Help your adult patients with Major Depressive Disorder (MDD) toward their treatment goals

GO forward with Pristiq

Results from PRISTIQ 50 mg clinical studies:

- An SNRI with proven efficacy[1]
- Demonstrated improvement in functional outcomes—work, leisure, and home activities as measured by the Sheehan Disability Scale* total score[2]
- Discontinuation rate due to adverse events comparable to placebo[3]
- No significant weight gain versus placebo and low incidence of sexual side effects[3]

The most commonly observed adverse reactions in patients taking PRISTIQ (incidence ≥5% and ≥2x the rate of placebo) were nausea, dizziness, hyperhidrosis, constipation, and decreased appetite.

*A validated, self-rated measure of functional impairment.[4]

To learn more about PRISTIQ, go to www.pristiqhcp.com

Pristiq® desvenlafaxine 50 mg
EXTENDED-RELEASE TABLETS

PRISTIQ is indicated for the treatment of major depressive disorder in adults.

Important Safety Information for PRISTIQ

WARNING: SUICIDALITY AND ANTIDEPRESSANT DRUGS

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

Contraindications

- PRISTIQ is contraindicated in patients with a known hypersensitivity to PRISTIQ or venlafaxine.
- PRISTIQ must not be used concomitantly with an MAOI or within 14 days of stopping an MAOI. Allow 7 days after stopping PRISTIQ before starting an MAOI.

Warnings and Precautions

- **All patients treated with antidepressants should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the first few months of treatment and when changing the dose.** Consider changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse or includes symptoms of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, mania, or suicidality that are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants should be alerted about the need to monitor patients.**
- Development of a potentially life-threatening serotonin syndrome or Neuroleptic Malignant Syndrome-like reactions have been reported with SNRIs and SSRIs alone, including PRISTIQ treatment, but particularly with concomitant use of serotonergic drugs, including triptans, with drugs that impair the metabolism of serotonin (including MAOIs), or with antipsychotics or other dopamine antagonists. If concomitant use with a triptan is clinically warranted, careful observation of the patient is advised, particularly during treatment initiation and dose increases. Concomitant use of PRISTIQ with serotonin precursors is not recommended.
- Patients receiving PRISTIQ should have regular monitoring of blood pressure since increases in blood pressure were observed in clinical studies. Pre-existing hypertension should be controlled before starting PRISTIQ. Caution should be exercised in treating patients with pre-existing hypertension or other underlying conditions that might be compromised by increases in blood pressure. Cases of elevated blood pressure requiring immediate treatment have been reported. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.
- SSRIs and SNRIs, including PRISTIQ, may increase the risk of bleeding events. Concomitant use of aspirin, NSAIDs, warfarin, and other anticoagulants may add to this risk.
- Mydriasis has been reported in association with PRISTIQ; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.
- PRISTIQ is not approved for use in bipolar depression. Prior to initiating treatment with an antidepressant, patients should be adequately screened to determine the risk of bipolar disorder.
- As with all antidepressants, PRISTIQ should be used cautiously in patients with a history or family history of mania or hypomania, or with a history of seizure disorder.
- Caution is advised in administering PRISTIQ to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders. Increases in blood pressure and small increases in heart rate were observed in clinical studies with PRISTIQ. PRISTIQ has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease.
- Dose-related elevations in fasting serum total cholesterol, LDL (low density lipoprotein) cholesterol, and triglycerides were observed in clinical studies. Measurement of serum lipids should be considered during PRISTIQ treatment.
- On discontinuation, adverse events, some of which may be serious, have been reported with PRISTIQ and other SSRIs and SNRIs. Abrupt discontinuation of PRISTIQ has been associated with the appearance of new symptoms. Patients should be monitored for symptoms when discontinuing treatment. A gradual reduction in dose rather than abrupt cessation is recommended whenever possible.
- The recommended dose in patients with severe renal impairment or end-stage renal disease (ESRD) is 50 mg every other day. The dose should not be escalated in patients with moderate or severe renal impairment or ESRD.
- Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with PRISTIQ.
- Hyponatremia may occur as a result of treatment with SSRIs and SNRIs, including PRISTIQ. Discontinuation of PRISTIQ should be considered in patients with symptomatic hyponatremia.
- Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of PRISTIQ) therapy have been rarely reported.

Adverse Reactions

- The most commonly observed adverse reactions in patients taking PRISTIQ vs placebo for MDD in short-term fixed-dose premarketing studies (incidence ≥5% and ≥2x the rate of placebo in the 50-mg dose group) were nausea (22% vs 10%), dizziness (13% vs 5%), hyperhidrosis (10% vs 4%), constipation (9% vs 4%), and decreased appetite (5% vs 2%).

References: 1. Thase ME, Kornstein SG, Germain JM, Jiang Q, Guico-Pabia C, Ninan PT. An integrated analysis of the efficacy of desvenlafaxine compared with placebo in patients with major depressive disorder. *CNS Spectr.* 2009;14(3):144-154. **2.** Soares CN, Kornstein SG, Thase ME, Jiang Q, Guico-Pabia CJ. Assessing the efficacy of desvenlafaxine for improving functioning and well-being outcome measures in patients with major depressive disorder: a pooled analysis of 9 double-blind, placebo-controlled, 8-week clinical trials. *J Clin Psychiatry.* 2009;70(10):1365-1371. **3.** Clayton AH, Kornstein SG, Rosas G, Guico-Pabia C, Tourian KA. An integrated analysis of the safety and tolerability of desvenlafaxine compared with placebo in the treatment of major depressive disorder. *CNS Spectr.* 2009;14(4):183-195. **4.** Leon AC, Olfson M, Portera L, Farber L, Sheehan DV. Assessing psychiatric impairment in primary care with the Sheehan Disability Scale. *Int J Psychiatry Med.* 1997;27:93-105.

Please see brief summary of Prescribing Information on adjacent pages.

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dose-dependent increase in the proportion of patients who developed sustained hypertension. **Abnormal Bleeding-** SSRIs and SNRIs can increase the risk of bleeding events. Concomitant use of aspirin, other drugs that affect platelet function, nonsteroidal anti-inflammatory drugs, warfarin, and other anticoagulants can add to this risk. Bleeding events related to SSRIs and SNRIs have ranged from ecchymosis, hematoma, epistaxis, and petechiae to life-threatening hemorrhages. Patients should be cautioned about the risk of bleeding associated with the concomitant use of Pristiq and NSAIDs, aspirin, or other drugs that affect coagulation or bleeding. **Narrow-angle Glaucoma-**Mydriasis has been reported in association with Pristiq; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored. **Activation of Mania/Hypomania-**During all MDD and VMS (vasomotor symptoms) phase 2 and phase 3 studies, mania was reported for approximately 0.1% of patients treated with Pristiq. Activation of mania/hypomania has also been reported in a small proportion of patients with major affective disorder who were treated with other marketed antidepressants. As with all antidepressants, Pristiq should be used cautiously in patients with a history or family history of mania or hypomania. **Cardiovascular/Cerebrovascular Disease-**Caution is advised in administering Pristiq to patients with cardiovascular, cerebrovascular, or lipid metabolism disorders [*see Adverse Reactions (6.1)*]. Increases in blood pressure and heart rate were observed in clinical studies with Pristiq. Pristiq has not been evaluated systematically in patients with a recent history of myocardial infarction, unstable heart disease, uncontrolled hypertension, or cerebrovascular disease. Patients with these diagnoses, except for cerebrovascular disease, were excluded from clinical studies. **Serum Cholesterol and Triglyceride Elevation-** Dose-related elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides were observed in the controlled studies. Measurement of serum lipids should be considered during treatment with Pristiq [*see Adverse Reactions (6.1)*]. **Discontinuation of Treatment with Pristiq-** Discontinuation symptoms have been systematically and prospectively evaluated in patients treated with Pristiq during clinical studies in major depressive disorder. Abrupt discontinuation or dose reduction has been associated with the appearance of new symptoms that include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, fatigue, abnormal dreams, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy. During marketing of SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors) and SSRIs (Selective Serotonin Reuptake Inhibitors), there have been spontaneous reports of adverse events occurring upon discontinuation of these drugs, particularly when abrupt, including the following: dysphoric mood, irritability, agitation, dizziness, sensory disturbances (eg, paresthesia, such as electric shock sensations), anxiety, confusion, headache, lethargy, emotional lability, insomnia, hypomania, tinnitus, and seizures. While these events are generally self-limiting, there have been reports of serious discontinuation symptoms. Patients should be monitored for these symptoms when discontinuing treatment with Pristiq. A gradual reduction in the dose rather than abrupt cessation is recommended whenever possible. If intolerable symptoms occur following a decrease in the dose or upon discontinuation of treatment, then resuming the previously prescribed dose may be considered. Subsequently, the physician may continue decreasing the dose, but at a more gradual rate [*see Dosage and Administration (2.4) and Adverse Reactions (6.1) in full prescribing information*]. **Renal Impairment-**In patients with moderate or severe renal impairment or end-stage renal disease (ESRD) the clearance of Pristiq was decreased, thus prolonging the elimination half-life of the drug. As a result, there were potentially clinically significant increases in exposures to Pristiq [*see Clinical Pharmacology (12.6) in full prescribing information*]. Dosage adjustment (50 mg every other day) is necessary in patients with severe renal impairment or ESRD. The doses should not be escalated in patients with moderate or severe renal impairment or ESRD [*see Dosage and Administration (2.2) in full prescribing information*]. **Seizure-**Cases of seizure have been reported in premarketing clinical studies with Pristiq. Pristiq should be prescribed with caution in patients with a seizure disorder. **Hyponatremia-** Hyponatremia can occur as a result of treatment with SSRIs and SNRIs, including Pristiq. In many cases, this hyponatremia appears to be the result of the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Elderly patients can be at greater risk of developing hyponatremia with SSRIs and SNRIs. Also, patients taking diuretics or who are otherwise volume depleted can be at greater risk [*see Use in Specific Populations (8.5) and Clinical Pharmacology (12.6) in full prescribing information*]. Discontinuation of Pristiq should be considered in patients with symptomatic hyponatremia and appropriate medical intervention should be instituted. **Coadministration of Drugs Containing Desvenlafaxine and Venlafaxine-** Desvenlafaxine is the major active metabolite of venlafaxine. Products containing desvenlafaxine and products containing venlafaxine should not be used concomitantly with Pristiq. **Interstitial Lung Disease and Eosinophilic Pneumonia-** Interstitial lung disease and eosinophilic pneumonia associated with venlafaxine (the parent drug of Pristiq) therapy have been rarely reported. The possibility of these adverse events should be considered in patients treated with Pristiq who present with progressive dyspnea, cough, or chest discomfort. Such patients should undergo a prompt medical evaluation, and discontinuation of Pristiq should be considered.

ADVERSE REACTIONS: Clinical Studies Experience: The most commonly observed adverse reactions in Pristiq-treated MDD patients in short-term fixed-dose studies (incidence ≥5% and at least twice the rate of placebo in the 50- or 100-mg dose groups) were nausea, dizziness, insomnia, hyperhidrosis, constipation, somnolence, decreased appetite, anxiety, and specific male sexual function disorders. Adverse reactions reported as reasons for discontinuation of treatment- The most common adverse reactions leading to discontinuation in at least 2% of the Pristiq-treated patients in the short-term studies, up to 8 weeks, were nausea (4%); dizziness, headache and vomiting (2% each); in the long-term study, up to 9 months, the most common was vomiting (2%). Common adverse reactions in placebo-controlled MDD studies- Table 3 in full PI shows the incidence of common adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients at any dose in the 8-week, placebo-controlled, fixed-dose, premarketing clinical studies. In general, the adverse reactions were most frequent in the first week of treatment. Cardiac disorders: Palpitations, Tachycardia, Blood pressure increased; Gastrointestinal disorders: Nausea, Dry mouth, Diarrhea, Constipation, Vomiting; General disorders and administration site conditions: Fatigue, Chills, Feeling jittery, Asthenia; Metabolism and nutrition disorders: Decreased appetite, weight decreased; Nervous system disorders: Dizziness, Somnolence, Headache, Tremor, Paraesthesia, Disturbance in attention; Psychiatric Disorders: Insomnia, Anxiety, Nervousness, Irritability, Abnormal dreams; Renal and urinary disorders: Urinary hesitation; Respiratory, thoracic, and mediastinal disorders: Yawning; Skin and subcutaneous tissue disorders: Hyperhidrosis, Rash; Special Senses: Vision blurred; Mydriasis, Vertigo, Tinnitus, Dysgeusia; Vascular Disorders: Hot flush. Sexual function adverse reactions-Table 4 shows the incidence of sexual function adverse reactions that occurred in ≥2% of Pristiq-treated MDD patients in any fixed-dose group (8-week, placebo-controlled, fixed and flexible-dose, premarketing clinical studies). Men Only: Anorgasmia, Libido decreased, Orgasm abnormal, Ejaculation delayed, Erectile dysfunction, Ejaculation disorder, Ejaculation failure, Sexual dysfunction; Women Only: Anorgasmia; Other adverse reactions observed in premarketing clinical studies: Other infrequent adverse reactions occurring at an incidence of <2% in MDD patients treated with Pristiq were: *Immune system disorders* – Hypersensitivity. *Investigations* – Weight increased, liver function test abnormal, blood prolactin increased. *Nervous system disorders* – Convulsion, syncope, extrapyramidal disorder. *Musculoskeletal and connective tissue disorders* – Musculoskeletal stiffness. *Psychiatric disorders* – Depersonalization, hypomania, bruxism. *Respiratory, thoracic and mediastinal disorders* – Epistaxis. *Vascular disorders* – Orthostatic hypotension. In clinical studies, there were uncommon reports of ischemic cardiac adverse events, including myocardial ischemia, myocardial infarction, and coronary occlusion requiring revascularization; these patients had multiple underlying cardiac risk factors. More patients experienced these events during Pristiq treatment as compared to placebo [*see Warnings and Precautions (5.7)*]. Discontinuation events-Adverse events reported in association with abrupt discontinuation, dose reduction or tapering of treatment in MDD clinical studies at a rate of ≥5% include dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. In general, discontinuation events occurred more frequently with longer duration of therapy [*see Dosage and Administration (2.4) and Warnings and Precautions (5.9) in full prescribing information*]. Laboratory, ECG and vital sign changes observed in MDD clinical studies-The following changes were observed in placebo-controlled, short-term, premarketing MDD studies with Pristiq. *Lipids*-Elevations in fasting serum total cholesterol, LDL (low-density lipoprotein) cholesterol, and triglycerides occurred in the controlled studies. Some of these abnormalities were considered potentially clinically significant [*see Warnings and Precautions (5.8)*]. *Proteinuria*-Proteinuria, greater than or equal to trace, was observed in the fixed-dose controlled studies (see Table 6 in full prescribing information). This proteinuria was not associated with increases in BUN or creatinine and was generally transient. *ECG changes*-Electrocardiograms were obtained from 1,492 Pristiq-treated patients with major depressive disorder and 984 placebo-treated patients in clinical studies lasting up to 8 weeks. No clinically relevant differences were observed between Pristiq-treated and placebo-treated patients for QT, QTc, PR, and QRS intervals. In a thorough QTc study with prospectively determined criteria, desvenlafaxine did not cause QT prolongation. No difference was observed between placebo and desvenlafaxine treatments for the QRS interval. *Vital sign changes*-Table 7 summarizes the changes that were observed in placebo-controlled, short-term, premarketing studies with Pristiq in patients with MDD (doses 50 to 400 mg). Relative to placebo, Pristiq was associated with mean increase of up to 2.1 mm Hg in systolic blood pressure, 2.3 mm Hg in diastolic blood pressure, and 4.1 bpm with supine pulse. At the final on-therapy assessment in the 6-month, double-blind, placebo-controlled phase of a long-term study in patients who had responded to Pristiq during the initial 12-week, open-label phase, there was no statistical difference in mean weight gain between Pristiq- and placebo-treated patients. *Orthostatic hypotension*- In the short-term, placebo-controlled clinical studies with doses of 50-400 mg, systolic orthostatic hypotension (decrease ≥30 mm Hg from supine to standing position) occurred more frequently in patients ≥65 years of age receiving Pristiq (8.0%, 7/87) versus placebo (2.5%, 1/40), compared to patients <65 years of age receiving Pristiq (0.9%, 18/1,937) versus placebo (0.7%, 8/1,218). **Adverse Reactions Identified During Post-Approval Use-** The following adverse reaction has been identified during post-approval use of Pristiq. Because post-approval 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: *Skin and subcutaneous tissue disorders* – Angioedema. **Adverse Reactions Reported With Other SNRIs**- Although the following are not considered adverse reactions for desvenlafaxine succinate, they are adverse reactions for other SNRIs and may also occur with desvenlafaxine succinate: gastrointestinal bleeding, hallucinations, photosensitivity reactions and severe cutaneous reactions (such as Steven-Johnson Syndrome, toxic epidermal necrolysis, and/or erythemia multiforme). **DRUG INTERACTIONS: Central Nervous System (CNS)-Active Agents-**The risk of using Pristiq in combination with other CNS-active drugs has not been systematically evaluated. Consequently, caution is advised when Pristiq is taken in combination with other CNS-active drugs [*see Warnings and Precautions (5.13)*]. **Monoamine Oxidase Inhibitors (MAOIs)-** Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from a monoamine oxidase inhibitor (MAOI) and started on antidepressants with pharmacological properties similar to Pristiq (SNRIs or SSRIs), or who have recently had SNRI or SSRI therapy discontinued prior to initiation of an MAOI [*see Contraindications (4.2)*]. **Serotonergic Drugs-** Based on the mechanism of action of Pristiq and the potential for serotonin syndrome, caution is advised when Pristiq is coadministered with other drugs that may affect the serotonergic neurotransmitter systems [*see Warnings and Precautions (5.2)*]. **Drugs that Interfere with Hemostasis (eg, NSAIDs, Aspirin, and Warfarin)-** Serotonin release by platelets plays an important role in hemostasis. Epidemiological studies of case-control and cohort design have demonstrated an association between use of psychotropic drugs that interfere with serotonin reuptake and the occurrence of upper gastrointestinal bleeding. These studies have also shown that concurrent use of an NSAID or aspirin may potentiate this risk of bleeding. Altered anticoagulant effects, including increased bleeding, have been reported when SSRIs and SNRIs are coadministered with warfarin. Patients receiving warfarin therapy should be carefully monitored when Pristiq is initiated or discontinued. **Ethanol-** A clinical study has shown that desvenlafaxine does not increase the impairment of mental and motor skills caused by ethanol. However, as with all CNS-active drugs, patients should be advised to avoid alcohol consumption while taking Pristiq. **Potential for Other Drugs to Affect Desvenlafaxine-**Inhibitors of CYP3A4 (ketoconazole)- CYP3A4 is a minor pathway for the metabolism of Pristiq. Concomitant use of Pristiq with potent inhibitors of CYP3A4 may result in higher concentrations of Pristiq. Inhibitors of other CYP enzymes- Based on *in vitro* data, drugs that inhibit CYP isozymes 1A1, 1A2, 2A6, 2D6, 2C8, 2C9, 2C19, and 2E1 are not expected to have significant impact on the pharmacokinetic profile of Pristiq. **Potential for Desvenlafaxine to Affect Other Drugs-** Drugs metabolized by CYP2D6 (desipramine)- *In vitro* studies showed minimal inhibitory effect of desvenlafaxine on CYP2D6. Clinical studies have shown that desvenlafaxine does not have a clinically relevant effect on CYP2D6 metabolism at the dose of 100 mg daily. Concomitant use of desvenlafaxine with a drug metabolized by CYP2D6 can result in higher concentrations of that drug. Drugs metabolized by CYP3A4 (midazolam)- *In vitro*, desvenlafaxine does not inhibit or induce the CYP3A4 isozyme. Concomitant use of Pristiq with a drug metabolized by CYP3A4 can result in lower exposures to that drug. Drugs metabolized by CYP1A2, 2A6, 2C8, 2C9 and 2C19- *In vitro*, desvenlafaxine does not inhibit CYP1A2, 2A6, 2C8, 2C9, and 2C19 isozymes and would not be expected to affect the pharmacokinetics of drugs that are metabolized by these CYP isozymes. **P-glycoprotein Transporter-** *In vitro*, desvenlafaxine is not a substrate or an inhibitor for the P-glycoprotein transporter. The pharmacokinetics of Pristiq are unlikely to be affected by drugs that inhibit the P-glycoprotein transporter, and desvenlafaxine is not likely to affect the pharmacokinetics of drugs that are substrates of the P-glycoprotein transporter. **Electroconvulsive Therapy-** There are no clinical data establishing the risks and/or benefits of electroconvulsive therapy combined with Pristiq treatment. **Drug-Laboratory Test Interactions-** False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine. This is due to lack of specificity of the screening tests. False positive test results may be expected for several days following discontinuation of desvenlafaxine therapy. Confirmatory tests, such as gas chromatography/mass spectrometry, will distinguish desvenlafaxine from PCP and amphetamine. **USE IN SPECIFIC POPULATIONS: Pregnancy-** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Teratogenic effects– Pregnancy Category C- There are no adequate and well-controlled studies of Pristiq in pregnant women. Therefore, Pristiq should be used during pregnancy only if the potential benefits justify the potential risks. Non-teratogenic effects- Neonates exposed to SNRIs (Serotonin and Norepinephrine Reuptake Inhibitors), or SSRIs (Selective Serotonin Reuptake Inhibitors), late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding. Such complications can arise immediately upon delivery. Reported clinical findings have included respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying. These features are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome. It should be noted that, in some cases, the clinical picture is consistent with serotonin syndrome [*see Warnings and Precautions (5.2)*]. When treating a pregnant woman with Pristiq during the third trimester, the physician should carefully consider the potential risks and benefits of treatment [*see Dosage and Administration (2.2)*]. **Labor and Delivery-** The effect of Pristiq on labor and delivery in humans is unknown. Pristiq should be used during labor and delivery only if the potential benefits justify the potential risks. **Nursing Mothers-** Desvenlafaxine (O-desmethylvenlafaxine) is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Pristiq, a decision should be made whether or not to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. Only administer Pristiq to breastfeeding women if the expected benefits outweigh any possible risk. **Pediatric Use-** Safety and effectiveness in the pediatric population have not been established [*see Box Warning and Warnings and Precautions (5.1)*]. Anyone considering the use of Pristiq in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use-** Of the 3,292 patients in clinical studies with Pristiq, 5% were 65 years of age or older. No overall differences in safety or efficacy were observed between these patients and younger patients; however, in the short-term, placebo-controlled studies, there was a higher incidence of systolic orthostatic hypotension in patients ≥65 years of age compared to patients <65 years of age treated with Pristiq [*see Adverse Reactions (6)*]. For elderly patients, possible reduced renal clearance of desvenlafaxine should be considered when determining dose [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6)*]. If Pristiq is poorly tolerated, every other day dosing can be considered. SSRIs and SNRIs, including Pristiq, have been associated with cases of clinically significant hyponatremia in elderly patients, who may be at greater risk for this adverse event [*see Warnings and Precautions (5.12)*]. Greater sensitivity of some older individuals cannot be ruled out. **Renal Impairment-** In subjects with renal impairment the clearance of Pristiq was decreased. In subjects with severe renal impairment (24-hr CrCl < 30 mL/min) and end-stage renal disease, elimination half-lives were significantly prolonged, increasing exposures to Pristiq; therefore, dosage adjustment is recommended in these patients [*see Dosage and Administration (2.2) and Clinical Pharmacology (12.6) in the full prescribing information*]. **Hepatic Impairment-** The mean $t_{1/2}$ changed from approximately 10 hours in healthy subjects and subjects with mild hepatic impairment to 13 and 14 hours in moderate and severe hepatic impairment, respectively. The recommended dose in patients with hepatic impairment is 50 mg/day. Dose escalation above 100 mg/day is not recommended [*see Clinical Pharmacology (12.6)*].

OVERDOSAGE: Human Experience with Overdosage- There is limited clinical experience with desvenlafaxine succinate overdosage in humans. In premarketing clinical studies, no cases of fatal acute overdose of desvenlafaxine were reported. The adverse reactions reported within 5 days of an overdose > 600 mg that were possibly related to Pristiq included headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, and tachycardia. Desvenlafaxine (Pristiq) is the major active metabolite of venlafaxine. Overdose experience reported with venlafaxine (the parent drug of Pristiq) is presented below; the identical information can be found in the *Overdosage* section of the venlafaxine package insert. In postmarketing experience, overdose with venlafaxine (the parent drug of Pristiq) has occurred predominantly in combination with alcohol and/or other drugs. The most commonly reported events in overdosage include tachycardia, changes in level of consciousness (ranging from somnolence to coma), mydriasis, seizures, and vomiting. Electrocardiogram changes (eg, prolongation of QT interval, bundle branch block, QRS prolongation), sinus and ventricular tachycardia, bradycardia, hypotension, rhabdomyolysis, vertigo, liver necrosis, serotonin syndrome, and death have been reported. Published retrospective studies report that venlafaxine overdosage may be associated with an increased risk of fatal outcomes compared to that observed with SSRI antidepressant products, but lower than that for tricyclic antidepressants. Epidemiological studies have shown that venlafaxine-treated patients have a higher pre-existing burden of suicide risk factors than SSRI-treated patients. The extent to which the finding of an increased risk of fatal outcomes can be attributed to the toxicity of venlafaxine in overdosage, as opposed to some characteristic(s) of venlafaxine-treated patients, is not clear. Prescriptions for Pristiq should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Management of Overdosage-** Treatment should consist of those general measures employed in the management of overdosage with any SSRI/SNRI. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. General supportive and symptomatic measures are also recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. Induction of emesis is not recommended. Because of the moderate volume of distribution of this drug, forced diuresis, dialysis, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for desvenlafaxine are known. In managing an overdose, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the Physicians Desk Reference (PDR®).

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THE AMERICAN JOURNAL OF
PSYCHIATRY

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Cover

In this issue, the Journal Editors select those articles published in 2012 that shone brightest in guiding the field (p. 1233). Photo of Little Sable Point Light Station, a 107-foot tower built in 1874 located in Silver Lake State Park on the eastern shore of Lake Michigan. Photo from Dreamstime.com.

Audio	this article is featured in *AJP Audio*: a downloadable .mp3 file available at ajp.psychiatryonline.com
Clinical Guidance	this article offers clinical guidance (see "In this Issue" page or end of article)
CME	a course covering the content of this article is available online for paid subscribers to the AJP CME Course Program
Editorial	this article is discussed in one of the issue's editorials

This issue's Table of Contents is available in Spanish.

Presented in collaboration with the Office of Global Health, UMDNJ-Robert Wood Johnson Medical School

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David Myland Kaufman, MD

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Andrea J. Weiss, MD and David Myland Kaufman, MD

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For the treatment of schizophrenia

LATUDA can help put your patients back together

- Symptom improvement was established in several pivotal trials[1]
- The safety and tolerability of LATUDA were evaluated in pivotal trials and multiple studies up to 52 weeks[1]
- The recommended starting dose, 40 mg/day, is an effective dose with no initial dose titration required. The maximum recommended dose is 160 mg/day[1]
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  - LATUDA should not be used in combination with strong CYP3A4 inhibitors such as ketoconazole or strong CYP3A4 inducers such as rifampin. When coadministered with a moderate CYP3A4 inhibitor such as diltiazem, the recommended starting dose of LATUDA is 20 mg/day and the maximum recommended dose is 80 mg/day

INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic indicated for the treatment of patients with schizophrenia. Efficacy was established in five 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

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.**

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

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Latuda®
(lurasidone HCl) tablets
20mg | 40mg | 80mg | 120mg

INDICATIONS AND USAGE

LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in five 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.

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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.**

CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole).
- Concomitant use with 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.

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. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

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

Potential for Cognitive and Motor Impairment: In short-term, placebo-controlled trials, somnolence was reported in 17.0% (256/1508) of patients treated with LATUDA compared to 7.1% (50/708) of placebo patients, respectively. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

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

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS

Commonly Observed Adverse Reactions: (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism.

Please see brief summary of prescribing information on adjacent pages, including **Boxed Warning**.

Reference: 1. LATUDA prescribing information. Sunovion Pharmaceuticals Inc. May 2012.

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

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 *[see Warnings and Precautions (5.1)]*.**
- **LATUDA is not approved for use in 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 five 6-week controlled studies of adult patients with schizophrenia *[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)]*.

4 CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone *[see Adverse Reactions (6.1)]*.
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) *[see Drug Interactions (7.1)]*.
- Concomitant use with 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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of between 1.6- to 1.7- times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis *[see Boxed Warning]*.

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

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

5.3 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

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

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

Dyslipidemia

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

Table 2: Change in Fasting Lipids

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

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

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 0.43 kg for LATUDA-treated patients compared to –0.02 kg for placebo-treated patients. Change in weight from baseline for olanzapine was 4.15 kg and for quetiapine extended-release was 2.09 kg in Studies 3 and 5 *[see Clinical Studies (14.1)]*, respectively. The proportion of patients with a ≥ 7% increase in body weight (at Endpoint) was 4.8% for LATUDA-treated patients versus 3.3% for placebo-treated patients.

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

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

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

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 0.4 ng/mL and was –1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was 0.5 ng/mL and for females was –0.2 ng/mL. Median changes for prolactin by dose are shown in Table 5.

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

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

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

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

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/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 [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)]. Assessment of orthostatic hypotension was 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, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications), and in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), or cerebrovascular disease.

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% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) 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 by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients. 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 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

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

5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant illnesses is limited *[see Clinical Pharmacology (12.3)]*.

Patients with Parkinson's Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neuroleptic malignant syndrome.

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 trials. Because of the risk of orthostatic hypotension with LATUDA, caution should be observed in patients with known cardiovascular disease *[see Warnings and Precautions (5.8)]*.

6 ADVERSE REACTIONS

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)]*

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from a clinical study database for LATUDA consisting of 2905 patients with schizophrenia exposed to one or more doses with a total experience of 985.3 patient-years. Of these patients, 1508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. A total of 769 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

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

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

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

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

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients: Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 5.

Table 5: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

	Percentage of Patients Reporting Reaction	
Body System or Organ Class Dictionary-derived Term	**Placebo (N=708)**	**All LATUDA (N=1508)**
Gastrointestinal Disorders		
Nausea	5	10
Vomiting	6	8
Dyspepsia	5	6
Salivary Hypersecretion	<1	2
Musculoskeletal and Connective Tissue Disorders		
Back Pain	2	3
Nervous System Disorders		
Somnolence*	7	17
Akathisia	3	13
Parkinsonism**	5	10
Dizziness	2	4
Dystonia***	<1	4
Psychiatric Disorders		
Insomnia	8	10
Agitation	4	5
Anxiety	4	5
Restlessness	1	2

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

Dose-Related Adverse Reactions

In pooled data from the short-term, placebo-controlled, fixed-dose studies, there were no dose-related adverse reactions (greater than 5% incidence) in patients treated with LATUDA across the 20 mg/day to 160 mg/day dose range. However, the frequency of akathisia increased with dose up to 120 mg/day (5.6% LATUDA 20 mg, 10.7% LATUDA 40 mg, 12.3% LATUDA 80 mg, 22.0% LATUDA 120 mg); akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo.

Extrapyramidal Symptoms

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restlessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 7.

Table 6: Incidence of EPS Compared to Placebo

		LATUDA				
Adverse Event Term	**Placebo (N=709) (%)**	**20 mg/day (N=71) (%)**	**40 mg/day (N=487) (%)**	**80 mg/day (N=538) (%)**	**120 mg/day (N=291) (%)**	**160 mg/day (N=121) (%)**
All EPS events	**9**	**10**	**21**	**23**	**39**	**20**
All EPS events, excluding Akathisia/ Restlessness	**6**	**6**	**11**	**12**	**22**	**13**
Akathisia	3	6	11	12	22	7
Dystonia*	<1	0	4	5	7	2
Parkinsonism**	5	6	9	8	17	11
Restlessness	1	1	3	1	3	2

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

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, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%) and the SAS (LATUDA, 5.0%; placebo, 2.3%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles, sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

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

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2905 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 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

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

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

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

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

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

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

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

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

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

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

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

Psychiatric Disorders: ***Infrequent:*** *abnormal dreams, panic attack, sleep disorde;*

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

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

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

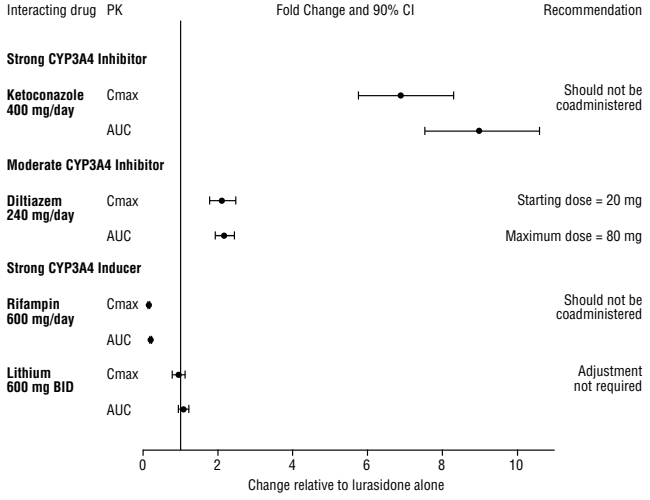
Vascular Disorders: ***Frequent:*** *hypertension*

7 DRUG INTERACTIONS

7.1 Potential for Other Drugs to Affect LATUDA

LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme *[see Contraindications (4)]* and dose should be limited when used in combination with moderate inhibitors of CYP3A4 *[see Dosage and Administration (2.4)]*. No dose adjustment is needed with concomitant use of lithium (see Figure 1).

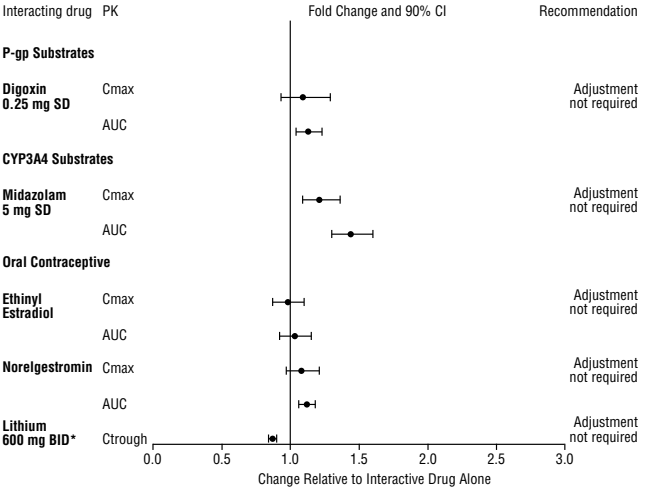
Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics



7.2 Potential for LATUDA to Affect Other Drugs

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

Figure 2: Impact of LATUDA on Other Drugs



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

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects

Pregnancy Category B

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

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.

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

Animal Data

No adverse developmental effects were seen in a study in which pregnant rats were given LATUDA during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately half of the MRHD based on body surface area.

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

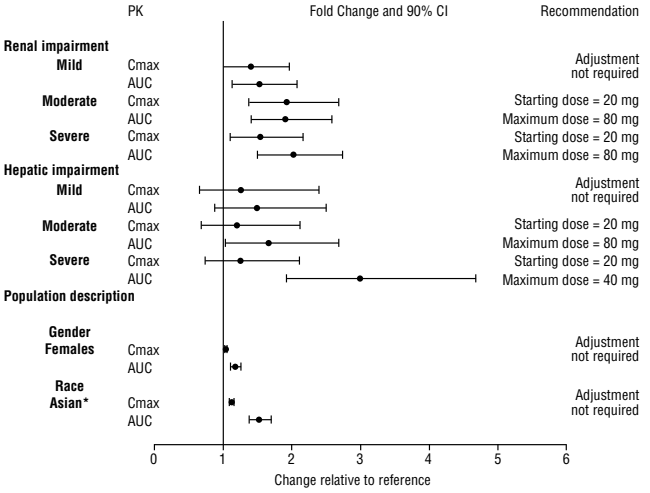
Clinical studies of LATUDA in the treatment of schizophrenia did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects *[see Clinical Pharmacology (12.3)]*. No dose adjustment is necessary in elderly patients (Figure 2).

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

8.6 Other Patient Factors

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

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics



*Compare to Caucasian

10 OVERDOSAGE

10.1 Human Experience

In premarketing clinical studies involving 2905 patients, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

10.2 Management of Overdosage

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

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

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

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

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

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Calendar, American Journal of Psychiatry, 1000 Wilson Boulevard, Suite 1825, Arlington, VA 22209-3901, swestrate@psych.org (e-mail).

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DECEMBER 2012

December 6–9, 23rd Annual Meeting and Symposium, American Academy of Addiction Psychiatry, Turnberry Isle Hotel Miami, Aventura, Florida. Contact: Isabel Vieira, 400 Massasoit Ave, Suite 307 (2nd floor), East Providence, RI 02914; (401) 524-3076 (tel); www.aaap.org/meetings-and-events (web site).

FEBRUARY

February 13-17, 18th Annual Psychopharmacology Update, Nevada Psychiatric Association (district branch of APA), Paris Las Vegas Hotel, Las Vegas, NV. Contact: (877) 493-0007 (tel); conference@nvpsychiatry.org (email); www.nvpsychiatry.org (web site).

MAY

May 18–22, 166th Annual Meeting, American Psychiatric Association, San Francisco, Calif. Contact: APA Annual Meetings Dept., 1000 Wilson Blvd, Suite 1825, Arlington, VA 22209; (703) 907-7815 (tel); http://www.psych.org/learn/annual-meeting (web site).

JUNE

June 6–9, 4th World Congress on ADHD: From Childhood to Adult Disease, Milan, Italy. Contact Congress Organizer, +49-40-670 88 20 (tel); adhd2013@cpo-hanser.de (email); www.adhd-congress.org (web site).

JULY

July 8–13, 28th International Congress of Applied Psychology, Palais des Congrès de Paris, France. Contact exh@icap2014.com (email); www.icap2014.com (web site).

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THE AMERICAN JOURNAL OF
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DSM-5 Field Trials in the United States and Canada, Part I: Study Design, Sampling Strategy, Implementation, and Analytic Approach

D.E. Clarke, W.E. Narrow, D.A. Regier, S.J. Kuramoto, D.J. Kupfer, E.A. Kuhl, L. Greiner, and H.C. Kraemer

DSM-5 Field Trials in the United States and Canada, Part II: Test-Retest Reliability of Selected Categorical Diagnoses

D.A. Regier, W.E. Narrow, D.E. Clarke, H.C. Kraemer, S.J. Kuramoto, E.A. Kuhl, and D.J. Kupfer

DSM-5 Field Trials in the United States and Canada, Part III: Development and Reliability Testing of a Cross-Cutting Symptom Assessment for DSM-5

W.E. Narrow, D.E. Clarke, S.J. Kuramoto, H.C. Kraemer, D.J. Kupfer, L. Greiner, and D.A. Regier

Effect of a Paraprofessional Home-Visiting Intervention on American Indian Teen Mothers' and Infants' Behavioral Risks: A Randomized Controlled Trial

A. Barlow, B. Mullany, S. Compton, A. Carter, R. Hastings, T. Billy, V. Coho-Mescal, S. Lorenzo, and J.T. Walkup

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WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy.

- Quillivant XR is contraindicated in patients with known hypersensitivity to methylphenidate or product components, and in patients who are taking concurrent treatment with a monoamine oxidase inhibitor (MAOI), or have used an MAOI within the preceding 14 days
- Sudden death has been reported in association with CNS stimulants at recommended doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart arrhythmias, or coronary artery disease
- Monitor blood pressure and pulse. Consider the benefits and risks in patients for whom an increase in blood pressure or heart rate would be problematic
- Use of stimulants may cause psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Evaluate for bipolar disorder prior to Quillivant XR use
- Monitor height and weight at appropriate intervals in pediatric patients for long-term suppression of growth
- Based on accumulated data from other methylphenidate products, the most common adverse reactions are appetite decreased, insomnia, nausea, vomiting, dyspepsia, abdominal pain, weight decreased, anxiety, dizziness, irritability, affect lability, tachycardia, and blood pressure increased
- Based on animal data, use of Quillivant XR during pregnancy may cause fetal harm. Nursing mothers should be advised to discontinue drug or discontinue nursing, taking into consideration the importance of the drug to the mother

*Please see Brief Summary of Prescribing Information, including **BOXED WARNING** regarding Abuse and Dependence, on following page.*

NextWave™ PHARMACEUTICALS

Quillivant XR™ (methylphenidate HCl) for extended-release oral suspension, CII Rx only
BRIEF SUMMARY: Consult Full Prescribing Information for Complete Product Information.

WARNING: ABUSE AND DEPENDENCE

CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warnings and Precautions, Drug Abuse and Dependence].*

INDICATIONS AND USAGE

Quillivant XR is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Quillivant XR was established in a 2-week, placebo-controlled, laboratory classroom, crossover study in children aged 6-12 years with a diagnosis of ADHD. Patients in the trial met DSM-IV-TR® criteria for ADHD. Accumulated efficacy data from other methylphenidate products were also considered.

CONTRAINDICATIONS

Hypersensitivity to Methylphenidate or other Components of Quillivant XR. Quillivant XR is contraindicated in patients known to be hypersensitive to methylphenidate, or other components of Quillivant XR. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with other methylphenidate products.

Monoamine Oxidase Inhibitors Quillivant XR is contraindicated during treatment with monoamine oxidase inhibitors, and also within 14 days following discontinuation of treatment with a monoamine oxidase inhibitor (MAOI), because of the risk of hypertensive crisis.

WARNINGS AND PRECAUTIONS

Potential for Abuse and Dependence CNS stimulants, including Quillivant XR, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy [*see Drug Abuse and Dependence*].

Serious Cardiovascular Reactions Stroke and myocardial infarction have occurred in adults treated with CNS stimulants at recommended doses. Sudden death has occurred in children and adolescents with structural cardiac abnormalities and other serious cardiac problems, and in adults taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious cardiac arrhythmias, coronary artery disease, or other serious cardiac problems. Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during treatment with Quillivant XR.

Blood Pressure and Heart Rate Increases CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

Psychiatric Adverse Reactions Exacerbation of Pre-Existing Psychosis CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder CNS stimulants may induce a manic or mixed episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing Quillivant XR. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

Long-Term Suppression of Growth CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients. Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including Quillivant XR. Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause a similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

ADVERSE REACTIONS

Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice. *Clinical Trials Experience with Other Methylphenidate Products in Children, Adolescents, and Adults with ADHD* Commonly reported (≥2% of the methylphenidate group and at least twice the rate of the placebo group) adverse reactions from placebo-controlled trials of methylphenidate products include: appetite decreased, weight decreased, nausea, abdominal pain, dyspepsia, dry mouth, vomiting, insomnia, anxiety, nervousness, restlessness, affect lability, agitation, irritability, dizziness, vertigo, tremor, blurred vision, blood pressure increased, heart rate increased, tachycardia, palpitations, hyperhidrosis, and pyrexia. *Clinical Trials Experience with Quillivant XR in Children and Adolescents with ADHD.* There is limited experience with Quillivant XR in controlled trials. Based on this limited experience, the adverse reaction profile of Quillivant XR appears similar to other methylphenidate extended-release products. The most common (≥2% in the Quillivant XR group and greater than placebo) adverse reactions reported in the Phase 3 controlled study conducted in 45 ADHD patients (ages 6-12 years) were affect lability, excoriation, initial insomnia, tic, decreased appetite, vomiting, motion sickness, eye pain, and rash.

Table 2. Common Adverse Reactions occurring in ≥2% of subjects on Quillivant XR and greater than placebo during the controlled cross-over phase

Adverse reaction	Quillivant XR (N=45)	Placebo (N=45)
Affect lability	9%	2%
Excoriation	4%	0%
Initial Insomnia	2%	0%
Tic	2%	0%
Decreased appetite	2%	0%
Vomiting	2%	0%
Motion sickness	2%	0%
Eye pain	2%	0%
Rash	2%	0%

Postmarketing Experience The following adverse reactions have been identified during post approval use of methylphenidate products. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure. These adverse reactions are as follows:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystole, Supraventricular tachycardia, Ventricular extrasystole
Eye Disorders: Diplopia, Mydriasis, Visual impairment
General Disorders: Chest pain, Chest discomfort, Hyperpyrexia
Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC
Investigations: Alkaline phosphatase increased, Bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal
Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching
Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia
Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania
Urogenital System: Priapism
Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema
Vascular Disorders: Raynaud's phenomenon

DRUG INTERACTIONS

MAO Inhibitors Do not administer Quillivant XR concomitantly with monoamine oxidase inhibitors or within 14 days after discontinuing MAOI treatment. Concomitant use of MAOIs and CNS stimulants can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C Risk Summary There are no adequate or well-controlled studies with Quillivant XR in pregnant women. Adverse pregnancy outcomes, including premature delivery and low birth weight, have been seen in mothers dependent on other stimulant products such as amphetamines. Methylphenidate showed some potential for teratogenicity when pregnant animals were treated during organogenesis: an increased incidence of fetal spina bifida in rabbits at 40 times the maximum recommended human dose (MRHD), on a mg/m^2 basis, and an increased incidence of fetal skeletal variations in rats at 7 times the MRHD. A decrease in body weight gain was seen in the offspring of rats treated with methylphenidate throughout pregnancy and lactation at 4 times the MRHD. Quillivant XR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Clinical Considerations Stimulant medications, such as Quillivant XR, cause vasoconstriction and thereby decrease placental perfusion. Infants born to amphetamine dependent mothers have an increased risk of premature delivery and low birth weight. Monitor infants for symptoms of withdrawal such as feeding difficulties, irritability, agitation, and excessive drowsiness. Animal Data In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal

Quillivant XR™ (methylphenidate HCl) Brief Summary continued...
development were observed. The no effect level for pre- and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis). **Nursing Mothers** Methylphenidate is present in human milk. Long-term neurodevelopmental effects on infants from stimulant exposure are unknown. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and effectiveness of Quillivant XR have been established in pediatric patients ages 6 to 17 years. Use of Quillivant XR in pediatric patients 6 to 12 years of age is supported by adequate and well-controlled studies. Use in 12 to 17 year olds is supported by the adequate and well-controlled studies of Quillivant XR in younger pediatric patients and additional pharmacokinetic data in adolescents, along with safety information from other methylphenidate-containing products. The long-term efficacy of methylphenidate in pediatric patients has not been established. Safety and efficacy in pediatric patients below the age of 6 years have not been established. Long Term Suppression of Growth Growth should be monitored during treatment with stimulants, including Quillivant XR. Children who are not growing or gaining weight as expected may need to have their treatment interrupted [*see Warnings and Precautions*]. Juvenile Animal Data Rats treated with methylphenidate early in the postnatal period through sexual maturation demonstrated a decrease in spontaneous locomotor activity in adulthood. A deficit in acquisition of a specific learning task was observed in females only. The doses at which these findings were observed are at least 6 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. In the study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (postnatal day 7) and continuing through sexual maturity (postnatal week 10). When these animals were tested as adults (postnatal weeks 13-14), decreased spontaneous locomotor activity was observed in males and females previously treated with 50 mg/kg/day (approximately 6 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was observed in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown. **Geriatric Use** Quillivant XR has not been studied in patients over the age of 65 years.

DRUG ABUSE AND DEPENDENCE
Controlled Substance Quillivant XR contains methylphenidate, a Schedule II controlled substance.
Abuse Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which can result in overdose and death [*see Overdosage*]. To reduce the abuse of CNS stimulants including Quillivant XR, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants, monitor for signs of abuse while on therapy, and re-evaluate the need for Quillivant XR use.
Dependence Tolerance Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants including Quillivant XR. Dependence Physical dependence (a state of adaptation manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) can occur in patients treated with CNS stimulants including Quillivant XR. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include extreme fatigue and depression.

OVERDOSAGE
Signs and Symptoms Signs and symptoms of acute methylphenidate overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, and dryness of mucous membranes.
Management of Overdose Consult with a Certified Poison Control Center for up-to-date guidance and advice on the management of overdosage with methylphenidate (1-800-222-1222.) Provide supportive care, including close medical supervision and monitoring. Treatment should consist of those general measures employed in the management of overdosage with any drug. Consider the possibility of multiple drug overdosage. Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. Use supportive and symptomatic measures.

NextWave™ PHARMACEUTICALS

The Residents' Journal

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The American Journal of Psychiatry

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Inside

In This Issue

This issue of the *Residents' Journal* highlights articles on the theme of psychosomatic medicine. In a commentary, David Hsu, M.D., describes his experiences in a dual residency program focusing on psychiatry and internal medicine. Kristopher Klem, B.A., presents a case report on prolonged QTc in a hemodialysis patient receiving antidepressant treatment for bipolar disorder. Harita Raja, M.D., discusses prenatal and postpartum depression and provides information on epidemiology, screening tools, and treatment. Lastly, Dr. Hsu contributes a book review of *Why Psychiatry Is a Branch of Medicine*.

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See the September 2010 issue for details on the new peer review process.

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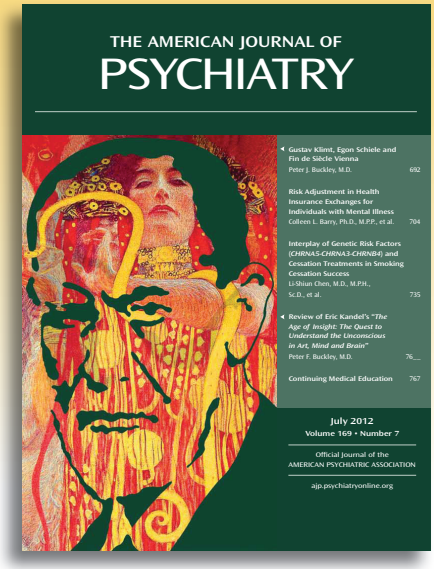

Official Journal of the American Psychiatric Association

Edited by Robert Freedman, M.D.

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