

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 Schizophrenia¹

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

¹Reactions 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 (≥ 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 ≥ 126 mg/dl or a non fasting blood glucose ≥ 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 ≥ 200 mg/dl was 1.7% and the incidence of a fasting treatment-emergent blood glucose level ≥ 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/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., 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 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 behaviour). **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 α -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 β stimulation may worsen hypotension in the setting of quetiapine fumarate-induced α 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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