

Late-Onset GAD More Common Than Thought

BY JANE SALODOF MACNEIL

Southwest Bureau

PARIS — Generalized anxiety disorder occurs as a late-onset condition more often than is recognized, according to investigators who presented the first large treatment trial in elderly patients during the annual congress of the European College of Neuropsychopharmacology.

Dr. Francesca Baldinetti reported that the average age of onset was 56 years in

273 outpatients with generalized anxiety disorder (GAD) who were aged at least 65 years and who enrolled in the placebo-controlled trial. The study found pregabalin (Lyrica) to be at least as effective in the elderly as in previous trials with younger patients.

“In reality, there is a late onset of generalized anxiety disorder in the later stage of life,” said Dr. Baldinetti, medical director of worldwide neuroscience at Pfizer Inc., in a presentation of the new data at

a session on psychiatric disorders in older people.

“That is not in the literature,” added the lead author, Dr. Stuart A. Montgomery, a professor emeritus of psychiatry at the Imperial College London.

Commenting from the audience at Dr. Montgomery’s invitation, an investigator of pregabalin in adult patients described the characterization of GAD as an early-onset disorder as a misconception. Most patients develop the full syndrome after the age of 30, according to Dr. Hans-Ulrich Wittchen, professor of clinical psychology and epidemiology at the Technische Universität Dresden (Germany).

He urged careful questioning of newly diagnosed older GAD patients who report they first had symptoms as children. “It may be that there are anxiety disorders preceding that [new] development ... But if you probe the GAD symptomatology, this is another disorder,” he said. “This is not an early anxiety disorder.”

In her presentation, Dr. Baldinetti said that at least half of all newly diagnosed cases of GAD occur after age 30 years and a third after age 40.

Five different studies from the United States and Europe have shown prevalence rates ranging from 1.9% to 7.2% in the elderly, she said.

All patients in the pregabalin study had Hamilton Rating Scale for Anxiety (HAM-A) scores of 20 or more, with a baseline average of 26.6 for 177 patients randomized to pregabalin and 26.1 for 96 patients on placebo. Patients with major depression and other anxiety or substance abuse disorders were excluded. The participants had three to four prior episodes of GAD on average, with the current episode lasting about 15 months. The average age was 72 years, as about a third of the population was 75 years of age or older. About three-fourths of those enrolled were female.

A flexible-dose regimen started the active drug group on 150 mg per day of pre-

gabalin, which clinicians could titrate up to 600 mg by week 6 of the 8-week trial. The average dose used was 270 mg.

Dr. Baldinetti suggested that the flexible dosing probably was responsible for the main difference in outcomes relative to the earlier adult trials. Whereas younger patients on pregabalin had a significantly better response than did those on placebo during week 1, elderly patients on pregabalin began to show significant improvement compared with the control group during week 2.

By the elderly trial’s end, 64.2% of the pregabalin cohort had responded versus 50% of the control group. Total HAM-A scores fell by more than 12 points in the pregabalin group, versus more than 10 points with placebo in a last-observation-carried-forward (LOCF) analysis.

The effect was seen in HAM-A psychic and HAM-A somatic scores. HAM-A psychic scores fell by 7.8 points with pre-

gabalin versus 6.3 points with placebo. HAM-A somatic scores fell by 6.6 points with pregabalin versus 5.4 points with placebo.

Dr. Baldinetti noted that the drug’s benefits were significant in subgroups of patients with severe anxiety and with subsyndromal depression.

About a quarter of the patients—28% of those on placebo and 25% of the pregabalin group—dropped out of the study. Only 7% on placebo and 4% on pregabalin did so for lack of efficacy. Adverse events caused discontinuation by 11% of the pregabalin group and 9% on placebo. The most common adverse events with pregabalin were dizziness (20.3%), somnolence (13%), headache (10.2%), nausea (9%), and infection (5.6%).

An anticonvulsant with anxiolytic and analgesic properties, pregabalin is approved in the United States for treatment of neuropathic pain and seizures. It is also under study for fibromyalgia.

SEROQUEL® (quetiapine fumarate) Tablets

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

adverse events 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. **Treatment-Emergent Adverse Experience Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials for the Treatment of Schizophrenia and Bipolar Mania (monotherapy):** Body as a Whole: Headache, Pain, Asthenia, Abdominal Back Pain, Fever, Cardiovascular: Tachycardia, Postural Hypotension; Digestive: Dry Mouth, Constipation, Vomiting, Dyspepsia, Gastroenteritis, Gamma Glutamyl Transpeptidase Increased; Metabolic: Weight Gain, SGPT increased, SGOT increased; Nervous: Agitation, Somnolence, Dizziness, Anxiety; Respiratory: Pharyngitis, Rhinitis; Skin and Appendages: Rash; Special Senses: Amblyopia. 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%). († 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, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.) Table 2, from the full Prescribing Information, 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. **Treatment-Emergent Adverse Experience Incidence in 3-Week Placebo-Controlled Clinical Trials for the Treatment of Bipolar Mania (Adjunct Therapy):** Body as a Whole: Headache, Asthenia, Abdominal Pain, Back Pain, Cardiovascular: Postural Hypotension; Digestive: Dry Mouth, Constipation; Metabolic and Nutritional: Weight Gain; Nervous: Somnolence, Dizziness, Tremor, Agitation; Respiratory: Pharyngitis. 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 dry mouth (44%), sedation (30%), somnolence (28%), dizziness (18%), constipation (10%), lethargy (5%), and nasal congestion (5%). († Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: nausea, upper respiratory tract infection, and headache.) Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors. **Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials:** Dose-related Adverse Events: Logistic regression analyses revealed a positive dose response ($p < 0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain. **Extrapyramidal Symptoms:** Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS. In six additional placebo-controlled clinical trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS. In two placebo-controlled clinical trials for the treatment of bipolar depression using 300 mg and 600 mg of SEROQUEL, the incidence of adverse events potentially related to EPS was 12% in both dose groups and 6% in the placebo group. In these studies, the incidence of the individual adverse events (eg, akathisia, extrapyramidal disorder, tremor, dyskinesia, dystonia, restlessness, muscle contractions involuntary, psychomotor hyperactivity and muscle rigidity) were generally low and did not exceed 4% in any treatment group. The 3 treatment groups were similar in mean change in SAS total score and BARS Global Assessment score at the end of treatment. The use of concomitant anticholinergic medications was infrequent and similar across the three treatment groups. **Vital Signs and Laboratory Studies: Vital Sign Changes:** SEROQUEL is associated with orthostatic hypotension (see PRECAUTIONS). **Weight Gain:** 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 significantly greater incidence of weight gain for SEROQUEL (23% compared to placebo (6%)). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight gain criterion were 13% compared to 4% for placebo. In bipolar depression trials, the proportions of patients meeting the same weight gain criterion were 8% compared to 2% for placebo. **Laboratory Changes:** An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see PRECAUTIONS). **ECG Changes:** Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. In bipolar depression trials, no patients had heart rate increases to > 120 beats per minute. 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. This slight tendency to tachycardia may be related to SEROQUEL’s potential for inducing orthostatic changes (see PRECAUTIONS). **Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL:** Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. **Nervous System: Frequent:** hyperreflexia, dizziness, dysarthria; **Infrequent:** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid ideation, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, cataplexy reaction, hemiparesis; **Rare:** apathia, autopsychic syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma. **Body as a Whole: Frequent:** flu syndrome; **Infrequent:** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; **Rare:** abdomen enlarged; **Digestive System: Frequent:** anorexia; **Infrequent:** increased salivation, increased appetite, gamma glutamyl transpeptidase increased, gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; **Rare:** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis; **Cardiovascular System: Frequent:** palpitation; **Infrequent:** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; **Rare:** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration; **Respiratory System: Frequent:** pharyngitis, rhinitis, cough increased, dyspnea; **Infrequent:** pneumonia, epistaxis, asthma; **Rare:** hiccups, hyperventilation; **Metabolic and Nutritional System: Frequent:** peripheral edema; **Infrequent:** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; **Rare:** glycosuria, gout, hand edema, hypokalemia, water intoxication. **Skin and Appendages System: Frequent:** sweating; **Infrequent:** pruritus, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; **Rare:** exfoliative dermatitis, psoriasis, skin discoloration. **Urogenital System: Infrequent:** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; (*adjusted for gender). **Rare:** gynecomastia*, nocturia, polyuria, acute kidney failure. **Special Senses: Infrequent:** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; **Rare:** abnormality of accommodation, deafness, glaucoma. **Musculoskeletal System: Infrequent:** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain; **Hemic and Lymphatic System: Frequent:** leukopenia; **Infrequent:** leukocytosis, anemia, ecchymosis, asinophilia, hypochromic anemia; lymphadenopathy, cyanosis; **Rare:** hemolysis, thrombocytopenia. **Endocrine System: Infrequent:** hypothyroidism, diabetes mellitus; **Rare:** hyperthyroidism. **Post Marketing Experience:** Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: 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 events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE: Controlled Substance Class: SEROQUEL is not a controlled substance. **Physical and Psychologic Dependence:** SEROQUEL 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 any 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, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE: Human experience: Experience with SEROQUEL in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug’s known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. 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 Overdosage:** In case of acute overdosage, 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 overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic blocking properties of tetrylium might be additive to those of quetiapine, resulting in problematic hypotension. There is no specific antidote to SEROQUEL. 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-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.

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Elderly patients on pregabalin began to show significant improvement during week 2.

DR. BALDINETTI

noted that the drug’s benefits were significant in subgroups of patients with severe anxiety and with subsyndromal depression.

Occupational Therapy Improves Daily Functioning in Dementia

Occupational therapy improves the daily functioning of patients with mild to moderate dementia, results of a randomized, controlled trial show.

“We believe that, in the long term, occupational therapy will result in less dependence on social and health care resources and less need for institutionalization,” reported Maud J.L. Graff, of the Research Group for Allied Health Care at University Medical Center Nijmegen, the Netherlands, and her associates (BMJ 2006 Nov. 17 [Epub doi:10.1136/bmj.39001.688843.BE]).

In the study, dementia patients were randomized to an occupational therapy treatment group (68) or to a control group

(67). Study participants had to be aged 65 years or older, diagnosed with mild or moderate dementia, and cared for once a week or more by a primary caregiver.

At 6 weeks, those in the intervention group had statistically significant improvements over the controls on three tests. Patients in the therapy group had a mean score that was 1 point higher on the 8-point motor and process skills test and 10.9 points higher on the 44-point performance interview. Caregivers in the therapy group had a mean score 16.2 points higher on the 135-point competence questionnaire.

One limitation of the study was that it was not double blinded.

—Jonathan Gardner