1 / H1 Visa applicants are welcome. Outpatient, in-patient, and combination of both are available. Psychiatrists will also provide consults; on-call and some weekend duty may be required.

Our Coastal Community:
- Close to the beach
- Growing Population of 154,579
- 30 Miles of Wide, Unspoiled Beaches on Atlantic Ocean
- Coastal Activities Offer Unique Shopping and Family Entertainment
- Ranked 24th Out of 301 Surveyed Metropolitan Areas as **"Best Place to Raise a Family"** According to Reader's Digest
- 6 Private Schools Available and Excellent Public Schools

Benefits:
- Competitive salary; range of $200K to $350K annually
- Excellent benefit package, including professional liability insurance.

Send CV's to blind.ad.nc@gmail.com.

NORTH DAKOTA

North Dakota - Sanford Health Fargo Region is expanding its Child/Adolescent Behavioral Health Services and currently seeking a **Child/Adolescent Psychiatrist** interested in a rewarding practice as well as department chair leadership. The department is staffed with three child psychiatrists, four child psychologists, one child and adolescent trained psychology resident and one master level therapist. Located in Fargo, ND, this outpatient practice includes opportunity for practice in both the behavioral health clinic and in a collaborative model with Sanford pediatricians at two clinic locations. Sanford psychiatrists also have the opportunity to teach University of North Dakota psychiatry residents. To learn more about Sanford Health Fargo visit: **www.sanfordhealth.org**.

Fargo, ND is a metropolitan, tri-college community of 190,000 where high quality elementary and secondary education is a priority. Close proximity to Minnesota lake country offers access to a multitude of four season outdoor activities. To learn more about the Fargo community visit: www.culturepulse.org and www.fmchamber.com.

Contact:
Jean Keller, Physician Recruiter
Sanford Physician Placement
Phone: 701-280-4853, Fax: 701-280-4136
Email: Jean.Keller@sanfordhealth.org. Visit our website at
EOE/AA Not subject to H1 Caps.

OHIO

Addiction Psychiatrist

The Department of Psychiatry at The MetroHealth System, a major teaching hospital of Case Western Reserve University, is expanding under the leadership of the new Chair, Ewald Horwath, M.D. We are currently seeking a board-certified (or board eligible) addiction psychiatrist, who will provide clinical care, teaching of residents and students and have the opportunity for academic and career development at the largest medical research institution in Ohio and a top1% ranked hospital. Benefits include a competitive salary, incentive potential, health insurance, paid time off, liability insurance, an academic appointment and CME opportunities.

In employment, as in education, MetroHealth System and Case Western Reserve University are committed to Equal Opportunity and World Class Diversity. Please send CV and a letter outlining clinical and academic interests to ehorwath@metrohealth.org.

Child and Adolescent Psychiatrist

The Department of Psychiatry at The MetroHealth System, a major teaching hospital of Case Western Reserve University, is expanding under the leadership of the new Chair, Ewald Horwath, M.D. We are currently seeking a board-certified (or board eligible) child and adolescent psychiatrist, who will provide clinical care, teaching of residents and students and have the opportunity for academic and career development at the largest medical research institution in Ohio and a top1% ranked hospital. Benefits include a competitive salary, incentive potential, health insurance, paid time off, liability insurance, an academic appointment and CME opportunities.

In employment, as in education, MetroHealth System and Case Western Reserve University are committed to Equal Opportunity and World Class Diversity. Please send CV and a letter outlining clinical and academic interests to ehorwath@metrohealth.org.

Part-time Child Psychiatrist

The person in this position is responsible for performing psychiatric assessments and delivering psychiatric services to Southeast clients. This person also is responsible for making referrals for medical evaluations and follow-up with clients' test results. Consultation with Medical Director, Associate and Clinical Directors and other Southeast staff members is also an important function of this position.

We offer many great benefits, including health, dental, vision, 401(k), an on-site fitness room, and generous time off. If you are interested in learning more about opportunities available at Southeast, Inc. send resume to: Southeast Inc., HR Dept., 16 W. Long St., Columbus, OH 43215 or e-mail at hr.applications@southeastinc.com. EOE.

CLEVELAND: Child Psychiatrist - Inpatient Services. Salary, benefits, bonus opportunity. Phone call only 1:5. Estabilised programs and collegial staff. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

PENNSYLVANIA

Psychiatrists:

Currently we have exciting full- and part-time positions in a rapidly expanding department. Opportunities include responsibilities in and outside our five-hospital health system. There are immediate openings for child/adolescent, adult and addictions psychiatrists.

There are also practice options in a traditional psychotherapy model. Psychiatric Hospitalist positions are available for weekday and weekend rounding and Crisis. Excellent salaries, no on-call nor rounding responsibilities ever and exceptional benefits package offered. Send CV to Kevin Caputo, M.D., Vice President and Chairman, Department of Psychiatry, Crozer-Keystone Health System, One Medical Center Blvd., Upland, PA 19013 or contact the department manager, Kathy Waring at 610-619-7413.

Warren State Hospital has two immediate openings for Staff Psychiatrist position(s). The Joint Commission accredited Pennsylvania state-run 190 bed adult psychiatric facility is located a short distance from Erie, PA in Northwestern Pennsylvania. Applicant must be Board Certified or Board Eligible. Benefit package includes full-time benefits, including healthcare with dental and vision coverage, as well as life insurance and a retirement plan. Competitive salary. Pennsylvania State Civil Service covered position.

Interested candidates fax CV to Asha Prabhu, MD at (814)726-4447 or call (814)726-4189 - aprabhu@state.pa.us or contact: Human Resources -WARREN STATE HOSPITAL- 33 Main Drive- N. Warren, PA 16365 mlodowski@state.pa.us.

The Commonwealth of Pennsylvania is an Equal Opportunity Employer/Program.

PENNSTATE HERSHEY
Milton S. Hershey Medical Center

The Penn State Department of Psychiatry is recruiting psychiatrists for its growing department. With our clinical partner, Pennsylvania Psychiatric Institute, the Department staffs four clinics, with outpatient and partial hospital programs for children and adults, 58 adult and 16 child/adolescent beds, ECT and other neurostimulation services, and psychiatric consultation for 3 hospitals. Our current psychiatry faculty numbers 52, with planned increases, plus 24 residents and fellows. We have a growing research portfolio, with basic and clinical research and close collaboration with allied neuroscience disciplines at several Penn State campuses. We plan expansion in teaching programs as well.

Successful candidates should have strong clinical and teaching skills and, optimally, potential for scientific and scholarly achievement.

Candidates with interest and skills in these areas should send a curriculum vitae and cover letter to:

Alan J. Gelenberg, M.D.
Professor and Chair
Penn State Hershey Medical Center
Department of Psychiatry, H073
500 University Drive, P.O. Box 850
Hershey, PA 17033
Phone: 717.531.8516
Fax: 717.531.6491
agelenberg@hmc.psu.edu

Penn State Hershey Medical Center is committed to affirmative action, equal opportunity and the diversity of its workforce

PHILADELPHIA
General Psychiatrists - Adult Inpatient Services and Admission/Intake Services - no call.
Child Psychiatrists - Inpatient / RTC position and Partial Hospital O/P only (can be part-time). Salary, benefits, bonus opportunity offered. Contact Joy Lankswert, In-house recruiter @ 866-227-5415 OR email joy.lankswert@uhsinc.com.

Stroudsburg, PA

Full time outpatient Adult/Child Psychiatrist, ISL Psychiatric Services is looking to recruit additional psychiatrists to join our excellent group of 20 psychiatrists and other mental health workers. Starting salary of 170k and an excellent benefit package. Please send CV to (570) 424-6271, or call (570) 424-6187.

TENNESSEE

PSYCHIATRIST

Western Mental Health Institute, a Joint Commission accredited psychiatric hospital with an all board certified medical staff, has an opening for a full time BE/BC psychiatrist. All patient services are delivered in a newly built state of the art hospital located in a beautiful country setting only 65 miles east of Memphis, TN. Competitive salary: 37.5 hour work week, opportunity to earn significant additional income through voluntary on-call system. Excellent State benefits including an employer funded benefit pension plan. Contact Rita Kennedy at 731-228-2028 or e-mail to rita.kennedy@tn.gov.

Can you go home and leave your work behind?

Your relocation comparison checklist:

- Paid malpractice coverage
- 37.5 hour work week
- 100% employer funded pension
- 80% of health insurance premiums covered
- No state or city income tax
- Most competitive state for business
- 5th best state in the nation for Quality of Life
- 2nd best state in the nation for the business climate
- **2009 "State of the Year"** for the number of new jobs created

Lakeshore offers all this and more. Lakeshore has a full-time position open for a BC/BE Psychiatrist in a 115-bed facility with a mountain view setting overlooking the picturesque Tennessee River. Lakeshore is located in Knoxville, Tennessee, one of the most affordable cities in the U.S.

Nestled in the foothills of the Great Smoky Mountains National Park, rugged mountains, lush valleys, abundant fresh-water fishing streams and lakes and breath-taking vistas plus miles of hiking trails, dozens of campsites and boundless opportunities to "get away from it all" are just minutes from downtown.

Knoxville is also home to a rich arts community, diverse range of restaurants and entertainment, shopping and sporting events, and the Southeast's booming high-tech Innovation Valley. Knoxville and the Innovation Valley truly provide cosmopolitan amenities with a hometown atmosphere. With several of the state's top ranked primary/secondary schools, and the highly rated flagship campus of the University of Tennessee, East Tennessee offers a topnotch education for everyone.

Earn extra money through voluntary on-call coverage. Excellent benefits which includes malpractice coverage, 100% employer funded pension, 401k tax deferred retirement with employer contribution, health insurance, paid sick leave, paid vacation, paid time off for CME, and 11 paid holidays per year.

Contact Bert Simpson, MD, Clinical Director, today to discuss this unique opportunity at (865) 583-8768. Come enjoy your work and enjoy your life. Pre-employment drug testing required. The State of TN is an Equal Opportunity, Equal Access, Affirmative Action Employer.

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. 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.

VERMONT

Inpatient/Outpatient Psychiatry

Exciting opportunity to practice in a well established, hospital based Psychiatry Department. Fulltime, employed position with excellent benefits at second largest hospital in the state, and among the highest salaries offered in the state. 19 bed inpatient unit, and new outpatient program. Weekend call 1:6, week nights 1:5 with overnight phone call only. Strong crisis team covers intake in ED.

Enjoy the magic of classic New England towns, quiet roads, and make Vermont your year round home. Imagine yourself in the vibrant beauty of our fall foliage, the warmth of ending a day of skiing by a roaring fire, or a lazy summer day on a lake. Only hours from NYC, Boston & Montreal. Send CV to Rebecca Banco, Inhouse Physician Recruiter for Rutland Regional Medical Center, bbanco@rrmc.org.

VIRGINIA

Board Eligible/Board Certified Full time Psychiatrist

The City of Chesapeake VA, Community Services Board is seeking a Full Time Psychiatrist. You will provide vital psychiatric services to include psychiatric evaluations, ongoing medication management, crisis intervention sessions, as well as individual, family, and group services as needed. Coordination/collaboration of care is required with a variety of staff, family members, guardians, and other concerned parties. M.D. or D.O. degree with completion of residency in psychiatry and progressively responsible experience in providing outpatient/hospital psychiatric services are required. Applicant must possess a current, valid license to practice medicine in the Commonwealth of Virginia and a current, valid DEA Registration. Board Certification in psychiatry is preferred but will consider Board Eligible applicants. The City of Chesapeake provides an excellent benefit package. Salary is competitive and commensurate with experience. View application at **www.jobs.cityofchesapeake.net**. For questions call 757-547-9334, ask for George Ennelf. Deadline 6/15/11.

CSB/District 19 - Community Psychiatrist Position: F3211

ACADEMIC AMBULATORY PSYCHIATRY: VA Commonwealth University recruiting BE/BC Psychiatrist with community psychiatry and academic career interests to provide outpatient clinical care and supervise/teach residents/medical students. The clinical experiences include: City community psychiatry clinic and hospital-based teaching clinic. VCU Department of Psychiatry employs over 80 fulltime faculty and has well-funded research in genetics, addictions, child and women's mental health and psychopharmacology. VCU is a large urban university with robust health science campus and 750-bed university hospital. Richmond, the State Capital, has moderate climate and rich mix of history with modern facilities, excellent suburban housing, public/private schools. J-1 applicants welcome.

Send CV to Tammy M. Newcomb, Human Resources, Department of Psychiatry, VCU, Box 980710, Richmond, VA 23298 (Fax 804-628-1247). VCU is an Equal Opportunity/Affirmative Action employer. Women, minorities, and persons with disabilities are encouraged to apply.

WEST VIRGINIA

Psychiatrist, BC/BE, treating primarily children & adolescents for practice w/ locations in Huntington, Wayne, & Branchland, West Virginia. Outpatient & inpatient responsibilities. Send CV to Jerri Tyson-Rollins, Prestera Center for Mental Health Services, Inc., 5600 U.S. Rt. 60 East Huntington, WV 25703.

SWEEPING CURVES, ROLLING HILLS AND SCENIC MOUNTAIN VISTAS MAKES WEST VIRGINIA A TERRIFIC PLACE TO PRACTICE MEDICINE!

DIRECTOR OF PSYCHIATRY NORTH CENTRAL WEST VIRGINIA

A Director of Psychiatry is needed to practice General Psychiatry and guide a 30-bed inpatient Psychiatric Unit located in a 207-bed community hospital. Enjoy leadership responsibilities and practice medicine. Call will be 1:4 and is shared with two other Psychiatrists and a Physician Assistant. A new 18-bed geriatric Psychiatric Unit opened in December 2010. This exquisite community surrounded by beautiful lakes and rolling hills is less than 20 minutes from Morgantown and Clarksburg, 2 1/2 hours from Pittsburgh and 3 hours from Washington, D.C. Each year thousands of outdoor enthusiasts converge on West Virginia's rivers, streams and woodlands to fish, hunt, canoe, boat, white-water raft and jet ski. Historic museums, concerts, stage plays and numerous other cultural activities offer fun for the whole family. Opportunity, lifestyle all come together at this thriving medical facility. It is a place to grow and stay.

Contact George at (800) 243-4353 or givekich@strelcheck.com **TODAY**!

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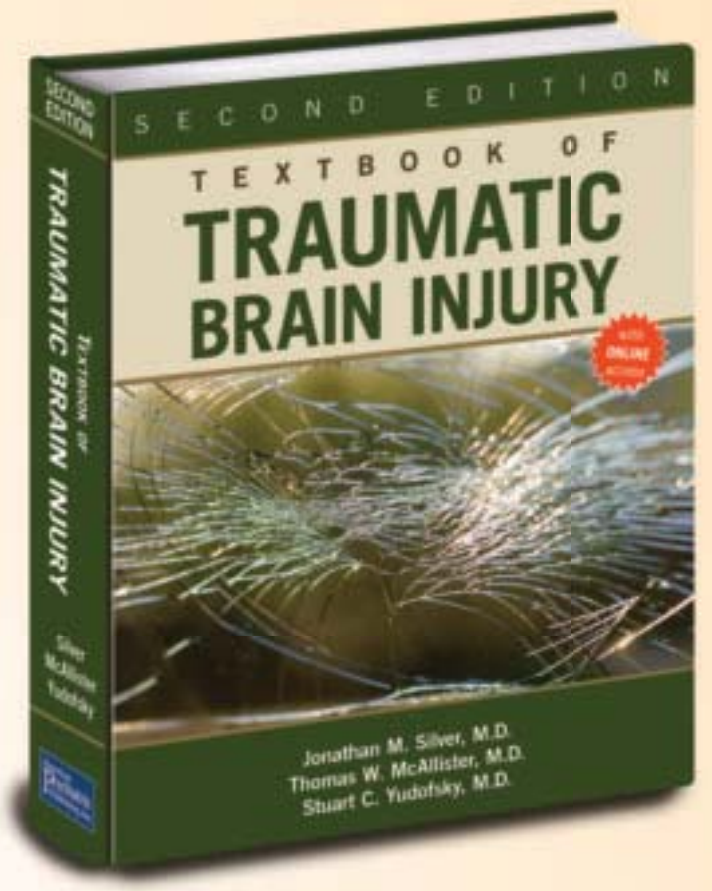

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As soldiers and combat veterans have returned from the wars in Iraq and Afghanistan traumatic brain injury (TBI) has been identified as the "signature injury" of those wars. This new edition of *Textbook of Traumatic Brain Injury* has been thoroughly revised and updated from the 2005 first edition to reflect the exponential expansion of research and clinical data amassed in the intervening years. Each chapter was written and reviewed by the foremost authorities in neuropsychiatry, neurology, rehabilitation medicine, and the other specialties who assess, diagnose, and treat these patients.

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- Enhanced coverage of psychopharmacology and psychotherapy for the psychiatric symptoms associated with TBI
- Information on the social ramifications of TBI so that clinicians will better understand and help their patients cope with the complex legal, financial, and insurance-based struggles their patients who have sustained TBI encounter
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- A Foreword written by Bob Woodruff (the ABC World News correspondent who sustained a TBI while covering the war in Iraq) and his wife, Lee Woodruff, who underscore that although this volume is intended to be read primarily by professionals, patients and families may also find the information in the textbook to be of keen interest and practical application.

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