

# Study Elucidates Menopause-Related Sleep Issues

BY HEIDI SPLETE  
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MINNEAPOLIS — Women with no history of sleep disorders often report sleep problems—especially difficulty falling asleep—as they undergo menopause. Their complaints were validated by a sleep study of more than 700 women presented at the annual meeting of the Association of Professional Sleep Societies.

“These data provide, for the first time,

objective findings to support this common sleep complaint in postmenopausal women,” asserted Edward O. Bixler, Ph.D., who is vice chair of the sleep research division at Pennsylvania State University in Hershey.

To confirm the association between menopause and poor sleep and to seek a possible mechanism for this connection, Dr. Bixler and his colleagues conducted single-night polysomnographies on 715 women with a mean age of 49 years. Of

these, 400 women were premenopausal, 120 were postmenopausal and using hormone therapy (HT), and 195 were postmenopausal but not using HT.

Women sleep as well as or better than men until they reach menopause, but sleep needs change with age, Dr. Bixler noted.

With this fact in mind, the researchers used a group of 609 men who were at least 45 years old (with an average age of 49 years) as controls for the study. The av-

erage body mass index for both genders was 26.9 kg/m<sup>2</sup>. All of the study participants had a low score (less than 5) on the apnea-hypopnea index and did not complain of insomnia or excessive daytime sleepiness.

The results of the single-night sleep test showed that the postmenopausal women who were not on hormone therapy took an average of 15 minutes longer to fall asleep, compared with women who were on HT, and an average of 10

## SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets BRIEF SUMMARY of Prescribing Information—Before prescribing, please consult complete Prescribing Information.

**WARNING: 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 XR is not approved for the treatment of patients with Dementia-Related Psychosis.

**INDICATIONS AND USAGE:** SEROQUEL XR is indicated for the treatment of schizophrenia. The efficacy of SEROQUEL XR in schizophrenia was established in part, on the basis of extrapolation from the established effectiveness of SEROQUEL. In addition, the efficacy of SEROQUEL XR was demonstrated in 1 short-term (6-week) controlled trial of schizophrenic inpatients and outpatients. The effectiveness of SEROQUEL XR 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 XR for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see *Dosage and Administration*).

**DOSAGE AND ADMINISTRATION: Usual Dose:** SEROQUEL XR should be administered once daily, preferably in the evening. The recommended initial dose is 300 mg/day. Patients should be titrated within a dose range of 400 – 800 mg/day depending on the response and tolerance of the individual patient. Dose increases can be made at intervals as short as 1 day and in increments of up to 300 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials. SEROQUEL XR tablets should be swallowed whole and not split, chewed or crushed. It is recommended that SEROQUEL XR be taken without food or with a light meal (approximately 300 calories). **Dosing in Special Populations:** Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see *Use in Specific Populations*). When indicated, dose escalation should be performed with caution in these patients. For those patients who require less than 200 mg per dose of SEROQUEL XR during the initial titration, use the immediate release formulation. Elderly patients should be started on SEROQUEL immediate release formulation 25 mg/day and the dose can be increased in increments of 25-50 mg/day depending on the response and tolerance of the individual patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose (see *Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets*). Patients with hepatic impairment should be started on SEROQUEL immediate release formulation 25 mg/day. The dose can be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerance of the patient. When an effective dose has been reached, the patient may be switched to SEROQUEL XR at an equivalent total daily dose (see *Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets*). The elimination of quetiapine fumarate was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine fumarate may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (see *Drug Interactions*). **Maintenance Treatment:** While there is no body of evidence available to specifically address how long the patient treated with SEROQUEL XR should remain on it, it is recommended that responding patients be continued on SEROQUEL XR, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment. **Re-initiation of Treatment in Patients Previously Discontinued:** Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting therapy of patients who have been off SEROQUEL XR for more than one week, the initial dosing schedule should be followed. When restarting patients who have been off SEROQUEL XR for less than one week, gradual dose escalation may not be required and the maintenance dose may be reinitiated. **Switching Patients from SEROQUEL Tablets to SEROQUEL XR Tablets:** Schizophrenic patients who are currently being treated with divided doses of SEROQUEL (immediate release formulation, eg, 2 to 3 times per day) may be switched to SEROQUEL XR at the equivalent total daily dose taken once daily. Individual dosage adjustments may be necessary. **Switching from Antipsychotics:** There are no systematically collected data to specifically address switching patients with schizophrenia from other antipsychotics to SEROQUEL XR, or concerning concomitant administration with other antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL XR therapy in place of the next scheduled injection. The need for continuing existing extrapyramidal syndrome medication should be re-evaluated periodically.

**CONTRAINDICATIONS:** None

**WARNINGS AND PRECAUTIONS: 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 XR (quetiapine fumarate) is not approved for the treatment of patients with dementia-related psychosis (see *Boxed Warning*). **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 quetiapine fumarate (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 reactions is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse reactions in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse reactions 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 anti-diabetic treatment despite discontinuation of the suspect drug. **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 quetiapine fumarate. Rare cases of NMS have been reported with quetiapine fumarate. 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 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 (eg, 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 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. **Orthostatic Hypotension:** Quetiapine fumarate may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its  $\alpha$ -1-adrenergic antagonist properties. Syncope was reported in 0.3% (3/951) of the patients treated with SEROQUEL XR, compared with 0.3% (1/319) on placebo. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo. Quetiapine fumarate 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). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate. **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, quetiapine fumarate 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 quetiapine fumarate, drug discontinuation should be considered. However, some patients may require treatment with quetiapine fumarate despite the presence of the syndrome. **Cataracts:** The development of cataracts was observed in association with quetiapine fumarate treatment in chronic dog studies. Lens changes have also been observed in patients during long-term quetiapine fumarate treatment, but a causal relationship to quetiapine fumarate 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 with SEROQUEL XR, seizures occurred in 0.1% (1/951) of patients treated with SEROQUEL XR compared to 0.9% (3/319) on placebo. During clinical trials with SEROQUEL, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo. As with other antipsychotics, quetiapine fumarate 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:** In SEROQUEL XR clinical trials, 0.5% (4/806) of patients on SEROQUEL XR vs. 0% (0/262) on placebo experienced decreased free thyroxine and 2.7% (21/786) on SEROQUEL XR vs. 1.2% (3/256) on placebo experienced increased TSH; however, no patients experienced a combination of clinically significant decreased free thyroxine and increased TSH. No patients had reactions of 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 quetiapine fumarate treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of these patients with TSH increases needed replacement thyroid treatment. **Cholesterol and Triglyceride Elevations:** In schizophrenia clinical trials, SEROQUEL XR treated patients had increases from baseline in mean cholesterol and triglycerides of 4% and 15%, respectively compared to decreases from baseline in mean cholesterol and triglycerides of 2% and 6% for placebo treated patients. In schizophrenia clinical trials, SEROQUEL treated patients had increases from baseline in mean cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. **Hyperprolactinemia:** An elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL XR as compared with placebo. Increased prolactin levels with quetiapine fumarate were observed in rat toxicity studies, and were associated with an increase in mammary gland neoplasia in rats. 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. **Transaminase Elevations:** Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. The proportions of patients with transaminase elevations of >3 times the upper limits of the normal reference range in a pool of 6-week placebo controlled schizophrenia trials were approximately 1% for SEROQUEL XR compared to 2% for placebo. 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. 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. **Potential for Cognitive and Motor Impairment:** Somnolence was a commonly reported adverse event reported in patients treated with quetiapine fumarate especially during the 3-day period of initial dose titration. In schizophrenia trials, somnolence and sedation were reported in 12% and 13% of patients on SEROQUEL XR respectively compared to 4% and 7% of placebo patients. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. Since quetiapine fumarate 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 quetiapine fumarate therapy does not affect them adversely. **Priapism:** One case of priapism in a patient receiving quetiapine fumarate was reported prior to market introduction. While a causal relationship to use of quetiapine fumarate has not been established, other drugs with  $\alpha$ -adrenergic blocking effects have been reported to induce priapism, and it is possible that quetiapine fumarate may share this capacity. Severe priapism may require surgical intervention. **Body Temperature Regulation:** Disruption of the body's ability to sever core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL XR for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, eg, 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 XR and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia. **Suicide:** The possibility of a suicide attempt is inherent in schizophrenia; close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL XR should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose. In three, 6-week clinical studies in patients with schizophrenia (N=951) the incidence of treatment emergent suicidal ideation or suicide attempt, as measured by the Columbia Analysis of Suicidal Behavior, was low in SEROQUEL XR treated patients (0.6%) and similar to placebo (0.9%). **Use in Patients with Concomitant Illness:** Clinical experience with SEROQUEL XR in patients with certain concomitant systemic illnesses is limited. SEROQUEL XR 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 XR, caution should be observed in cardiac patients (see *Warnings and Precautions*). **Withdrawal:** Acute withdrawal symptoms, such as nausea, vomiting, and insomnia have very rarely been described after abrupt cessation of atypical antipsychotic drugs, including quetiapine fumarate. Gradual withdrawal is advised.

**ADVERSE REACTIONS: Clinical Studies Experience:** Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice. The information below is derived from a clinical trial database for SEROQUEL XR consisting of 951 patients exposed to SEROQUEL XR for the treatment of schizophrenia in placebo controlled trials. This experience corresponds to approximately 82.9 patient-years. Adverse reactions were assessed by collecting adverse reactions, results of physical examinations, vital signs, body weights, laboratory analyses, and ECG results. Adverse reactions 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 reactions without first grouping similar types of reactions into a smaller number of standardized event categories. In the tables and tabulations that follow, standard MedDRA terminology has been used to classify reported adverse reactions. The stated frequencies of adverse reactions represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. **Adverse Reactions Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials:** There was no difference in the incidence and type of adverse reactions associated with discontinuation (6.4% for SEROQUEL XR vs. 7.5% for placebo) in a pool of controlled trials. **Adverse Reactions Occurring at an Incidence of 5% or More Among SEROQUEL XR Treated Patients in Short-Term, Placebo-Controlled Trials:** Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse reactions that occurred during acute therapy of schizophrenia (up to 6 weeks) in  $\geq 5\%$  patients treated with SEROQUEL XR (doses ranging from 300 to 800 mg/day) where the incidence in patients treated with SEROQUEL XR was greater than the incidence in

continued

minutes longer to fall asleep compared with the men. These differences were statistically significant.

The average time it took for the male controls to fall asleep was not significantly different from that of premenopausal women (a difference of 1.6 minutes) or of postmenopausal women who were taking hormone therapy (a difference of 5.6 minutes).

“What was unexpected was that we didn’t find an increase in daytime sleepiness,” Dr. Bixler noted. He proposed that the lack of daytime sleepiness might be a result of the reduced need for sleep that is a natural part of aging. “As you

age, you are less likely to be sleepy during the day even though you are sleeping less at night,” he said.

When the researchers looked at slow wave sleep, which is associated with the brain’s ability to recharge, think, and remember, they found no differences between premenopausal women and male controls.

Postmenopausal women who didn’t use HT, however, were twice as likely to have slow wave sleep as were male controls, and postmenopausal women who used HT were four times as likely to have slow wave sleep as were male controls. Therefore, postmenopausal women who

used HT were twice as likely to have slow wave sleep as were women who didn’t use HT.

The data suggest that sleep latency is a valid symptom among menopausal women without a history of sleep disorders, especially among those who are not using HT. Based on these findings, menopausal women may be at increased risk for developing chronic insomnia that may require treatment, Dr. Bixler added.

“We would speculate that [menopausal changes] may be triggers for the onset of primary insomnia in vulnerable women,” he said. ■

# Depression Affects Heart Rate Variability

BY MARY ANN MOON  
Contributing Writer

Depression severely impairs the recovery of heart rate variability after acute coronary syndrome, reported Dr. Alexander H. Glassman of Columbia University, New York, and his associates.

In addition, heart rate variability (HRV) continues to decline in patients whose depression does not respond to sertraline (Zoloft), while it ceases to decline in those who do respond to sertraline. It is not yet known whether this cardiac benefit is attributable to a pharmacologic effect of the antidepressant, to improvement of the depressive illness, or to a combination of both, the researchers said.

“What is clear is that depression is associated with biological changes involving increased heart rate, inflammatory response, plasma norepinephrine, platelet reactivity, decreased heart rate variability, and now, absent post-ACS-HRV recovery, all of which [are] associated with life-threatening consequences,” said Dr. Glassman and his associates.

“From a clinician’s point of view, patients with depression after myocardial infarction . . . should be both carefully watched and aggressively treated, because they are at an elevated cardiac risk and less likely to get better spontaneously,” they noted (Arch. Gen. Psychiatry 2007;64:1025-31).

The researchers used data from 258 subjects who participated in the SADHART study to examine the effects of depression and of antidepressant therapy on heart rate variability. SADHART (Sertraline Antidepressant Heart Attack Randomized Trial), which took place in 1997-2001, compared sertraline with placebo in patients with major depressive disorder who were hospitalized after ACS.

In the general population, HRV falls abruptly during acute coronary episodes and recovers gradually but incompletely in the following weeks. However, Dr. Glassman and his associates found that HRV failed to recover in ACS patients with major depression.

The decline in HRV leveled off or improved slightly in those who responded to sertraline and in those whose mood improved spontaneously, but continued to decline in patients who received placebo or who failed to respond to sertraline, the investigators said.

Even patients who responded to sertraline showed only one-third as much HRV recovery as is reported in the literature among ACS patients who do not have depression. Thus, even successful selective serotonin reuptake inhibitor therapy “may not fully eliminate the autonomic risk associated with major depressive disorder,” the investigators added.

Dr. Glassman served as a member of the steering committee for SADHART. He also has been a consultant for and has received honoraria from Pfizer Inc., which markets sertraline and provided partial support for the study. ■

## SEROQUEL XR™ (quetiapine fumarate) Extended-Release Tablets

BRIEF SUMMARY of Prescribing Information (continued)—Before prescribing, please consult complete Prescribing Information.

placebo-treated patients.

Table 1. Treatment-Emergent Adverse Experience Incidence in 6-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia<sup>1</sup>

Body System/ Preferred Term	SEROQUEL XR (n=951)	PLACEBO (n=319)
<b>Gastrointestinal Disorders</b>		
Dry mouth	12%	1%
Constipation	6%	5%
Dyspepsia	5%	2%
<b>Nervous System Disorders</b>		
Sedation	13%	7%
Somnolence	12%	4%
Dizziness	10%	4%
<b>Vascular Disorders</b>		
Orthostatic hypotension	7%	5%

<sup>1</sup>Reactions for which the SEROQUEL XR incidence was equal to or less than placebo are not listed in the table, but included the following: headache, insomnia, and nausea.

In these studies, the most commonly observed adverse reactions associated with the use of SEROQUEL XR (incidence of 5% or greater) and observed at a rate on SEROQUEL XR at least twice that of placebo were dry mouth (12%), somnolence (12%), dizziness (10%), and dyspepsia (5%). **Adverse Reactions that occurred in <5% of patients and were considered drug-related (incidence greater than placebo and consistent with known pharmacology of drug class) in order of decreasing frequency:** Heart rate increased, hypotension, weight increased, tremor, akathisia, increased appetite, blurred vision, postural dizziness, pyrexia, dysarthria, dystonia, drooling, syncope, tardive dyskinesia, dysphagia, leukopenia, and rash. **Adverse Reactions that have historically been associated with the use of SEROQUEL and not listed elsewhere in the label:** The following adverse reactions have also been reported with SEROQUEL: anaphylactic reaction, peripheral edema, rhinitis, eosinophilia, hypersensitivity, elevations in gamma-GT levels and restless legs syndrome. **Extrapyramidal Symptoms:** Four methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) Barnes Akathisia Rating Scale (BARS) Global Assessment Score (3) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertension, hypokinesia, neck rigidity, and tremor), and (4) use of anticholinergic medications to treat emergent EPS. In three-arm placebo-controlled clinical trials for the treatment of schizophrenia, utilizing doses between 300 mg and 800 mg of SEROQUEL XR, the incidence of any adverse reactions potentially related to EPS was 8% for SEROQUEL XR and 8% for SEROQUEL (without evidence of being dose related), and 5% in the placebo group. In these studies, the incidence of the individual adverse reactions (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, and muscle rigidity) was generally low and did not exceed 3% for any treatment group. At the end of treatment, the mean change from baseline in SAS total score and BARS Global Assessment score was similar across the treatment groups. The use of concomitant anticholinergic medications was infrequent and similar across the treatment groups. The incidence of extrapyramidal symptoms was consistent with that seen with the profile of SEROQUEL in schizophrenia patients. **Vital Signs and Laboratory Studies: Vital Sign Changes:** Quetiapine fumarate is associated with orthostatic hypotension (see *Warnings and Precautions*). **Weight Gain:** In schizophrenia trials with SEROQUEL XR, the proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight was 10% for SEROQUEL XR compared to 5% for placebo. In schizophrenia trials the proportions of patients meeting a weight gain criterion of  $\geq 7\%$  of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significant greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). **Laboratory Changes:** An assessment of the pre-marketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in ALT and increases in both total cholesterol and triglycerides (see *Warnings and Precautions*). In post-marketing clinical trials, elevations in total cholesterol (predominantly LDL cholesterol) have been observed. In three-arm SEROQUEL XR placebo controlled monotherapy clinical trials, among patients with a baseline neutrophil count  $\geq 1.5 \times 10^9/L$ , the incidence of at least one occurrence of neutrophil count  $< 1.5 \times 10^9/L$  was 1.5% in patients treated with SEROQUEL XR and 1.5% for SEROQUEL, compared to 0.8% in placebo-treated patients. **Hyperglycemia:** In 2 long-term placebo-controlled clinical trials, mean exposure 213 days for SEROQUEL (646 patients) and 152 days for placebo (680 patients), the exposure-adjusted rate of any increased blood glucose level ( $\geq 126$  mg/dl) for patients more than 8 hours since a meal was 18.0 per 100 patient years for SEROQUEL (10.7% of patients) and 9.5 for placebo per 100 patient years (4.6% of patients). In short-term (12 weeks duration or less) placebo-controlled clinical trials (3342 patients treated with SEROQUEL and 1490 treated with placebo), the percent of patients who had a fasting blood glucose  $\geq 126$  mg/dl or a non fasting blood glucose  $\geq 200$  mg/dl was 3.5% for quetiapine and 2.1% for placebo. In a 24 week trial (active-controlled, 115 patients treated with SEROQUEL) designed to evaluate glycemic status with oral glucose tolerance testing of all patients, at week 24 the incidence of a treatment-emergent post-glucose challenge glucose level  $\geq 200$  mg/dl was 1.7% and the incidence of a fasting treatment-emergent blood glucose level  $\geq 126$  mg/dl was 2.6%. **ECG Changes:** 0.8% of SEROQUEL XR patients, and no placebo patients, had tachycardia ( $> 120$  bpm) at any time during the trials. SEROQUEL XR was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean decrease of 1 beat per minute for placebo. This is consistent with the rates of SEROQUEL. The incidence of adverse reactions of tachycardia was 3% for SEROQUEL XR compared to 1% for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. The slight tendency for tachycardia may be related to quetiapine fumarate’s potential for inducing orthostatic changes (see *Warnings and Precautions*). **Post Marketing Experience:** The following adverse reactions were identified during post approval use of SEROQUEL. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Adverse reactions reported since market introduction which were temporally related to SEROQUEL therapy include: anaphylactic reaction, restless legs, and leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia. Other adverse reactions reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, cardiomyopathy hyponatremia, myocarditis rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Stevens-Johnson syndrome (SJS).

**DRUG INTERACTIONS:** The risks of using SEROQUEL XR in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL XR, caution should be used when it is taken in combination with other centrally acting drugs. Quetiapine fumarate potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be limited while taking quetiapine fumarate. Because of its potential for inducing hypotension, SEROQUEL XR may enhance the effects of certain antihypertensive agents. SEROQUEL XR may antagonize the effects of levodopa and dopamine agonists. **The Effect of Other Drugs on Quetiapine Fumarate: Phenytoin:** Coadministration of quetiapine fumarate (250 mg three times/day) and phenytoin (100 mg three times/day) increased the mean oral clearance of quetiapine fumarate by 5-fold. Increased doses of SEROQUEL XR may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine fumarate and phenytoin, or other hepatic enzyme inducers (eg, carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (eg, valproate) (see *Dosage and Administration*). **Divalproex:** Coadministration of quetiapine fumarate (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine fumarate 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 fumarate (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 fumarate (150 mg tid). Dosage adjustment for quetiapine fumarate 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 fumarate by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine fumarate. Caution (reduced dosage) is indicated when SEROQUEL XR is administered with ketoconazole and other inhibitors of cytochrome P450 3A (eg, itraconazole, fluconazole, erythromycin, 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 fumarate (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine fumarate. **Effect of Quetiapine Fumarate on Other Drugs: Lorazepam:** The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine fumarate 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 fumarate (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 fumarate (150 mg bid). The changes were not significant. **Lithium:** Concomitant administration of quetiapine fumarate (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium. **Antipyrene:** Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine fumarate to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrene or urinary recovery of antipyrene metabolites. These results indicate that quetiapine fumarate does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrene.

**USE IN SPECIFIC POPULATIONS: Pregnancy:** Pregnancy Category C: The teratogenic potential of quetiapine fumarate 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/m<sup>2</sup> basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m<sup>2</sup> 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/m<sup>2</sup> 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/m<sup>2</sup> basis). Evidence of maternal toxicity (i.e., 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/m<sup>2</sup> 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/m<sup>2</sup> basis. There are no adequate and well-controlled studies in pregnant women and quetiapine fumarate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Labor and Delivery:** The effect of SEROQUEL XR on labor and delivery in humans is unknown. **Nursing Mothers:** SEROQUEL XR was excreted in milk of treated animals during lactation. It is not known if SEROQUEL XR is excreted in human milk. It is recommended that women receiving SEROQUEL XR should not breast feed. **Pediatric Use:** The safety and effectiveness of SEROQUEL XR in pediatric patients have not been established. **Geriatric Use:** Sixty-eight patients in clinical studies with SEROQUEL XR were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL XR in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL XR, 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 quetiapine fumarate was reduced by 30% to 50% in elderly patients when compared to younger patients (see *Use in Special Populations*). **Renal Impairment:** Clinical experience with SEROQUEL XR in patients with renal impairment is limited. **Hepatic Impairment:** Since quetiapine fumarate is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (see *Dosing and Administration*).

**DRUG ABUSE AND DEPENDENCE: Controlled Substance:** SEROQUEL XR is not a controlled substance. **Abuse:** SEROQUEL XR has not been systematically studied in animals or humans for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL XR, (eg, development of tolerance, increases in dose, drug-seeking behavior).

**OVERDOSAGE: Human Experience:** In clinical trials, survival has been reported in acute overdoses of up to 30 grams of quetiapine fumarate. Most patients who overdosed experienced no adverse events or recovered fully from the reported events. Death has been reported in a clinical trial following an overdose of 13.6 grams of quetiapine fumarate alone. In general, reported signs and symptoms were those resulting from an exaggeration of the drug’s known pharmacological effects, ie, drowsiness and sedation, tachycardia and hypotension. Patients with pre-existing severe cardiovascular disease may be at an increased risk of the effects of overdose (see *Warnings and Precautions*). One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma, or QTc prolongation. **Management of Overdose:** In case of acute overdose, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect 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 acute overdose of SEROQUEL XR. Similarly it is reasonable to expect that the  $\alpha$ -adrenergic-blocking properties of bretylium might be additive to those of quetiapine fumarate, resulting in problematic hypotension. There is no specific antidote to SEROQUEL XR. Therefore, appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since  $\beta$  stimulation may worsen hypotension in the setting of quetiapine fumarate-induced  $\alpha$  blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

**PATIENT COUNSELING INFORMATION: Hyperglycemia and Diabetes Mellitus:** Patients should be aware of the symptoms of hyperglycemia (high blood sugar, polydipsia, polyuria, polyphagia, and weakness) and be advised regarding the risk of diabetes mellitus. Patients who are diagnosed with diabetes, those with risk factors for diabetes, or those that develop these symptoms during treatment should be monitored. **Increased Mortality in Elderly Patients with Dementia-Related Psychosis:** Patients and caregivers should be advised that elderly patients with dementia-related psychoses treated with atypical antipsychotic drugs are at increased risk of death compared with placebo. Quetiapine fumarate is not approved for elderly patients with dementia-related psychosis. **Orthostatic Hypotension:** Patients should be advised of the risk of orthostatic hypotension (symptoms include feeling dizzy or lightheaded upon standing) especially during the period of initial dose titration, and also at times of re-initiating treatment or increases in dose. **Interference with Cognitive and Motor Performance:** Patients should be advised of the risk of somnolence or sedation, especially during the 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 machinery, until they are reasonably certain quetiapine fumarate therapy does not affect them adversely. Patients should limit consumption of alcohol during treatment with quetiapine fumarate. **Pregnancy and Nursing:** Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy. Patients should be advised not to breast feed if they are taking quetiapine fumarate. **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. **Heat Exposure and Dehydration:** Patients should be advised regarding appropriate care in avoiding overheating and dehydration. **Neuroleptic Malignant Syndrome (NMS):** Patients should be advised to report to their physician any signs or symptoms that may be related to NMS. These may include muscle stiffness and high fever.

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