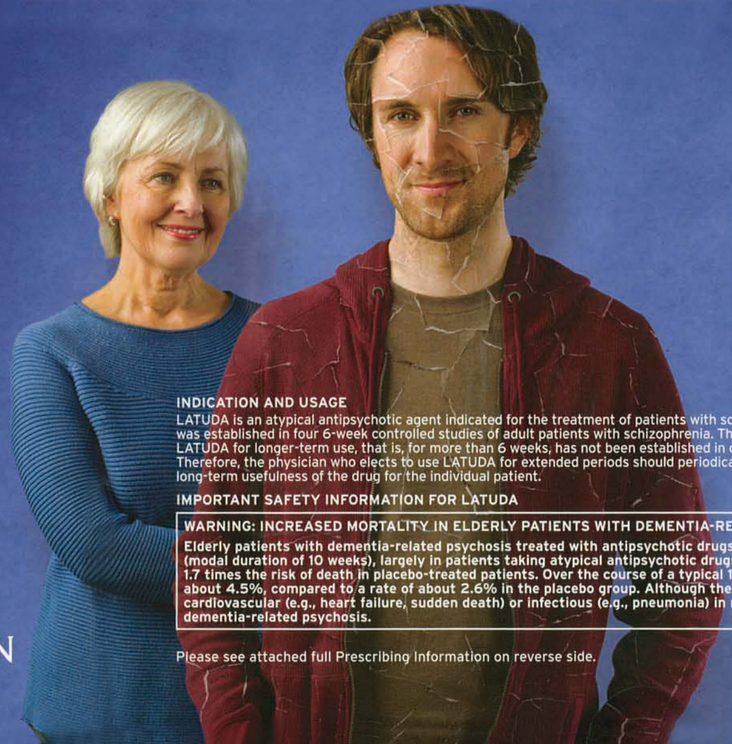
SUNOVION



A new treatment option for schizophrenia

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.

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 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 attached full Prescribing Information on reverse side.

Look inside for more information.

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*

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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.

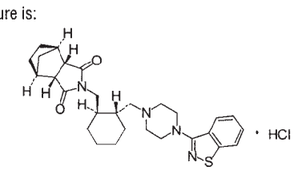
The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.

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 $C_{28}H_{36}N_4O_2S{\cdot}HCl$ 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)]*.

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American
Psychiatric
Association

PSYCHIATRIC NEWS

www.psychnews.org

THIS ISSUE CONTAINS THE EXHIBITS GUIDE FOR APA'S 2011 ANNUAL MEETING • SEE PAGE 11

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PERIODICALS:
TIME-SENSITIVE MATERIALS

Credit: David Hathcox

Jeffrey Borenstein, M.D., chair of the Ad Hoc Work Group on *Psychiatric News,* presents a series of recommendations to the Board of Trustees last month to improve APA communications to members. The major recommendation was to expand *Psychiatric News'* electronic presence by enhancing its Web site and adding an electronic newsletter and other products. The Board met last month to discuss these and other issues. See story on page 14.

Slightly Fewer Graduates Chose Psychiatry In Recent Match

Following recent resident match results, a psychiatric educator says the identity of psychiatry, especially the role of psychotherapy as a core skill of psychiatrists, is crucial to the profession's long-term vitality.

BY MARK MORAN

A total of 640 U.S. graduating medical students matched into psychiatry training programs in this year's National Resident Matching Program (NRMP), down from last year's figure of 670 who matched into psychiatry.

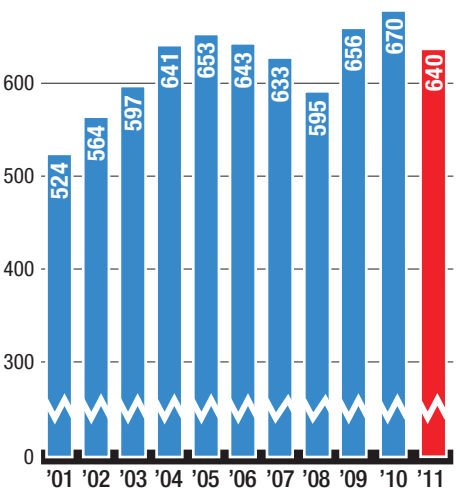
Those 640 graduates represent 4.1 percent of all U.S. seniors who matched into residency positions this year, falling from 4.5 percent last year. For the past five years, the percentage of graduates matching into psychiatry has remained between 4.1 and 4.6 percent (the percentage was 4.1 in 2008 as well as this year).

A total of 1,069 psychiatry positions were filled this year (out of 1,097 offered). As in past years, positions not filled by U.S. graduating seniors were filled by international medical graduates (including U.S. and non-U.S. citizens), Canadian students,

please see ***Match*** *on page 34*

U.S. Grads Matching Into Psychiatry Down

While the number of U.S. medical school seniors matching into psychiatry took a dip this year, it is still well above the lows experienced at the beginning of the last decade. One of the notable outcomes of this year's match was the increase in the number of students matching into primary care residencies.



Source: National Resident Matching Program, 2011

Overlooked Psychotherapy Effective in Depression

For years IPT was primarily a research treatment tested in randomized, controlled trials and hence has not gained widespread dissemination despite its inclusion as a recommended treatment in APA treatment guidelines for depression.

BY MARK MORAN

Interpersonal psychotherapy (IPT) is effective in the treatment of depression both as an independent treatment and in combination with psychopharmacology.

These were key findings from a meta-analysis of 38 studies published online March 1 in *AJP in Advance*. The analysis included studies examining the effect of IPT as an acute treatment and as a maintenance treatment after successful recovery from a depressive disorder; studies comparing IPT with a control condition (such as waiting list, usual care, or placebo); and studies comparing IPT with another psychotherapy, with combination treatment, and with pharmacology alone.

A previous, smaller meta-analysis published online in the *European Archives of Psychiatry and Clinical Neuroscience* (October 4, 2007) found significant and large effects for IPT compared with placebo or no treatment, and superior effects for IPT compared with cognitive-behavioral therapy (CBT).

A substantial number of studies of IPT have been published since, and authors of the new analysis said that the earlier meta-analysis did not examine some potential confounding factors. The new, larger analysis underscores the efficacy of IPT, which the authors said is underused despite being recommended in APA guidelines and those of other organizations as a treatment for depression.

"What this report does is to consolidate previous research and to confirm the utility of IPT as an antidepressant treatment," co-author John Markowitz, M.D., told *Psychiatric News*. "Hopefully the paper will remind clinicians of the availability of IPT."

Markowitz is a research psychiatrist at the New York State Psychiatric Institute and a professor of clinical psychiatry at Columbia University College of Physicians and Surgeons.

please see ***Psychotherapy*** *on page 28*

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Psychological Association Members File Suit Over Special Assessment

The suit against the American Psychological Association highlights the sensitive nature of organizations that advocate for the political interests of a profession and the need for transparency about how those organizations are funded.

BY MARK MORAN

Some members of the American Psychological Association are filing a class-action lawsuit against that organization for alleged misrepresentation of the nature of a financial assessment designed to finance political advocacy on behalf of clinical psychologists.

The suit, brought by three members of the association purportedly on behalf of all of the psychological association's members who paid the assessment after 2000, alleges that the organization has misled members by characterizing as "mandatory" a special assessment—over and above the dues required for membership in the organization—used to finance a separate organization known as the American Psychological Association Practice Organization (APAPO), which is devoted to legislative and political advocacy.

Though run by the psychological association's leadership, the APAPO is a separate organization, classified as a 501(c)(6) entity by the Internal Revenue Service (IRS). The APAPO is not a political action committee. The IRS defines a 501(c)(6) entity as a "business league" that is "devoted to improving business conditions of one or more lines of business as distinguished from performing particular services for individual persons."

(The American Psychological Association is a 501(c)(3) organization, a tax status that limits its lobbying activities and prohibits financial support of candidates for political office.)

The case is being heard in the U.S. District Court for the District of Columbia. The American Psychological Association has filed a motion to dismiss the case, and a decision is not expected sooner than May, according to a lawyer for the plaintiffs.

In the suit, the plaintiffs state that "since at least 2002, the [psychological association] has falsely represented to its members that a 'mandatory' practice or special assessment over and above the annual dues was required for membership in the [psychological association]. In fact, that assessment (which currently amounts to approximately $140 per member per year) is completely voluntary and solely required for membership in the 501(c)(6) organization, the APAPO."

And the plaintiffs maintained that the assessment amounts collected have

please see ***Psychological*** *on page 34*

Important Annual Meeting Announcements

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  You can register online at <www.psych.org/annualmeeting> or on site at the Hawaii Convention Center.
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- **Great Opportunity for Tours!**
  Pre- and post-meeting tours will be offered to the outer Hawaiian islands. While in Honolulu, be sure to take advantage of the many tours and fun activities available for the whole family. Don't be left out—sign up now! Information on tour packages is posted on APA's Web site.

More information is available by calling the APA Meetings and Conventions Department at (703) 907-7822 or by e-mailing apa@psych.org.

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What Does the Parity Law Mean For You and Your Patients?

BY CAROL A. BERNSTEIN, M.D.

As you all know, when the Paul Wellstone and Pete Domenici Mental Health Parity and Addiction Equality Act became law in October 2008, it was a major victory, gained after years of lobbying by APA and other mental health advocacy groups. The central provision of the law is the requirement that when mental health and substance use benefits are offered as part of a health plan, they must be offered with no greater financial requirements or treatment limitations than those that are applied to the plans' medical/surgical benefits for both in-network and out-of-network care. Although the law has no requirement that mental health or substance use benefits be provided, most health plans already include either one or both of these benefits, and the parity law's importance in assuring that these benefits are provided in a nondiscriminatory fashion imbue it with landmark status. The Affordable Care Act (ACA), which was passed last year, will extend the reach of the parity law's requirements.

Although the parity law went into effect on January 1, 2010, enforcement was delayed until 2011. I am writing about it now because it is critical that we all understand what this law should mean for our patients and our practices and so that we can assist our patients in ensuring that their health plans are in compliance.

The regulations governing the parity law are groundbreaking because they define not only quantitative limitations to care, but also nonquantitative limitations. These are limitations that cannot be quantified numerically such as the number of days allowed for inpatient treatment, but also benefits that limit the scope or duration of benefits when compared with other medical or surgical benefits. While the quantitative limitations include such issues as copays for in-network and out-of-network care and limitations on the number of visits permitted, nonquantitative limitations are less straightforward and include concepts such as medical management standards that are used to limit or exclude benefits based on medical necessity or whether a treatment is experimental or investigative. Other examples of nonquantitiative issues include the methodologies used to determine usual, customary, and reasonable charges; the standards used to establish provider eligibility for network participation; and the imposition of step-therapy, or fail-first protocols, that demand that a lower-cost therapy must be proved ineffective before a higher-cost one may be prescribed.

The parity law has not only the capacity to improve patient access to psychiatric care, but also the potential to improve psychiatric practice management. APA recently sent a letter to the insurance commissioner of each state to clarify that the terms of the parity law require that psychiatrists be reimbursed for providing the medical evaluation and management services for which other physicians are paid. For health plans to limit payment for care by psychiatrists to the CPT procedural codes in the psychiatry section of CPT is to limit psychiatric patients' access to care that is medically necessary. This has been an issue for psychiatry for many years. I am pleased to report that progress was made recently in New York state when, at the behest of the New York State Psychiatric Association, the Health Bureau of the New York Insurance Department sent a circular letter to all insurers in the state reminding them they are not permitted to discriminate against psychiatrists in this way *(Psychiatric News*, February 4). With the regulatory weight of the parity law behind us, we may be successful in ending this type of discrimination in every state.

Since the parity law's passage, APA's Office of Healthcare Systems and Financing has been critically instrumental in the effort to ensure that the law will be administered in a manner that best serves psychiatrists and their patients. In 2009, APA was a leader in the creation of the Parity Implementation Coalition (PIC), which provided a legal analysis of the parity law and its regulations. In addition to APA, the PIC includes the American Academy of Child and Adolescent Psychiatry, American Society of Addiction Medicine, Betty Ford Center, Cumberland Heights, Faces and Voices of Recovery, Hazelden, Mental Health America, National Alliance on Mental Illness, National Association of Psychiatric Health Systems, National Council for Community Behavioral Healthcare, and the Watershed Addiction Treatment Programs. The coalition is now engaged in a variety of parity compliance and enforcement activities.

Please take the opportunity to educate yourself about the parity law and contact APA with any questions that you may have. The Office of Healthcare Systems and Financing manages the PIC's parity Web site, <www.mentalhealthparitywatch.org>. It contains all the information available about the parity law, as well as information on how to get in touch with APA to report problems with any health plans whose policies seem to be out of compliance with the law, so that any infractions can be communicated to the Department of Labor for enforcement. You can contact APA's Office of Healthcare Systems and Financing directly by contacting the Practice Management Help Line at (800) 343-4671 or hsf@psych.org. ■

Her Studies Uncovered BPD's Neurobiological Secrets

With a "relentlessly empirical" approach to patients, Antonia New, M.D., has used brain imaging to help establish the neurobiological basis for the troubling behavior associated with borderline personality disorder. This is the third part of a four-part series.

BY MARK MORAN

"Listen to your patients and use your best intelligence."

That's what Antonia New's father told her when she informed him that after an internship in internal medicine, she would be doing her residency in psychiatry. Two days before she entered training, Bertrand New, M.D.—her father and a child psychiatrist and psychoanalyst—died after a long illness.

Her father's words along with her own background in internal medicine and the influence of her mother, Maria New, M.D., a researcher in pediatric endocrinology, reinforced for the young psychiatry trainee what she called a "relentlessly empirical" approach to patients.

"My father told me he had loved what he'd done as an analyst, but he wasn't sure all the tenets were right," New recalled. "His words resonated with me as I entered my psychiatry training, enhancing my acute sense of wanting to observe the patients around me. And I very much carried my [general] medical background with me into the care of psychiatric patients."

Antonia New, M.D., has been a trailblazer in a research field dominated by men and has mentored young women psychiatrists who want to do research.

Early in training she became drawn to a particularly troubled group of patients: highly emotional, sometimes aggressive, and frequently self-harming, these patients with borderline personality disorder (BPD) were also often stigmatized within the emergency hospital setting where they were commonly seen.

"I was attracted to the emotional intensity of these patients," New said. "I was drawn to these women who would come into the hospital absolutely desperate, with very intense emotional responses to the people around them. Many of them cut themselves, and I remember asking a 17-year-old girl why she did that. She told me, 'It was the only way I could think of to make myself feel better.'

"I had this experience again and again with these patients who grew more and more desperate until they turned to this behavior as a way to cope," New said. "It was the first cohort of people I knew I wanted to study."

Her empathic fascination and "relentlessly empirical" approach would lead New over time to become one of the foremost researchers in the neurobiology of a disorder that had until then been the domain of psychoanalysts. Beginning with familial studies in an effort to discern the genetics of BPD, she moved on to use functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) scans to study the neurobiology of specific domains of the borderline pathology, especially impulsive aggression and impaired emotion processing.

WORKING ON THE BORDERLINE

Her work has contributed in great part to a new clinical appreciation of the person behind a disorder that had long been considered trouble. "In my training, I saw that these patients were terribly stigmatized," New said. "The worst thing you could call a patient was borderline."

The Narrative Brain Is Not Active

A New Yorker born and raised, and having already started a family of her own there, New wanted to stay in the city after her training and so began a fellowship at Mount Sinai Medical Center with a mentor, psychiatrist Larry Siever, M.D. It was Siever, today vice chair for VA Affairs at Mount Sinai School of Medicine, who encouraged her to delve into what was at the time still a nascent field of inquiry.

"The idea appealed to me of taking a neurobiological approach to a disorder that had been largely ignored from that point of view," New told *Psychiatric News*.

She turned to using brain imaging to study specific domains of pathology, especially impulsive aggression, that would reveal a crucial neurobiological trait of BPD: impaired connectivity between the amygdala—the seat of emotion and the so-called "reptilian brain"—and the prefrontal cortex, seat of reason and executive function.

In a study published in the January 2007 *Neuropsychopharmacology*, New and colleagues used measures of relative glucose metabolic rate in subregions of the prefrontal cortex and amygdala to study connectivity of those regions in BPD patients and healthy controls; they demonstrated a tight coupling of metabolic activity between the right orbitofrontal cortex and ventral amygdala in healthy subjects that was not present in patients with BPD.

In a remarkable study appearing in *Biological Psychiatry* in December 2009, New and colleagues used PET scans and a novel instrument for inducing aggression in the laboratory to study the neuroanatomy of aggression in patients with BPD. Patients and healthy controls were administered the Point Subtraction Aggression Paradigm, a computer game that measures a participant's aggressive responses to the subtraction of "points" worth money that he or she has accumulated during a 35-minute testing session; the losses are blamed on the erroneous responses of a fictitious other person.

New and colleagues found that patients with BPD showed significantly greater aggression in response to the paradigm and increased glucose metabolic rates in the orbitofrontal cortex and amygdala when provoked. Healthy controls, in turn, showed decreased glucose metabolic rates in those areas, but an increase in activity in anterior, medial, and dorsolateral prefrontal regions—brain regions involved in top-down cognitive control of aggression and emotion.

These results were among the first evidence of a neurobiological underpinning of the aggressive behavior seen in borderline patients. "The frontal lobe that puts the brakes on emotion seems to be offline in borderline patients and only comes online with a significant provocation," New explained. "So for these patients, the thinking or narrative brain is not active. And we showed a dysfunction in connectivity, the way the prefrontal cortex and amygdala are not coordinated, as they are in healthy people."

A Woman's Disorder Only?

With the establishment of a neurobiological basis for the impulsive aggression and emotional dysregulation characteristic of BPD, New said that she and other researchers are now turning to social cognition and the ways in which borderline patients can disastrously misinterpret the intentions of those closest to them and the larger world around them. She cited, as an example, the work of Reed Montague, Ph.D., who has used the "economic exchange" game to show that patients with BPD have a neuroanatomically impaired ability to cooperate with others for mutual benefit.

"We can show that patients are poor at cooperating and have subtle difficulty reading emotions in others," she said. "Ultimately, we want to use these kinds of brain-imaging tests to develop pharmacologic approaches and to determine which patients will respond best to psychotherapy."

Conventional wisdom has held that BPD is a disorder dramatically skewed toward women—according to *DSM-IV*, 75 percent of cases are women—but New said the true picture is not quite so stark. "It *is* a disorder more commonly seen in women, but not nearly so much as the research literature assumes," she told *Psychiatric News*. "Empirical research using diagnostic interviews in the community suggests that the ratio of women to men with BPD is approximately 2 to 1."

Mentoring Other Women

Quite aside from her accomplishments, New's status as a woman in neurobiological research makes her a maverick. "My mother is a researcher, so I had her as model," she said. "I haven't had the explicit obstacles to overcome that my mother did, but I have not had female researchers senior to me that I have been able to turn to.

"It's really rare for women psychiatrists to stay in research when they are mothers," says New, the mother of three daughters. "I think that is changing. I've told my senior colleagues, 'I'm not looking for the fast track, but the slow track, so I can be present for my children.' "

And she has made it a priority to mentor young women researchers and to advocate for allowing researchers the time to be with their families. "It's an incredibly challenging path to stop your career, have a baby, and then come back and try to jump right back in. I think we need to create opportunities to allow people in this career track to have families."

"Amygdala-Prefrontal Disconnection in Borderline Personality Disorder" is posted at <www.nature.com/npp/journal/v32/n7/abs/1301283a.html>. "Laboratory Induced Aggression: A Positron Emission Tomography Study of Aggressive Individuals With Borderline Personality Disorder" is posted at <www.ncbi.nlm.nih.gov/pubmed/19748078>.

The fourth installment in this series will profile BPD researcher John Gunderson, M.D. ■

Women to Women

Women psychiatrists who would like to mentor other women psychiatrists or be mentored are invited to attend the Women in Psychiatry Mentoring Breakfast at APA's 2011 annual meeting in Hawaii. It has been scheduled for Wednesday, May 18, from 7:30 a.m. to 9 a.m. in the Kahili Suite in the Kalia Executive Conference Center, Hilton Hawaiian Village Hotel.

The breakfast is being held in honor of the late Tana Grady-Weliky, M.D., who was the chair of the annual meeting's Scientific Program Committee.

APA is holding the breakfast in collaboration with the Association of Women Psychiatrists, American College of Psychiatrists, Association for Academic Psychiatry, and American Association of Directors of Psychiatric Residency Training.

Those who plan to attend should RSVP to Alison Bondurant at (703) 907-8639 or abondurant@psych.org.

Obamas Shine Spotlight On Prevention of Bullying

The Obamas have brought national attention to the problem of bullying, making it the subject of a White House conference. Concerns about this behavior have become more pervasive with the advent of cyberbullying.

BY RICHARD FAUST

In the wake of several high-profile national news stories on tragedies related to bullying, the President and First Lady invited parents, students, and teachers to join policymakers and advocates at a White House conference on bullying prevention.

Speakers focused on the effects of bullying, as well as on mitigation programs being implemented around the country. Conference co-sponsors Education Secretary Arne Duncan and Health and Human Services Secretary Kathleen Sebelius spoke about existing federal efforts and new Obama administration initiatives.

Credit: AP Photo/Charles Dharapak

President Obama tells attendees at a White House conference on bullying prevention last month that he was a victim of bullying. Bullying, he pointed out, is not a "harmless rite of passage."

Having a conference hosted by the Obamas raises the issue of bullying to a more visible level. Louis Kraus, M.D., chief of child and adolescent psychiatry at Rush University and a member of the APA Council on Children, Adolescents, and Their Families, said in an interview with *Psychiatric News* that the White House event "is extremely important in raising the profile of the cause."

All Adults Have Role to Play

Michelle Obama opened the conference by stressing that prevention of bullying goes beyond just parents and requires that adults monitor their own behavior. "We all need to play a role—as teachers, coaches, faith leaders, elected officials, and anyone who's involved in our children's lives. And that doesn't just mean working to change our kids' behavior and recognize and reward kids who are already doing the right thing. It means thinking about our own behavior as adults as well."

The president noted that to understand the seriousness of the issue, people have to get past the "myth that bullying is just a harmless rite of passage or an inevitable part of growing up." Striking a personal note, he said that he "didn't emerge unscathed," saying that "with big ears and the name that I have, I wasn't immune."

Obama marshaled statistics to illustrate the scope of the problem. "A third of middle-school students have reported being bullied during the school year. Almost 3 million students have said they were pushed, shoved, tripped, or even spit on."

Gender Differences Apparent

The physical aspects of bullying are usually thought of in relation to boys, but Kraus said that a significant amount of bullying occurs among girls, though it frequently takes different forms. Girls often bully and are bullied on an emotional level and through peer relationships. "For young girls, exclusion and isolation from peer groups can be devastating. This is not to say that physical bullying between girls does not exist or that its effects should be diminished in any way," Kraus noted.

Besides the horrific stories of children driven to suicide or suffering serious injuries, the repercussions of bullying are many. The president noted that "bullying has been shown to lead to absences and poor performance in the classroom. And that alone should give us pause since no child should be afraid to go to school in this country."

Kraus pointed out that bullied children have a higher frequency of mental health

please see ***Bullying*** *on page 9*

APA Gives Back

Once again, APA invites you to contribute to a special program that will benefit a charity in the city hosting the annual meeting. The charity selected for this year's program is Mental Health Kokua. This organization assists people recovering from serious mental illness to achieve their optimum level of independent living in the community. Services include housing, case management, psychosocial rehabilitation, psychiatric care, and counseling. More information about Mental Health Kokua is posted at <www.mentalhealthkokua.org/aboutus.html>.

Donations can be made at the time you register for the meeting or by using the form posted at <www.psych.org/MainMenu/EducationCareerDevelopment/Meetings/2011-Annual-Meeting/Annual-Meeting-Donation-Form.aspx?FT=.pdf?>.

Last year's drive raised $7,000 for the Mission in New Orleans.

Evidence for Prevention Efficacy Said to Be Strong and Growing

Preventive mental health programs have the potential to impact lives and save money. The authors of a new report say the time is now and the future is bright for prevention.

BY RICHARD FAUST

A report in the March *Psychiatric Services* summarizes the evolution of evidence for the prevention of psychiatric disorders.

In the article, William Beardslee, M.D., Peter Chien, M.D., and Carl Bell, M.D., offer recommendations for implementing measures to prevent mental illness and urge systemic changes geared toward prioritizing prevention efforts and encouraging further research on preventive practices.

According to Chien, "the good news is that the evidence [for the effectiveness of prevention strategies] is stronger than most people believe and that it is mounting. The opportunities are there."

This state of preventive mental health programs did not always warrant such an optimistic outlook. In September 1989, the then General Accounting Office (GAO) issued a report in response to a congressional request for information on the status of implementing preventive mental health initiatives under the Public Health Service Act and subsequent 1980 and 1983 amendments detailing prevention-program requirements.

The GAO report, "Mental Health: Prevention of Mental Disorders and Research on Stress-Related Disorders," found that the prevention-related requirements had not been met and recommended programs had not been established. This report prompted a national conference on prevention research, leading to the Institute of Medicine (IOM) releasing its first report on prevention in 1994, "Reducing Risks for Mental Disorders: Frontiers for Prevention Research." The report recommended increases in both research on and implementation of preventive mental health programs.

Since the 1994 report, there has been an explosion in randomized, controlled studies in prevention, leading Bell to comment to *Psychiatric* News that "these studies have led to the increasing view that it is unethical to not do prevention in some areas." The evidence from these studies prompted the IOM to produce another report on the issue in 2009, titled "Preventing Mental, Emotional, and Behavioral Disorders Among Young People: Progress and Possibilities." Beardslee, Chien, and Bell believe this report shows that prevention in psychiatry is possible, and it prompted them to marshal the evidence and offer recommendations in their article.

Preventive mental health programs serve two purposes. From a health care perspective, these programs address risk factors to individuals, providing for better long-term prognoses. In addition, the authors contended that preventive mental health programs accrue economic benefits. They marshalled statistics to illustrate that prevention is often less expensive than the economic and societal costs once an illness has manifested.

Prevention requires a paradigm shift, however. Mental, emotional, and behavioral disorders are predominantly developmental, and thus for maximum impact prevention must focus on the young. The authors noted that "half of lifetime cases of mental, emotional, and behavioral disorders start by age 14, and three-fourths of disorders start by age 24." The shift needs to occur in considering the needs of children. Chien pointed out that "when you see [adult] patients in the office, it is hard to do primary prevention because they already have a diagnosable disorder, but you can do primary prevention for their children. Think about their family." Beardslee agreed, noting that the same clinician can do both treatment and prevention.

> **"These studies have led to the increasing view that it is unethical to not do prevention in some areas."**

In an interview with *Psychiatric News*, Beardslee said an interdisciplinary approach is needed and gave the example of the threat of homelessness for an increasing number of people in these economic times. The potential psychiatric problems from homelessness are many for the adults, families, and children. "Housing insecurity is a risk factor, while housing stability accrues numerous long-term benefits. It's a protective factor."

The interdisciplinary approach to prevention leads to the aforementioned economic benefits. The authors noted that the 2009 IOM report estimated that the costs associated with mental and behavioral disorders in young people totaled $247 billion in 2007. This took into account treatment, crime, and lost productivity. Prevention programs cost considerably less. They pointed to the Strengthening Families Program, which "realized reduced drug use, reduced delinquency, and increased academic performance" and highlighted that its interdisciplinary and preventive nature realized an estimated savings of $8 for every $1 invested.

The Strengthening Families Program has been implemented all around the country. It was created through a NIDA research grant in the early 1980s. The Web site is <www.strengtheningfamiliesprogram.org>.

All three authors are optimistic about the current direction of preventive mental health care. Bell said that originally it was not clear that the 2009 IOM report was getting any traction, but now he believes that the government, and the Substance Abuse and Mental Health Services Administration in particular, is moving in the right direction. The surgeon general is heading a prevention task force. Several provisions of the Patient Protection and Affordable Care Act—the Obama health care reform law—look back to the 2009 study, providing $3 billion for home visitation and $15 billion for a Prevention Intervention Council.

"Prevention is all coming together. Everyone is on the same page," said Bell.

An abstract of "Prevention of Mental Disorders, Substance Abuse, and Problem Behaviors: A Developmental Perspective" is posted at <http://psychservices.psychiatryonline.org/cgi/content/abstract/62/3/247>. The IOM report "Reducing Risks for Mental Disorders: Frontiers for Prevention Research can be purchased at <http://iom.edu/Reports/1994/Reducing-Risks-for-Mental-Disorders-Frontiers-for-Preventive-Intervention-Research.aspx>. The IOM report "Preventing Mental, Emotional, and Behavioral Disorders Among Young People: Progress and Possibilities" can be purchased at <http://iom.edu/Reports/2009/Preventing-Mental-Emotional-and-Behavioral-Disorders-Among-Young-People-Progress-and-Possibilities.aspx>. ■

Medicare Payment Commission Urges Minor Boost, Not Huge Cut

In testimony before Congress, the MedPAC chair highlighted concerns that the long-running uncertainty about payment rates could affect the long-term stability of the program.

BY MARK MORAN

Medicare payments to physicians should be increased next year by 1 percent, according to a report last month to Congress by the Medicare Payment Advisory Commission (MedPAC).

The committee's recommendations came just days after the federal Centers for Medicare and Medicaid Services (CMS) forecast a massive 29.5 percent cut next year for physician payment under the sustainable growth rate (SGR) formula.

In its report, the commission stated that "available data find that, overall, Medicare payments [at current levels] for physician and other health professional services are adequate. Access, supply, quality, and volume measures suggest that most Medicare beneficiaries are able to obtain physician services with few or no problems."

The report added that a 2010 patient survey by the commission found that "Medicare beneficiaries (age 65 or older) were more likely to report better access to physicians than privately insured individuals (age 50 to 64)."

However, the commission noted that "relative to current law, this recommendation [for a 1 percent update] is estimated to increase federal program spending by more than $2 billion in the first year and by more than $10 billion over five years."

Physician payment under the Medicare program has evolved into a repetitive drama, with increasingly draconian cuts being forecast each year by CMS followed by vigorous protests from physician groups and last-minute reprieves granted by Congress. Last year Congress extended 2010 Medicare physician payment rates through the rest of 2011, blocking a dramatic 25 percent across-the-board cut that was to have taken effect January 1 (*Psychiatric News*, January 7).

The MedPAC recommendation is not binding on Congress, but is used as a starting point for negotiations. The 2012 reduction is the largest that physicians have faced.

APA, the AMA, and other physician and senior groups such as AARP have consistently argued that the entire formula—especially the sustainable growth rate component, which requires increases in Medicare volume to be compensated for by decreases in payment—needs to be reformed.

"The AMA concurs with MedPAC's conclusion that the nearly 30 percent cut built into Medicare's payment system for 2012 would jeopardize access to physician services for many patients and should be replaced with a positive update to help offset increases in practice costs," said AMA President Cecil Wilson, M.D., in a statement.

In testimony before Congress, MedPAC Chair Glenn Hackbarth, J.D., discussed the flaws of the SGR formula and the concern that continued uncertainty about payment rates can have on the stability of the Medicare program.

"A main flaw of the SGR is it neither rewards individual providers who restrain unnecessary volume growth nor penalizes those who contribute most to inappropriate volume increases," he said. "Indeed, volume growth has been a major factor in the prescribed SGR payment cuts—cuts expected to be at least 25 percent in 2012.

"There is general consensus that fee cuts of that magnitude would be detrimental to beneficiary access to care, and legislative overrides of the SGR have averted payment cuts in recent years," Hackbarth said. "However, these overrides are merely temporary, leading to mounting frustration among physicians, other health professionals, and their patients and to a desire for a longer-term remedy. However, the high budgetary cost of eliminating some or all of the scheduled fee cuts in the longer term has prevented such proposals from becoming law. . . . The commission plans to continue to work on SGR payment policies and consider various approaches for updating Medicare's physician fee schedule."

The MedPAC report and the chair's testimony to Congress is posted at <www.medpac.gov/documents/Mar11_EntireReport.pdf>. ■

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Designer Drug's Rapid Spread Causes Alarm on Several Fronts

The DEA recently took control of five forms of synthetic cannabis, but the next group of synthetic drugs of abuse has already appeared on the regulatory horizon.

BY LESLIE SINCLAIR

They're called "bath salts," but these are not your grandmother's epsom salts or your mom's Calgon: They are synthetic stimulants, usually mephedrone, but sometimes methylenedioxypyrovalerone (MDPV) or its metabolite, pyrovalerone. To avoid detection and control, the products are sold as a powdery substance in small-volume packets labeled as "bath salts" or "plant fertilizer" and marketed with a variety of colorful names, including "Ivory Wave," "Purple Wave," Red Dove," "Blue Silk," "Zoom," "Bloom," "Cloud Nine," "Ocean Snow," "Lunar Wave," "Vanilla Sky," "White Lightning," "Scarface," and "Hurricane Charlie."

Although the packages are marked "not for human ingestion," the products are ingested by swallowing or snorting, and they can cause chest pains, increased blood pressure, increased heart rate, agitation, hallucinations, extreme paranoia, and delusions.

Reports of harm include cases like that of Neil Brown of Fulton, Miss., who slit his face and stomach repeatedly with a skinning knife after ingesting bath salts (Brown survived his injuries), and Cynthia Palmer, a mother of two from Calvert, Ky., who said she hallucinated after snorting bath salts. Kentucky State Police say they found a 2-year-old boy with a head injury lying on the inside edge of I-24 in Marshall County and his mother carrying a 5-year-old child in the median; Palmer had dropped the younger child after stopping her car and attempting to carry both children across the roadway.

"These chemicals act in the brain like stimulant drugs—cocaine substitutes—and present a high abuse and addiction liability," said National Institute on Drug Abuse (NIDA) Director Nora Volkow, M.D., in a message issued in late February about these emerging and dangerous products.

These particular drugs, known as methcathinones, are similar to cathinone, a central nervous system stimulant found in the leaves of the "khat" bush (Catha edulis). Methcathinones are derived in a manner similar to methamphetamines: Ephedrine and pseudoephedrine undergo reduction to yield methamphetamine or oxidation to yield methcathinone. And, like methamphetamines, methcathinones can be readily produced in a makeshift laboratory. The comparisons to cocaine are also inescapable: "Mephedrone appears to be used primarily intranasally and to have comparable abuse potential to cocaine, with more than half of those who use both reporting that mephedrone gives a better quality high," said Adam Winstock, M.B.B.S., and his colleagues in the January *Addiction*. They reported the results of a cross-sectional anonymous online survey of mephedrone use as part of a larger study exploring patterns of drug use among those associated with the dance music scene.

For the time being, these compounds are legal—and easy to get—in many parts of the United States, although Michigan, North Dakota, Louisiana, and Florida have outlawed them. The Federal Analog Act, part of the Comprehensive Drug Abuse Prevention and Control Act of 1970, allows any chemical "substantially similar" to an illegal drug (in Schedule I or II) to be treated as if it were also in Schedule I or II, but only if it is intended for human consumption, hence the designation on all bath salts that they are "not for human ingestion."

Bath salts are sold online and in drug paraphernalia stores, convenience stores, discount tobacco outlets, gas stations, pawn shops, tattoo parlors, and truck stops, among other locations. They have been slow to arrive in the United States: Sweden, Norway, Denmark, the Netherlands, Finland, Croatia, and Estonia had declared them to be controlled substances by late 2009, and the United Kingdom classified them as Class B drugs under the Misuse of Drugs Act in April 2010. Cathinone-type drugs have been seen in Canada since 2006 and are regulated there under the Controlled Drugs and Substances Act.

"Most new designer drugs are prepared to circumvent existing legislation, to create new drugs with desirable pharmacological properties, and/or to avoid detection through normal testing protocols," explained Chad Maheux, M.Sc., of the Canada Border Services Agency and his colleagues in the December 2010 *Microgram Journal*, and the methcathinones appear to be doing all of those things successfully. A group of British criminologists, evaluating the rise and subsequent illegalization of mephedrone that occurred in the United Kingdom from 2009 to 2010, have suggested that the popularity of mephedrone has more to do with events in the current drug climate than the drug itself. They blame significantly reduced availability—leading to reduced purity—of cocaine and ecstasy for users' "displacement" to more readily available "legal highs" such as mephedrone and other cathinones.

"It is exactly because users' desire for intoxication is constrained by concerns about availability, purity, legality, and price that mephedrone has risen to its current popularity," according to Fiona Measham, a senior lecturer in criminology at Lancaster University in Lancashire, England, and her colleagues in the March 2010 *Drugs and Alcohol Today*.

Perhaps the most alarming feature of these designer drugs is the role the Web plays in their rapid appearance and rise in popularity. "The recreational drug market . . . is constantly evolving, with the Internet playing an increasingly dominant role," said researchers with the Psychonaut Web Mapping Project, a two-year European Union–funded project (January 2008-December 2009) with the aim of developing a Web-scanning system to identify and categorize novel recreational drugs/psychoactive compounds and new trends in drug use based on information available on the Internet. The researchers presented their findings at the 21st International Harm Reduction Association's Annual Conference in April 2010 in Liverpool, England, where they pointed out that "from a harm-reduction perspective, the rapid rate of diffusion of these new drugs is a challenge for health professionals, as there is often very little, if any, evidence-based literature about the substances available."

NIDA agreed: "We will continue to monitor the situation and promote research on the extent, pharmacology, and consequences of bath salts abuse," said Volkow. "In the meantime, I would like to urge parents, teachers, and the public at large to be aware of the potential dangers associated with the use of these drugs and to exercise a judicious level of vigilance that will help us deal with this problem most effectively."

The "Message From the NIDA Director on 'Bath Salts'—Emerging and Dangerous Products" is posted at <http://drugabuse.gov/about/welcome/MessageBathSalts211.html>. ■

DEA Cracks Down on Fake Pot

On March 1, the U.S. Drug Enforcement Administration (DEA) exercised its emergency scheduling authority to control five chemicals (JWH-018, JWH-073, JWH-200, CP-47,497, and cannabicyclohexanol) known as synthetic cannabinoids used to make so-called "fake pot" products.

Except as authorized by law, this action makes possessing and selling these chemicals, or the products that contain them, illegal in the United States. "The action was necessary to prevent an imminent threat to public health and safety," the DEA said in a news release. "The temporary scheduling action will remain in effect for at least one year while DEA and the U.S. Department of Health and Human Services study whether these chemicals should be permanently controlled."

Already outlawed in many European countries, at least 18 U.S. states, and all branches of the U.S. military, the chemicals were placed in the Schedule I category, the most restrictive under the Controlled Substances Act.

The emergence of these five synthetic cannabinoids represents a recent phenomenon in the U.S. designer-drug market, said the DEA. Although these chemicals have not been approved for human consumption, they have become readily available in just a few short years. Synthetic cannabinoids are a large family of chemically unrelated structures biologically similar to tetrahydrocannibinol (THC), the active principal component of marijuana. Dissolved in solvents such as acetone and sprayed onto plant material, they are marketed as smokeable herbal products and known most commonly by the names "spice" and "K2."

Many synthetic cannabinoids originated in the laboratory of John William Huffman, an organic chemist at Clemson University since 1960, where more than 470 analogs and metabolites of THC have been synthesized. Huffman's research goals included the potential development of new pharmaceutical products and exploration of the geometry of both the cannabinoid brain (CB1) and peripheral (CB2) receptors. Huffman's lab developed JWH-018 in 1995, and he describes it as "quite potent and easy to make."

The synthetic cannabinoids first appeared in the United States as potential drugs of abuse in November 2008 when U.S. Customs and Border Protection first encountered them. The increasing abuse of synthetic cannabinoids is demonstrated by the increase in federal, state, and local law-enforcement activity associated with these substances. Since 2009, the DEA has received an increasing number of reports from poison-control centers, hospitals, and law-enforcement agencies regarding these products.

In addition, emergency-room physicians have reported that individuals who use these products experience serious side effects that include convulsions, anxiety attacks, dangerously elevated heart rates, increased blood pressure, vomiting, and disorientation. The risk of adverse health effects is further increased because similar products vary in the composition and concentration of synthetic cannabinoids spiked on the plant material, and products may contain other unknown chemicals with undetermined effects. "These five substances have the potential to be extremely harmful and, therefore, pose an imminent hazard to the public safety," the DEA stated.

Suspension

David Earl Linden, M.D., has been suspended for five years from APA and the Oklahoma Psychiatric Physicians Association. Linden was found to have violated sections 1, 2, 3, and 4 of the *Principles of Medical Ethics With Annotations Especially Applicable to Psychiatry* by the ethics committees of the district branch and APA. He was found to have committed a boundary violation and prescribed medications without sufficient examination and the establishment of a valid physician-patient relationship. ■


Schizophrenia
can tear
patients
apart

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.

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 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.

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.

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

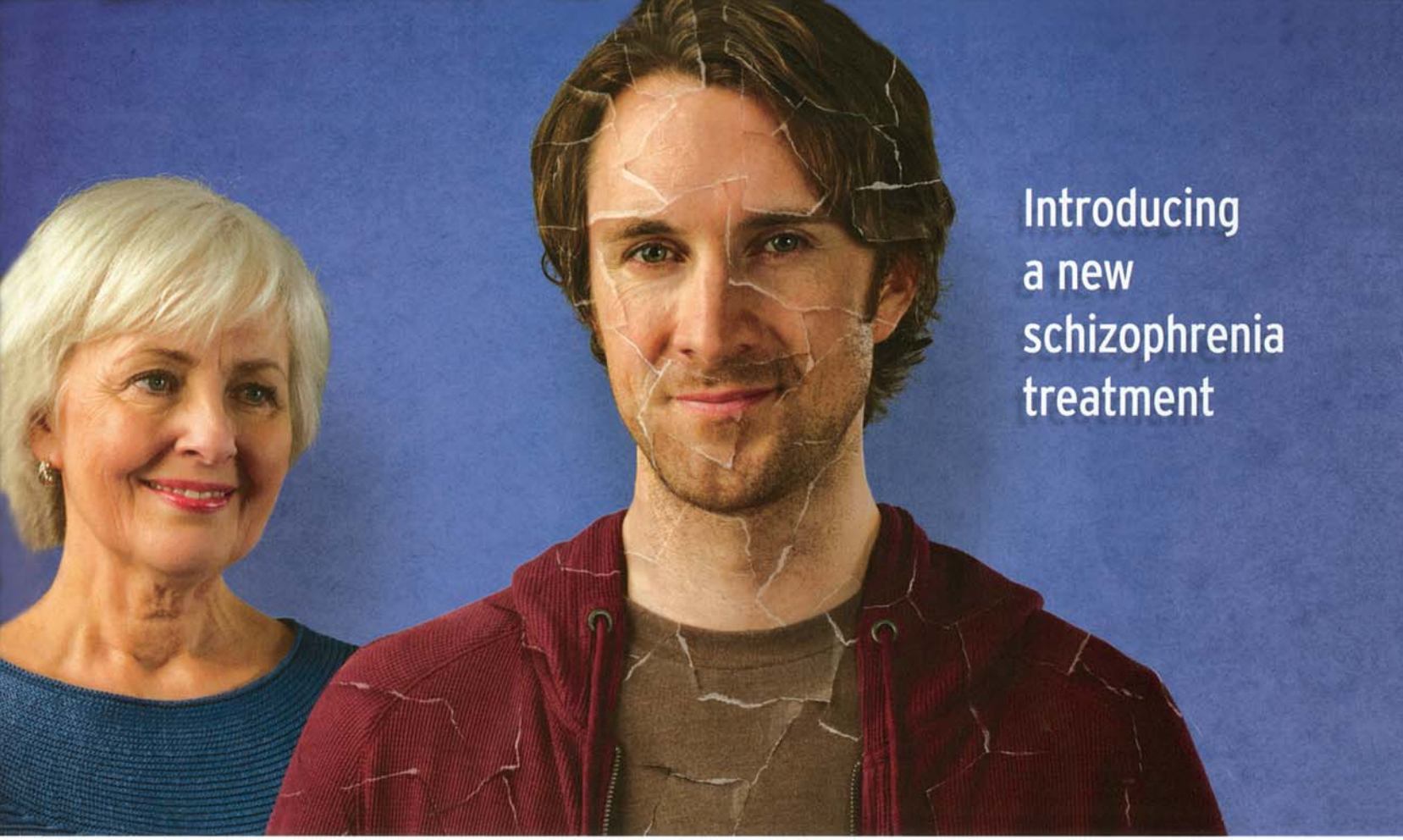
Drug Interactions: Given the primary CNS effects of LATUDA, caution should be used when it is taken in combination with other centrally acting drugs and alcohol.

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**.



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.

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 ($Cl_{cr} \geq 10$ 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.

SUNOVION

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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
901456R01

Courts Will Have to Decide Who Owns Prescription Data

The country's two largest drug-store chains are sued in separate cases involving their sale of consumers' prescription data, in one case to pharmaceutical manufacturers and in the other to data-mining companies.

BY KEN HAUSMAN

A parent who had his two daughters' prescriptions filled through a Walgreen Company drugstore has sued the company, charging that it had no legal right to sell the girls' prescription information to so-called data-mining companies that then sell it to pharmaceutical companies for marketing purposes.

In the class-action suit, which was filed in California in March, plaintiff Todd Murphy insists that such information is the property of the patient who pays for the prescription, and thus Walgreen sold something it did not own. This is a change of tactics from other lawsuits challenging the legality of data-mining practices, which were based on breaches of confidentiality of physician prescribing information.

As an indication of the value of the information Walgreen sells to data-mining companies, Murphy's suit indicates that Walgreen put a 2010 value of $749 million on the data in the company's report to the Securities and Exchange Commission, according to a March 11 report from Reuters. The suit was filed in California Superior Court, County of San Diego [*Murphy et al. v. Walgreen Corp. et al.*, San Diego Superior Court, No. 37-2011-87162].

The information Walgreen sells to data-mining companies does not cite the name of a patient for whom a medication was prescribed, but does include, in addition to the name of the medication, the patient's gender, age group, and state of residence, as well as the ID number of the physician who wrote the prescription.

Murphy's suit against Walgreen is not the only recent one challenging the legality of selling prescription data. On March 7 the Philadelphia Federation of Teachers Health and Welfare Fund and Pennsylvania resident Arthur Steinberg sued CVS Caremark Corp., parent of the huge CVS drugstore chain, for allegedly selling customers' private information to four major pharmaceutical companies—Lilly, Merck, AstraZeneca, and Bayer.

The plaintiffs maintain that CVS profited from the sale of "confidential prescription information obtained from consumers and third-party payors purchasing or reimbursing prescriptions filled by" CVS, a practice that under Pennsylvania law "constitutes unfair and deceptive practices. . . as well as unjust enrichment."

Specifically, the civil suit alleges that "in exchange for the receipt of funds, direct promotional letters were sent to physicians of consumers by Defendant CVS Caremark in order to promote and tout specific prescription drugs of pharmaceutical manufacturers who contract with [CVS] for the sale and/or use of prescription information."

The plaintiffs, who are seeking financial damages from the company and return of profits earned through this practice, want the court to grant their suit class-action status [*Arthur Steinberg and Philadelphia Federation of Teachers Health and Welfare Fund v. CVS Caremark Corporation*, Philadelphia Court of Common Pleas, No. 110300253].

In another case arising from prescription-related data-mining practices, in January the U.S. Supreme Court agreed to hear an appeal from Vermont regarding that state's law banning third-party access to physician prescribing data. A federal appeals court had struck down the law in November 2010, ruling that it violated the data-mining companies' commercial free-speech rights. Vermont had argued that its data-mining prohibition did not restrict constitutionally protected free speech, but rather the buying and selling of a commodity, namely prescribing data, which is within a state's regulatory rights (*Psychiatric News*, February 4).

Prior to the appeals court's rejection of the Vermont law's constitutionality, however, another federal appeals court had upheld the constitutionality of data-mining laws in New Hampshire and Maine.

The filing in the Pennsylvania case is posted at <www.courthousenews.com/2011/03/08/cvscaremark.pdf>. ■

Bullying

continued from page 5

issues. Bullies also have more mental health issues, but "the nature of the cycle is not understood yet. Were they previously bullied, did they have mental health issues before becoming a bully?" Many of the mental health issues related to bullying can be avoided, he noted, once there is a more complete understanding of bullying than is now the case.

A disturbing new twist on bullying is the advent of cyberbullying. "Today, bullying doesn't even end at the school bell—it can follow our children from the hallways to their cell phones to their computer screens," said the president.

Kraus agreed that cyberbullying is arising as a major issue. "It is pervasive, and the impact can be equally as severe as face-to-face bullying, as has been seen in recent high-profile cases." Tina Meier, whose 13-year-old daughter committed suicide after becoming the victim of an Internet hoax, told the conference audience that it was unrealistic to believe that the modern communications tools used in cyberbullying can just be turned off. "Technology is out there. We cannot shut it off." She stressed how important it is for parents to "understand what's going on in their children's online world."

The conference also included breakout sessions to cover policies and programs to prevent bullying, including those that are run by schools, community organizations, and college groups.

Initiatives by the Obama administration to combat bullying include launching the Web site, StopBullying.com, which provides information from various government agencies on methods and programs to deal with and stop bullying. In addition, the Department of Education's Office of Civil Rights has sent a "Dear Colleague" letter to schools, colleges, and universities clarifying federal protections for students from bullying, and Duncan sent a letter to every state school chief outlining each state's antibullying laws.

On the legislative front, a new bipartisan bill in the Senate looks to establish guidelines and requirements for reducing bullying in schools. Sens. Mark Kirk (R-Ill.) and Bob Casey (D-Pa.) introduced the Safe Schools Improvement Act. If that bill is passed, schools receiving designated federal funds would be "required to adopt codes of conduct specifically prohibiting bullying and harassment, including conduct based on a student's actual or perceived race, color, national origin, sex, disability, sexual orientation, gender identity, or religion." States would also be required "to report data on incidences of bullying and harassment to the Department of Education." When reached for comment, Kirk said "our children need to feel protected and safe so they can learn. My hope is that the Casey/Kirk bill will encourage schools and districts to develop effective prevention and responsible protocols."

Remarks of the president and Michelle Obama are posted at <www.whitehouse.gov/the-press-office/2011/03/10/remarks-president-and-first-lady-white-house-conference-bullying-prevent>. The Safe Schools Improvement Act is posted at <http://thomas.gov/cgi-bin/query/z?c111:S.3739:>. ■

Drug Firm to Pay Huge Fine In Illegal Marketing Case

A major pharmaceutical maker agrees to its second multimillion-dollar settlement in two years over charges that it engaged in illegal marketing practices for its antipsychotic drug.

BY KEN HAUSMAN

The District of Columbia and the 37 states that sued the pharmaceutical firm AstraZeneca over charges of deceptive marketing practices will divide $68.5 million, according to a settlement to which the company agreed in early March.

The charges involved the company's promotion of the atypical antipsychotic drug Seroquel (quetiapine) for off-label uses, including for treatment of sleep disorders, anxiety, and Alzheimer's disease and other dementias—uses not approved by the Food and Drug Administration (FDA) for Seroquel. Physicians are allowed to prescribe a medication for uses not approved by the FDA, but it is illegal for drug companies to promote the drug for such nonapproved, or off-label, uses.

The FDA has approved Seroquel to treat schizophrenia, as well as both acute manic and depressive episodes in bipolar disorder.

Charges against AstraZeneca also included failure to warn of potential side effects such as weight gain, hyperglycemia, and diabetes and withholding some data relating to the drug's safety and effectiveness.

Despite its agreeing to the settlement, AstraZeneca issued a statement saying that it denied the allegations, but "believes that it is important to bring these matters to a close and move forward with our business of providing medicines to patients."

In addition to the financial payments the company will make to the 38 jurisdictions that were plaintiffs in the lawsuit, it has agreed as part of the settlement to post on a Web site the payments for various professional activities that it makes to physicians and to guarantee that it will not pay any of its marketing representatives for recommending the drug for off-label uses. The company also agreed to refer to the indications for Seroquel's use that have been approved by the FDA when discussing symptoms the drug can treat and to avoid focusing discussions with health care providers on symptoms alone.

Similar lawsuits against AstraZeneca over Seroquel marketing have been filed in seven states in addition to the 37 covered by the March settlement. Those are Alaska, Arkansas, Mississippi, Montana, New Mexico, South Carolina, and Utah.

In April 2010 AstraZeneca agreed to pay the U.S. government and state Medicaid programs $520 million to settle a lawsuit filed against it by the Justice Department based on similar charges regarding the company's promotion of several nonapproved uses for Seroquel, including for Alzheimer's, aggressive behaviors, depression, and posttraumatic stress disorder. In agreeing to that settlement, the company also denied the allegations of illegal activities (*Psychiatric News*, June 18, 2010). It still faces thousands of civil lawsuits filed by individuals who allege serious adverse effects stemming from their use of Seroquel. ■

States Receive Guidance On Health-Reform Waivers

APA supports the requirement that states seeking waivers from the health care reform law conform to the law's goals regarding coverage, cost-sharing, and comprehensiveness.

BY RICHARD FAUST

In March the departments of Health and Human Services (HHS) and Education issued a proposed rule for states applying for waivers from provisions of the Affordable Care Act (ACA). In addition, President Obama has announced his support for bipartisan legislation that would move the timeline for availability of state waivers from 2017 to 2014.

In January's State of the Union Address, the president stressed that he was open to new ideas for improving the health care reform law. Echoing this commitment, HHS Secretary Kathleen Sebelius stated in a press release announcing the new rule that "Innovation Waivers empower states to take the lead on implementing the Affordable Care Act."

The waivers are designed to give states the latitude to implement their own health care policies, which may differ from those in the ACA as long as they meet specified criteria. The press release lays out the criteria contained in the proposed rule, requiring states to provide coverage that meet these requirements:

- It must be at least as comprehensive as that offered through health insurance exchanges—new competitive, private health insurance marketplaces.
- It must be at least as affordable as the cost-sharing protections through the exchanges.
- It must provide coverage to at least as many residents as otherwise would have been covered under the Affordable Care Act.
- It must not increase the federal deficit.

An HHS fact sheet on the proposed rule notes that states receiving waivers would also be required to submit quarterly and annual reports tracking measures in the four areas listed above and that the regulations suggest areas for continued monitoring of the waivers, such as choice of health plans and coverage of individuals with preexisting conditions.

The president has thrown his support behind a bipartisan bill to move the start date for implementation of state waivers from 2017 to 2014. The start date is important because many of the provisions of the ACA do not go into effect until 2014. If states can receive wavers at that time, they can continue with any innovations they already have in the works without stopping to switch to implementing the federal requirements.

Sens. Ron Wyden (D-Ore.) and Scott Brown (R-Mass.) first introduced the Empowering States to Innovate Act last November. In a press release Wyden stated that "some of the most innovative approaches to health policy have originated at the local level, where lawmakers have a unique insight into their constituents' lives, and the state waiver simply gives states the bandwidth to pursue those kinds of approaches." Brown said that "states shouldn't be forced by the federal government to adopt a one-size-fits-all health care plan."

Julie Clements, deputy director for regulatory affairs in APA's Department of Government Relations, stated that "we support the secretary's requirement that any innovative state programs substituting for Affordable Care Act provisions must still satisfy the ACA's goals of coverage, cost-sharing, and comprehensive benefits. These requirements preclude the waiver program from being a means to circumvent the goals of ACA regarding coverage, cost-sharing, and comprehensiveness." APA will likely submit brief comments to the Centers for Medicare and Medicaid Services reiterating support for the goals of ACA and the hope that states that "do innovate will go above and beyond the more positive aspects of the ACA and how it treats mental health."

The comment period on the proposed rule is open until May 13.

The proposed waiver rule is posted at <www.ofr.gov/OFRUpload/OFRData/2011-05583_PI.pdf>. The* Federal Register *listing for the rule is posted at <http://frwebgate1.access.gpo.gov/cgi-bin/PDFgate.cgi?WAISdocID=l5Bajp/0/2/0&WAISaction=retrieve>. The HHS fact sheet on the proposed rule is posted at <www.healthcare.gov/news/factsheets/stateinnovation03102011a.html>. The Empowering States to Innovate Act is posted at <http://thomas.loc.gov/cgi-bin/query/D?c112:2:./temp/~c1125CYkB8::>. ■

M.D. Groups Hope Ruling on Lawyers Will Also Apply to Physicians

The Federal Trade Commission could conceivably try to include physicians in the Red Flags Rule using entirely different criteria, but that would require a new ruling with a comment period, and physician groups would likely initiate renewed legal action.

BY MARK MORAN

A federal appeals court decision in March means physicians cannot be subject—at least for now—to the so-called Red Flags Rule.

The rule is a 2008 Federal Trade Commission (FTC) regulation stemming from the commission's interpretation of the Fair and Accurate Transactions Act of 2003, designed to tighten security of financial information held by banks and credit-card companies. Under the FTC's interpretation, physicians were classified as "creditors" because physicians bill people for services after they are provided and because physicians sometimes allow payment plans; under these conditions, they would therefore be required to comply with certain identity-theft-protection measures such as installing software security programs.

The next development in this saga occurred in March when the United States Court of Appeals for the District of Columbia Circuit found the application of the current FTC Red Flags regulations to attorneys to be invalid in light of the Red Flags Program Clarification Act of 2010, which was passed by Congress last December (*Psychiatric News*, March 4). That act, signed into law by President Obama in January, narrowed the term "creditor" to include only entities that use consumer reports, furnish information to consumer reporting agencies, or extend credit.

In revising the definition, the new legislation also undermined the basis for the application of the Red Flags Rule to physicians and other professionals. The appeals court decision was rendered in a suit brought by the American Bar Association, representing lawyers who had also been included as "creditors" in the FTC definition because they bill for services after they are rendered.

According to the court's ruling, "[T]he Clarification Act makes it plain that the granting of a right to 'purchase property or services and defer payment therefore' is no longer enough to make a person or firm subject to the FTC's red flags rule—there must now be an explicit advancement of funds. In other words, the FTC's assertion that the term 'creditor,' as used in the red flags rule includes 'all entities that regularly permit deferred payments for goods or services,' including professionals 'such as lawyers or health care providers, who bill their clients after services are rendered,'…is no longer viable."

The decision was welcomed by APA, the AMA, and other professional organizations that have argued that the FTC's interpretation was a bureaucratic burden for doctors already subject to regulations that ensure the safety of patient information. Last year, the AMA—along with APA and some two dozen other medical groups—filed suit against the agency to exempt their member physicians.

"The court's decision reinforces the intent of a new law clarifying the scope of the Red Flags Rule and helps eliminate any further confusion about the rule's application to physicians," said AMA President Cecil Wilson, M.D., in a statement released by the AMA. "The AMA will remain vigilant that the FTC respects the meaning and intent of the Clarification Act."

In an interview with *Psychiatric News*, Robert Portman, J.D., a lawyer representing APA and other specialty societies that have joined in the AMA suit, said, "The appeals court decision is a victory for doctors because it holds that the criteria by which the FTC was applying the rule to attorneys are no longer valid, and since those are the same criteria being applied to physicians, it means doctors can no longer be subject to the current rule."

But Portman said the door wasn't permanently shut on the issue. While the basis for the original inclusion of physicians and attorneys in the Red Flags Rule—that they bill for services after they are rendered—has been ruled inapplicable, he said it is conceivable that the agency, which is charged with protecting consumers from fraud and identity theft in the course of financial transactions, could still find that some physicians fall within the narrower definition of a "creditor" as defined by the Clarification Act. But he said that would require a new ruling and a comment period, with the likelihood of renewed legal action.

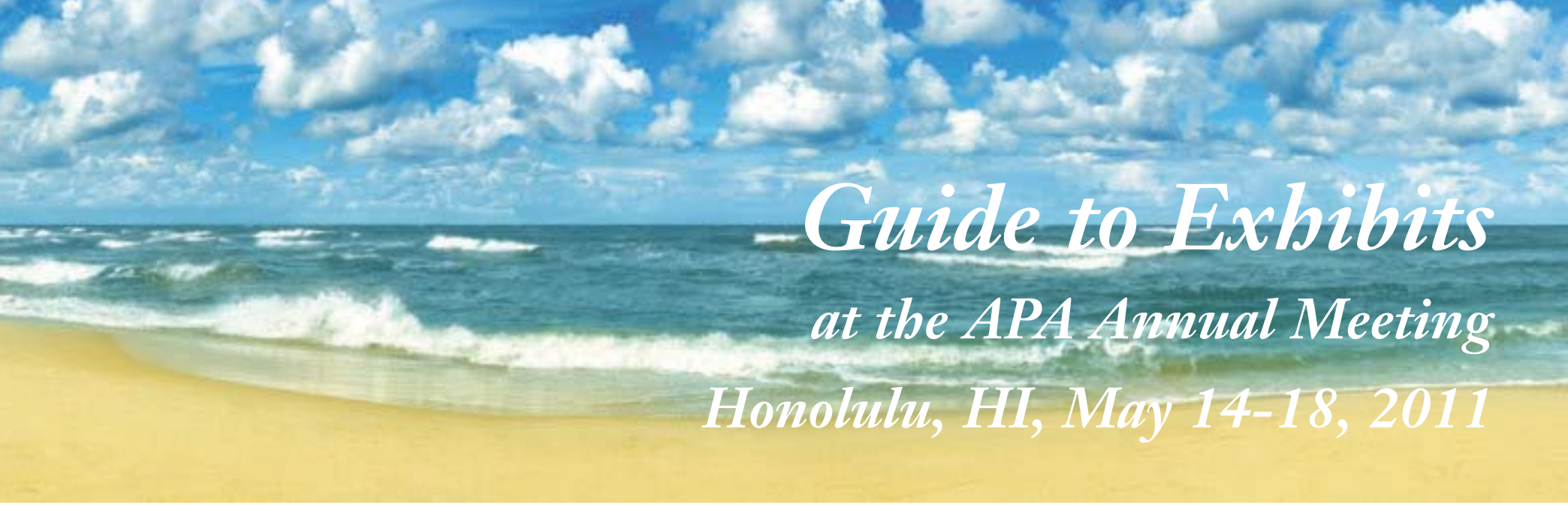
More information on the Red Flags Rule is posted at <www.ama-assn.org/ama/pub/physician-resources/solutions-managing-your-practice/practice-management-center/data-security/red-flags-rule.shtml> and <http://business.ftc.gov/privacy-and-security/red-flags-rule>. ■

Get a Head Start On Annual Meeting News

If you are attending next month's annual meeting in Honolulu, you'll want to jumpstart your meeting experience by reading through the new electronic preview issue of the *Daily Bulletin*. It's posted at <www.nxtbook.com/tristar/apa/preview_2011/index.php#/0>.

As meeting goers know, the *Daily Bulletin* is the annual meeting's onsite newspaper, providing information about meeting highlights, special events and scientific sessions, and general news about the meeting and local attractions.

The preview issue contains information about how to earn up to 8 CME credits by taking a self-assessment exam online as well as the special meeting features offered this year. Also, there will be a mobile version of the *Daily Bulletin* to keep you plugged in throughout the day. Instructions on how to download the annual meeting mobile app (APA 2011) appear on page 9 of the preview issue. Enjoy the *Daily Bulletin* preview issue, and see you in Honolulu!



Guide to Exhibits
at the APA Annual Meeting
Honolulu, HI, May 14-18, 2011

This abbreviated Guide to Exhibits introduces you to many exciting exhibits at the 164th APA Annual meeting in Honolulu. Exhibitors holding space as of March 31, 2011 are listed by product and service beginning on the following page. Exhibitors' product and services advertised in this issue appear in bold, followed by the page number.

The exhibits focus on specialized products and services for the psychiatric profession, including computer software, media products, online services, pharmaceutical products, diagnostic tools, ECT instruments, publishers and booksellers, insurance, financial services, management companies and services, market research, medical devices, electronic medical records, phototherapy, psychiatric facilities, treatment programs, recruiters, locum tenens, state and federal agencies, educational/professional support organizations and many more.

There are three special areas in the exhibit hall: the APA Member Center, Career Fair and Publishers' Book Fair.

APA Member Center

The APA Member Center opens Saturday, May 14 at 8:00 a.m. and is located in the exhibit hall, next to the American Psychiatric Publishing, Inc. bookstore. Whether you are a psychiatrist in patient care, administration, research, teaching or a resident/medical student, the APA Member Center has relevant information for you. Browse the new APA Store where APA-branded merchandise is available for sale. Discover all the advantages of APA membership, apply for membership, update your online APA membership profile and learn about cost saving members-only benefits. Find out about resident fellowship opportunities, the APA Job Bank, career and practice management information, legislative updates, and CME programs. Visit the American Psychiatric Institute for Research and Education for an update on DSM-V activities, the American Psychiatric Foundation to learn how the foundation is raising awareness that mental illnesses are real and can be effectively treated, and American Psychiatric Publishing, Inc. for the latest psychiatric books and journals.

Career Fair

The Career Fair includes exhibitors from psychiatric facilities, government agencies, hospitals, recruitment firms, and locum tenens seeking psychiatrists to fill open positions.

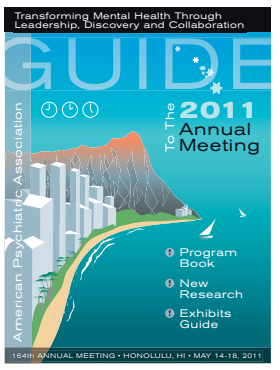
Publishers' Book Fair

The Publishers' Book Fair opens Saturday, May 14 at 8:00 a.m. Take advantage of the early opening to visit publishers with an outstanding collection of the latest professional books and journals in the psychiatric field.

Opening

The first exhibit areas to open are the APA Member Center, Career Fair and Publishers' Book Fair on Saturday, May 14, at 8 a.m. All exhibits open Sunday, May 15, at 8:00 a.m. Refer to the listing on the right for daily hours.

Guide to the 2011 APA Annual Meeting



At the meeting, registrants receive a copy of the *Guide to the 2011 APA Annual Meeting*. The *Guide* combines the APA Annual Meeting Exhibit Guide, Program Book, and New Research into one, comprehensive full color guide book. Easy to use fold-out tab dividers separate the Program Book, New Research and Exhibit Guide sections. Floor plans of the Exhibit Hall and Honolulu Convention Center, shuttle bus service, city map and other information are also included.

Photos by David Hathcox

Open Saturday, May 14
8:00 a.m. to 3:00 p.m.
Honolulu Convention Center
Exhibit Hall

APA Member Center

Lifelong Learning
Advocacy
Practice Tools
Quality Patient Care
Member Services
Job Bank
APA Store
American Psychiatric Foundation
American Psychiatric Institute for Research and Education (APIRE)

Career Fair

Publishers' Book Fair

All Exhibits Open Sunday, May 15
8:00 a.m. to 3:00 p.m.
Honolulu Convention Center
Exhibit Hall

APA Annual Meeting Exhibitors

by Product and Service

(as of March 31, 2011)

CME Provider

Neuroscience Education Institute 1124

Computer Software

CNS Vital Signs 939

Diagnostic Tool

AssureRx Health 843
MagVenture, Inc. 1038

ECT

MECTA Corporation 700
Somatics, LLC 1430

Education

Audio Digest Foundation 1420
NPIstanbul Hospital 1231
Tourette Syndrome Association 833

Electronic Medical Record

H&T Medical Solutions, LLC 1513
TheraManager, LLC 1616
Valant Medical Solutions 704

Healthcare

Kahi Mohala Behavioral Healthcare 1133

Hospital

NewYork-Presbyterian Hospital 609

Hospital/Residential and Outpatient Clinics

McLean Hospital 1432

Insurance

American Professional Agency, Inc. (7) 1621
The Psychiatrists' Program (27) 708

Life Sciences Data Company

CNS Response 1331

Medical Device

Electromedical Products International, Inc. 1425
Neuronetics, Inc. 1339
Rogue Resolutions 1135

Medical Education

15th World Congress of Psychiatry 1025
American Physician Institute for Advanced Professional Studies 615
Canadian Consortium for the Investigation of Cannibinoids 1134
Global Initiative on Psychiatry 1019
Sociedad Espanola de Patologia Dual - II International Congress Dual Pathology 1023

Mental Health Services

Adult Mental Health Division Department of Health 1606
Substance Abuse and Mental Health Services Administration (SAMHSA) 1031

Mobile Reference Software

Epocrates, Inc. 1522

Non-Profit Self-Help Group or Professional Association

American Board of Psychiatry and Neurology, Inc. ..... .934
American College of Psychiatrists 932
Christian Medical Association Psychiatry Section 835
NARSAD/NARSAD Artworks 1035
National Institute of Mental Health 1130
National Institute on Alcohol Abuse and Alcoholism 832
Physicians for a National Health Program 1132

Payment Processing

Solveras Payment Solutions 621

Pharmaceutical

Alkermes, Inc. 1419
Angelini Labopharm 403
AstraZeneca Pharmaceuticals 711
Avanir Pharmaceuticals 309
Bristol-Myers Squibb/Otsuka America Pharmaceuticals, Inc. 1039
Forest Pharmaceuticals, Inc. (29-33) 631
Janssen, Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc. 739, 839
Lilly USA, LLC (18-24) 701
Merck 508
Novartis Pharmaceuticals 1139, 1232
OmegaBrite 1233
Pamlab, LLC 1539
Pfizer, Inc. 1429
Reckitt Benckiser Pharmaceuticals 501
Shire Pharmaceuticals 520
Shionogi, Inc. 429
Somaxon Pharmaceuticals, Inc. 1439
Sunovion Pharmaceuticals, Inc. (cover-tip, 8a-h) 721, 733
TEVA Biologics and Specialty Products 303

Phototherapy

Northern Light Technologies 605

Professional Congress Organizer

World Psychiatric Association 1021

Professional Support/Organization

2nd International Congress on Borderline Personality Disorder 1024
24th ECNP Congress-European College of Neuropsychopharmacology 1022
Association of Gay and Lesbian Psychiatrists 1033

Psychiatric Facility

CBR Youth Connect 632
Homewood Health Centre 1333
Mayo Clinic 933
The Menninger Clinic (3) 726
North Shore LIJ Health System (36)
The Zucker Hillside Hospital 505
Truxtun Psychiatric Medical Group, LP/ Good Samaritan Hospital 1423

Publisher/Bookseller

BioMed Central 1225
Cambridge University Press 1118
Current Psychiatry/Quadrant Healthcom, Inc. 613
Elsevier 1224
Guilford Publications 1218
Hogrefe Publishing 1319
JAMA & Archives Journals 1223
Johns Hopkins University Press 1424
La Lettre Du Psychiatre 601
Lippincott Williams & Wilkins/Wolters-Kluwer Health 1318
The New York Times 1324
Oxford University Press 1220
Psychiatric Times 529
Psychotherapy.net 1418
Rapid Psychler Press 1125
Routledge 1123
Routledge Journals 1119
Wiley-Blackwell 1323

Recruitment

Army Medical Recruitment 1603
Army National Guard (25) 724
Global Medical Staffing 1602
Hospital Corporation of America 1608
International Medical Recruitment 1509
Jackson & Coker 1230
Kaiser Permanente/Permanente Medical Groups (37) 1704
LocumTenens.com (37) 628
Maxim Physician Resources 1604
Medical Doctor Associates 1330
Psychiatrists Only (35) 1131
QTC Medical Services, Inc. 1720
Registry of Physician Specialists 1507
Staff Care, Inc. 627
U.S. Army Medicine Civilian Corps 1505
U.S. Department of Veterans Affairs (HRRO) 1708
U.S. Navy Recruiting Command 1607
U.S. Public Health Service 1609
University of Vermont, Department of Psychiatry 1702
VISTA Medical Solutions 931

State/Federal

Army Medical Recruitment 1603
National Institute on Drug Abuse 1030
Office of Medical Services, U.S. Department of State 1503

Substance Abuse

Clarity Way 602

Telemedicine Equipment

GBH Communications, Inc. 606

Telepsychiatry

Forefront Behavioral TeleCare, Inc. 604

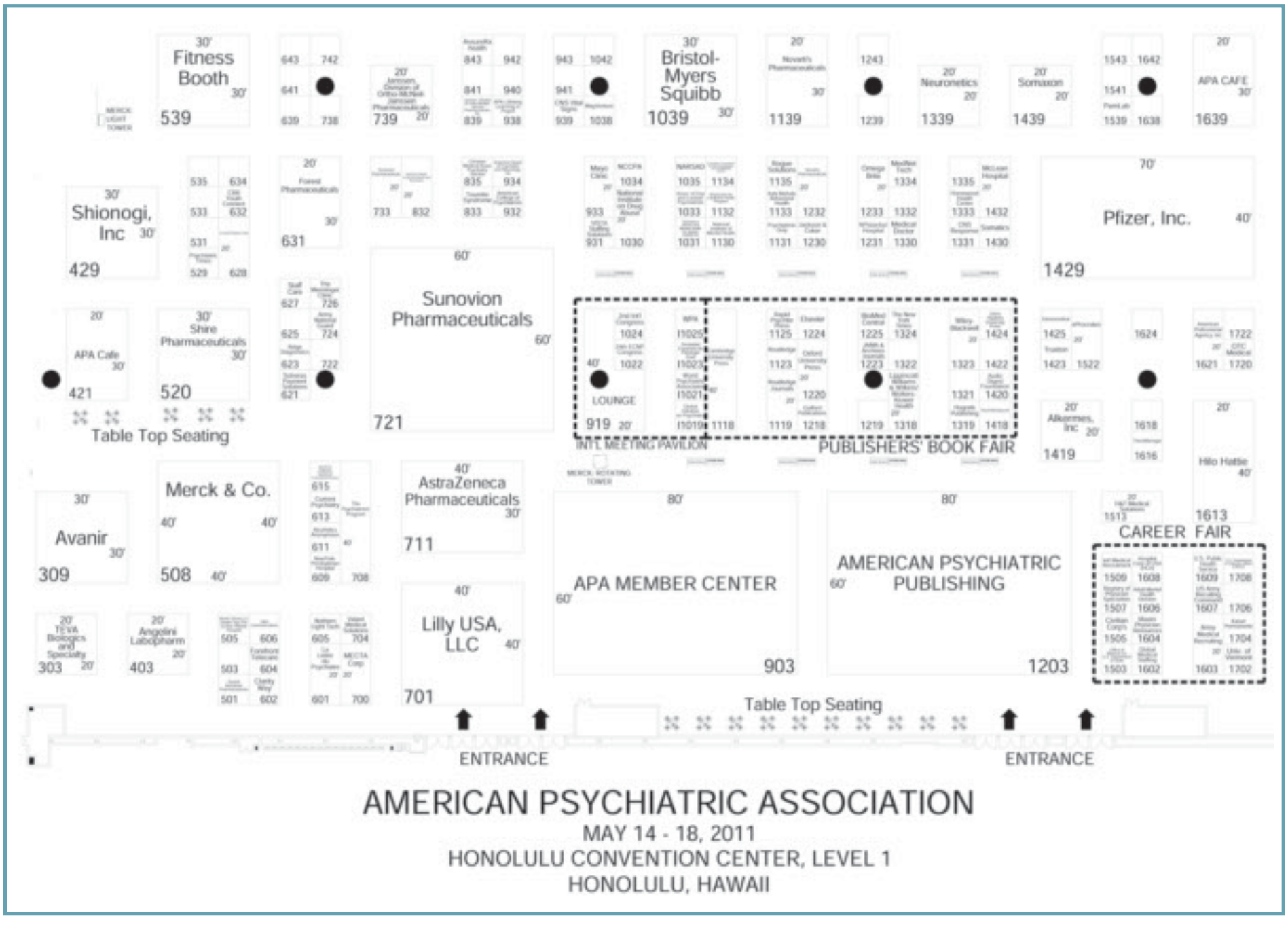
Twelve Step Fellowship

Alcoholics Anonymous 611

Website Design

MedNet Technologies, Inc. 1334

Honolulu Convention Center Exhibit Hall



AMERICAN PSYCHIATRIC ASSOCIATION

MAY 14 - 18, 2011
HONOLULU CONVENTION CENTER, LEVEL 1
HONOLULU, HAWAII

The APA Job Bank is located in the APA Member Center in the Exhibit Hall of the Honolulu Convention Center.

Hours:
Saturday, May 14
8:00 am - 3:00 pm

Sunday, May 15
8:00 am - 3:00 pm

Monday, May 16
8:00 am - 3:00 pm

Tuesday, May 17
8:00 am - 3:00 pm

Candidates and Employers Connect through the APA Job Bank

at the APA Annual Meeting
May 14-17 in Honolulu, Hawaii
psych.org/jobbank

- Use the APA Job Bank "Event Connection" tool at psych.org/jobank to set up interviews with a prospective employer or candidate attending the meeting. When you sign up for the "Event Connection" you are eligible to win a $100 gift card.
- Visit the new and improved APA Job Bank portal to search the most comprehensive online listing of psychiatric positions.
- During the meeting ask APA Job Bank representatives for a demonstration of new site Features, get answers to your questions, and submit a new employment announcement.
- Employers-find out how to save 10% on each ad that runs in *Psychiatric News* or *Psychiatric Services* and the Job Bank.

Contact: **Lindsey Fox**
Phone: **703-907-7331**
Fax: **703-907-1093**
E-mail: **lfox@psych.org**

Board Approves Changes For *Psychiatric News*

Among other actions, the Board of Trustees votes to make it easier for APA members to achieve fellowship status and decides on the schedule for electing its first position for a minority/underrepresented group trustee.

BY KEN HAUSMAN

At its March meeting in Arlington, Va., the APA Board of Trustees voted to approve several items related to the future of *Psychiatric News*. A work group appointed last year by then APA President Alan Schatzberg, M.D., and chaired by Jeffrey Borenstein, M.D., chair of APA's Council on Communications, was tasked with making recommendations about the future of APA's newspaper, in particular how it might expand to incorporate more digital options as readers get an increasing share of their professional and other information through those resources.

Credit: David Hathcox

Dilip Jeste, M.D., who at the close of next month's annual meeting in Honolulu will become the APA president-elect, discusses proposed changes to the criteria members will need to meet to achieve fellowship status in the Association, while Area 2 Trustee James Nininger, M.D., looks on.

At last month's meeting the Board voted to support a move by *Psychiatric News* to greatly expand its digital presence to complement the print version of the paper. The Board also approved a proposal to integrate APA's many newsletters into *Psychiatric News* in tabbed sections of an expanded online edition of the paper that will soon be developed. (The online edition of *Psychiatric News* is posted at <pn.psychiatryonline.org>.) In addition, the Board approved funds for a redesign of the newspaper's print version that can be adapted for its digital products.

To give the paper's circulation a sizable boost that will make it more attractive to advertisers, some of whom have shifted their advertising to competing psychiatric publications with far more readers, the Board endorsed a proposal to send the paper to 10,000 nonmember psychiatrists. This will put its circulation on a par with those for the monthly publications *Psychiatric Times* and *Clinical Psychiatry News* and give APA an additional opportunity to convey information about its activities and accomplishments to nonmembers and in so doing interest them in joining APA.

APA President Carol Bernstein, M.D., agreed to appoint, in conjunction with President-elect John Oldham, M.D., a search committee that will recommend to the Board no later than September 1 the names of candidates for the next editor in chief of *Psychiatric News*. That position became vacant when James Krajeski, M.D., stepped down last May after 12 years in the job. Former APA President Carolyn Robinowitz, M.D., has been serving as interim editor in chief until Krajeski's successor is chosen.

Fellowship Criteria Change

On a membership-related issue, the Board decided to back a proposal from the Membership Committee to eliminate the requirement that APA members applying for fellowship status in the Association must have two letters of recommendation from current APA fellows. The other fellowship criteria will remain the same, that is, board certification, APA membership for at least five years, and a 30-day review by the applicant's district branch. The Board charged the Membership Committee with reviewing fellowship criteria again in two years to assess whether any additional revisions may be in order.

Credit: David Hathcox

Sandra Walker, M.D., chair of APA's Council on Minority Mental Health and Health Disparities, comments on the schedule that will be implemented for electing the new minority/underrepresented group trustee and the restored trustee-at-large position.

Minority-Trustee Election Procedures

Also on the Board's agenda last month was approving changes to APA Bylaws that are needed to reflect the Trustees' decision last year to add a minority/underrepresented (M/UR) group trustee and to reinstate an at-large trustee position.

Under the revised procedure, there will be an election for the trustee-at-large in the next election, which will be held in 2012. The first M/UR trustee will be elected in the following election cycle. Both the at-large trustee and the M/UR trustee will serve two-year terms.

Trustees also got an update on APA's activities concerning development of regulations to implement the federal parity law from Paul Wick, M.D., chair of the Board Work Group on Health Reform and Parity and a member of the Council on Healthcare Systems and Financing. Wick noted that the group is focusing on both "general issues of significance," such as the scope of services health plans have to provide under the law, and "specific issues that directly impact psychiatry," for example, reimbursement rates for psychiatrist-provided services.

In the next six to nine months, the work group, along with the Council on Healthcare Systems and Financing, will concentrate on how the parity law requirements apply to managed Medicaid plans and on what mental health services must be included in the "essential health benefit package" that health plans offer so that they comply with the parity law. The work group will also address with federal regulators "undue utilization review requirements for inpatient and outpatient care," Wick noted.

On another matter, the Board voted to give $50,000 in American Psychiatric Foundation funds to help sponsor the "Next Frontier, One Mind for Brain Research" campaign, which is being spearheaded by former Rep. Patrick Kennedy and has a goal of raising $1 billion for research into brain disorders (see next issue).

In addition, Trustees agreed to endorse "The Parents' Medication Guide for Bipolar Disorder in Children and Adolescents," which was developed by the American Academy of Child and Adolescent Psychiatry and released last August. The guide is posted at <www.aacap.org/galleries/default-file/aacap_bipolar_medication_guide.pdf>.

A draft summary of actions from the March Board meeting is posted at <www.psych.org/Resources/Governance/BoardofTrustees/ArchivesofMeetingsoftheBOT/March-2011-Board-of-Trustees-Meeting.aspx>. ■

Assembly Election Candidates

The APA Assembly will hold its annual election next month at its three-day meeting held in conjunction with APA's 2011 annual meeting in Honolulu.

In the race to be the next speaker-elect are R. Scott Benson, M.D., of Florida, and John Gaston, M.D., of Georgia. Benson is the recorder of the Assembly, and Gaston is the Assembly's Area 5 representative.

Vying to replace Benson as recorder are Ramaswamy Viswanathan, M.D., and Melinda Young, M.D. Viswanathan is one of the Assembly representatives from Area 2 (the New York State Psychiatric Association), and Young is a representative from Area 6 (the California Psychiatric Association).

At the end of the 2011 annual meeting, the current speaker-elect, Ann Sullivan, M.D., will begin a one-year term as speaker.

APA members are encouraged to contact their Assembly representatives if they have any comments about the election or the candidates.

Fellows Named

Five psychiatry residents have been selected for the 2011-2012 APA Child and Adolescent Psychiatry Fellowship.

The fellowship is awarded each year to PGY-1 to PGY-3 psychiatry residents to support their attendance at two APA annual meetings and to further develop their interests in pursuing careers in child and adolescent psychiatry. These residents are mentored by noted child and adolescent psychiatrists. Here are the names of the new fellows and their training affiliation:

- Christopher Hammond, M.D., Yale-New Haven Hospital
- Jared Kiddoe, M.D., Duke University
- Chinedu Onyedike, M.D., Johns Hopkins University
- Melissa Rooney, M.D., New York Presbyterian Hospital
- Darryl Smith, M.D., Howard University ■

Hispanic Psychiatrists To Meet in Hawaii

The American Society of Hispanic Psychiatry will hold its 2011 annual conference at APA's annual meeting in Honolulu on Saturday, May 14. The theme of the conference is "Evidence-Based Treatments for Latinos With Schizophrenia, Mood, and Impulse Disorders and ADHD."

The location is the Molokai Room at the Sheraton Waikiki. Registration will open at noon, and the conference will begin at 1 p.m. A cocktail reception will follow that evening, from 6 p.m. to 7 p.m.

Registration is required, but there is no registration fee. More information is available from Maria Sciancalepore at (732) 690-4507 or mcesteve896@aol.com. ■

Musicians Sought

The Medical Musical Group (MMG) Symphony Orchestra and Chorale seek new participants. In 2011, MMG plans twin "Healing for the Nations" concerts in Washington, D.C., and Geneva, Switzerland, on November 9 and 15, respectively. More information may be obtained by calling (202) 797-0700 or sending an e-mail message to vanmmg@hotmail.com.

Seeking Pampering or Adventure? Here's Where to Find Them

Whether you're looking to enhance your Honolulu annual meeting experience with expert relaxation or more active pursuits, a local psychiatrist offers an array of prescriptions.

BY JEFFREY AKAKA, M.D.

Credit: Hawaii Tourism Japan

The diverse plants of Oahu are on display at the Waimea Valley Audubon Center.

Want to experience Hawaii for a few days longer, away from the crowded bustle of Waikiki?

This is the reality of the Turtle Bay Resort on the North Shore of Oahu in Kahuku (808-203-3650; <TurtleBay Resort.com>). With a rocky peninsula dividing surfable waves on its western side from a gentle, sandy beach bay on its eastern side, you would be hard pressed to find a better escape on Oahu than this resort. Its spacious feel is enhanced by panoramic ocean views from every guest room. Your days will be as free or as filled with activity as you wish. For those who prefer being pampered, great food, an extensive kids program, jacuzzis, and a full-service spa are there for your enjoyment. Visitors who prefer a more active vacation experience can take advantage of 12 miles of oceanfront trails for hiking, jogging, or horseback riding; the 80-foot waterslide; two oceanfront swimming pools; surfing lessons; tennis courts; and a fitness center. Visitors can even book a helicopter tour that departs from the on-site landing pad. The Arnold Palmer golf course, with a Scottish links front nine and a tropical forest, marsh, wetlands, and ironwood back nine, water coming into play on 14 of its holes—including the ocean backdropped signature 17th, is one of my favorites. (You may recognize it from a scene in the television show "Lost" in which Sayid shoots both a ball and a bullet.)

Credit: Hawaii Tourism Authority (HTA) /Tor Johnson

Beautiful Waimea Bay on Oahu's North Shore is a popular venue for surfing competitions and movie filming.

The resort's second golf course, designed by Fazio, has wider fairways, but with too much sand in wide bunkers, it steals many of your golf balls.

A few minutes' drive to the west is famous Waimea Bay on the North Shore of Oahu, popularized by the 1960s movie "Ride the Wild Surf." Winter waves 30 to 40 feet high attract high-surf specialists and their fans. By the time you arrive in May, calmer waters will entice more casual swimmers to frolic on its sizable beach.

Waimea Bay and Waimea Valley were of great religious and political significance to the Kahuna (high priests) and Ali'i (high chiefs) of old Hawaii, including King Kamehameha the Great, whose unstoppable war machine transformed the Hawaiian Islands from multiple chiefdoms into a single Hawaiian nation. On the plateau above Waimea Bay, reached via a winding paved road, respectful visitors are welcome to experience the spiritual power of the Pu'u Mahuku Heiau, one of the largest partially restored Heiau (temples of worship) in Hawaii. It has been reported that Hewahewa, a Kahuna Nui (high priest) for Kamehameha, performed rituals including human sacrifices here. Waimea Valley, Mauka of the bay, was known for its great agricultural bounty. Once filled with taro (a root starch similar to a potato), the valley is now a botanical garden with thousands of plants, some found nowhere else in the world. There is a fee to enter, but the 3/4 mile paved road through the garden (bring mosquito repellant) rewards the stroller with a waterfall-fed pool safe enough for swimming.

Want another way to escape Waikiki other than by plane to a neighbor island or by driving an hour and a half to the North Shore? How about chartering a private yacht? I'd recommend, from personal experience, making a reservation for a gourmet dinner off Waikiki for you and family or several close friends, yacht included, with Chad Allenbaugh of Hawaii Yachts (808-222-9768; <www.Hawaii Yachts.com>). With a fleet of seven motor and sailing yachts of 50 to 60 feet, Chad and his captains will arrange transportation to Kewalo Basin Marina (about a mile Waianae of the Hawaii Convention Center) and then take you on a private cruise for as little as a few hours off Waikiki, to a few days around the Hawaiian Islands chain, or to as much as a few weeks to sail you from San Diego to the APA annual meeting in Honolulu. Take your choice among the yachts he provided for various royalty, Muhammad Ali, and Bill and Hillary Clinton, among others. A family friend treated my family and me to the private Waikiki dinner experience—fantastic!

So much to share, so little time. Come to Hawaii for the annual meeting, recharge your academic and clinical batteries, and restore yourselves and your families in our island paradise. ■

Jeffrey Akaka, M.D., is president of the Hawaii Psychiatric Medical Association and a past speaker of the APA Assembly.

HONOLULU MAY 14-18: REGISTER NOW FOR THE ANNUAL MEETING!

Although you can no longer register by mail or fax for APA's 2011 annual meeting, you can register online at <www.psych.org/annualmeeting> or on site at the Hawaii Convention Center.

Here are some of the special meeting features that await you:

- 20 percent discount for APA members at the APPI Bookstore; 25 percent for members-in-training.
- 20 percent discount on Hilo Hattie merchandise, located in the Exhibit Hall. Hilo Hattie is the world's largest manufacturer of Hawaiian and resort fashions.
- Food voucher for all paid attndees good in all Exhibit Hall food courts during exhibit hours.
- Networking lounge in Exhibit Hall with free wi-fi.
- Fitness Pavilion with Nintendo Wii.
- Coffee lounges throughout the Exhibit Hall.

APA Lifers Plan Active Schedule At Annual Meeting

The APA members of this organization have signed on for life—and welcome others to join them. Here is information about the group and the activities it has planned for the annual meeting.

BY LINDA BUENO

The Lifers of APA welcomes all eligible APA members to join the organization and attend the activities that it has planned for APA's 2011 annual meeting in Honolulu. (A schedule appears below.)

Linda Bueno is director of industry relations for the American Psychiatric Foundation.

The mission of the APA Lifers is to assist in APA's work to further the quality of patient care and advance the future of psychiatric research and services; engage in related charitable, educational and/or social endeavors in psychiatry; and bring into closer fellowship interaction among APA's distinguished life members, distinguished life fellows, distinguished fellows, and life associate members.

The officers of the Lifers are Stephen Scheiber, M.D., president; Paul Wick, M.D., vice president; Bernard Katz, M.D., treasurer; Maria Lymberis, M.D., secretary, and Sheila Hafter Gray, M.D., past president.

Friday, May 13

5:30 p.m.: The **Assembly Caucus** will meet at the Hilton Hawaiian Village in the Iolani Suite at 7 p.m. Discussions on new initiatives and timely topics will be led by the Lifers' Assembly liaison, Bert Warren, M.D.

please see ***Lifers*** *on page 34*

Analyzing 'In Treatment' And Its Termination

BY HARVEY GREENBERG, M.D.

During my Bellevue C/L training, I was asked to evaluate a classic alcoholic with DTs and chronic cardiac and renal disease. Besides being exuberantly paranoid and profane, the patient reeked of booze and body odor. "Why are we knocking ourselves out with this guy?" asked an annoyed intern, "He's just another bum." The chief resident angrily retorted: "There's no room for bum treatment in the treatment of bums!"

Several years ago, I criticized Tony Soprano's long-suffering therapist, Dr. Jennifer Melfi, for giving her badfella client the bum's rush as the HBO series ended. Melfi probably should never have taken on Tony in the first place for moral as well as legal reasons. But, as Al Capone said about the rackets, once you're in, you're in, and there's no getting out. At first hugely resistive, Tony had come to trust Melfi over several years, even benefit from her help. In this context, ejecting him from treatment was callous and unethical.

The third and last season of the HBO series "In Treatment" recently concluded with another therapeutic bum's rush. During the previous seasons, Dr. Paul Weston, a gifted but deeply flawed psychoanalyst, was treated by his former mentor, Gina. Their relationship was complex. Her interventions were sometimes questionable. She was guilty of several major boundary violations, as was Weston himself in his work. But Gina's respect of and concern for Weston seemed genuine. Although he left treatment with his doubts about the value of psychotherapy unresolved, he parted on warm terms with her.

I speculate that the creators of "In Treatment," in the context of flagging interest in the series, imagined that going deeper into Weston's neurotic conflicts would make for more gripping melodrama. Unfortunately, they converted their sympathetic wounded healer into an unappealing whiner, awash in maudlin self-pity. His work with his latest crop of patients—a depressed Indian ex-patriot, a famous actress who couldn't remember her lines, and a provocative gay adolescent—was more uneven than ever and compromised by his gnawing skepticism.

Weston returned to treatment yet again after discovering that Gina had painted a mean and recognizable portrait of him in a novel. This time around, he was careful to choose Adele, a brilliant young psychoanalyst with impeccable credentials, utterly incapable of Gina's countertransferential contretemps.

Adele quickly winkled out Weston's rescue fantasies, his overweening need to be needed, and his hidden sense of entitlement. She adroitly turned away—and interpreted—his clumsy proposition to take their relationship out of the office. But despite her finely honed skills, Adele was a Freudian ice queen. With all her avowals of sympathy, she was emotionally tone-deaf to his suffering.

Dr. Melfi whacked Tony Soprano out of therapy crudely—and uneasily. But Adele's bum's rush of Weston was so subtle, so well rationalized by her stringent obedience to ultraorthodox analytic principles as to go unrecognized by her. Weston suffered a narcissistic meltdown when he discovered Adele was pregnant. In their last session, his composure and dignity restored to something of his healthier self of the first two seasons, he asked her to reveal the circumstances of her pregnancy. Was she married? Living with someone? Or was there no father, rather insemination in the abstract?

Weston made it clear that he neither wanted nor needed many details about her private life. He just feared that her refusal to reveal the simple truth about her pregnancy would precipitate an interminable analysis of his fantasies about her, while more pressing issues in the real world would go unaddressed.

I believe his request deserved an answer. For the concluding season's immature and unmoored Weston has, at base, been an adolescent in an adult's body. To treat teenagers—and perennial adolescents like Weston—the therapist must share something, though not much, of his or her outside life. It's mightily therapeutic to know you are sharing your problems with a fully fleshed human being, and not some Rogerian robot.

Predictably, Adele remained as mum about her pregnancy as about the rest of her world. Although she rendered Weston more honest service than slippery Gina, her "appropriate" analytic stance is as cruel as Melfi's coarse rejection of Tony Soprano. Weston does well to flee Adele's juiceless care. Her parting words—"my door is always open to you"—go down as easy as oysters. Her smile is a pleasant rictus. Come back tomorrow and get more of the rigid, frigid same. ■

Harvey Greenberg, M.D., is a clinical professor of psychiatry at Albert Einstein College of Medicine. He publishes frequently on media, cinema, and popular culture.

MindGames Finalists for 2011: Which Team Will Reign Supreme?

The three finalist teams for APA's annual MindGames competition were announced last month at the meeting of the American Association of Directors of Psychiatric Residency Training. The teams are from Boston University Medical Center, New York Presbyterian Hospital-Cornell Campus, and University of Pittsburgh/Western Psychiatric Institute and Clinic.

The teams will face off in a "Jeopardy"-style competition at APA's annual meeting on Tuesday, May 17, from 10 a.m. to 11 a.m. in Room 323A-C of the Hawaii Convention Center. Glen Gabbard, M.D., will once again take on the role of Alex Trebek in the final round.

The MindGames competition began in February with a preliminary qualifying phase in which residency programs chose a team of three residents to take an online quiz with questions based loosely on the ABPN Part 1 content outline and additional questions on neurology and psychiatry history. Each team had to answer 150 online questions in 60 minutes.

MindGames is a collaboration between APA and the American College of Psychiatrists and supported by an unrestricted educational grant from AstraZeneca.

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

Representatives of the winning teams hold mock checks for travel funds to attend the MindGames final next month at APA's annual meeting. Top left, left to right: From New York Presbyterian Hospital-Cornell are Elizabeth Auchincloss, M.D., director of residency training; team members Conor Liston, M.D., Ph.D., Jennifer Bernstein, M.D., and Benjamin Zebley, M.D.; and Sibel Klimstra, M.D., associate director of residency training. Top right, left to right: The University of Pittsburgh team members are Sarah Wolfe, M.D., Shannon Allen, M.D., and Ryan Herringa, M.D., Ph.D. Bottom left, left to right: From Boston University Medical Center are residency program director Janet Osterman, M.D., and team members Ana Ivkovic, M.D., Brie Beaudoin, M.D., and Mark Oldham, M.D.

Join in Discussion On Integrated Care

Join in the discussion group for psychiatrists working at the interface of primary care and mental and behavioral health at APA's 2011 annual meeting in Honolulu on Sunday, May 15. The session will be held from 9 a.m. to 10:30 a.m. in the Ilima Room on the second floor of the Ala Moana Hotel.

This forum will allow for dialogue about both the work psychiatrists do with primary care colleagues in integrated settings and the primary care considerations facing psychiatrists in mental health practices. Psychiatrists working in these settings will have an opportunity to exchange ideas and network.

Leading the annual meeting discussion will be Jurgen Unutzer, M.D., the principal investigator for Project IMPACT and vice chair of psychiatry at the University of Washington, and Lori Raney, M.D., the medical director of Axis Health System in Durango, Colo. Project IMPACT, at <http://impact-uw.org>, is responsible for the model of care most frequently used in integrated settings.

The conversation is sure to be timely and useful in this era of health care reform. Psychiatric leadership is crucial to making health care reform successful and to attaining the long-sought goal of closing the mortality gap for persons with mental illness.

APA's Council on Healthcare Systems and Financing recently created an electronic forum for members interested in learning more about integrated care and how it relates to psychiatry. It now has about 160 members.

More information about the forum and the annual meeting discussion is available by contacting Karen Sanders at (703) 907-8590 or ksanders@psych.org. ■

Gene Data Suggest Obesity Linked to Food Addictions

If you like sweets, perhaps you should attribute it not to a "sweet tooth," but to having two copies of a variant of the mu opioid receptor gene.

BY JOAN AREHART-TREICHEL

Could obesity be due to a food addiction?

In some cases that is a distinct possibility, Nora Volkow, M.D., director of the National Institute on Drug Abuse, stated in an editorial in the May 2007 *American Journal of Psychiatry*. Obesity, she said, "is not only a metabolic disorder, but also a brain disorder. . . [and] we propose that some forms of obesity are driven by an excessive motivational drive for food and should be included as a mental disorder in *DSM-V*."

Since then, evidence has been building that some cases of obesity are indeed due to a food addiction. For example, the endogenous opioid system, which is implicated in alcoholism and heroin abuse, is also known to stimulate food intake. Opioid circuitry in both the nucleus accumbens and ventral palladium regions of the brain appears to mediate taste responses. Impulsivity and the tendency to act on cravings have been linked with higher mu opioid receptor concentrations and greater opioid system activation.

And recently people who possess two copies of a variant of the mu opioid receptor gene have been found to have a greater weakness for sweet and fatty foods than people who have only one copy of the variant or another variant of that gene. A preference for sweet and fatty foods in turn has been linked with emotional eating, binge eating, and hedonic eating (which the researchers defined as appetitive responsiveness to food independent of actual consumption). And these three types of eating in turn have been linked with obesity.

The findings were reported online January 25 in the *International Journal of Obesity*. The lead investigator was Caroline Davis, Ph.D., a professor of health at York University in Toronto, and the senior investigator was J.L. Kennedy, M.D., of the University of Toronto's Centre for Addiction and Mental Health.

Three hundred men and women aged 24 to 50 recruited from universities, hospitals, newspaper ads, and other venues took part in the study. The sample had a broad range of body mass index (BMI) values, with a distribution representative of the general adult population. None of the subjects had a psychotic disorder, an alcohol use disorder, a substance use disorder, or a serious medical illness.

Subjects filled out the Food Preference Questionnaire, indicating their preference for various foods on a nine-point scale. Subjects' tendencies to binge eat were evaluated with the Binge Eating Questionnaire. Their appetitive responsiveness to food—for instance, "If I see or smell a food I like, I get a powerful urge to have some"—was assessed with the Power of Food Scale. And their tendency to eat when prompted by emotions such as tension and worry was evaluated with the Eating Behavior Patterns Questionnaire.

Subjects were genotyped for the mu opioid receptor gene. A total of 226 of the subjects (75 percent) possessed two copies of the A variant of the gene, 62 (21 percent) possessed one A variant of the gene and one G variant of the gene, and the remaining 12 (4 percent) possessed two copies of the G variant of the gene.

The researchers compared the three gene groups on their preferences for sweet foods, fatty foods, or both and found that the GG group scored significantly higher on the preference for sweets, fatty foods, or both than the other two gene variant groups did. (The latter two groups' preferences for sweet and fatty foods were comparable.)

Moreover, they found that a preference for sweet and fatty foods was positively correlated with hedonic eating, emotional eating, and binge eating, and that all three of these forms of consumption in turn contributed to a subject's BMI.

It thus looks as if individuals with two copies of the G variant of the mu opioid receptor gene are particularly vulnerable to consuming sweet and fatty foods and ultimately to obesity—"a biological liability that is easily exploited in our fast-food culture and toxic-food environment," Davis and her colleagues stated.

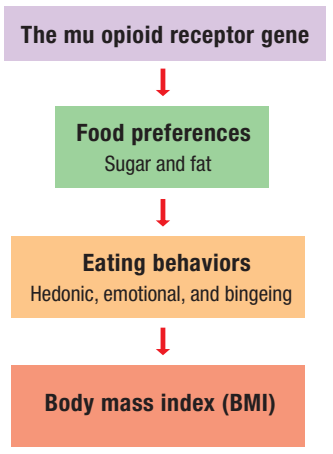
Yet while having two copies of the G variant of the mu opioid receptor gene may explain certain individuals' obesity problems, it may be only a minor culprit in society's overall obesity crisis, Davis indicated to *Psychiatric News*. One reason for this belief is that only 4 percent of subjects in this study had two copies of the G variant of the gene. Another reason is that hedonic eating, emotional eating, and binge eating explained only 51 percent of the BMI of subjects in this study. In other words, "Lots of factors, most of which are probably unknown to us," explained the remaining 49 percent, Davis said.

The study was funded by the Canadian Institute of Health Research.

An abstract of "Opiates, Overeating, and Obesity: A Psychogenetic Analysis" is posted at <www.nature.com/ijo/journalvaop/ncurrent/abs/ijo2010276a.html>. ■

The Path From Gene to Obesity

This diagram shows how having two copies of a particular variant of the mu opioid receptor gene (G variant) can lead to a preference for sugar and fat, which in turn can lead to hedonic, emotional, and binge eating, and finally to an expanding body mass index (obesity).



Source: Caroline Davis, Ph.D., et al., *International Journal of Obesity*, January 25, 2011

Mutation Implicated in Psychosis Points to Drug-Development Target

Elucidating the genetic basis for schizophrenia is turning out to be as difficult as understanding the condition itself. A recent development appears to be only a small piece of the puzzle but could represent a much larger section of the bigger picture.

BY LESLIE SINCLAIR

It's been 100 years since Swiss psychiatrist Eugen Bleuler coined the term "schizophrenia," renaming the symptoms German physician Emile Kraepelin in 1887 had initially called "dementia praecox." It was beginning to appear as if it might take another century to decipher the genetic basis of schizophrenia.

Efforts until now have suggested that the brain disorder that affects about 1 percent of adults might, in many cases, be rooted in different genetic causes in each affected individual, complicating prospects for elucidating the source of schizophrenia-spectrum disorders and delaying the search for cures.

But a recent National Institutes of Health–funded study published in the February 23 *Nature* may have yielded a tiny clue that has huge potential for furthering understanding of schizophrenia-spectrum disorders and possibly creating effective treatments. For the study, 30 investigators collaborated to analyze the genomic makeup of 15,721 individuals—8,290 of whom had been diagnosed with schizophrenia.

The size of the study is impressive: "Sample sizes like this are required in order to make progress. You really can't do this with a handful of families; you need thousands," said Jonathan Sebat, Ph.D., an assistant professor at the University of California, San Diego, chief of the Beyster Center of Molecular Genomics for Neuropsychiatric Diseases, and leader of the study team, in an interview with *Psychiatric News*.

The results of the study are equally impressive: Sebat and his colleagues found that patients with schizophrenia were 14 times more likely than controls to have mutations—specifically, mutations that are known as copy number variations (CNVs)—of the vasoactive intestinal peptide receptor gene VIPR2. The researchers say these findings implicate altered vasoactive intestinal peptide signaling in the pathogenesis of schizophrenia and point to the vasoactive intestinal peptide receptor VPAC2 as a potential target for the development of new antipsychotic drugs.

VIPR2 does a lot of exciting things in the brain, but it has been overlooked. That its name is misleading "is one reason why it hasn't already been on everyone's list of candidate genes," said Sebat. VIPR2 regulates patterns of activity in sleep, mediates important events during the development of the nervous system, and regulates learning and behavior. "It's been postulated to be involved in autism, Down syndrome, and fetal alcohol syndrome. But this is the first time it's been genetically linked to mental illness."

"In our previous smaller study (published in the April 2008 *Science*), we could see there was a contribution from rare mutations, but it wasn't clear which regions were the culprits," said Sebat. "At that time, it seemed that the mutations were often specific to single cases or families. Virtually every mutation we detected was different in a sample of 150 adults with schizophrenia and 268 healthy controls."

This larger study, however, has pointed the finger of responsibility, at least for a small percentage of patients with schizophrenia, at the VIPR2 gene, and that has exciting implications for the development of treatments for schizophrenia, with the VPAC2 receptor as a potential target.

"VIPR2 is a drop in the bucket in terms of genetic causes of schizophrenia, but it's a good one because it's a potential drug target. So it raises the possibility of a novel approach to drug development: Target a rare mutation the way you would develop an orphan drug, only expecting success with small markets," Sebat suggested. "Because some of these common neuropsychiatric disorders may be a constellation of rare genetic disorders, it may be feasible to establish efficacy in a small group of individuals, prove efficacy in small trials, then expand that drug to evaluate its applicability to a broader range of patients. Genomics is key to enabling this kind of treatment."

An abstract of "Duplications of the Neuropeptide Receptor Gene VIPR2 Confer Significant Risk for Schizophrenia" is posted at <www.nature.com/nature/journal/vaop/ncurrent/full/nature09884.html>. ■

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 general 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).

I Will:

*O*ffer educational resources that may support your patients

*R*ealize I'm not the most important person you'll see today

*R*emember that small talk is best in small doses

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duloxetine HCl

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

We provide clinical 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 visit insidecymbalta.com.

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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duloxetine HCl

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.

DD HCP ISI 4NOV10

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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.

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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.

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Major Study Finds Most Youth Fail to Get Needed MH Care

A national survey finds startling rates of psychiatric disorders in U.S. youth, often higher than for illnesses such as diabetes and asthma, but most of these youth go without needed mental health care.

BY AARON LEVIN

More than 20 percent of U.S. teenagers experience a mental disorder with severe distress or impairment, but only 36 percent of them receive mental health services, according to a study of more than 10,000 young people by the National Institute of Mental Health (NIMH).

"This is the first nationally representative sample of American adolescents and covers a full range of psychiatric disorders," study leader Kathleen Merikangas, Ph.D., told *Psychiatric News*. Merikangas is chief of the Genetic Epidemiology Research Branch in the intramural research program at NIMH.

"There is an increasing gap between what mental health professionals see and what's out there, and this study shows many people could use good mental health treatment," said Merikangas. "Substantial unmet needs for care persist."

She and her colleagues used data from the National Comorbidity Survey–Adolescent Supplement (NCS-A). They published the first two articles on prevalence and treatment in the *Journal of the American Academy of Child and Adolescent Psychiatry* in October 2010 and January 2011. Analyses covering anxiety, depression, substance abuse, and medication use data drawn from the same survey are in preparation.

The survey consisted of face-to-face interviews with 10,123 adolescents aged 13 to 18 and questionnaires completed by 6,491 of their parents. The team at NIMH worked closely with psychiatrists who have extensive clinical experience to develop the questions used in the NCS-A, said Merikangas.

The results were striking.

"The prevalence of severe emotional and behavioral disorders is even higher than [that of] the most frequent major physical conditions in adolescence, including asthma or diabetes, which have received widespread public attention," wrote the authors.

Lifetime prevalence rates varied among disorder categories, they found.

Most common were anxiety disorders, for which 31.9 percent of the adolescents met diagnostic criteria. About 14.3 percent met *DSM-IV* criteria for mood disorders, 8.7 percent for attention-deficit/hyperactivity disorder (ADHD), and 11.4 percent for substance use disorders.

Overall, 49.5 percent of the sample met criteria at some time in their young lives for a mental disorder. About 40 percent of those met criteria for at least one additional psychiatric diagnosis.

Prevalence varied by sex, age, and some demographic factors. Girls had double the rate of unipolar mood disorders, while boys were three times as likely to have ADHD.

The median age of onset was 6 for anxiety disorders, 11 for behavior disorders, 13 for mood disorders, and 15 for substance use disorders.

Parental divorce or separation was associated with higher rates of anxiety, behavior, and substance use disorders compared with adolescents who had married or cohabiting parents. Rates of all categories of disorders were higher among youth whose parents were not college graduates.

Non-Hispanic black respondents showed lower rates of substance use disorders and higher rates of anxiety disorders than their white counterparts. Hispanic youth had higher rates of mood disorders than did whites.

"The prevalence rates reported here closely approximate those of our nationally representative sample of adults using nearly identical methods, suggesting that the majority of mental disorders in adults emerge before adulthood," wrote the authors.

A study about eating disorders based on the NCS-A appeared online in the March *Archives of General Psychiatry*. The prevalence of anorexia nervosa was 0.3 percent, bulimia nervosa 0.9 percent, and binge-eating disorder 1.6 percent. Rates were higher for subthreshold anorexia and binge eating.

Those rates may seem low, but the adolescents with eating disorders also reported high levels of impairment and worrisome levels of lifetime suicidality. Half of those with bulimia and about one-third of those with anorexia or binge-eating disorder reported suicidal ideation.

Service use among those with eating disorders followed an unusual pattern. Between 76 percent and 88 percent

please see ***Youth*** *on page 28*

Father's Depression Affects Behavior Toward Infant

Whether fathers have depression or are free from the disorder, they are equally likely to play with or sing to their young children and accompany them to pediatrician visits. The same does not hold true, however, where punishment is concerned.

BY AARON LEVIN

Depressed fathers of 1-year-old children were less likely to read to their children and four times more likely to spank them than nondepressed fathers, and that may be a signal to pediatricians to screen fathers as well as mothers at well-child visits.

"Irritability and anger, common symptoms of depression, may be implicated in the increased likelihood of depressed fathers spanking their 1-year-old children," wrote R. Neal Davis, M.D., M.Sc., of Intermountain Healthcare in Murray, Utah, and his former colleagues at the University of Michigan Health System in Ann Arbor, in the April *Pediatrics*.

The researchers used data from 1,746 fathers interviewed in the Fragile Families and Child Wellbeing Study (FFCWS), the aim of which was to examine associations between positive and negative parenting behaviors.

The study follows nearly 5,000 children born in large U.S. cities from 1998 to 2000. About three-quarters of those children were born to unmarried parents, who are at greater risk of breaking up and living in poverty than are what the authors call "more traditional families."

Unlike many other studies, the FFCWS interviewed fathers directly rather than relying on maternal reports for information on child-rearing practices, Davis said. These fathers said they were living with their children "all or most of the time."

When the children were a year old, the researchers assessed the fathers with the World Health Organization's Composite International Diagnostic Interview Short Form, asking if they had a major depressive episode in the previous year. Those who indicated that they had had such an episode were then asked a further series of questions based on *DSM-IV* depression criteria.

About 7 percent of the fathers reported a major depressive episode in the prior year. Fathers who reported major depression were more likely to be unemployed and to report substance abuse than were nondepressed fathers.

Many factors may contribute to the increase in depression surrounding the birth of a child, suggested child psychologist James Paulson, Ph.D., an associate professor of pediatrics at Eastern Virginia Medical School in Norfolk. Paulson has studied perinatal depression in fathers but was not involved in the current study.

"It's a time of transition in life roles," said Paulson in an interview with *Psychiatric News*. "Parents may lose sleep or worry about money. The marital relationship may change too."

Fathers in the study were also asked about how many days a week they played simple games (like "peek-a-boo") with their children, how often they sang songs or recited nursery rhymes to them, and how often they read to them.

Results showed that both groups of fathers played or sang songs with their children at equal rates. However, fathers with depression read to their children less often (41 percent read to them) than nondepressed fathers (58 percent). Anhedonia may affect the extent to which depressed fathers read to their children, suggested the authors.

"You don't need tools or planning for peek-a-boo," said Paulson. "Reading requires settling into a chair and picking up a book, demanding an effort that may be too much for a depressed parent."

Respondents were also asked if they had spanked misbehaving children within the previous month. Only 13 percent of nondepressed fathers said they had spanked their children, compared with 41 percent of depressed fathers.

"Although associations between spanking and maternal depression have been previously reported, this is the first study, to our knowledge, to report an association between spanking and paternal depression," said the authors.

In an encouraging finding, 82 percent of the fathers participating in the study said they had spoken with their child's pediatrician in the previous year, and there were

please see ***Fathers*** *on page 28*

Depression Alters Dads' Behavior With Children

Depressed fathers of 1-year-old children are more likely to spank their children and less likely to read to them than fathers without depression.

Parenting behavior	Unadjusted odds ratio	Adjusted odds ratio
Play games[1]	1.08	0.97*
Sing songs[1]	0.96	0.98*
Read stories[1]	0.49	0.38
Spank[2]	4.60	3.92

*not significant
[1]Three or more days in a typical week
[2]In the prevous month

Source: R. Neal Davis, M.D., et al., *Pediatrics*, April 2011

Psychiatric Illness Risk Grows After Traumatic Injury in Youth

Physicians are urged to screen young patients for a history of injury and refer them for specialized care when they spot signs of posttrauma psychiatric disturbances.

BY AARON LEVIN

Children and adolescents who suffer serious physical injuries appear to have a greater chance of developing psychiatric symptoms over the ensuing three years.

Analysis of data from 20,507 young people aged 10 to 19 enrolled in the Group Health Cooperative's health plan in Washington state showed that the odds of being diagnosed with anxiety, depression, or substance use were higher among youth who had sustained traumatic injuries. They also were more likely to receive a prescription for a psychotropic medication, wrote Douglas Zatzick, M.D., and David Grossman, M.D., M.P.H., in their report in the March *Psychiatric Services*.

"This study shows that systems of care are needed to integrate injury into a care plan and service delivery," said Frederick J. Stoddard Jr., M.D., an associate clinical professor at Harvard Medical School, a psychiatrist at the Massachusetts General Hospital, and chief of psychiatry at the Shriners Burns Hospital for Children. The main focus of Stoddard's clinical care, teaching, and research is with children and adolescents with burn injuries, but he was not involved in Zatzick and Grossman's study.

The elevation of risk was important because most of the injuries were not severe, said the authors.

Zatzick is a professor of psychiatry and behavioral science and medical director of the inpatient consultation-liaison service at the University of Washington School of Medicine. Grossman is a professor of health services and an adjunct professor of pediatrics there.

They reviewed data from 1998 to 2004 and divided the youth into two groups based on whether they had an *ICD-9-CM* coded injury visit in 2001. In that year, the youngsters' average age was 14, and 30 percent (n=6,116) recorded at least one injury visit.

About 13 percent of the injured youth received a psychiatric diagnosis in 2002, 14.2 percent did so in 2003, and 14.5 percent did so in 2004. Over that same time, from 10.8 percent to 11.7 percent received at least one prescription for a psychotropic medication.

After adjusting for clinical and demographic factors, the researchers found that the injured youngsters had increased odds of receiving a diagnosis of anxiety and acute stress disorders, depressive disorders, or substance use disorders. They also had greater odds of being prescribed a psychotropic medication.

The youth who had suffered a traumatic brain injury also had elevated rates of depression or substance use disorder diagnoses and of psychotropic medication prescriptions, compared with uninjured youth. However, they showed no greater odds of developing a psychiatric disorder than did youth whose injuries were other than traumatic brain injuries.

The researchers found a correlation between pre-injury psychiatric history and psychiatric diagnoses after injury in 2001, but that wasn't the full story.

"We adjusted for prior psychiatric diagnosis and found that injury contributes to later diagnosis above and beyond pre-event diagnosis," Zatzick told *Psychiatric News*. Injury could not, however, be established as a cause of the psychiatric diagnosis, he said.

"But injury is a good proxy for children who need psychiatric screening for psychiatric disorders and may need treatment," said Stoddard.

Posttraumatic stress disorder was diagnosed "infrequently" over the three-year follow-up period and so was included among other anxiety disorders in their classification, said the authors.

They recommended a stepped-care model with initial population-based screening, followed by treatment in pediatric primary care, with referral to mental health specialists for youth with persistent symptoms, said Zatzick.

Other specialists can be involved as well, even if that requires a little innovation, he added.

"Psychiatrists are accustomed to working with primary care doctors, but not often with surgeons," noted Stoddard.

Zatzick has been doing just that. He collaborated with University of Wash-

please see ***Traumatic Injury*** *on page 28*

Injuries Correlate With Later Psychiatric Diagnoses

In a study of 20,507 adolescents, researchers found that suffering a traumatic injury was associated with a greater chance of being diagnosed with certain psychiatric disorders and being prescribed a psychotropic drug. Numbers below are odds ratios.

	Any injury	Traumatic brain injury	All other injury (non-TBI)
Anxiety and acute stress disorders	1.21	1.19	1.21
Depressive disorders	1.30	1.66	1.30
Substance use disorders	1.56	2.20	1.55
Disruptive behavior disorders*	1.10	1.29	1.10
Psychotropic medication prescription	1.37	2.16	1.37

*Not significant
Adjusted for age, gender, one or more psychiatric diagnoses in 1998–2000, one or more psychotropic medication prescriptions in 1998–2000, traumatic brain injury (TBI) or any non-TBI injury incurred in 1998–2000, and injury severity for injuries incurred from 1998 to 2000 and in the index year of 2001. The reference group for comparisons in all regressions is noninjured youths.

Source: Douglas Zatzick, M.D., et al., *Psychiatric Services*, March 2011

Can Your Neighborhood Raise Risk For Cognitive Function Decline?

Having the APOE e4 gene variant plus living in a neighborhood hazardous to residents' health appears to harm cognition. But could such a gene-environment interaction lead to Alzheimer's disease?

BY JOAN AREHART-TREICHEL

What happens when people possessing the Alzheimer's risk gene variant APOE e4 live in a neighborhood fraught with multiple physical and psychological perils? It may impair their cognitive abilities, a new study suggests.

The lead researcher on the study was Brian Lee, Ph.D., an assistant professor of epidemiology and biostatistics at the Drexel University School of Public Health in Philadelphia. The results were published in the March *Archives of General Psychiatry*.

More than 1,000 people aged 50 to 70 living in 63 neighborhoods in Baltimore participated in the study. Fifty-four percent of the sample was white, 42 percent African American, and the rest Asian or of mixed race.

Each of the 63 neighborhoods was rated with a tool called the Neighborhood Psychosocial Hazards Scale, which evaluates potential psychological and physical hazards such as lack of education, single-parent families, economic deprivation, vacant houses, violent crime, and the number of 911 calls made annually by neighborhood residents.

The subjects were genotyped for APOE e4. The researchers found that 37 percent of the African-American subjects had one copy of the variant, and 25 percent of the white subjects did.

Each subject's cognitive performance was measured with various tests to obtain scores regarding language, reaction time, eye-hand coordination, verbal memory and learning, visual memory, visuoconstruction, abstract reasoning, decision making, and other aspects of executive function.

Finally, the researchers assessed whether possession of the APOE e4 variant, living in a hazardous neighborhood, or both was associated with cognitive test scores.

Specifically, they compared the cognitive test scores of those having the e4 variant and living in a nonhazardous neighborhood, the cognitive test scores of those not having the e4 variant and living in a hazardous neighborhood, and the cognitive test scores of those both having the e4 variant and living in a hazardous neighborhood with the cognitive test scores of those who neither possessed the variant nor lived in a hazardous neighborhood (the reference group). They also took possibly confounding variables such as age, gender, race/ethnicity, education, and household income into consideration.

Subjects who had the e4 variant and lived in a nonhazardous neighborhood did not perform worse than the reference group in any cognitive domain. That was also the case for subjects who did not have the e4 variant and lived in a hazardous neighborhood.

However, subjects who both had the e4 variant and lived in a hazardous neighborhood performed significantly worse than the reference group in two cognitive domains—processing speed and executive function. Suggestive evidence was also found for eye-hand coordination differences.

Thus, having the e4 variant and living in a hazardous neighborhood seemed to be a risk factor for poor cognitive function—in other words, the result of a gene-environment interaction, the researchers concluded.

This finding could have important clinical implications, Lee and his colleagues believe. Since the e4 variant is a strong predictor of increased risk for Alzheimer's disease, and even small decrements in cognitive function predict dementia risk, it could well be that people who have the e4 variant and who live in a hazardous neighborhood are in even greater danger of developing Alzheimer's than individuals who simply have the e4 variant and who do not live in a hazardous neighborhood.

Lee and his team are going to follow their subjects to see whether those who have the e4 variant and live in a hazardous neighborhood are at particularly high risk of being diagnosed with Alzheimer's, he told *Psychiatric News*. "However, our study sample is relatively young (50 to 70 years of age at baseline)" for developing Alzheimer's, so "we may not have sufficient numbers of cases to study by the time the study ends," he pointed out.

The findings by Lee and his group complement some that Guerry Peavy, Ph.D., an assistant clinical professor of psychiatry at the University of California, San Diego, and colleagues reported in the September 1, 2007, *Biological Psychiatry*. Peavy and his colleagues found that nondemented seniors who possessed the e4 variant and who were exposed to prolonged stress experienced memory impairment. This new study by Lee and colleagues, Peavy told *Psychiatric News*, "could help identify those at heightened risk for cognitive decline due to age, genetic status, and exposure to the chronic stress of psychosocial hazards. Interventions to minimize the impact of the stress by reducing the hazards or by improving coping strategies could help prevent or delay cognitive decline in those individuals who are most vulnerable."

The study was funded by the National Institutes of Health and the Johns Hopkins Bayview Medical Center General Clinical Research Center.

An abstract of "Neighborhood Psychosocial Environment, Apolipoprotein E Genotype, and Cognitive Function in Older Adults" is posted at <http://archpsyc.ama-assn.org/cgi/content/abstract/68/3/314>. ■

Youth

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of these youth said they had sought some form of general mental health treatment. However, many fewer (3 percent to 27 percent) had addressed eating or weight problems with a professional.

"For some reason, eating disorders are not well recognized," said Merikangas. Denial, shame, and stigma may keep adolescents from talking about eating problems. Families get blamed but may not be aware of what their child is doing.

"And clinicians complain that with perhaps 30 minutes available for an intake interview, they can't ask about everything," she said.

Despite this demonstrated need for care, wrote Merikangas and colleagues in their article on service utilization, ". . . most youth with mental disorders *do not* receive mental health treatment for their symptoms."

Half of those with comorbid and severely impairing disorders had never gotten treatment. Members of racial or ethnic minorities were less likely to be treated than whites, particularly in regard to internalizing disorders.

Youth with externalizing disorders got the most attention.

"This suggests that aggressive, impulsive, and disruptive behaviors tend to drive or attract mental health care treatment seeking of adolescents," they wrote.

Highest service rates were found for youth with ADHD (59.8 percent) and behavioral disorders (45.2 percent), while youth with mood disorders (37.7 percent), anxiety disorders (17.8 percent), or substance use disorders (15.4 percent) were less likely to receive treatment.

"[T]hese findings underscore the key public health importance of mental health in American youth," the researchers said. Their conclusions can help facilitate getting young people into treatment, direct future prospective research, and guide health policymakers in trying to alleviate the economic and personal burden of mental disorders among adolescents, they said.

The studies by Merikangas and colleagues were funded by the Intramural Research Program at NIMH. Funding for the NCS-A came from NIMH, the National Institute on Drug Abuse, the Substance Abuse and Mental Health Services Administration, Robert Wood Johnson Foundation, and John W. Alden Trust.

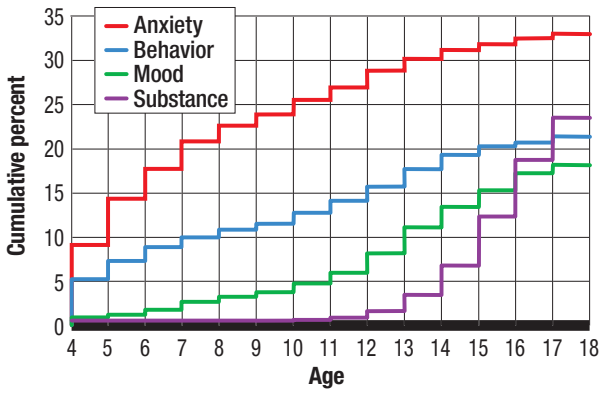
An abstract of "Service Utilization for Lifetime Mental Disorders in U.S. Adolescents: Results of the National Comorbidity Survey–Adolescent Supplement (NCS-A)" is posted at <www.jaacap.com/search/quick#>.

An abstract of "Lifetime Prevalence of Mental Disorders in U.S. Adolescents: Results from the National Comorbidity Survey Replication–Adolescent Supplement (NCS-A)" is posted at <www.jaacap.com/search/quick#>.

An abstract of "Prevalence and Correlates of Eating Disorders in Adolescents" is posted at <http://archpsyc.ama-assn.org/cgi/content/short/archgenpsychiatry.2011.22>. ■

Mental Illness Common in Childhood, Teen Years

The chart below shows the cumulative lifetime prevalence of major classes of *DSM-IV* disorders among adolescents. The data are from the National Comorbidity Survey Replication-Adolescent Supplement.



Source: Kathleen Merikangas, Ph.D., *J Am Acad Child Adolesc Psychiatry,* October 2010

Fathers

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no significant differences between the depressed and nondepressed fathers. That may offer an opportunity for pediatricians to screen fathers for symptoms of depression and refer them for treatment, a practice that has been shown to work with mothers.

"I have begun asking fathers how they are handling the added stress of having an infant in the home," said Davis in an interview. "I mention that recent research suggests that about 1 in 10 dads can experience symptoms of depression, such as sadness or irritability, and that these symptoms can affect how fathers interact with their children."

He is considering adding the validated PHQ-2 depression screening tool to his clinic's intake forms, with sections for mothers, fathers, and other caregivers to answer, he said. "Positive responses could be discussed during the clinic visit."

In addition, children's doctors can use those interactions to counsel fathers about why they should not use corporal punishment and better ways to discipline children and deal with their own feelings of frustration when a child misbehaves.

Increasing positive interactions and reducing negative ones between fathers and young children could improve children's mental and physical health throughout the development process, suggested the authors.

"We've known about the negative effects of mothers' depression on parenting," said Paulson. "In the past 10 years we've learned about fathers' increased risk for perinatal depression, but this study documents that fact in a compelling way."

An abstract of "Fathers' Depression Related to Positive and Negative Parenting Behaviors With 1-Year-Old Children" is posted at <http://pediatrics.aappublications.org/cgi/content/abstract/peds.2010-1779v1>. ■

Psychotherapy

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The analysis found a small initial benefit for pharmacotherapy alone over IPT, while combination maintenance treatment with pharmacotherapy and IPT was more effective in preventing relapse than pharmacotherapy alone.

"The difference between pharmacotherapy and IPT alone was small," Markowitz said. "You'd need to treat 10 patients to see a difference in one.

"Basically, both treatments worked," he said. "Medication and psychotherapy presumably treat depression in different ways, so it's not surprising that there might be a synergy in combining IPT and medication. Whereas antidepressant medication relieves symptoms, it doesn't help you figure out how to handle social situations. Previous studies in the literature indicate that combined treatment never does worse than monotherapy for depression, and sometimes—particularly if there is sufficient statistical power—looks better."

IPT is a time-limited, diagnosis-targeted treatment that focuses on a specific interpersonal crisis such as complicated bereavement, a role dispute, or a role transition. Initially developed by Myrna Weissman, Ph.D., and the late Gerald Klerman, M.D., for major depression, it has since shown utility for other disorders as well. (Weissman is a professor of epidemiology and psychiatry at Columbia University, and Klerman, who died in 1992, was an expert on depression and schizophrenia and served as head of the Alcohol, Drug Abuse, and Mental Health Administration from 1977 through 1980.)

Markowitz said the therapy defines major depression as a treatable illness that is not the patient's fault. "This provides hope, helps the patient to separate symptoms from self, and particularly eases the self-blame that plagues depressed individuals."

He added that the IPT therapist helps patients focus on their feelings and recognize that those feelings are not "bad" but rather are reactions to social encounters. "Thus anger, anxiety, and sadness can become useful signposts of interpersonal encounters that patients can learn to express and to use to handle life better. This leads to better social functioning, which helps mood. And it's no wonder that IPT has been shown to build social skills, given that that's what the treatment focuses on."

Other components of the therapy include mobilization of social supports and the imposition of a time limit on the course of therapy, which encourages patients to work fast to resolve the current crisis. "Thus the treatment is organized, but not overly structured, and the patient has a clear sense of where he or she is and what is to come," Markowitz said.

The 38 studies included 4,356 patients: 1,338 in the IPT conditions, 812 in control conditions, 713 in pharmacotherapy conditions, 468 in other psychotherapy conditions, 510 in combination treatment with IPT and pharmacotherapy, and 515 in maintenance studies. Thirty-three of the 38 studies examined the effects of IPT as an acute treatment, and the remaining five examined IPT as a maintenance treatment after successful recovery from a depressive disorder.

Markowitz said that for most of the period since Klerman and Weissman developed IPT, it was a research treatment not widely disseminated to practicing clinicians—a fact that may account for what Markowitz and fellow authors said is an underutilization of the therapy. But he said that in the last decade it has begun to spread, and he cited as evidence the establishment of the International Society for Interpersonal Psychotherapy, which will be holding its fourth annual meeting this year in June in Amsterdam.

"Interpersonal Psychotherapy for Depression: A Meta-Analysis" is posted at <http://ajp.psychiatryonline.org/cgi/reprint/appi.ajp.2010.10101411v1>. ■

Traumatic Injury

continued from page 26

ington Harborview colleagues, including trauma surgeons Gregory Jurkovich, M.D., and Larry Gentilello, M.D., on a review of the scientific evidence on alcohol screening and brief intervention. Their work helped persuade the American College of Surgeons (ACS) to mandate alcohol screening and intervention services at accredited U.S. level I and II trauma centers.

The team is working now toward developing similar ACS guidelines for PTSD screening and intervention at U.S. trauma centers.

Stoddard agreed.

"Psychiatrists whose practices do not ordinarily involve injury patients should inquire about a possible history of injury, either as a possible etiological factor for a psychiatric disorder such as PTSD, or as a potential problem in treatment such as an added source of stigma or disability, or a factor contributing to depression or self-esteem problems related to body image," said Stoddard.

"Association Between Traumatic Injury and Psychiatric Disorders and Medication Prescription to Youths Aged 10–19" is posted at <http://ps.psychiatryonline.org/cgi/content/full/62/3/264>. ■

Caucus Schedule Changes

The start times of two of the APA caucus meetings being held at APA's 2011 annual meeting in Honolulu have been changed. Both meetings are being held on Sunday, May 15.

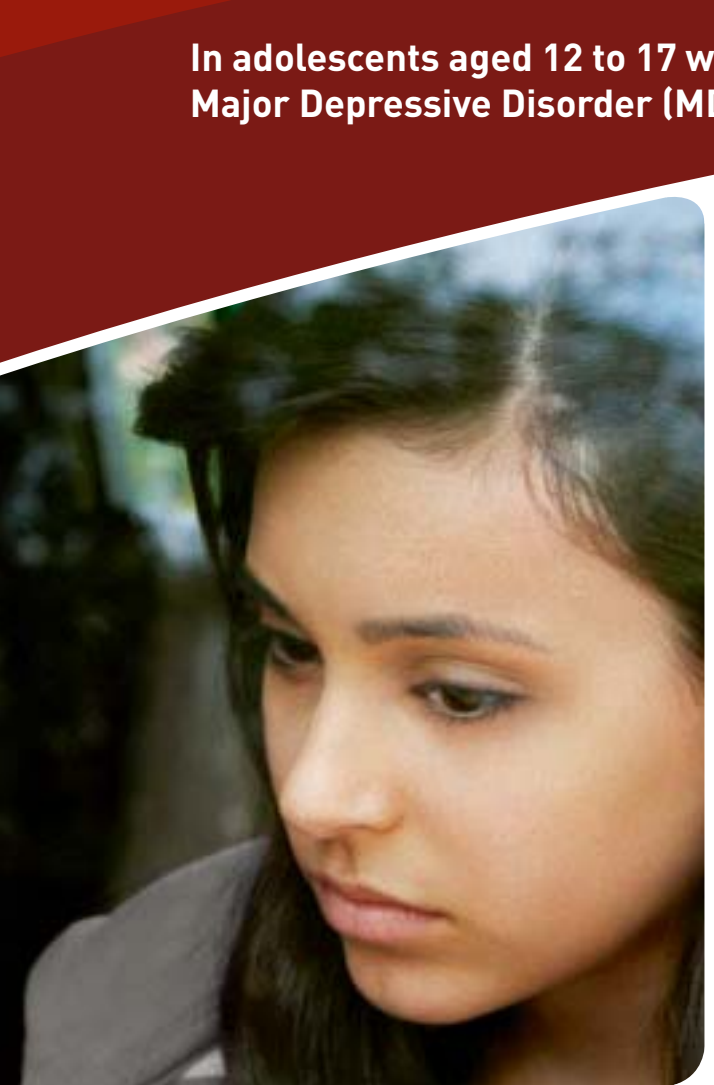
The joint meeting of the APA Caucus of Gay, Lesbian, and Bisexual Psychiatrists and the Association of Gay and Lesbian Psychiatrists will begin at 3 p.m. instead of 1:30 p.m. The meeting will be held in the Roof Garden of the Moana Surfrider Hotel.

The meeting of the Caucus of Hispanic Psychiatrists will begin at 4 p.m. instead of 5 p.m. It will be held in the Waialua Room of the Sheraton Waikiki Hotel.

Treat your patients with the demonstrated efficacy of LEXAPRO[1-5]

In adolescents aged 12 to 17 with Major Depressive Disorder (MDD)[1]

In adults with MDD and Generalized Anxiety Disorder (GAD)[1]



Lexapro® escitalopram oxalate

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

Please see additional Important Safety Information on following pages.

There is no generic available for LEXAPRO

- Significantly improved MDD symptoms in adolescents[2]

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

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

IMPORTANT SAFETY INFORMATION (continued)

Contraindications

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

Warnings and Precautions

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

- Significantly higher rates of response and remission vs placebo in MDD and GAD in adults[4,5]

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

Please see Boxed Warning on first page and additional Important Safety Information on next page.

Lexapro®
escitalopram oxalate

Visit the LEXAPRO website at www.lexapro.com

LEXAPRO: Proven efficacy in MDD in adolescents aged 12 to 17, and in MDD and GAD in adults[1-5]

Warnings and Precautions (continued)

- SSRIs (including Lexapro) and SNRIs may increase the risk of bleeding. Patients should be cautioned that concomitant use of aspirin, NSAIDs, warfarin or other anticoagulants may add to the risk.
- Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that Lexapro does not affect their ability to engage in such activities.
- Lexapro should be used with caution in patients with severe renal impairment or with diseases or conditions that alter metabolism or hemodynamic responses. In subjects with hepatic impairment, clearance of racemic citalopram was decreased and plasma concentrations were increased. The recommended dose of Lexapro in hepatically impaired patients is 10 mg/day.
- For pregnant or nursing mothers, Lexapro should be used only if the potential benefit justifies the potential risk to the fetus or child.

Adverse Reactions

- In clinical trials of MDD, the most common adverse reactions in adults treated with Lexapro (approximately 5% or greater and at least twice the incidence of placebo) were nausea (15% vs 7%), insomnia (9% vs 4%), ejaculation disorder (9% vs <1%), fatigue (5% vs 2%), somnolence (6% vs 2%), and increased sweating (5% vs 2%). In pediatric patients, the overall profile of adverse reactions was similar to that seen in adults; however, the following additional adverse reactions were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion.
- In clinical trials of GAD, the most common adverse reactions in adults treated with Lexapro (approximately 5% or greater and at least twice the incidence of placebo) were nausea (18% vs 8%), ejaculation disorder (14% vs 2%), insomnia (12% vs 6%), fatigue (8% vs 2%), decreased libido (7% vs 2%) and anorgasmia (6% vs <1%).

Please see accompanying brief summary of Prescribing Information for LEXAPRO, including Boxed Warning.

References: 1. LEXAPRO [package insert]. St. Louis, Mo: Forest Pharmaceuticals, Inc.; 2009. **2.** Emslie GJ, Ventura D, Korotzer A, Tourkodimitris S. Escitalopram in the treatment of adolescent depression: a randomized placebo-controlled multisite trial. *J Am Acad Child Adolesc Psychiatry*. 2009;48:721-729. **3.** Burke WJ, Gergel I, Bose A. Fixed-dose trial of the single isomer SSRI escitalopram in depressed outpatients. *J Clin Psychiatry*. 2002;63:331-336. **4.** Davidson JRT, Bose A, Korotzer A, Zheng H. Escitalopram in the treatment of generalized anxiety disorder: double-blind, placebo controlled, flexible dose study. *Depress Anxiety*. 2004;19:234-240. **5.** Wade A, Lemming OM, Hedegaard KB. Escitalopram 10 mg/day is effective and well tolerated in a placebo-controlled study in depression in primary care. *Int Clin Psychopharmacol*. 2002;17:95-102.

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Lexapro® escitalopram oxalate

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

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

WARNINGS: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

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

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

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

TABLE 1

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

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

fatal, reactions including hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. These reactions have also been reported in patients who have recently discontinued SSRI treatment and have been started on an MAOI. Some cases presented with features resembling neuroleptic malignant syndrome. Furthermore, limited animal data on the effects of combined use of SSRIs and MAOIs suggest that these drugs may act synergistically to elevate blood pressure and evoke behavioral excitation. Therefore, it is recommended that Lexapro should not be used in combination with an MAOI, or within 14 days of discontinuing treatment with an MAOI. Similarly, at least 14 days should be allowed after stopping Lexapro before starting an MAOI. Serotonin syndrome has been reported in two patients who were concomitantly receiving linezolid, an antibiotic which is a reversible non-selective MAOI.

ADVERSE REACTIONS: Clinical Trials Experience-Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. **Clinical Trial Data Sources; Pediatrics (6 -17 years)**-Adverse events were collected in 576 pediatric patients (286 Lexapro, 290 placebo) with major depressive disorder in double-blind placebo-controlled studies. Safety and effectiveness of Lexapro in pediatric patients less than 12 years of age has not been established. **Adults**-Adverse events information for Lexapro was collected from 715 patients with major depressive disorder who were exposed to escitalopram and from 592 patients who were exposed to placebo in double-blind, placebo-controlled trials. An additional 284 patients with major depressive disorder were newly exposed to escitalopram in open-label trials. The adverse event information for Lexapro in patients with GAD was collected from 429 patients exposed to escitalopram and from 427 patients exposed to placebo in double-blind, placebo-controlled trials. Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard World Health Organization (WHO) terminology has been used to classify reported adverse events. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Events Associated with Discontinuation of Treatment; Major Depressive Disorder; Pediatrics (6 -17 years)**-Adverse events were associated with discontinuation of 3.5% of 286 patients receiving Lexapro and 1% of 290 patients receiving placebo. The most common adverse event (incidence at least 1% for Lexapro and greater than placebo) associated with discontinuation was insomnia (1% Lexapro, 0% placebo). **Adults**-Among the 715 depressed patients who received Lexapro in placebo-controlled trials, 6% discontinued treatment due to an adverse event, as compared to 2% of 592 patients receiving placebo. In two fixed-dose studies, the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro was not significantly different from the rate of discontinuation for adverse events in patients receiving placebo. The rate of discontinuation for adverse events in patients assigned to a fixed dose of 20 mg/day Lexapro was 10%, which was significantly different from the rate of discontinuation for adverse events in patients receiving 10 mg/day Lexapro (4%) and placebo (3%). Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice that of placebo, were nausea (2%) and ejaculation disorder (2% of male patients). **Generalized Anxiety Disorder; Adults**-Among the 429 GAD patients who received Lexapro 10-20 mg/day in placebo-controlled trials, 8% discontinued treatment due to an adverse event, as compared to 4% of 427 patients receiving placebo. Adverse events that were associated with the discontinuation of at least 1% of patients treated with Lexapro, and for which the rate was at least twice the placebo rate, were nausea (2%), insomnia (1%), and fatigue (1%). **Incidence of Adverse Reactions in Placebo-Controlled Clinical Trials; Major Depressive Disorder; Pediatrics (6 -17 years)**-The overall profile of adverse reactions in pediatric patients was generally similar to that seen in adult studies, as shown in Table 2. However, the following adverse reactions (excluding those which appear in Table 2 and those for which the coded terms were uninformative or misleading) were reported at an incidence of at least 2% for Lexapro and greater than placebo: back pain, urinary tract infection, vomiting, and nasal congestion. **Adults**-The most commonly observed adverse reactions in Lexapro patients (incidence of approximately 5% or greater and approximately twice the incidence in placebo patients) were insomnia, ejaculation disorder (primarily ejaculatory delay), nausea, sweating increased, fatigue, and somnolence. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred among 715 depressed patients who received Lexapro at doses ranging from 10 to 20 mg/day in placebo-controlled trials. Events included are those occurring in 2% or more of patients treated with Lexapro and for which the incidence in patients treated with Lexapro was greater than the incidence in placebo-treated patients.

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

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

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

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

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

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

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

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

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

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

Male and Female Sexual Dysfunction with SSRIs-Although changes in sexual desire, sexual performance, and sexual satisfaction often occur as manifestations of a psychiatric disorder, they may also be a consequence of pharmacologic treatment. In particular, some evidence suggests that SSRIs can cause such untoward sexual experiences. Reliable estimates of the incidence and severity of untoward experiences involving sexual desire, performance, and satisfaction are difficult to obtain, however, in part because patients and physicians may be reluctant to discuss them. Accordingly, estimates of the incidence of untoward sexual experience and performance cited in product labeling are likely to underestimate their actual incidence.

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

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

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

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

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

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

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

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Match

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graduates of osteopathic schools, and students who graduated from medical school in previous years.

The match—in which the choices of graduating medical students are "matched" with those of residency programs—is typically watched as an indicator of workforce size and makeup of the various medical specialties for the coming years.

Like last year, one of the notable results of this year's match was the increase in the number of students entering primary care specialties. Of these, family medicine experienced the largest growth, with an 11 percent increase over 2010.

The two other primary care specialties, pediatrics and internal medicine, also increased in popularity. U.S. seniors matched to 1,768 of the 2,482 pediatric positions offered, a 3 percent increase over 2010. In internal medicine, U.S. seniors filled 2,940 of 5,121 positions, an 8 percent increase over last year.

In addition to primary care, other specialties that had a larger number of residency positions filled by U.S. seniors in this year's match included emergency medicine, anesthesiology, and neurology.

While the drop in students entering psychiatry is not dramatic, educators said it is worth attention. "This change is within the variance we have seen for the last six years," said former APA Trustee Sidney Weissman, M.D., a past president of the American Association of Directors of Psychiatric Residency Training, who has maintained a keen interest in workforce issues. "For this reason this change may not have a long-term meaning. However, we must be concerned that it is not the first step in a trend."

He continued, "Senior U.S. medical students select careers for many reasons. We need to assess the factors that today lead to the selection of psychiatric careers. Frequently we hear that students select psychiatric careers because psychiatry offers them an opportunity to become more engaged with their patients. We need to learn more about the coming generation of psychiatrists and their practice desires and those of the current generation of medical students."

Weissman added that it is not yet clear that the jump in primary care matches necessarily represents a dramatic shift away from specialty medicine.

"If you look at the actual numbers of students now going into primary care, the increase is not as great as the hype," he said. "In family medicine, the increase from last year is only 132 students, or less than 1 percent of all senior students. I suspect the increase might include some students who may previously have entered psychiatry, but it mainly relates to the expansion of medical school positions and publicity about the need for primary care."

In a statement following the release of match numbers, J. Fred Ralston Jr., M.D., president of the American College of Physicians, said, "This is good news for internal medicine and adult patient care in the U.S. The American College of Physicians has consistently called for health care reforms that support internal medicine as a career path, including increasing support for primary care training programs, increasing Medicaid and Medicare reimbursement to primary care physicians, and expanding pilot testing and implementation of new models of patient care."

Jerald Kay, M.D., professor and chair of psychiatry at the Boonshoft School of Medicine at Wright State University, suggested that the trend seems to contradict the notion that student indebtedness drives new doctors into more high-paying specialties.

Also, he agreed that the number entering psychiatry is still within the range of the last several years and may not be a cause for immediate concern.

More important for the long-term vitality of the profession, he said, is the overall identity of psychiatry and how it is perceived by students in medical school. He urgently underscored the need to maintain psychotherapy as a core skill of psychiatry.

"At Wright State, we have a very strong psychotherapy program, and a lot of our students are keenly interested in psychotherapy," Kay said. "I have long asserted that it is very shortsighted for the profession to jettison psychotherapy as a core clinical skill. Much of the richness of our field, and its attraction to young medical students, has to do with the ability of psychiatrists to immerse themselves in the lives of their patients."

Kay drew attention to an article that appeared in the *New York Times* on March 5 under the headline "Talk Doesn't Pay So Psychiatry Turns to Drug Therapy." The article chronicled a senior Pennsylvania psychiatrist who had long practiced psychotherapy but had turned to providing 15-minute med checks because of inadequate insurance reimbursement for psychotherapy.

"We urgently need to pay attention to this and its possible effect on the future students entering our profession," Kay said.

Data from the NRMP are posted at <www.nrmp.org/data/2011Adv%20Data%20Tbl.pdf>. The* New York Times *article is posted at <www.nytimes.com/2011/03/06/health/policy/06doctors.html?_r=1>. ■

Psychological

continued from page 2

totaled approximately $6 million a year.

The suit highlights the sensitive nature of organizations created to advocate for the political interests of a business or profession and the need for transparency in how such organizations are funded.

In a statement provided to *Psychiatric News*, Rhea Farberman, director of the Office of Public Affairs for the American Psychological Association, states that the assessment is "mandatory" but also that members retain their membership in the association even if they don't pay it.

"The practice assessment was established in 1985 as a mandatory payment. All [American Psychological Association] members who are licensed health service providers are billed the assessment and are expected to pay it. [M]embers who pay the assessment become members of the American Psychological Association Practice Organization (APAPO) in addition to their membership in the [psychological association]. Licensed members who pay dues but fail to pay the assessment (most members do pay) lose their access to APAPO services and benefits, but their [American Psychological Association] membership continues unaffected."

She added, "Concerning the lawsuit, we believe it to be totally baseless. [The American Psychological Association] and APAPO have filed a motion to dismiss the complaint. If our motion is denied, we will oppose class certification and continue to vigorously defend against any remaining claims."

But in an interview with *Psychiatric News*, Hassan Zavareei, a lawyer with the firm Tycko and Zavareei, which is representing the plaintiffs, drew attention to the difficulty of characterizing something as "mandatory" while acknowledging that members could decline to pay the assessment without affecting their membership in the psychological association.

"Their argument is too cute by half," he said. "They are saying the assessment is mandatory, but that 'mandatory' doesn't mean there are consequences. So they are playing word games.

"Our position is simpler," Zavareei said. "The plaintiffs allege that they were given the impression that if they didn't pay the assessment, they couldn't be members of the association, when in fact that is not the case."

Documents submitted by the plaintiffs to the District Court include remarks made by a member of the board of trustees of the psychological association, Glenn Ally, Psy.D., on a list serve in May 2010, following attempts by that board to clarify to membership the nature of the special assessment.

"I'm assuming you know the statistics that psychologist [sic] are at the bottom of the list of professions regarding voluntary contributions, even political advocacy contributions," Ally wrote on the list serve. "What you are suggesting here is to make the primary and largest advocacy arm of our organization dependent on the voluntary contributions of the cheapest profession around. . . . The [APAPO] is a business and [it is] in the business of advocating for practice. We have decided we need this, and we decided long ago that we were not getting enough advocacy when we had to depend on the larger [psychological association]. . . . That 'business' has to depend on a relatively stable revenue source." ■

annual meeting

Lifers

continued from page 15

Sunday, May 15

1 p.m.-3 p.m.: The **Lifers Executive Committee** will meet. In addition to the officers and Warren, the committee members include Pierre Loebel, M.D., a member of the Membership Committee; Irvin Cohen, M.D., chair of the Awards Committee; Norman Clemens, M.D., chair of the Bylaws Committee; Herbert Peyser, M.D., chair of the Legislation and Policy Committee; Philip Margolis, M.D., chair and editor of the Lifers newsletter, *Lifersline*; and Arthur Meyerson, M.D., associate newsletter editor. Other committees chaired by officers include Sheila Hafter Gray, M.D., chair of the Annual Meeting Program Committee, Nominating Committee, and Practice Guidelines Response Team; Bernard Katz, M.D., chair of the Finance Committee; and Paul Wick, M.D., chair of the Membership Committee. The Lifers thrives through members' participation on the committees. Members interested in serving on a committee are encouraged to contact Scheiber.

Tuesday, May 17

7 a.m.: The workshop **"How May Military Leaders Optimize Mental Health Services to Serve Members?"** will be held in Room 327 at the Hawaii Convention Center.

9:30 a.m.: The **Lifers annual business meeting** will be held at the Sheraton Waikiki 'Iao Needle/Akaka Falls Room. APA President Carol Bernstein, M.D., will be the guest speaker. Among the topics to be discussed will be the Berson Award and how the award committee should be guided in its work. Nada Stotland, M.D., will discuss how Lifers interested in becoming mentors for existing APA programs can be linked with these programs. Wick will talk about membership initiatives and how other organizations such as the AMA have organized activities for senior members. Pierre Loebel, M.D., will speak about linkages with the American Association of Geriatric Psychiatry. Peyser will discuss retirement issues, and Margolis will speak about future editions of *Lifersline.*

7 p.m.: The annual **Lifers reception** will take place at the Ala Moana Hotel in the Plumeria Room. In addition to providing lots of time to socialize with colleagues and friends, the reception is an opportunity to meet new and aspiring members of the Lifers. The Berson Award will be presented.

Other News

Lifersline is now available on the Web; it is linked to the site of the American Psychiatric Foundation at <www.psychfoundation.org/News/Publications.aspx> under "Lifers" and is available two to three times a year. Past issues of the newsletter are also posted on the Web site. One of the newsletter's newest features is Joel Yager, M.D.'s book reviews. In memoriam submissions, such as the one for Gerald Flamm, M.D., are encouraged.

In addition to the workshop that the Lifers will present in Hawaii, the Lifers will be presenting a workshop at APA's Institute on Psychiatric Services in San Francisco in October, according to Hafter Gray, M.D. More information will appear in a future issue.

The executive committee voted to have the membership year run from January to December. Dues are $50 a year. A membership information form can be accessed at the Web site of the American Psychiatric Foundation at <www.psychfoundation.org>.

The Lifers play a vital role in supporting the work of its parent organization, APA. Those who are interested in joining should send a check for $50 to Linda Bueno, director of industry relations at the American Psychiatric Foundation, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901.

More information is available by contacting Bueno at LBueno@psych.org. Tax-deductible contributions are also welcome. ■

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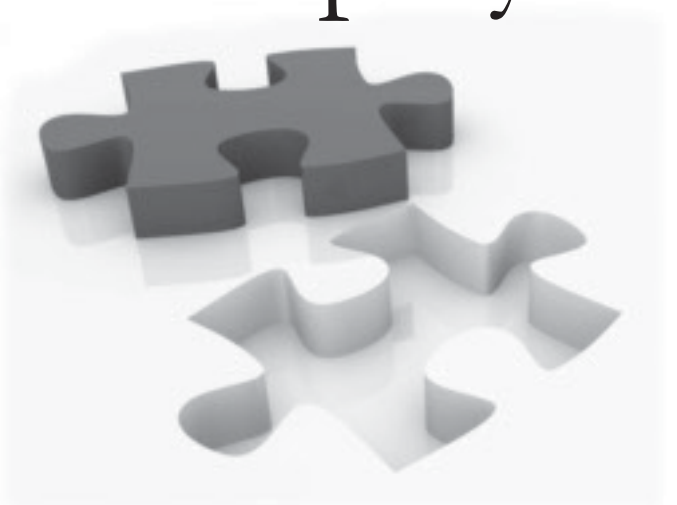

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Human Rights Award

Purpose:

The Human Rights Award was established to recognize an individual and an organization whose efforts exemplify the capacity of human beings to act courageously and effectively to prevent human rights violations, to protect others from human rights violations and their psychiatric consequences, and to help victims recover from human rights abuses.

Nomination Procedures:

APA members are asked to submit nominations by **July 1, 2011** to:

Council on Psychiatry and Law
American Psychiatric Association
c/o Lori Klinedinst, Staff Liaison
1000 Wilson Blvd., Suite 1825
Arlington, VA 22209
E-mail: advocacy@psych.org

The nomination letter should succinctly describe the contributions that are the basis for the nomination and be accompanied by a curriculum vitae of the nominee. The Council on Psychiatry and Law will serve as the award review panel in determining the recipients of this award. The recipients will receive a plaque which will be awarded during the Convocation at the APA's Annual Meeting in May.

Service Chief, Mental Health and Behavioral Sciences Service Line Manager
Department of Veterans Affairs Medical Center
White River Junction, VT

The Department of Veterans Affairs Medical Center in White River Junction (WRJ), Vermont and the Dartmouth Medical School in Hanover, NH, are seeking an outstanding candidate for Service Chief and Mental Health and Behavioral Sciences Service Line Manager. As the WRJ VAMC is an award winning Dean's Committee VA Medical Center, this individual will lead a dynamic service with a strong commitment to clinical, educational, and research missions. The WRJ VAMC is a major component of the Dartmouth Department of Psychiatry and the Mental Health Service Chief is a core member of the Department Chair's Advisory Group.

The WRJ VAMC is a 60-bed acute care facility providing healthcare to 23,000 Vermont and New Hampshire Veterans. The position offers opportunities to enhance patient care delivery and oversee a broad array of specialized programs, including the White River Primary Care-Mental Health Integration Program that has served as a model of integrated care nationally. The Service Chief/Service Line Manager oversees approximately 75 staff members and the training of medical students, psychiatry residents, geriatrics and addictions fellows, psychology interns and psychology post-doctoral fellows. The Service Chief interfaces with local and state agencies within Vermont and New Hampshire. He/she also oversees the growing mental health services in VA Community Based Outpatient Clinics and a telehealth outreach program. The WRJ VAMC has research collaboration with regional partners and throughout VHA. The WRJ VAMC is also home to the National Center for PTSD, National Patient Safety Program, and Quality Scholars Program and has close academic ties to The Dartmouth Institute, an innovative program dedicated to health care improvement.

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Interested candidates should forward a brief letter of interest, curriculum vitae and application to:

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Additional inquiries may be directed to the search chair, Thomas Parrino, MD, Chief of Staff, White River Junction VAMC, at (802) 295-9363, extension 6209.

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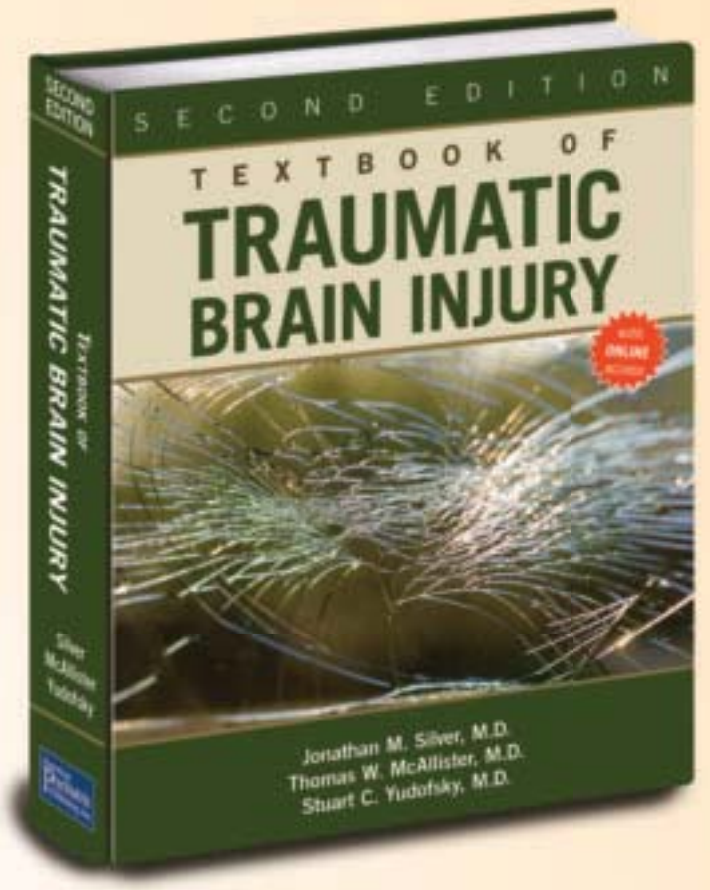

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164th ANNUAL MEETING MAY 14-18, 2011, HONOLULU, HAWAII

HIGHLIGHTS

Distinguished Psychiatrist Lecturers: Alan F. Schatzberg, M.D.; Laura W. Roberts, M.D.; Nancy C. Andreasen, M.D., Ph.D.; Loree K. Sutton, M.D.; Darrell G. Kirch, M.D.; and Sarah H. Lisanby, M.D.

Frontiers of Science Lecturers: Nora D. Volkow, M.D. Director, National Institute of Drug Abuse; Sabine Bahn, M.D., Ph.D. with The Cambridge Centre for Neuropsychiatric Research, The Bahn Laboratory; Ian Hickie, M.D., A.M. Executive Director, The Brain and Mind Research Institute.

Special Guest Lecturers: Barry C. Scheck, J.D., Director of the Innocence Project; Michael Owen, M.D., Ph.D., Director, Center for Neuropsychiatric Genetics and Genomics.

Advances in Series: Advances in Personality Disorders, John Oldham, M.D.; Advances in Psychotherapeutic Treatments, Glen O. Gabbard, M.D.; Advances in Substance Abuse Treatment, Marc Galanter, M.D. and Herbert Kleber, M.D.; Advances in Psychopharmacology, Alan F. Schatzberg, M.D., and Charles Nemeroff, M.D..

Advances in Medicine: Monique Yohanan, M.D., Internal Medicine; Robert McCarron, D.O., Medical Mysteries; Richard F. Arakaki, M.D., Seizure Disorders; Alan Stein, M.D., Diabetes.

Advances in Research: Herbert Pardes, M.D., CEO of the New York-Presbyterian Hospital.

- Come Early! Scientific Sessions will begin at 7:00 AM Sat., May 14, 2011 and end on Wed., May 18, 2011 at 12:30 PM
  Daily Programming Times: Scientific sessions run from 7:00 AM - 3:00 PM • Courses run from 7:00 AM - 3:30 PM
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American Psychiatric Association

164th ANNUAL MEETING MAY 14-18, 2011, HONOLULU, HAWAII

NIMH National Institute of Mental Health Track

SESSIONS

SATURDAY, MAY 14

Lecture: Re-Thinking Mental Illness
313A-C, Level 3, 8-9:30 a.m., Hawaii Convention Center
Thomas Insel, M.D., Director, NIMH

Symposium: Health Care Reform and Mental Health Care Financing
316A, Level 3, 12-3:00 p.m. Hawaii Convention Center
Chair: Agnes Rupp, Ph.D.

SUNDAY, MAY 15

Symposium: New Perspectives on Global Mental Health
316A, Level 3, 8-11 a.m., Hawaii Convention Center
Chair: Pamela Y. Collins, M.D.

Symposium: Novel Treatments for Neurodevelopmental Disorders
316A, Level 3, 12-3 p.m., Hawaii Convention Center
Chair: Chris Sarampote, Ph.D.

MONDAY, MAY 16

Lecture: Translating Neural Circuits into Novel Therapeutics for Schizophrenia
Scheduled 311, Level 3, 12-1:30 p.m., Hawaii Convention Center
David Lewis, M.D.

Symposium: Teaching What Every Psychiatrist Should Know About Neuroscience
314, Level 3, 8-11 a.m., Hawaii Convention Center
Chairs: Mayada Akil, M.D., Thomas Insel, M.D.

Symposium: Research Update – New Developments in the Treatment of Mood Disorders
314, Level 3 , 12-3 p.m., Hawaii Convention Center
Chairs: Matthew Rudorfer, M.D., Jing Du, M.D., Ph.D.

TUESDAY, MAY 17

Symposium: Brain Circuitry of Serious Mental Illnesses
316A, Level 3, 8-11 a.m., Hawaii Convention Center
Chair: Cameron S. Carter, M.D.

Symposium: Psychiatric Nosology: A Search for New Models
Scheduled 316A, Level 3, 12-3 p.m., Hawaii Convention Center
Chair: Nancy C. Andreasen, M.D.

- Come Early! Scientific Sessions will begin at 7:00 AM Sat., May 14, 2011 and end on Wed., May 18, 2011 at 12:30 PM
  Daily Programming Times: Scientific sessions run from 7:00 AM - 3:00 PM • Courses run from 7:00 AM - 3:30 PM
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Issue	Deadline (Friday, 5 p.m. E.T.)
May 6	April 22
May 20	May 6

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- **IDAHO-** Boise
- **ILLINOIS-** Chicago and Springfield (Academic Affiliation)
- **INDIANA- Bloomington-Outpatient only**
- **LOUISIANA-** Shreveport (J1 eligible)
- **MASSACHUSETTS-** BOSTON city & suburbs
- **MICHIGAN-** Detroit and Grand Rapids
- **MISSISSIPPI-** Meridian
- **NEW JERSEY-** Westampton (just east of Philadelphia)
- **NEW MEXICO-** Las Cruces- Medical Director
- **OHIO-** Cleveland
- **OKLAHOMA-** Oklahoma City
- **PENNSYLVANIA-** Philadelphia-State College-Clarion-Shippensburg
- **SOUTH CAROLINA-** Columbia-Aiken
- **TEXAS-** Austin, Dallas, San Angelo-Salaried Employment
- **VIRGINIA-** Leesburg AND Portsmouth/Norfolk
- **WEST VIRGINIA-** Huntington
- **WYOMING-** Casper & Cheyenne-Student Loan repayment

Competitive compensation packages and benefits if employed, including bonus and student loan assistance opportunity depending on location. See the UHS website: www.uhsinc.com for full list of our facility locations.

Psychiatrist needed for **Florida & Mississippi locations** working in Forensic Hospitals or Correctional Facility. The M.D. must be licensed in the state. Good compensation, paid insurances. Email Resume: shaddad@humancapitalmgnt.com or call Susan: 954-318-2309.

ALABAMA

MEDICAL DIRECTOR
Near Birmingham, Alabama

Horizon Health, in partnership with client hospital in Talladega, Alabama seeks a Psychiatrist as Medical Director for a 14-bed Geriatric Inpatient Psychiatric program. Hospital is a full service facility offering the latest in technology. Offering competitive stipend in an area with lucrative private practice potential. Located less than 1 hour from Birmingham, Alabama! Talladega is rich in history and tradition and home to the Talladega Superspeedway. Beautiful lake community only minutes away offering fishing, boating and swimming. For more information contact Diane Odom V: 972-921-9707 F: 972-499-1842, email:diane.odom@psysolutions.com .

ARIZONA

Neuropsychiatrist - Phoenix, Arizona

The Barrow Neurological Institute at St. Joseph's Hospital and Medical Center, recognized by U.S.News & World Report as one of the top 10 neuroscience programs in the country, is currently seeking a Neuropsychiatrist to join our new Center for Neuromodulation. Our neuromodulation program is already one of the busiest in the West, having performed more than 1,000 Deep Brain Stimulation (DBS) procedures in the last 10 years. With a very active clinical research program, we're exploring new indications for DBS, such as depression, bipolar disorder, Tourette syndrome, autism, anxiety, dementia and obesity. To ensure this endeavor is successful, we're looking for extensive support from a talented psychiatric professional like you.

As part of a multidisciplinary team, you will be involved with the application of neuromodulatory procedures (including DBS, rTMS, ECT and VNS) to neuropsychiatric disorders. You'll contribute to existing programs focused on the clinical and experimental use of neuromodulation through animal studies or human neuroimaging. You will also provide support with the establishment of an outpatient neuropsychiatry clinic, the recruitment of candidates for clinical trials, and the preoperative screening of candidates for neuromodulation procedures.

Qualifications include an M.D. or D.O. degree, board certification or eligibility for board certification in psychiatry, eligibility for Arizona psychiatry licensure, BNI credentials, and membership with relevant professional associations and societies. You also must be active academically and have a strong interest in expanding your clinical research base and increasing scholarly productivity. Academic faculty appointment is available at the Creighton University School of Medicine.

To apply, send your curriculum vitae along with a cover letter and the names of three references to: Jason Caplan, M.D., Chairman of Psychiatry, St. Joseph's Hospital and Medical Center, 500 W. Thomas Road, Phoenix, AZ 85013; or e-mail Jason.caplan@chw.edu.

UNIVERSITY OF 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. 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 current group of psychiatrists providing inpatient psychiatric services at the UPH Hospital, designated as a federally recognized underserved area. Opportunities may also exist for work in a new ambulatory Crisis Response Center. Incumbent will be responsible for 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. Salary: 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.

The largest private practice psychiatric group in **Orange County, California** offering comprehensive patient treatment in both outpatient and inpatient settings is seeking a board certified psychiatrist to join our growing group. Successful candidate will join an established team of board certified psychiatrists from varied backgrounds and experiences including forensic, child & adolescent, addiction, research and faculty psychiatry. Our group has become the premier psychiatric group over the past five years serving all of Orange County, CA with multiple outpatient locations and hospital affiliations.

Qualified candidates will possess an MD or DO, be board certified in psychiatry and hold a California medical license in order to be eligible for the position. A strong interest in inpatient psychiatry is recommended as well as a comprehensive approach to treating the psychiatric patient to provide excellent continuity of care.

Applicants please forward your interest statement, CV and references to: Lori Kelly, 28 Monarch Bay Plaza, Suite N, Dana Point, CA 92629 or fax to 949-493-9350.

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.

LICENSED CA. PSYCHIATRIST wanted for part-time PRIVATE PRACTICE POSITION. Flexible hours. Already on insurance panels a must. No inpatient work. Very little on call. AVERAGE $200 PER HOUR. Fax CV to 760-946-1215 or email desertbehavioralhlth@msn.com.

San Francisco Bay Area or Sacramento:
J1 and H1 applicants welcome.

Adult and child psychiatrists in out-patient or hospital practices in or near the San Francisco Bay Area or Sacramento, California. Locations meet criteria for designated shortage area. Please view our web site at CommunityPsychiatry.com or call (800) 244-5807, Fax: (916) 285-0338, Email StephaniMartinez@communitypsychiatry.com.

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.**

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

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. bayarea doctors@gmail.com.

CONNECTICUT

APT Foundation in New Haven CT, a non-profit substance abuse and mental health clinic, closely affiliated with Yale Dept of Psychiatry is seeking a full time addiction psychiatrist. APT provides outpatient and residential treatment, serves as a training site for Yale Addiction Psychiatry residents and post-doctoral trainees and conducts research aimed at improving treatment. The position includes treatment team leadership, direct care responsibilities, limited call, and supervision to trainees and fellows. Applicants must have successfully completed psychiatric residency training in an accredited US program, be board certified (or eligible), able to obtain a license to practice in Connecticut and have or be willing to obtain a DEA waiver for buprenorphine management. Preference will be given to candidates with BC/BE in addiction psychiatry or ASAM certification or the equivalent in experience.

The APT foundation offers competitive compensation, malpractice coverage and attractive benefits. Interested physicians should send a CV to: Jane Tendler, Human Resources at jtendler@aptfoundation.org, T:, 203-285-1792 F: 203-781-4622.

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.

DISTRICT OF COLUMBIA

Howard University, College of Medicine
Department of Psychiatry and
Behavioral Sciences
Addiction and Inpatient Psychiatrist

Howard University, College of Medicine, Department of Psychiatry and Behavioral Sciences invite applications for an Inpatient Psychiatrist and Addiction Psychiatrist position. Applicants must have an M.D. appropriate clinical skills and research interest, or experience. At time of the appointment, the applicant must have a DC license and be certified by the Board of Psychiatry and Neurology. This position will be filled at an academic rank commensurate with experience (Assistant-Full Professor), in either the Tenure or the Clinical Educator Track. Applicants are encouraged to submit their application electronically-including a CV, and four Letters of Recommendations to:

William B. Lawson MD, PhD, DF APA
Professor and Chair,
Department of Psychiatry
and Behavioral Sciences
Professor of Pharmacology and Psychology
Howard University, College of Medicine
2041 Georgia Ave. N.W.
Washington DC 20060

Equal Employment Opportunity: Howard University does not discriminate on the basis of race, color, national and ethnic origin, sex, marital status, religion, or disability.

FLORIDA

Part-time ASSOCIATE MEDICAL DIRECTOR-
CHILD & ADOLESCENT Board Certified

Excellent opportunity: The physician in this AMD position will have shared oversight of the UM and QI programs. This position provides a key interface between our managed behavioral health organization and our key providers, members and health plan customers. It provides the opportunity to develop clinical programs based on evidence based practices and to monitor clinical outcomes in service delivery across the membership. This position allows for excellent clinical skills to developed and broadened in innovative ways.

Position requires Florida licensure and ABPN Board Certification in Psychiatry, sub-specialty Child and Adolescent Psychiatry. Excellent base salary, paid benefits, and flexible hours within normal business hours.

Please apply to our Recruiter Terri Holub, Phone 916-859-5162 or e-mail tmholub@magellanhealth.com. www.magellanhealth.com.

PSYCHIATRISTS: Renaissance Behavioral Health Systems (RBHS), a Joint Commission accredited, comprehensive behavioral health center, is seeking Psychiatrists for its inpatient and outpatient programs in Jacksonville and Gainesville, Florida. Full-time positions with competitive salary and excellent benefits package. Must be Board Certified or Board Eligible and possess Florida medical license.

For more information, contact: Robert Sommers, Ph.D., President/CEO, RBHS, P.O. Box 19249, Jacksonville, FL 32245-9249. Phone: 904-743-1883, ext. 7103. Fax: 904-743-5109. Email: rbhspres@bellsouth.net.

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.

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

GEORGIA

PSYCHIATRIST to join a well-established multi-disciplinary private M/H practice in St. Marys, GA, 35 miles north of Jacksonville, FL. No start up money required. Full office & billing services provided for an immediate ft/pt caseload. We are a US Health Service Corp site with up to $170,000 in student loan forgiveness possible. For information, call Bryan P. Warren, M.D., DLFAPA at 912-882-4994. Email CV to practicemgr@tds.net.

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

TEACHING FACULTY POSITIONS
UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE AT PEORIA
METHODIST MEDICAL CENTER OF ILLINOIS

SEVERAL FULL TIME FACULTY POSITIONS AVAILABLE IN SUPPORT OF NEW PSYCHIATRY RESIDENCY TRAINING PROGRAM:

- Primary Responsibilities include education, supervision, and clinical care. Administrative, program development, & scholarship roles are also available.
- Directorship Opportunities available in the following clinical service areas: Adult Inpatient, Geriatrics, and Partial Hospitalization Program.
- Associate Program Director position is also available to persons interested in advancement to full Program Director.
- Competitive salary & benefits. Academic rank commensurate with experience.

The Methodist Medical Center of Illinois is a 329-bed teaching institution affiliated with the University of Illinois College of Medicine and provides complete support of the residency. Five state-of-the art inpatient behavioral health units, comprised of 63 patient beds, provide a positive environment and productive learning experience for residents and faculty.

The University has successfully hired several new faculty. The new positions are perfect opportunities for motivated educators interested in curriculum development, supervision of residents and medical students, and entry into academic medicine.

Please contact: Ryan Finkenbine, MD, Department of Psychiatry, University of Illinois College of Medicine at Peoria, 221 NE Glen Oak Ave., Peoria, IL 61636. Phone: 309-671-8393, Fax: 309-671-8384, e-mail: ryanf@uic.edu.

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.

The Department of Psychiatry & Behavioral Neuroscience at the University of Chicago is seeking an academically-oriented addiction psychiatrist to develop and lead a new clinical and translational research program. The candidate will also be involved in the training of medical students, psychiatric residents and fellows, and in patient management. The Department has a strong team of researchers and potential for collaborations in basic and animal research, human psychopharmacological studies, translational investigations, and efficacy and effectiveness trials for alcohol and tobacco disorders as well as other addictions. Applicants must have an M.D. or a combined M.D./Ph.D. degree. Candidates are required to be Board-Certified in Psychiatry and licensure as a Physician & Surgeon in IL at the time of hire. Excellent teaching skills required. Preference will be given to candidates with Board Certification in Addiction Disorders, a track record of peer-review publications, and a history of extramural funding. A start-up package is available in order to develop the clinical research program. Academic rank and compensation are dependent upon qualifications. Employees receive a generous package of fringe benefits.

Review of applications will commence **March 15, 2011**, and continue until the position is filled. To apply, visit The University of Chicago Academic Career Opportunities website at **http://tinyurl.com/4lev8zo**. to send cover letter and curriculum vitae. The University of Chicago is an Affirmative Action / Equal Opportunity Employer.

Older Adult Program

Expanding cutting edge state of the art practice in South West Suburb of Chicago (Orland Park) is seeking a general psychiatrist with experience working with geriatric population. Geriatric fellowship desirable but not essential. Primary outpatient practice, limited inpatient work at Ingalls Memorial Hospital and Silver Cross Hospital. Will help the development of an older adult program in the community providing consultation to a consortium of selected assisted living and sub-acute rehabilitation facilities. Will join other 6 psychiatrists and 10 therapists. TMS treatment available. Call every 4 or 5 weekends. Group practice will provide malpractice insurance and health benefits, as well as credentialing with insurance carriers. Please email CV to moigaviria@usa.net. Candidate must have license to practice in Illinois and be board certified or board eligible. Applications accepted until position is filled.

KANSAS

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**.

LOUISIANA

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.

The Department of Psychiatry and Behavioral Sciences at Tulane University School of Medicine is recruiting a geriatric psychiatrist for a full-time faculty position. The candidate will spend part of their time at the Southeast Louisiana Veterans Health Care System (SLVHCS) and will also be involved in the new initiatives in both clinical geriatric care and special geriatric education programs at Tulane. Responsibilities include patient care as well as contributing to the various teaching and training programs of Tulane University's Department of Psychiatry and Behavioral Sciences at the SLVHCS. He/she will be provided the opportunity to pursue their research interests. The person selected for this position must be professionally competent and be board eligible/certified in general psychiatry and in geriatric psychiatry. She/he must be eligible for medical licensure in the State of Louisiana and have a current state and federal narcotics number. In addition, candidates must be eligible for clinical privileges at Tulane University Hospital and Clinic under the appropriate staff category and must agree to abide by those privileges as outlined by the current bylaws of the institution. Salary will be competitive and commensurate with the level of the candidate's academic appointment. Applications will be accepted until a suitable qualified candidate is found.

Applicants should email (winstead@tulane.edu) or send letter of interest, updated 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. Interested and eligible candidates may obtain further information by contacting Daniel K. Winstead, MD at 504-988-5246 or winstead@tulane.edu. Tulane is strongly committed to policies of non-discrimination and affirmative action in student admissions and in employment.

DEPARTMENT OF PSYCHIATRY AND 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. 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 non-discrimination and affirmative action in student admission and in employment.

MAINE

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

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.

MARYLAND

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.

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.

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

PT psychiatrist needed in well established psychiatric practice in Gaithersburg, MD, 10-20 hours per week to treat adolescents and adults. Schedule is flexible, Board Certified Only, experience in meds management a must. Mail CV to GMPS at 9055 Shady Grove Court, Gaithersburg, MD 20877 or email to **glasser medical@verizon.net.**

MASSACHUSETTS

The Edith Nourse Rogers Memorial Veterans Hospital (ENRMVH) in Bedford, Massachusetts has a new position for an innovative psychiatrist who would like to assume leadership of our 30 bed acute inpatient unit and help lead a reconfiguration of that to a best practice inpatient milieu. This inpatient unit already has two Psychiatrists assigned as well as a full complement of experienced Mental Health staff. It is scheduled to undergo a physical renovation within the next few months to make it state-of-the art. Residents from Boston University School of Medicine Division of Psychiatry rotate on the unit for their PGY 1 and 2 experiences. The ENRMVH is a teaching hospital with research in Mental Health, Alzheimer's disease and Health Services Outcomes. It has a highly supportive and collegial environment in a delightful suburban setting. Academic appointments available commensurate with qualifications. ENRMVH is an Equal Opportunity Employer. Applications are subject to an employment physical examination and drug testing.

Interested candidates please contact:

Lawrence Herz, M.D.,
Acting Chief of Psychiatry
Edith Nourse Rogers Memorial Veterans Hospital
200 Springs Rd, Bedford, MA 01730
781-687-2363
Lawrence.Herz@va.gov

The Department of Psychiatry at the University of Massachusetts Medical School/UMass Memorial Medical Center is seeking a **BC/BE Psychiatrist** for its **University Hospital Outpatient Clinic**. Candidates should have an interest in available academic opportunities in either training or research. Academic rank commensurate with experience.

Interested applicants send CV to Alan P. Brown, M.D., Vice Chairman for Clinical Services, Department of Psychiatry, UMass Memorial Medical Center, 55 Lake Avenue North, Worcester, MA 01655 or email BrownA01@ummhc.org. AA/EOE.

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.

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.

Psychiatrist, Concord, Massachusetts

Full-time psychiatry salaried position for growing general hospital department of Psychiatry. Position includes inpatient responsibility for patients on our 31-bed inpatient unit, consultation and liaison services to the medical units, and shared on-call responsibilities as a member of the department of Psychiatry. Emerson Hospital is a recognized provider of high quality mental health and substance abuse services. We provide a stimulating and collegial atmosphere for the career-minded psychiatrist. Competitive salary and benefit package. Additional compensation available for added call responsibilities. The Concord area is an excellent environment to develop a vibrant supplemental private practice. Please contact Robert Stern, MD, chair, department of Psychiatry, 978-287-3512 or by email at rstern@emersonhosp.org. Geriatric expertise and ECT experience a plus.

Weekend coverage - Also seeking moonlighters to cover the inpatient service one weekend per month. Includes rounding on all inpatients and phone coverage from home. Please contact Robert Stern, MD, chair, department of Psychiatry, 978-287-3512 or by email at rstern@emersonhosp.org.

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.

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.

Exceptional Professional Opportunity for psychiatrist to provide high quality care as part of a well respected multidisciplinary private group practice loacted 2 hours north of NYC in Columbia County/Hudson Valley, NY and **neighboring Berkshire County, MA**. Inpt/outpt. Flexible hours.

Excellent salary packages $200,000 + (with opportunity for additional income). **Call Dennis Marcus, M.D.** at (413)528-1845, fax CV to (413)528-3667 or email to scppcmd@yahoo.com.

MICHIGAN

Hiawatha Behavioral Health is seeking a **Psychiatrist/Medical Director** to provide direct psychiatric services to adults, psychiatric assessments, and medication management as part of a multi-disciplinary team; assuring that all clients receive appropriate evaluation, diagnosis, treatment, medical screening, and psychiatric evaluation whenever indicated; and that clinical staff receives appropriate clinical supervision. Position may be full or part-time (negotiable with the successful applicant).

Hiawatha Behavioral Health is a progressive, nationally accredited Agency that provides a comprehensive array of services to persons with serious mental illness, developmental disabilities, and children with severe emotional disturbances in a rural setting. The Agency values opportunities to contribute to the growing body of knowledge of most effective treatments and supports toward recovery for individuals challenged by serious and persistent mental illness.

Applicants should be a **Board Certified/Board Eligible adult Psychiatrist**; and have, or the ability to obtain, State of Michigan licensure.

Hiawatha Behavioral Health is a Community Mental Health Agency that covers Chippewa, Mackinac, and Schoolcraft Counties in the picturesque Upper Peninsula of Michigan. The Upper Peninsula is a wonderful place to live and work, with great schools, family friendly communities, year-round recreational opportunities and natural beauty.

Send letter of interest and resume to: Hiawatha Behavioral Health, Human Resources Manager, 3865 S. Mackinac Trail, Sault Ste. Marie, fax to 906-635-3760, or e-mail: kjuda@hbhcmh.org. Applications will be accepted until position is filled. E.O.E.

J1 and H1 Opportunities near Ann Arbor, Michigan

Adult and child psychiatrists in out-patient or hospital practices, near Ann Arbor, Michigan. Locations meet criteria for designated shortage area. Please view our web site at Community-Psychiatry.com or call (800) 244-5807, Fax: (916) 285-0338, Email StephaniMartinez@communitypsychiatry.com.

Assistant Director of Psychiatry

Outpatient opportunity affiliated with the new medical school at CMU. Oversee and ensure the quality of Psychiatric training at this well respected program. Amazing academic and non academic support staff. Don't miss out on this great academic opportunity!

Contact: Courtney Tripp - ASA Partners
Courtney@asapartners.net
800-473-5460 Ext 112

MINNESOTA

General Outpatient Psychiatry Adult and Child Psychiatrist

The Park Nicollet Clinic Health Services Department of Mental Health seeks highly qualified applicants for positions in adult and child outpatient psychiatry. Successful candidates will join 14 adult psychiatrists and 2 child psychiatrists, along with nearly 30 clinical mental health professionals, in a growing practice which provides outstanding clinical services as well as opportunities for teaching and research. Park Nicollet Clinic Health Services is renowned for clinical excellence, innovation in service delivery and collegiality. We are a comprehensive, nonprofit healthcare system that contracts with all major insurers. Minneapolis, MN is famous for its cultural attractions, healthcare and educational systems, natural beauty and overall quality of life. Salary and benefits are highly competitive.

Please submit letter of interest and CV to Jenny Bredeson, Park Nicollet Health Services, 3800 Park Nicollet Blvd-7N, St. Louis Park, MN 55416; email: bredej@parknicollet.com or apply online at www.parknicollet.com. For more information call (952) 993-2804 or toll free (866) 874-3812. AA/EOE

NURSE PRACTITIONER

The Behavioral Health Department of the Mankato Clinic is looking for **Nurse Practitioners** to provide patient-centered, out-patient, psychiatric assessment and ongoing care services to clients between the ages of 6 - 18, 16+ or a mix of both. You will assess, plan, evaluate, implement and coordinate care of psychiatric patients with our fully implemented EMR, including medication management, education and support for patients, families in collaboration with psychiatry, psychology, and LICSW providers.

Enjoy our community with regional appeal and amenities.

- This growing river valley community has some of the state's best education;
- Named one of America's Promise **"100 of the Best Places for Youth"**;
- High school students are eligible to take college courses for credit while in 11th and 12th grades;
- Essential retail located in the community; Target, Best Buy, Lowe's, Sears, Old Navy, and more;
- Major shopping mall-easy one-hour drive: Macy's, Nordstrom, Bloomingdales, Apple Store, Burberry, Coach, etc.;
- State university with 14k students; 150 undergraduate/100 graduate/4 PhD programs; 1800 Faculty/Staff; 5 other local colleges;
- Affordable housing: 4-bed, 4.5 bath, 3,572 Sq/Ft. home - $264,900;
- Four season outdoor activity; over 50 miles of hiking/biking trails; hundreds of acres of community parks.

Contact Dennis Davito, Director of Provider Services, Mankato Clinic, 1230 East Main Street, Mankato, MN 56001. Phone: 507-389-8654. Fax: 507-625-4353.

MISSISSIPPI

Staff Psychiatrist
Mississippi State Hospital

Mississippi State Hospital is seeking a staff psychiatrist for its Inpatient Services Division. Located 15 minutes from downtown Jackson, the Joint Commission accredited facility has approximately 530 inpatient psychiatric beds. The position offers generous personal and medical leave, 12 paid holidays per year, health insurance, participation in the state of Mississippi retirement program, and other valuable benefits such as no call and no weekends. Rent-free housing is also available. We do not qualify as a J-1 visa site.

For further information, please contact:
Dr. Duncan Stone
Chief of the Medical Staff
PO Box 157-A
Whitfield, MS39193
Ph-601-351-8066
Fax-601-351-8257
Email: stonedu@msh.state.ms.us
Website: http://www.msh.state.ms.us/

Horizon Health seeks **Psychiatrists** for weekend call coverage for Adult and Geriatric inpatient psychiatric programs in **Batesville, MS.** For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

MISSOURI

Heart of Missouri! 30 Minutes or Less from Columbia-

Seeking additional Psychiatrist, salaried position with benefits, adult inpatient psychiatric unit in a very impressive hospital. Full-time or part-time. Join a great team. Student loan repayment plan may be an option. Please **contact Terry B. Good, Horizon Health, 1-804-684-5661**, fax 1-804-684-5663, or email terry.good@horizonhealth.com. EOE

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.

NEW MEXICO

LAS CRUCES: Medical Director - Private behavioral health hospital with I/P, RTC and O/P services. Salaried employment with benefits and bonus opportunity. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

NEW YORK CITY & AREA

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.

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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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

Seeking a **F/T Inpatient** and a **P/T Emergency Room Psychiatrist**. Competitive salaries and excellent benefits. Please fax CV to Seeth Vivek, M.D., Chairman, Department of Psychiatry to 718-206-7169 or SVivek@jhmc.org.

NEW YORK STATE

ELMIRA PSYCHIATRIC CENTER
Adult and Adolescent Psychiatrists

Board Certified - $172,269 - $176,903
Licensed Physician - $141,751
Limited Permit - $107, 318 - $115,905

- All positions M-F 8-4:30 with no managed care insurance demands
- Optional participation in a low stress on-call program with potential to earn up to an extra $74,000/year
- Student loan repayment available
- Excellent NYS benefits package
- Inpatient, Outpatient and Day Treatment services
- Our location offers: quality housing prices; little traffic; regional airport; Cornell University; 4hr drive to NYC, Toronto & Philadelphia; 5 ½ hr drive to Boston & DC; less than 1hr to Finger Lakes

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

Exceptional Professional Opportunity for psychiatrist to provide high quality care as part of a well respected multidisciplinary private group practice loacted 2 hours north of NYC in Columbia County/Hudson Valley, NY and **neighboring Berkshire County, MA**. Inpt/outpt. Flexible hours.

Excellent salary packages $200,000 + (with opportunity for additional income). **Call Dennis Marcus, M.D.** at (413)528-1845, fax CV to (413)528-3667 or email to scppcmd@yahoo.com.

Private Practice Psychiatrist

Upscale private practice office located near Buffalo is seeking a full-time psychiatrist to a join large, multidisciplinary group practice. Referrals are already built in and are clinically varied. Practice will pay guaranteed salary until billables are up to acceptable level, plus benefits and malpractice are paid. For immediate consideration, call Holly Dorna, MA, LPCC, President/CEO, PsychPros Executive Search, at 513-333-4770 (direct line) or e-mail CV to Holly@psychpros.com.

St. Lawrence Psychiatric Center, a fully accredited NYS Office of Mental Health facility, is seeking Licensed Psychiatrists for our Children and Youth, Forensics and Adult services. In addition to salary ($168,421 to $174,798) and guaranteed additional compensation for voluntary participation in an on-call program, benefits package includes medical/dental/vision insurance, paid vacation, holiday and sick time, an excellent retirement plan, and educational and professional leaves. SLPC is an EO/AAE, federally designated as MHPSA.

Located on the scenic St. Lawrence Seaway in northern New York, St. Lawrence Psychiatric Center is located within reasonable driving distance of many cultural, educational and economic opportunities, including metropolitan Ottawa and Montreal, Canada and Syracuse, NY. Close proximity to the Adirondack Mountains, including Lake Placid, offers easy access to a wide variety of unspoiled natural areas and provides abundant recreational opportunities throughout the year.

Submit letter of interest to: Rosella Turnbull, St. Lawrence Psychiatric Center, One Chimney Point Drive, Ogdensburg, NY 13669 or at Rosella.Turnbull@omh.ny.gov. If you have questions, please call (315) 541-2189.

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

Live and work near beautiful Lake Gaston, NC!

Employment opportunity with partnership potential. Adult, primarily outpatient. Admit to 20-bed behavioral health unit at **Halifax Regional**.

- **Paid vacation / CME**
- **Relocation package**
- **401(K)**
- **Competitive Salary**

Location: I-95 corridor, northeastern NC. 2.5 hours to Outer Banks, centrally located 1.5 hours from Raleigh-Durham, NC, Richmond, VA, and Norfolk, Va. Outstanding water recreation. Area population: 85K.

Send letter and CV to Pam Ballew
pballew@halifaxrmc.org
252-535-8795
www.halifaxregional.org
www.visithalifax.com

Medical Director-North Carolina

We are seeking a full time Adult or Child/Adolescent Psychiatrist for a Medical Director opportunity with MBHO in North Carolina. Medical Director will oversee the utilization review process and provide clinical supervision to clinical staff. In addition, this position serves as co-chair of the Quality Management and Utilization Management committees.

Contact Cheryl Rapier, Sr. Recruiting Manager, PsychPros, Inc. at 513-333-4780 or e-mail Cheryl@psychpros.com.

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

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.
EOE/AA Not subject to H1 Caps

OHIO

Outpatient Psychiatrist

Community mental health agency in Southeastern Ohio needs adult psychiatrist to serve adult patients and, if interested, to serve as Medical Director. Will consider full-time or at least 32 hours per week for full benefits and malpractice insurance paid, in addition to CMEs and other benefits. Above-market salary and flexible hours. For immediate consideration, call Holly Dorna, MA, LPCC, President/CEO, PsychPros Executive Search, at 513-333-4770 (direct line) or e-mail your CV and statement of interest to Holly@psychpros.com.

CLEVELAND: Child Psychiatrist - Inpatient Services. Salary, benefits, bonus offered. Phone call only 1:5. Salary, benefits, and bonus offered. Contact Joy Lankswert, In-house recruiter @ 866-227-5415; OR email joy.lankswert@uhsinc.com.

Medical Director

Community mental health agency near Cleveland is seeking a psychiatrist with child and adolescent experience to serve in a combined Medical Director/direct patient care role. Can be boarded in adult or child, but must have child experience. Excellent salary, plus full benefits and malpractice insurance paid. For more information, please call Holly Dorna, MA, LPCC, President/CEO, PsychPros Executive Search, at 513-333-4770 (direct line) or e-mail your CV and statement of interest to Holly@psychpros.com.

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.

PENNSYLVANIA

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.

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.

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

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PITTSBURGH Assertive Community Treatment - Opportunity for a FT ACT psychiatrist at Mercy Behavioral Health. Our financially solid organization, with 24 psychiatrists, offers competitive compensation and an excellent benefits package. Contact Jim Jacobson, MD at 412-488-4927 physician@mercybh.org.

Medical Director-Salary 255k-One Hour to PHILADELPHIA - Two Hours from WASHINGTON, DC -Pretty Area- Easy drive to several amazing metro areas. Salary $255k; Inpatient adult unit and geropsych unit in a med/surg hospital in eastern PA. Much opportunity for growth and the financial rewards that go with it. Please call **Terry B. Good** at 1-804-684-5661, Fax #: 804-684-5663; Email: **terry.good@horizonhealth.com**.

Join Our Team of Psychiatrists

Staff Psychiatrist position available at a Pennsylvania state-run 232 bed adult psychiatric facility located a short distance from the Pocono Mountains in Northeast Pennsylvania. Position enjoys full-time benefits, including healthcare with dental and vision coverage, as well as life insurance and a retirement plan. Salary based on education and experience. Interested candidates should send resume to:

Human Resources
Clarks Summit State Hospital
1451 Hillside Drive
Clarks Summit, PA 18411
Or E-mail Kathleen at kflatness@state.pa.us or fax to 570-587-7132
This is a Pennsylvania State Civil Service covered position.

SOUTH DAKOTA

IMMEDIATE OPENING

The South Dakota Human Services Center, a state-of-the-art 304-bed psychiatric and chemical dependency hospital serving acute, psychiatric rehabilitation, geriatric and adolescent patients, located in Yankton, South Dakota is seeking a BE/BC Psychiatrist to join a dynamic team of nine physicians.

The South Dakota Human Services Center is a teaching hospital affiliated with the Sanford School of Medicine at the University of South Dakota, Department of Psychiatry. Faculty appointment is available and encouraged for qualified candidates.

Comprehensive benefits package including three weeks paid vacation, ten paid holidays, fourteen days sick leave per year, health, life, retirement and flexible benefits. Salary range: $203,707.31-$229,170.73, DOQ/DOE. Typical working hours are 8:00 am - 5:00 pm, Monday through Friday, with on-call coverage from home of 1:7. State liability coverage is provided. Yankton is designated as an underserved area.

Historic Yankton is a family-oriented community located on the shores of Lewis & Clark Lake with excellent outdoor recreation including boating, camping, hunting, fishing and golfing. The Yankton area allows you to enjoy affordable housing with an excellent school system; live in a community with a four-year college; and, be within 25 minutes of a university which offers undergraduate, graduate and doctoral programs. The State of South Dakota does not have a personal income tax.

Forward CV to Holly Bodenstedt, Human Resources, PO Box 7600, Yankton, SD 57078 or fax to (605) 668-5415 or e-mail holly.bodenstedt@state.sd.us. Phone: (605) 668-3118; Web site: http://dhs.sd.gov/hsc.

TENNESSEE

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.

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.

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.

TEXAS

Vericare (www.vericare.com) is the leader in providing mental health services to residents of long term care. We have immediate needs for Adult or Geriatric Psychiatrists in **San Antonio, Houston, Dallas Ft. Worth and surrounding areas**. We offer flexible scheduling, 100% paid malpractice, administrative support, no on- call/weekend requirement and a complete benefits package. Board Certified preferred. Call **DebLee Tran** at **800-257-8715 x1146** or email your resume/inquiry to **dtran@vericare.com.**

VERMONT

Washington County Mental Health Services, nestled in the heart of the Green Mountains at Montpelier, Vermont's capitol, is seeking a full time psychiatrist to join its dedicated, team oriented, and high quality staff. WCMH is the second largest CMHC in Vermont with about 500 employees. In our rural setting we provide care for the full range of psychiatric difficulties. The position entails outpatient work with adult and geriatric patients suffering from major mental illnesses, developmental disorders, the effects of trauma, and substance abuse. Depending on qualifications an assistant medical director's position is also possible.

From its mountains and lakes to its universities and cultural events, and from its verdant summers to its white winters, Vermont is a wonderful place to live and work. **WCMH** offers a competitive salary with benefits, and is an EOE. Applicant must be BE/BC. Please send cover letter and CV to: Stuart Graves, MD, PO Box 647, Montpelier, VT, 05601, or e-mail Stuartg@wcmhs.org.

VIRGINIA

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.

GEROPSYCHIATRIST: Virginia Commonwealth University, Department of Psychiatry is recruiting a Virginia license eligible and board-eligible/certified Geropsychiatrist to be a program leader in providing clinical care, education and scholarship. Geropsychiatry fellowship and funded research preferred. J-1 will be considered. Clinical facilities include 12-bed geriatric inpatient team at the University hospital, geriatric clinic and large base of nursing home residents. Strong educational program with medical students, psychiatry residents and other trainees. Opportunity for collaborative and independent research available. Demonstrated experience working in and fostering a diverse faculty, staff, and student environment or commitment to do so as a faculty member at VCU.

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Send CV to Tammy Newcomb, Human Resources, Department of Psychiatry, VCU/MCV, Box 980710, Richmond, VA 23298. Virginia Commonwealth University is an equal opportunity/affirmative action employer. Women, minorities, persons with disabilities encouraged to apply.

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For more information contact: Mark Blakeney, Voice: 972-420-7473, Fax: 972-420-8233; email: mark.blakeney@horizonhealth.com EOE.

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For more information, contact Cyndi Edwards 800-573-2580, fax 715-838-6192, or e-mail edwards.cyndi@mayo.edu. You may also visit our website at **www.luthermidelfort.org.** EOE

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Ralph Hoffman, MD, and research assistant Joan Nye, view functional MR images of a patient's cortical activation during auditory hallucinations.

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