

New Treatment Options Can Help Smokers Quit

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Many new and effective treatment strategies are available that clinicians can employ to help patients quit tobacco use, according to an updated Clinical Practice Guideline released recently by the U.S. Public Health Service.

Use of multiple interventions, individual and group counseling, integration of effective therapies into routine health care

delivery, and insurance reimbursement increase the likelihood a patient with tobacco dependence can quit, according to the guideline.

Expanding tobacco dependence literature and new treatments available since 1999 led a consortium of eight federal agencies and nonprofit organizations to update the guideline for the first time since 2000. The new recognition of tobacco dependence as a chronic disease that generally requires ongoing assess-

ment and repeated intervention is central to the update.

A 24-member panel screened more than 8,700 publications on tobacco dependence and treatment published since 1975 in preparation for the update. A total of 81 outside peer experts reviewed the panel's findings.

The universal aim of the 276-page "Treating Tobacco Use and Dependence: 2008 Update" is assist clinicians in strongly recommending effective tobacco de-

pendence counseling and medications to patients who use tobacco. This includes consideration of seven first-line medications now approved by the Food and Drug Administration that "reliably increase long-term smoking abstinence rates." Those medications are bupropion SR, nicotine gum, nicotine inhaler, nicotine lozenge, nicotine nasal spray, nicotine patch, and varenicline (Chantix).

It is important to encourage use of effective medications alone or in combina-

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BRIEF SUMMARY: For full Prescribing Information, see package insert.

Increased Mortality in Elderly Patients with Dementia-Related Psychosis

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

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 SEROQUEL 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. SEROQUEL is not approved for use in pediatric patients. (See Warnings: Clinical Worsening and Suicide Risk, Precautions: Information for Patients, and Precautions: Pediatric Use)

INDICATIONS AND USAGE **Bipolar Disorder** SEROQUEL is indicated for the treatment of both: • depressive episodes associated with bipolar disorder; • acute manic episodes associated with bipolar I disorder as either monotherapy or adjunct therapy to lithium or divalproex. Depression The efficacy of SEROQUEL was established in two identical 8-week randomized, placebo-controlled double-blind clinical studies that included either bipolar I or II patients (see CLINICAL PHARMACOLOGY in full Prescribing Information). Effectiveness has not been systematically evaluated in clinical trials for more than 8 weeks. Mania The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (see CLINICAL PHARMACOLOGY in full Prescribing Information). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. The physician who elects to use SEROQUEL for extended periods in bipolar disorder should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see DOSAGE AND ADMINISTRATION). **Schizophrenia** SEROQUEL is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (see CLINICAL PHARMACOLOGY in full Prescribing Information). The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled 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 (see DOSAGE AND ADMINISTRATION).

CONTRAINDICATIONS SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

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

Table 1

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

No suicides occurred in any of the pediatric trials. There were suicides in the adult trials, but the number was not sufficient to reach any conclusion about drug effect on suicide. It is unknown whether the suicidality risk extends to longer-term use, i.e., beyond several months. However, there is substantial evidence from placebo-controlled maintenance trials in adults with depression that the use of antidepressants can delay the recurrence of depression. **All patients being treated with antidepressants for any indication should be monitored appropriately and observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially during the initial few months of a course of drug therapy, or at times of dose changes, either increases or decreases.** The following symptoms, anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, and mania, have been reported in adult and pediatric patients being treated with antidepressants for major depressive disorder as well as for other indications, both psychiatric and non-psychiatric. Although a causal link between the emergence of such symptoms and either the worsening of depression and/or the emergence of suicidal impulses has not been established, there is concern that such symptoms may represent precursors to emerging suicidality. Consideration should be given to changing the therapeutic regimen, including possibly discontinuing the medication, in patients whose depression is persistently worse, or who are experiencing emergent suicidality or symptoms that might be precursors to worsening depression or suicidality, especially if these symptoms are severe, abrupt in onset, or were not part of the patient's presenting symptoms. **Families and caregivers of patients being treated with antidepressants for major depressive disorder or other indications, both psychiatric and non-psychiatric, should be alerted about the need to monitor patients for the emergence of agitation, irritability, unusual changes in behavior, and the other symptoms described above, as well as the emergence of suicidality, and to report such symptoms immediately to health care providers. Such monitoring should include daily observation by families and caregivers.** Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose. **Screening Patients for Bipolar Disorder:** A major depressive episode may be the initial presentation of bipolar disorder. It is generally believed (though not established in controlled trials) that treating such an episode with an antidepressant alone may increase the likelihood of precipitation of a mixed/manic episode in patients at risk for bipolar disorder. Whether any of the symptoms described above represent such a conversion is unknown. However, prior to initiating treatment with an antidepressant, patients with depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression. It should be noted that SEROQUEL is approved for use in treating adult bipolar depression. **Neuroleptic Malignant Syndrome (NMS)** 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 hyperreflexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) 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 (CNS) pathology. The

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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. The patient should be carefully monitored since recurrences of NMS have been reported. **Tardive Dyskinesia** A syndrome of potentially irreversible, involuntary, dyskinetic movements may 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, SEROQUEL 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 appear to 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 SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome. **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, including Serquel (see ADVERSE REACTIONS, Hyperglycemia). 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. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. 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 (eg, 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 antidiabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS **General:** **Orthostatic Hypotension:** SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1 -adrenergic antagonist properties. Syncope was reported in 1% (28/3265) of the patients treated with SEROQUEL, compared with 0.2% (2/954) on placebo and about 0.4% (2/527) on active control drugs. SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (see DOSAGE AND ADMINISTRATION). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **Leukopenia, Neutropenia and Agranulocytosis:** In clinical trial and postmarketing experience, events of leukopenia/neutropenia have been reported temporally related to atypical antipsychotic agents, including SEROQUEL. Agranulocytosis (including fatal cases) has also been reported. Possible risk factors for leukopenia/neutropenia include pre-existing low white 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 should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count <1000/mm³) should discontinue SEROQUEL and have their WBC followed until recovery (see ADVERSE REACTIONS). **Cataracts:** The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, 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. **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 should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, eg, Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older. **Hypothyroidism:** Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of 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 without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.7% (26/3489) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels. **Cholesterol and Triglyceride Elevations:** In schizophrenia trials, the proportions of patients with elevations to levels of cholesterol ≥ 240 mg/dL and triglycerides ≥ 200 mg/dL were 16% and 23% for SEROQUEL treated patients respectively compared to 7% and 16% for placebo patients respectively. In bipolar depression trials, the proportion of patients with cholesterol and triglycerides elevations to these levels were 9% and 14% for SEROQUEL treated patients respectively, compared to 6% and 9% for placebo patients respectively. **Hyperprolactinemia:** Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see Carcinogenesis). 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 contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomatia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiological studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL. In bipolar depression trials, the proportions of patients with transaminase elevations of ≥ 3 times the upper limits of the normal reference range in two 8-week placebo-controlled trials was 1% for SEROQUEL and 2% for placebo. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. In bipolar depression trials, somnolence was reported in 28% of patients on SEROQUEL compared to 7% of placebo patients. In these trials, sedation was reported in 30% of patients on SEROQUEL compared to 8% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which 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. **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. SEROQUEL and other antipsychotic drugs

tion for all patients attempting to quit smoking, except when medically contraindicated, according to the guideline. Also, evidence is insufficient for effectiveness in specific populations, including pregnant women, smokeless tobacco users, light smokers, and adolescents.

However, it is not enough for clinicians to recommend these medications. Health systems, insurers, and purchasers need to increase availability and facilitate use of these therapies to help physicians help their patients. "Making tobacco dependence treatment a covered benefit of insurance plans increases the likelihood that a tobacco user will receive treatment and

quit successfully," the authors wrote.

Increased evidence that counseling, alone and especially with medication, greatly increases a person's chances of quitting tobacco is recognized. There is a new consensus that counseling efforts can be effective in adolescent tobacco users, for example. Also, quitlines such as 1-800-QUIT-NOW are an effective intervention that can reach a large number of the 70% of 45 million smokers in the United States who indicate a desire to quit, according to the guideline.

Individual and group counseling also are deemed effective, particularly with increasing treatment intensity. Practical

counseling (problem-solving/skills training) and social support delivered as part of treatment were found especially effective. Use these interventions when counseling patients making a quit attempt, the authors suggested.

Clinical interventions both for patients who are willing or unwilling to make a quit attempt at the time are outlined. Interventions for individuals with psychiatric disorders, including substance use disorders, are also recommended.

The guideline was sponsored by the Agency for Healthcare Research and Quality; the Centers for Disease Control and Prevention; the National Cancer Institute;

the National Heart, Lung, and Blood Institute; the National Institute on Drug Abuse; the American Legacy Foundation; the Robert Wood Johnson Foundation; and the University of Wisconsin School of Medicine and Public Health's Center for Tobacco Research and Intervention.

Of the 24 panel members, 21 had no significant financial interests. The three other panel members were recused from panel deliberations relating to their areas of conflict. ■

The Clinical Practice Guideline and related documents are available at www.surgeongeneral.gov/tobacco.

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should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. In 2 eight-week clinical studies in patients with bipolar depression (N=1048) the incidence of treatment emergent suicidal ideation or suicide attempt was low and similar to placebo, (SEROQUEL 300 mg, 6/350, 1.7%; SEROQUEL 600 mg, 9/348, 2.6%; Placebo, 7/347, 2.0%). **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations in full Prescribing Information) is limited. SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**). **Withdrawal:** Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including SEROQUEL. Gradual withdrawal is advised. **Information for Patients:** Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with SEROQUEL and should counsel them in its appropriate use. A patient Medication Guide about "Antidepressant Medicines, Depression and other Serious Mental Illness, and Suicidal Thoughts or Actions" is available for SEROQUEL. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document. Patients should be advised of the following issues and asked to alert their prescriber if these occur while taking SEROQUEL. **Clinical Worsening and Suicide Risk:** Patients, their families, and their caregivers should be encouraged to be alert to the emergence of anxiety, agitation, panic attacks, insomnia, irritability, hostility, aggressiveness, impulsivity, akathisia (psychomotor restlessness), hypomania, mania, other unusual changes in behavior, worsening of depression, and suicidal ideation, especially early during antidepressant treatment and when the dose is adjusted up or down. Families and caregivers of patients should be advised to look for the emergence of such symptoms on a day-to-day basis, since changes may be abrupt. Such symptoms should be reported to the patient's prescriber or health professional, especially if they are severe, abrupt in onset, or were not part of the patient's presenting symptoms. Symptoms such as these may be associated with an increased risk for suicidal thinking and behavior and indicate a need for very close monitoring and possibly changes in the medication. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely. **Pregnancy:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. **Nursing:** Patients should be advised not to breast feed if they are taking SEROQUEL. **Concomitant Medication:** As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs. **Alcohol:** Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Leukopenia/Neutropenia:** Patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia should be advised that they should have their CBC monitored while taking SEROQUEL. **Laboratory Tests:** 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 should discontinue SEROQUEL at the first sign of a decline in WBC in absence of other causative factors. (See **PRECAUTIONS: Leukopenia, neutropenia and agranulocytosis**.) **Drug Interactions:** The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL. Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents. SEROQUEL may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine Phenytoin:** Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**). **Divalproex:** Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady-state by 17% without affecting the extent of absorption or mean oral clearance. **Thioridazine:** Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%. **Cimetidine:** Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine. **P450 3A Inhibitors:** Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution (reduced dosage) is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, erythromycin, and protease inhibitors). **Fluoxetine, Imipramine, Haloperidol, and Risperidone:** Coadministration of fluoxetine (60 mg once daily), imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine. **Effect of Quetiapine on Other Drugs Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing. **Divalproex:** The mean maximum concentration and extent of absorption of total and free valproic acid at steady-state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrine:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine. **Carcinogenesis, Mutagenesis, Impairment of Fertility:** **Carcinogenesis:** Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m² basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m² basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m² basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m² basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m² basis). Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown. Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-year toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see **Hyperprolactinemia** in **PRECAUTIONS**, **General**). **Mutagenesis:** The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats. **Impairment of Fertility:** Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m² basis. Drug-related effects included decreases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m² basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m² basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m² basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m² basis. **Pregnancy Pregnancy Category C:** The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m² basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m² basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m² basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m² basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m² basis). Evidence of maternal toxicity (i.e.,

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decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m² basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m² basis. There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL in pediatric patients have not been established. Anyone considering the use of SEROQUEL in a child or adolescent must balance the potential risks with the clinical need. **Geriatric Use:** Of the approximately 3700 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see **Pharmacokinetics** under **CLINICAL PHARMACOLOGY** in full Prescribing Information and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3700 patients. This database includes 698 patients exposed to SEROQUEL for the treatment of bipolar depression, 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia. Of these approximately 3700 subjects, approximately 3400 (2300 in schizophrenia, 405 in acute bipolar mania, and 698 in bipolar depression) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 992.6 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations. Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events for schizophrenia and bipolar mania. MedDRA terminology has been used to classify reported adverse events for bipolar depression. The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Findings Observed in Short-Term, Controlled Trials Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials Bipolar Disorder:** Depression: Overall, discontinuations due to adverse events were 12.3% for SEROQUEL 300 mg vs 19.0% for SEROQUEL 600 mg and 5.2% for placebo. Mania: Overall, discontinuations due to adverse events were 5.7% for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy. **Schizophrenia:** Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the side effect incidence in the population studied. Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 2. Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

Body System/Preferred Term	SEROQUEL (n=719)	PLACEBO (n=404)	Body System/Preferred Term	SEROQUEL (n=719)	PLACEBO (n=404)
Body as a Whole			Metabolic and Nutritional		
Headache	21%	14%	Weight Gain	5%	1%
Pain	7%	5%	SGPT Increased	5%	1%
Asthenia	5%	3%	SGOT Increased	3%	1%
Abdominal Pain	4%	1%	Nervous		
Back Pain	3%	1%	Agitation	20%	17%
Fever	2%	1%	Somnolence	18%	8%
Cardiovascular			Dizziness	11%	5%
Tachycardia	6%	4%	Anxiety	4%	3%
Postural Hypotension	4%	1%	Respiratory		
Digestive			Pharyngitis	4%	3%
Dry Mouth	9%	3%	Rhinitis	3%	1%
Constipation	8%	3%	Skin and Appendages		
Vomiting	6%	5%	Rash	4%	2%
Dyspepsia	5%	1%	Special Senses		
Gastroenteritis	2%	0%	Amblyopia	2%	1%
Gamma Glutamyl Transpeptidase Increased	1%	0%			

¹ Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonion, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%). Table 3 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 3. Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy)

Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)	Body System/ Preferred Term	SEROQUEL (n=196)	PLACEBO (n=203)
Body as a Whole			Metabolic and Nutritional		
Headache	17%	13%	Weight Gain	6%	3%
Asthenia	10%	4%	Nervous		
Abdominal Pain	7%	3%	Somnolence	34%	9%
Back Pain	5%	3%	Dizziness	9%	6%
Cardiovascular			Tremor	8%	7%
Postural Hypotension	7%	2%	Agitation	6%	4%
Digestive			Respiratory		
Dry Mouth	19%	3%	Pharyngitis	6%	3%
Constipation	10%	5%			

¹ Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.