

# Comorbid Nighttime Agitation, Sleep Disturbance, and Restless Legs Syndrome

## What Next?

In 2016, President Obama launched the Precision Medicine Initiative with a \$215 million investment for research on treatments that take into account distinct differences in individual's genes, environments, and lifestyles (The White House Office of the Press Secretary, 2015). Most health care interventions are designed for the "usual" case or patient without considering that individual differences in patients may influence treatment needs. Nursing research has been ahead of the curve in designing and researching many interventions that are tailored to match select characteristics of each individual to aspects of the intervention. In addition to tailoring, designing interventions for subgroups who share similar characteristics or disorders is also needed to solve some vexing problems that impact older adults' health and quality of life. Unlike current "one-size-fits-all" interventions to treat agitated behavior and sleep problems of individuals with dementia, patients in pain have had their agitation and sleep problems successfully treated through better pain management (Kovach et al., 2012). There is a need to determine if other specific subgroups achieve better outcomes by treating specific disorders that may be causing the agitation and sleep disturbance. This editorial focuses on opportunities for investigating the sleep disorder restless legs syndrome (RLS) as a cause for nighttime agitation and sleep disturbance in individuals with Alzheimer's disease.

*Nighttime agitation*, also called "sundowning," is defined as the appearance or exacerbation of behavioral disturbances, such as wandering and aggression, in the afternoon and/or evening hours (Bachman & Rabins, 2006). Nighttime agitation is often associated with sleep disturbances, such as insufficient sleep, increased frequency of awakenings, more wake after sleep onset (i.e., minutes awake), and excessive daytime napping. From 2% to 66% of individuals with Alzheimer's disease have night-

time agitation, which causes patient suffering, caregiver burden, and is costly to manage (Beeri, Werner, Davidson, & Noy, 2002). Pharmacological interventions are primarily antipsychotic medications. The alarming statistics on the danger of antipsychotic agents and the prevalence of their use in nursing home and community settings has resulted in the National Plan to Address Alzheimer's Disease and The National Partnership to Improve Dementia Care prioritizing reduction in antipsychotic medication use (Alzheimer's Association National Plan Milestone Workgroup et al., 2014; Schneider, Dagerman, & Insel, 2006). Few nonpharmacological interventions for nighttime agitation have been empirically tested.

Developing tailored, effective, and sustainable treatments for nighttime agitation in individuals with Alzheimer's disease is difficult because of the limited knowledge of its etiology. Proposed etiologies, most with little to no evidence, include unmet needs due to reduced nighttime staffing, alterations in the suprachiasmatic nucleus, disorganized circadian rhythms, insufficient light, evening fatigue, diurnal mood variability, medication side effects, and the sleep disorders obstructive sleep apnea syndrome and RLS.

Patients with RLS report a nighttime urge to move associated with uncomfortable and unpleasant leg sensations, often described as painful. Discomfort from RLS is often relieved by moving or walking, perhaps manifested in individuals with Alzheimer's disease as wandering or elopement. The reported prevalence of RLS in the general population and older adults is 5% to 10% (Montplaisir, Allen, Walters, & Ferini-Strambi, 2011) and 10% to 14% (Rothdach, Trenkwalder, Haberstock, Keil, & Berger, 2000), respectively, but there is little information on prevalence in individuals with Alzheimer's disease because RLS diagnosis has been based on a clinical interview with the patient

and requires that the patient have the verbal and cognitive skills to precisely describe complex sensory symptoms. Often individuals with Alzheimer's disease cannot describe complex symptoms. Due to this problem, an objective tool, the Behavioral Indicators Test–Restless Legs, suitable for diagnosing RLS in this population (Richards et al., 2015), was recently developed and validated. This diagnostic tool provides the opportunity for urgently needed research in home and institutional settings on prevalence of RLS in individuals with Alzheimer's disease, sleep disturbance, and nighttime agitation, and strength of the relationships among these comorbid conditions.

Another research opportunity that may result in more precise interventions is the use of biomarkers and clinical data to determine the etiology of RLS in this population. RLS has two well-defined environmental risk factors: age and iron deficiency. Imaging studies consistently indicate dysfunction of dopaminergic pathways and the presence of a functional and metabolic impairment that involves a network or several connected networks in the brains of patients with RLS. A number of factors in older adults with Alzheimer's disease may activate various aspects of the RLS pathway and contribute to development of RLS. A major factor is anemia. Anemia, present in 48% to 63% of institutionalized older adults (Patel & Guralnik, 2009), is a well-established risk factor for RLS. Anemia is more common in females and older adults, and a majority of nursing home residents are female and older than 65. In addition, antidepressant and antipsychotic agents are often prescribed and they impact the RLS pathway. A systematic review identified strong evidence that escitalopram, fluoxetine, L-dopa/carbidopa and pergolide, L-thyroxine, mianserin, mirtazapine, olanzapine, and tramadol induce/exacerbate RLS (Hoque & Chesson, 2010). From a behavioral point of view, and considering the compulsive urge to move of patients with RLS, the lack of activity and prolonged bed rest common in institutionalized older adults with Alzheimer's disease may engender RLS by triggering the limbic/nociceptive pathway.

Finally, it is important to conduct clinical trials to identify effective, safe pharmacological and non-pharmacological treatments for nighttime agitation, sleep disturbance, and RLS in individuals with Alzheimer's disease. The outcomes of this line of research may be considerable for patients, caregivers, and society. Potential outcomes for patients include: (a) less discomfort, (b) fewer antipsychotic medication prescriptions, (c) less restrictive environments, (d) living at home longer, (e) fewer falls, (f) less injury from getting "lost" during nighttime wan-

dering, and (g) improved sleep, which may result in better cognitive function. Caregiver burden and costs for institutionalization may also be reduced.

In conclusion, the potential for research that focuses on subgroups with specific needs and disorders that underlie a complex problem challenges us to think in new ways about problems, the etiology of problems, and designing varied treatments for multiple causal paths. Through this type of research and thinking, a cadre of interventions can be developed that can be chosen for use based on which will work best for which individuals or subgroup. The effect sizes for research studies testing interventions to treat agitation and sleep disturbance in individuals with dementia are likely to increase through these more focused treatment efforts. Sustained effort and funding are needed to realize the potential for precision medicine to improve outcomes and decrease the use of ineffective and inappropriate treatments.

## REFERENCES

- Alzheimer's Association National Plan Milestone Workgroup, Fargo, K.N., Aisen, P., Albert, M., Au, R., Corrada, M.M.,...Carrillo, M.C. (2014). 2014 report on the milestones for the US National Plan to Address Alzheimer's Disease. *Alzheimer's & Dementia*, 10(5 Suppl.), S430-S452. doi:10.1016/j.jalz.2014.08.103
- Bachman, D., & Rabins, P. (2006). "Sundowning" and other temporally associated agitation states in dementia patients. *Annual Review of Medicine*, 57, 499-511. doi:10.1146/annurev.med.57.071604.141451
- Beeri, M.S., Werner, P., Davidson, M., & Noy, S. (2002). The cost of behavioral and psychological symptoms of dementia (BPSD) in community dwelling Alzheimer's disease patients. *International Journal of Geriatric Psychiatry*, 17, 403-408. doi:10.1002/gps.490
- Hoque, R., & Chesson, A.L., Jr. (2010). Pharmacologically induced/exacerbated restless legs syndrome, periodic limb movements of sleep, and REM behavior disorder/REM sleep without atonia: Literature review, qualitative scoring, and comparative analysis. *Journal of Clinical Sleep Medicine*, 6, 79-83.
- Kovach, C.R., Simpson, M.R., Joosse, L.L., Logan, B.R., Noonan, P.E., Reynolds, S.,...Raff, H. (2012). Comparison of the effectiveness of two protocols for treating nursing home residents with advanced dementia. *Research in Gerontological Nursing*, 5, 251-263. doi:10.3928/19404921-20120906-01
- Montplaisir, J.Y., Allen, R.P., Walters, A., & Ferini-Strambi, L. (2011). Restless legs syndrome and periodic limb movements during sleep. In M. Kryger, T. Roth, & W.C. Dement (Eds.), *Principles and practice of sleep medicine* (5th ed., pp. 1026-1037). St. Louis, MO: Elsevier Saunders.
- Patel, K.V., & Guralnik, J.M. (2009). Prognostic implications of anemia in older adults. *Haematologica*, 94(1), 1-2. doi:10.3324/haematol.2008.001289
- Richards, K.C., Bost, J.E., Rogers, V.E., Hutchison, L.C., Beck, C.K., Bliwise, D.L.,...Allen, R.P. (2015). Diagnostic accuracy of behavioral, activity, ferritin, and clinical indicators of restless legs syndrome. *Sleep*, 38, 371-380. doi:10.5665/sleep.4492
- Rothdach, A.J., Trenkwalder, C., Haberstock, J., Keil, U., & Berger, K. (2000). Prevalence and risk factors of RLS in an elderly popu-

lation: The MEMO study. Memory and morbidity in Augsburg elderly. *Neurology*, 54, 1064-1068.

Schneider, L.S., Dagerman, K., & Insel, P.S. (2006). Efficacy and adverse effects of atypical antipsychotics for dementia: Meta-analysis of randomized, placebo-controlled trials. *American Journal of Geriatric Psychiatry*, 14, 191-210.

The White House Office of the Press Secretary. (2015, January 30). *Fact sheet: President Obama's precision medicine initiative*. Retrieved from <https://www.whitehouse.gov/the-press-office/2015/01/30/fact-sheet-president-obama-s-precision-medicine-initiative>

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