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An Association of Intrusive, Repetitive Phrases with Lamotrigine Treatment in Bipolar II Disorder
D.E. Kemp, W.S. Gilmer, J. Fleck, and P.L. Dago

Do Children and Adolescents Have Differential Response Rates in Placebo-Controlled Trials of Fluoxetine?
T.L. Mayes, R. Tao, J.W. Rintelmann, T. Carmody, C.W. Hughes, B.D. Kennard, S.M. Stewart, and G.J. Emslie

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Alzheimer’s Disease: Progress in the Development of Anti-amyloid Disease-Modifying Therapies
D.D. Christensen

Compulsive Buying Disorder: A Review of the Evidence
D.W. Black

Psychosocial Treatment of Depression and Suicidality in Adolescents
A. Brunstein Klomek and B. Stanley

Factors in the Assessment of Suicidality in Youth
K. Posner, G.A. Melvin, B. Stanley, M.A. Oquendo, and M. Gould

NEW COLUMN

TRENDS IN PSYCHOPHARMACOLOGY

Overview of Trends in Modern Psychopharmacology
S.M. Stahl
In the treatment of ADHD...

Think Square

Think Daytrana™—The Methylphenidate Patch

Important Safety Information

Daytrana should not be used in patients with allergy to methylphenidate or patch components; marked anxiety, tension and agitation; glaucoma; tics, diagnosis or a family history of Tourette's syndrome; seizures; or during or within 14 days after treatment with monoamine oxidase inhibitors (MAOIs).

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses in ADHD. Physicians should take a careful patient history, including family history, and physical exam to assess the presence of cardiac disease. Patients who report symptoms of cardiac disease such as exertional chest pain and unexplained syncope should be promptly evaluated. Use with caution in patients whose underlying medical condition might be affected by increases in blood pressure or heart rate.

New psychosis, mania, aggression, growth suppression, and visual disturbances have been associated with the use of stimulants. Use with caution in patients with a history of: psychosis; EEG abnormalities; bipolar disorder; depression. Growth and hematologic monitoring is advised during prolonged treatment. Patients should avoid applying external heat to the Daytrana patch. Skin irritation or contact sensitization may occur.

Daytrana should be given cautiously to patients with a history of drug dependence and alcoholism. Chronic abuse can lead to marked tolerance and psychological dependence. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use, since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder.

Common adverse events reported by patients who received Daytrana in clinical trials were decreased appetite, insomnia, nausea, vomiting, decreased weight, tics, affect lability, and anorexia, consistent with adverse events commonly associated with the use of methylphenidate.

An individualized approach to treatment that has physicians, parents, patients, and teachers thinking along the same lines

- The next evolution in the delivery of methylphenidate
- Continuous delivery for smooth levels of medication
- Efficacy from the first time point measured (2 hours) through 12 hours, with the recommended 9-hour wear time
- Flexible wear time—up to 9 hours—allows for individualized duration of effect to meet the changing daily needs of patients and parents

Daytrana is indicated as an integral part of a comprehensive ADHD treatment program that may include other measures (psychological, educational, social). The efficacy of Daytrana was established in clinical trials in children aged 6 to 12 years.


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the presence of the required number of DSM-IV-TR characteristics. In a patient with prior EEG abnormalities In absence of seizures, and, very rarely, in patients without a history of seizures.

CONTRAINDICATIONS — Monoamine Oxidase Inhibitors). silicon adhesive, and fluoropolymer-coated polyester. Using Saytrana™ as prescribed, alternating application sites on the hip, no cases of contact sensitization were reported. However, since patients were not specifically assessed for sensitization in the clinical effectiveness studies, it is unknown what by exposure to Daytrana™ may not be able to take methylphenidate in any form. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% of subjects.
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Anxiety, insomnia, low energy
Currently on an SSRI
Still suffering
It may be time to make a change

Still depressed?

Break the Cycle with EFFEXOR XR

IMPORTANT TREATMENT CONSIDERATIONS

Suicidality in Children and Adolescents
Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of EFFEXOR XR or any other antidepressant in a child or adolescent must balance this risk with the clinical need. Patients who are started on therapy should be 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. EFFEXOR XR is not approved for use in pediatric patients.

• EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs).

• Adult and pediatric patients taking antidepressants can experience worsening of their depression and/or the emergence of suicidality. Patients should be observed closely for clinical worsening and suicidality, especially at the beginning of drug therapy, or at the time of increases or decreases in dose. Anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia, hypomania, and mania have been reported and may represent precursors to emerging suicidality. Stopping or modifying therapy should be considered especially when symptoms are severe, abrupt in onset, or not part of presenting symptoms.

The development of potentially life-threatening serotonin syndrome may occur when EFFEXOR XR is coadministered with other drugs that may affect the serotonergic neurotransmitter systems. Concomitant use of EFFEXOR XR with MAOIs is contraindicated. If concomitant use of EFFEXOR XR with an SSRI, SNRI, or a triptan is clinically warranted, careful observation of the patient is advised. Concomitant use of EFFEXOR XR with tryptophan supplements is not recommended.

• Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Postmarketing cases of elevated BP requiring immediate treatment have been reported. Pre-existing hypertension should be controlled. Regular BP monitoring is recommended.

• Mydriasis has been reported in association with venlafaxine; therefore, patients with raised intraocular pressure or those at risk of acute narrow-angle glaucoma (angle-closure glaucoma) should be monitored.

• Abrupt discontinuation or dose reduction has been associated with discontinuation symptoms. Patients should be counseled on possible discontinuation symptoms and monitored while discontinuing the drug; the dose should be tapered gradually.

Please see brief summary of Prescribing Information on adjacent pages.
...
were similar to that observed in adult patients. The precautions for adults apply to pediatric patients.

Associated with Discontinuation of Treatment — The most common adverse events reported in EFFEXOR XR short-term placebo-controlled depression, generalized anxiety disorder (GAD), social anxiety disorder (SAD), and/or panic disorder (PD) trials (incidence ≥10% and ≥2x that of placebo) were anorexia, asthenia, anxiety, dizziness, headache, nausea, nervousness, somnolence, and vomiting.

The most common adverse events reported in EFFEXOR XR clinical trials were dizziness, headache, nausea, somnolence, nervousness, and vomiting.

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TRENDS IN PSYCHOPHARMACOLOGY

103 Overview of Trends in Modern Psychopharmacology

Stephen M. Stahl, MD, PhD, University of California-San Diego

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Recent Advances in the Treatment and Management of Excessive Daytime Sleepiness

By Jed Black, MD, Stephen P. Duntley, MD, Richard K. Bogan, MD, FCCP, and Mary B. O’Malley, MD, PhD

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163 The quiz is CME-accredited by the Mount Sinai School of Medicine for 3.0 credit hours.

MISSION

CNS Spectrums’ editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal’s goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma. This month’s issue of CNS Spectrums, as well as a host of educational resources, enduring materials, and archived issues, is available at www.cnsspectrums.com.
NOW APPROVED for bipolar depression

• SEROQUEL is the ONLY monotherapy FDA-approved to treat both bipolar depression and mania¹

• Once-daily dosing at bedtime for bipolar depression*²

Still a first-line treatment for schizophrenia.²

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

*Dosing for bipolar mania and schizophrenia is twice daily.

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**Important Safety Information**

- SEROQUEL is indicated for the treatment of depressive episodes in bipolar disorder; acute manic episodes in bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex; and schizophrenia. Patients should be periodically reassessed to determine the need for treatment beyond the acute response.

- Elderly patients with dementia-related psychosis treated with atypical antipsychotic drugs are at an increased risk (1.6 to 1.7 times) of death compared to placebo (4.5% vs 2.6%, respectively). SEROQUEL is not approved for the treatment of patients with dementia-related psychosis. (See Boxed Warning)

- Suicidality in children and adolescents—antidepressants increased the risk of suicidal thinking and behavior (4% vs 2% for placebo) in short-term studies of 9 antidepressant drugs in children and adolescents with major depressive disorder and other psychiatric disorders. Patients started on therapy should be 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. SEROQUEL is not approved for use in pediatric patients. (See Boxed Warning)

- A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include immediate discontinuation of antipsychotic drugs.

- Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of TD.

- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing.

- Precautions include the risk of seizures, orthostatic hypotension, and cataracts. Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6-month intervals during chronic treatment.

- The most commonly observed adverse events associated with the use of SEROQUEL monotherapy versus placebo in clinical trials for schizophrenia and bipolar disorder were dry mouth (9-44% vs 3-13%), sedation (30% vs 8%), somnolence (18-28% vs 7-8%), dizziness (11-18% vs 5-7%), constipation (8-10% vs 3-4%), SGPT increase (5% vs 1%), dyspepsia (5-7% vs 1-4%), lethargy (5% vs 2%), and weight gain (5% vs 1%). The most commonly observed adverse events associated with the use of SEROQUEL versus placebo in clinical trials as adjunct therapy with lithium or divalproex in bipolar mania were somnolence (34% vs 9%), dry mouth (19% vs 3%), asthenia (10% vs 4%), constipation (10% vs 5%), abdominal pain (7% vs 3%), postural hypotension (7% vs 2%), pharyngitis (6% vs 3%), and weight gain (6% vs 3%).

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


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247388 1/07 www.SEROQUEL.com

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SEROQUEL® (quetiapine fumarate) Tablets

BRIEF SUMMARY OF PRESCRIBING INFORMATION—Before prescribing, please consult complete Prescribing Information.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis: Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death compared to placebo-treated patients. This increased mortality was seen in several studies where antipsychotics were compared to placebo without a concurrent control intervention. The risk was similar for all antipsychotic drug types used in the studies. The increased mortality in placebo-treated patients was approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained during the course of treatment. The risk did not diminish even with lower doses. In one 9-week study, SEROQUEL treatment was associated with a reduction in the risk of death compared to placebo, and the risk appeared to be similar for all antipsychotic drugs used in the study.

It is generally believed, although not proven, that this risk of death is possibly intrinsic in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy.

Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, it was a contributing factor in the increased mortality seen in these studies. Somnolence was more frequent in patients treated with SEROQUEL compared to placebo in several controlled clinical trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

INDICATIONS AND USAGE: Bipolar Disorder: SEROQUEL is indicated for the treatment of depressive episodes associated with bipolar disorder and acute manic episodes associated with bipolar 1 disorder as either monotherapy or adjunct therapy to lithium or valproate. Depression: The efficacy of SEROQUEL was established in two double-blind, 8-week randomized placebo-controlled trials in patients with bipolar depression. Patients were randomized to receive seroquel 200 mg twice daily, seroquel 600 mg once daily, or placebo. The primary efficacy measure was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at week 8. SEROQUEL significantly improved MADRS scores in both trials compared to placebo. The improvement was more apparent in patients with a history of antidepressant-responsive depression. The median time to response with SEROQUEL was approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained during the course of treatment. The risk did not diminish even with lower doses. In one 9-week study, SEROQUEL treatment was associated with a reduction in the risk of death compared to placebo, and the risk appeared to be similar for all antipsychotic drugs used in the study.

Seizures: Seizures during or after drug treatment with antipsychotic drugs are observed infrequently in patients with no history of epilepsy. However, serum levels of certain antipsychotic drugs are associated with the risk of seizures. SEROQUEL may induce seizures, especially with rapid dose escalation or during treatment with other substances that lower the seizure threshold (e.g., alcohol, benzodiazepines). Therefore, patients should be observed closely for seizures, especially during the initial dose-titration period, for weeks after the drug is discontinued, and for weeks after an abrupt dose reduction. If a seizure occurs, treatment with SEROQUEL should be discontinued and appropriate medical evaluation should be carried out. Seizures: During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL may also cause such events during treatment.

Mood Disorders: The efficacy of SEROQUEL for the treatment of mood disorders was not established in clinical trials.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially life-threatening syndrome that may occur during treatment with antipsychotic drugs, including SEROQUEL. While the syndrome may occur at any time during treatment, it is most likely to be seen at the beginning of treatment or following a dose increase. NMS is characterized by hyperpyrexia, muscle rigidity, disorientation, mental confusion, and autonomic instability. In some patients, the symptoms may include delirium, agitation, coma, or death. NMS can occur in patients with no prior history of neuroleptic exposure. The risk of NMS is increased by pre-existing conditions that can affect temperature regulation, such as hyperthyroidism, neuroleptic malignant syndrome, or other conditions associated with central nervous system depression. Patients with neuroleptic malignant syndrome or similar clinical syndromes should be observed for signs of hyperpyrexia, muscle rigidity, and autonomic instability, and appropriate medical evaluation should be carried out. If symptoms suggestive of NMS occur, treatment with SEROQUEL should be discontinued and appropriate medical evaluation should be carried out.

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APPLICATIONS: Bipolar Disorder: The efficacy of SEROQUEL was established in two double-blind, 8-week placebo-controlled trials in patients with bipolar depression. Patients were randomized to receive seroquel 200 mg twice daily, seroquel 600 mg once daily, or placebo. The primary efficacy measure was change from baseline in the Montgomery-Asberg Depression Rating Scale (MADRS) at week 8. SEROQUEL significantly improved MADRS scores in both trials compared to placebo. The improvement was more apparent in patients with a history of antidepressant-responsive depression. The median time to response with SEROQUEL was approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained during the course of treatment. The risk did not diminish even with lower doses. In one 9-week study, SEROQUEL treatment was associated with a reduction in the risk of death compared to placebo, and the risk appeared to be similar for all antipsychotic drugs used in the study.

Seizures: Seizures during or after drug treatment with antipsychotic drugs are observed infrequently in patients with no history of epilepsy. However, serum levels of certain antipsychotic drugs are associated with the risk of seizures. SEROQUEL may induce seizures, especially with rapid dose escalation or during treatment with other substances that lower the seizure threshold (e.g., alcohol, benzodiazepines). Therefore, patients should be observed closely for seizures, especially during the initial dose-titration period, for weeks after the drug is discontinued, and for weeks after an abrupt dose reduction. If a seizure occurs, treatment with SEROQUEL should be discontinued and appropriate medical evaluation should be carried out. Seizures: During clinical trials, seizures occurred in 0.5% (20/3490) of patients treated with SEROQUEL compared to 0.2% (2/954) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL may also cause such events during treatment.

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Serotonin Disrupts Blood Pressure, Skeletal Muscle Tone, Baroreflex Responsiveness, and Cardiac Function in Rats

Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter that plays a crucial role in modulating various physiological functions, including cardiovascular control. In rats, serotonin has been shown to influence blood pressure, skeletal muscle tone, baroreflex responsiveness, and cardiac function. These effects are mediated through serotonergic receptors located in the cardiovascular and autonomic nervous systems. Understanding these mechanisms is essential for developing effective treatments for conditions such as hypertension and cardiac arrhythmias.