

Lively Limbs Limit Sleep in Cognitively Impaired

BY HEIDI SPLETE
Senior Writer

Frequent nighttime leg movements were significantly associated with sleep disturbance and less total sleep in a study of 102 elderly people with cognitive impairment.

Previous research had shown that sleep time varies from approximately 6 to 10 hours in nursing home residents who have moderate to severe cognitive impairment,

and that this sleep is quite fragmented.

However, an association between periodic limb movements in sleep and total sleep time in older people with cognitive impairment hadn't been established.

The nature of the association—which emerged both among people living in nursing homes and in those in the community—remains unclear.

Kathy C. Richards, Ph.D., of the Polisher Research Institute, Horsham, Pa., and her colleagues measured sleep vari-

ables in 58 men and 44 women of average age 82 years. Of those, 66 people lived in nursing homes or assisted-living facilities and the rest resided at home.

The participants scored an average of 17.3 on the Mini-Mental State Examination (MMSE), in which a score of 30 signifies the highest cognitive function.

The exam rated seven people as having profound cognitive impairment, 14 with severe cognitive impairment, and 33 with the criteria for moderate cognitive im-

pairment. The test rated 21 people as mildly impaired and 27 with early cognitive impairment.

The researchers then used polysomnography to collect data on variables including leg movement, oxygen saturation, time spent in bed, total sleep time, and the apnea-hypopnea index. The team conducted the test during 1 night in each person's usual sleep setting.

The study participants averaged 5.5 hours of total sleep time, ranging from

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- A target dose of 300 mg/day by Day 4 for bipolar depression with **once-daily dosing at bedtime**, and a target dose of 600 mg/day[‡] by Day 5 in bipolar mania with **BID[§] dosing**^{2,6}

Important Safety Information (continued)

- A potentially fatal symptom complex, sometimes referred to as Neuroleptic Malignant Syndrome (NMS), has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The management of NMS should include immediate discontinuation of antipsychotic drugs
- Tardive dyskinesia (TD), a potentially irreversible syndrome of involuntary dyskinetic movements, may develop in patients treated with antipsychotic drugs. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic drugs administered to the patient increase. TD may remit, partially or completely, if antipsychotic treatment is withdrawn. SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of TD
- Hyperglycemia, in some cases extreme and associated with ketoacidosis, hyperosmolar coma, or death, has been reported in patients treated with atypical antipsychotics, including SEROQUEL. The relationship of atypical use and glucose abnormalities is complicated by the possibility of increased risk of diabetes in the schizophrenic population and the increasing incidence of diabetes in the general population. However, epidemiological studies suggest an increased risk of treatment-emergent, hyperglycemia-related adverse events in patients treated with atypical antipsychotics. Patients starting treatment with atypical antipsychotics who have or are at risk for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Patients who develop symptoms of hyperglycemia should also undergo fasting blood glucose testing
- Leukopenia, neutropenia, and agranulocytosis (including fatal cases), have been reported temporally related to atypical antipsychotics, including SEROQUEL. Patients with a pre-existing low white blood cell (WBC) count or a history of drug induced leukopenia/neutropenia should have their complete blood count monitored frequently during the first few months of therapy. In these patients, SEROQUEL should be discontinued at the first sign of a decline in WBC absent other causative factors. Patients with neutropenia should be carefully monitored, and SEROQUEL should be discontinued in any patient if the absolute neutrophil count is < 1000/mm³
- Precautions include the risk of seizures, orthostatic hypotension, and cataracts. Examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment, or shortly thereafter, and at 6-month intervals during chronic treatment

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less than 1 hour to nearly 9 hours. Although the average time spent in bed was 8 hours, only 67% of that time was spent sleeping, and nonrapid eye movement sleep made up 87% of the total sleep time. The study subjects awoke an average of 34 times during the night, but only an average of 1.8 awakenings was related to leg movements (Sleep 2008;31:224-30).

Participants' scores on the Periodic Leg Movement Index (PLMI) ranged from 0 to 112, with an average of 17. A total of 34 persons (33%) had PLMI scores greater than 15, which is the cutoff point for a diagnosis of periodic limb movement disorder.

Overall, people with a PLMI greater than 15 experienced significantly more minutes awake; less total sleep time and nonrapid eye movement sleep; less sleep efficiency; and a lower apnea-hypopnea index than did study participants with lower PLMI.

When the researchers controlled for multiple variables, a combination of time spent in bed, older age, and higher PLMI accounted for 44% of the study population's variance in total sleep time.

On the other hand, the analysis found no relationship between PLMI and other sleep variables or participants' age or MMSE scores.

The study showed no significant difference in total sleep time between people in private homes and those in nursing homes or assisted-living facilities.

"This was surprising considering the pervasive nursing care practices in nursing homes of awakening residents for incontinence and other care and the noise from other residents and staff," the researchers noted.

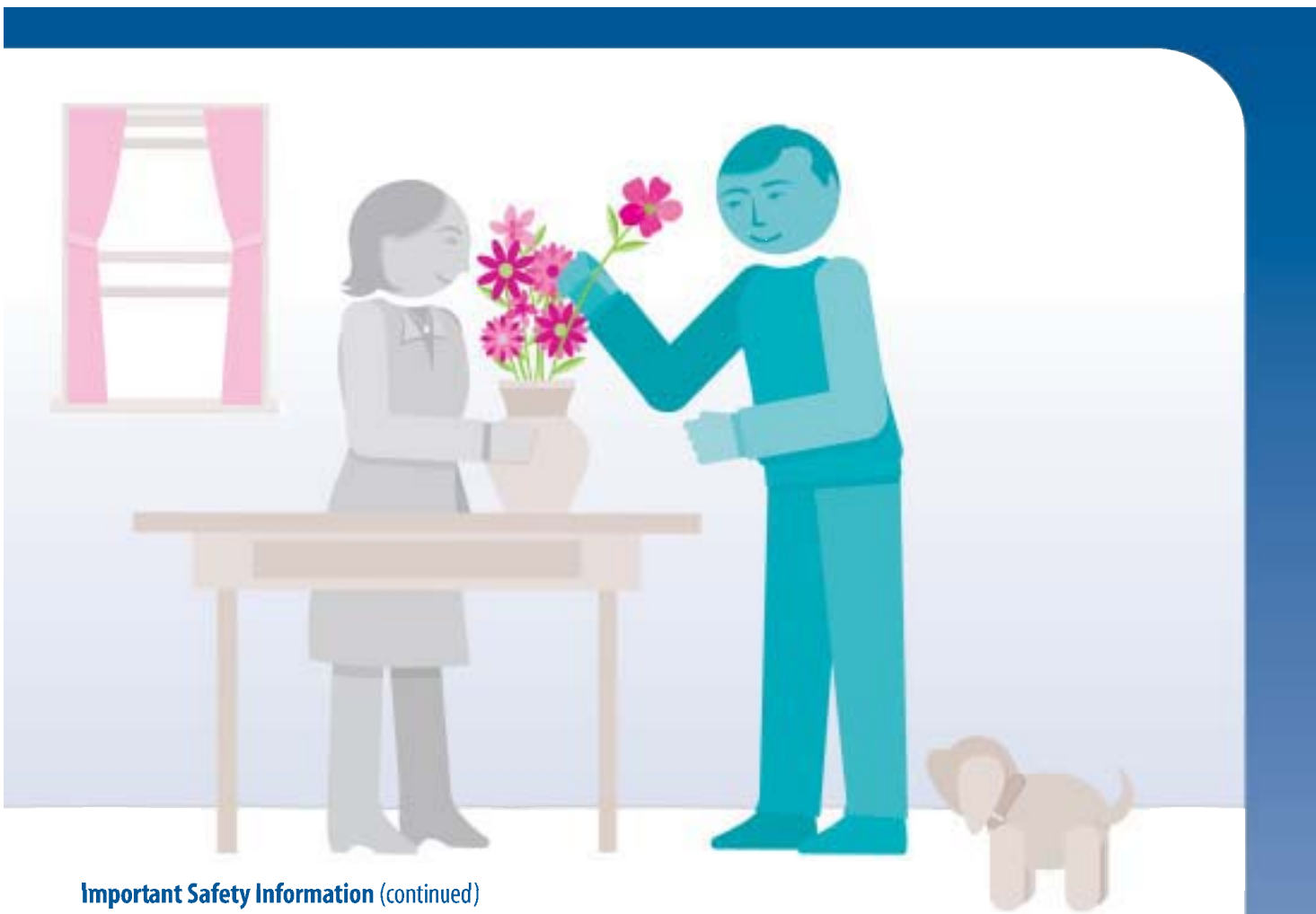
"An elevated PLMI was associated with a consistent pattern of sleep disturbance, suggesting that [periodic leg movements] or other related comorbidities, such as restless leg syndrome, may be a cause for poor sleep in elders with cognitive im-

pairment," Dr. Richards and her colleagues wrote.

In a statement, Dr. Richards called that finding "important because treatment of periodic leg movements may result in improved nighttime sleep and improved quality of life in this vulnerable population."

The study was limited by a lack of data on the potential role of upper airway resistance as a cause of nighttime leg movement, according to Dr. Richards and her colleagues.

Dr. Richards has received research support from Beverly Healthcare Corp., but the study had no industry sponsorship. ■



Important Safety Information (continued)

- The most commonly observed adverse events associated with the use of SEROQUEL monotherapy versus placebo in clinical trials for schizophrenia and bipolar disorder were dry mouth (9%-44% vs 3%-13%), sedation (30% vs 8%), somnolence (18%-28% vs 7%-8%), dizziness (11%-18% vs 5%-7%), constipation (8%-10% vs 3%-4%), SGPT increase (5% vs 1%), dyspepsia (5%-7% vs 1%-4%), lethargy (5% vs 2%), and weight gain (5% vs 1%). The most commonly observed adverse events associated with the use of SEROQUEL versus placebo in clinical trials as adjunct therapy with lithium or divalproex in bipolar mania were somnolence (34% vs 9%), dry mouth (19% vs 3%), asthenia (10% vs 4%), constipation (10% vs 5%), abdominal pain (7% vs 3%), postural hypotension (7% vs 2%), pharyngitis (6% vs 3%), and weight gain (6% vs 3%).
- In long-term clinical trials of quetiapine, hyperglycemia (fasting glucose ≥ 126 mg/dL) was observed in 10.7% of patients receiving quetiapine (mean exposure 213 days) vs 4.6% in patients receiving placebo (mean exposure 152 days)

* Data combined from two 8-week, multicenter, randomized, double-blind, placebo-controlled, monotherapy bipolar depression trials. SEROQUEL (300 mg/day; n=327) showed significant improvement from baseline in Montgomery-Asberg Depression Rating Scale total score at Week 1 continuing through Week 8 vs placebo (n=330; P values ≤ 0.0001).

† Data combined from two 12-week, multicenter, randomized, double-blind, placebo-controlled, monotherapy mania trials. SEROQUEL (n=208) showed significant improvement from baseline in Young Mania Rating Scale (YMRS) total score at Day 4 continuing through Day 84 vs placebo (n=195; P values ≤ 0.05).

‡ In pivotal mania trials, the average dose in responders (patients with $\geq 50\%$ improvement in YMRS total score) was 600 mg/day.

§ Twice daily.

References: 1. Data on file, AstraZeneca Pharmaceuticals LP, DA-SER-51. 2. Prescribing Information for SEROQUEL. 3. Calabrese JR, Keck PE, Macfadden W, et al. *Am J Psychiatry*. 2005;162:1351-1360. 4. Thase ME, Macfadden W, Weisler RH, et al, for the BOLDER II Study Group. *J Clin Psychopharmacol*. 2006;26:600-609. 5. Endicott J, Rajagopalan K, Minkwitz M, et al, for the BOLDER Study Group. *Int Clin Psychopharmacol*. 2007;22:29-37. 6. Vieta E, Mullen J, Brecher M, et al. *Curr Med Res Opin*. 2005;21:923-934. 7. Sachs G, Chengappa KNR, Suppes T, et al. *Bipolar Disord*. 2004;6:213-223. 8. Data on file, AstraZeneca Pharmaceuticals LP, DA-SER-45.

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