

# **Chronic Insomnia in Primary Care: The Role of Insomnia as an Indicator of Mental and Medical Co-morbidities**

## **Why health care providers need a better understanding of chronic insomnia**

### **Introduction**

Insomnia is closely associated with mental disorders such as major depressive disorder (MDD) and anxiety, cardiovascular and neurological disorders, diabetes, cognitive impairment, chronic pain, and many other debilitating conditions. (Roth T, 2007) In recent years it has become clear that what we call 'sleep' is not a continuous state, but a complex continuum of processes. Research is revealing physiological links between sleep and overall health, in turn leading to correlations between specific stages of sleep and the underlying conditions that lead to specific disorders. (Banks S, Dinges DF, 2007; Basta M, et al, 2007; Datta S, MacLean RR, 2007; Roth T, et al, 2008) This is shifting how sleep specialists assess and research insomnia and its manifestation in different patient populations. Insomnia is estimated to effect up to 30% of the population, or approximately 70 million Americans (Wallander et al, 2007), 10-15% of that number on a chronic basis. The prevalence of insomnia rises in some estimates up to 57% in elderly populations (McCall, 2004), and our overall population is an aging one—the 2000 Census showed over 35 million people over age 65, a 12% increase over 1990. Incidence of obesity and diabetes (closely associated with sleep disorders) is rising across all age groups. It is vital that primary care physicians and psychiatrists have a clear understanding of the baseline role that sleep plays in maintaining physical and mental health.

### **Target CME Audience**

Primary care physicians and psychiatrists assessing patients with insomnia.

### **Methods**

The gap analysis and educational needs portion of this report were generated based on the following methods:

- Literature review
- Governmental source review
- Physician interview with Dr. M.B. Scharf, MD

### **Gap Analysis**

Chronic insomnia has been recognized as a "significant economic burden" due to its effects on productivity, costing United States employers an estimated 4.4 days of wages per untreated individual over a period of 6 months. (Rosenthal LD, et al, 2008) Medical costs associated with elderly insomnia sufferers are estimated at between \$92.5 and \$107.5 billion annually. (Reeder et al, 2007) However, these numbers may not reflect the approximately 10 million people diagnosed with depression, or the approximately 11 million diagnosed with fibromyalgia, two of the many chronic and debilitating diseases that current research show to be deeply interconnected with insomnia. Historically there has been difficulty in coming up with definitive definitions of insomnia (Dohjramji K, 2006; Roth T, 2007), not surprising given the complexity of neurological, endocrine, genetic, environmental and other

factors that affect sleeping and waking processes. (Datta S, MacLean RR, 2007) Many conditions associated with chronic insomnia, such as obesity, diabetes, Alzheimer's disease, Parkinson's, depression, fibromyalgia, cardiovascular disease, and anxiety have become major health problems in the industrialized world within the last 20-30 years, a time frame that has also shown a drop in average sleep hours for American adults from greater than to less than 7 hours nightly. (Banks S, Dinges DF, 2007; Knutson KL, et al 2007) Consistent sleep time of less than 7 hours a night seems to be a threshold for chronic sleep deprivation (ie, chronic insomnia), which in turn appears to be the common thread in how sleep is implicated in the disorders referenced. Adequate and restful sleep is as vital to physical and mental health as drinking water or eating, and has a significant statistical impact on mortality rates. (Basner M, et al, 2007; Ferrie JE, et al, 2007; Wallander MA, et al 2007)

However, patients routinely underreport insomnia and many primary care

settings do not screen for sleep patterns. Often up to 60% of general care patients with insomnia are not treated. (Basta M et al, 2007; Fogel, 2003; Univ. of Pennsylvania Sleep Gene Study, 2008) Misperceptions upon the part of both primary care physicians and patients play into these figures. First, the importance of good sleep habits to health is not fully appreciated. A simple example is driving ability. Experiments found that restricting subjects to 4 or 6 hours of sleep per night over 14 days resulted in behavioral alertness

impairments equivalent to 1, 2 and even 3 nights of total sleep deprivation. Since chronic sleep deprivation produces smaller changes in sleepiness, fatigue and cognitive ability than total sleep deprivation, subjects tended to underestimate the effects on their performance readiness. Real-world studies found decreased

driving ability and increased incidence of sleep-related crashes in drivers reporting an average of less than 7 hours of sleep per night. (Banks S, Dinges DF, 2007)

A second factor in the under-treatment of insomnia is that there is a lingering reluctance, despite pharmacological advances in recent years, to medicate chronic insomnia, based on experiences of extreme dependence with first-generation sleep medications like glutethimide or ethchlorvynol. The next generation, benzodiazepine receptor agonists such as **temazepam**, **triazolam** or **flurazepam**, was safer, but still presented problems of dependence, tolerance, and debilitating side effects. Newer drugs include **eszopiclone**, **zolpidem** and **zaleplon**, which act as benzodiazepine receptors but have a nonbenzodiazepine structure, and a lower risk of tolerance, dependence, abuse, and residual effects than the benzodiazepines.

Even more recently, **ramelteon**, an unscheduled, novel melatonin-receptor agonist, has been indicated for sleep-onset. Also unscheduled, low-dose (3mg and 6 mg) **doxepin HCl**, a histamine antagonist long used in treating depression, has been the subject of studies, including recent Phase III clinical trials, indicating that doxepin may provide long-term, low-risk efficacy. Options in insomnia medication therefore now include drugs with no seeming risk of dependence, a huge change from even a few years ago that has yet to be fully accepted by the medical community. (Ancoli-Israel et al 2008; Kavey N, et al, 1997; Lankford et al 2008; Lieberman JA, 2006; Medical News Today #41444, April 12, 2006; Roth T, 2007; Roth et al, 2008; ) Almost equally important in managing pharmacological treatment is how dosing strategy has evolved in response to greater understanding of the

MALINCKRODT RESTORIL/ Temazepam Benzodiazepine
PFIZER HALCION/Triazolam Benzodiazepine
VALEANT DALMANE/ Flurazepam hydrochloride Benzodiazepine
SEPRACOR LUNESTA/ Eszopiclone Nonbenzodiazepine sedative-hypnotic
SANOPI/AVENTIS AMBIEN CPR/Zolpidem tartrate Nonbenzodiazepine sedative-hypnotic

KING SONATA/Zaleplon Nonbenzodiazepine sedative-hypnotic
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TAKEDA ROZEREM/ Ramelteon Melatonin-receptor agonist
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SOMAXEN SILENOR/Doxepin HCl Tricyclic antidepressant
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etiology of insomnia. (Hajak G et al, 2002; Roth T et al, 2007; Walsh JK et al, 2007) Thus, the conception of insomnia as a problem primarily of sleep onset and maintenance is shifting to a consideration of how intermittent and lower-dosage intervention might be used to address specific sleep-state disorders.

To sum up: general medical and public opinion regarding insomnia treatment has not caught up with current reality. Because the real cost of insomnia (medically and socially) is not understood, and because medication for insomnia continues to be perceived as high-risk, patients don't tell, doctors don't ask, and insurers will often not cover long-term use of medications prescribed for chronic insomnia.

### ***Educational Needs***

Sleep affects every organ in the body, from the skin to the brain to the heart. Sleep is affected by our habits and our environment, including smoking and alcohol use, exercise, length of commute and working hours, television and computers, traffic noise and street lights shining in the bedroom window. It is only through maintaining sleep over an extended period (7 or more hours) that the variously restorative and regenerative processes that make up "sleep" occur and work together to ensure and reinforce their benefits. Primary care physicians and psychiatrists need to be sure to assess patients' sleep patterns. A number of clinical tools are available, including (although not limited to) the Insomnia Severity Index (ISS), Medical Outcomes Study (MOS) Sleep Scale, Pittsburgh Sleep Diary (PSD), Pittsburgh Sleep Quality Index (PSQI), the Clinical Global Impressions (CGI) Scale, the Minnesota Multiphasic Personality Inventory (MMPI), Multiple Sleep Latency Test (MSLT), polysomnography, patient-generated sleep diaries, genetic studies, EEG readings. (Busner J, Targum SD, 2007; Fogel 2003; Morin et al, 2007)

There is a need to educate primary care physicians, psychiatrists, and patients about the direct correlation between adequate sleep and quality of life.

Knowledge about sleep stages and their functions is far from complete. However, there has been important recent research. For the purposes of this needs assessment, aspects of the growing understanding about the benefits of slow-wave sleep (SWS) will be examined.

A subset of non-rapid eye movement (NREM) sleep, SWS is identified by the presence of low-frequency, high-amplitude oscillations in the EEG that reflect the field potentials associated with synchronized burst-phase firing patterns in cortical neurons. SWS is reduced due to a variety of circumstances including normal aging, anxiety, habitual chronic sleep deprivation—for example among American teenagers whose natural circadian clocks are in direct conflict with most school schedules—and gender (men of all ages have less SWS than women). (Dijk DJ, 2008)

Onset of SWS coincides with hormonal changes that affect glucose regulation. Suppression of SWS, without any change in total sleep time, may contribute to increase in the risk of type 2 diabetes. Although the rise in type 2 diabetes is generally attributed to the rise in obesity and the overall aging of the U.S. population, in fact, failure to sleep well for 2-3 nights has the same negative effect on the body's ability to manage insulin as gaining 20-30 pounds. Failure to sleep is also implicated in weight gain, both because of changes in appetite due to daytime

fatigue and because of changes in hormone secretions governing appetite. Studies have linked childhood sleep deprivation to subsequent childhood obesity. (Knutson, KL, et al, 2007; Sinton CM, et al, 1999; Tasali E, et al, 2008) Since growth hormone secretion is also linked to SWS, lack of SWS in children affects bone and muscle development, and athletic ability and activity (also related to obesity). 80% of daily growth hormone in adults goes to insuring physical maintenance such as bone density and disturbance in growth hormone secretion may be linked to rheumatoid arthritis and osteoporosis. (Blackman MR, et al, 2007)

Declarative memory consolidation is associated with SWS. Acetylcholine (ACh), a neurotransmitter known to be related to Alzheimer's disease, is involved in regulation of sleep cycles through cholinergic activation of the central nervous system. High cholinergic activity during time awake means new memories can be gathered, and low cholinergic activity during SWS allows the spontaneous replay of new information within the hippocampus. This replay is believed to lead to information transfer from the hippocampus to permanent neocortical storage and thus to memory consolidation. (Gais S, Born J, 2004)

Non-Restorative Sleep (NRS) is characterized by sleep that, no matter how long it lasts, is not restful. Based on polysomnographic evidence, NRS seems to involve alpha wave intrusion into SWS. If present, NRS is chronic, occurring every night. NRS does not seem to be specific for any one disorder, however 70-80% of fibromyalgia patients suffer from NRS. Recent research into reducing the pain associated with fibromyalgia show a correlation between inhibiting alpha wave intrusion, more restful sleep, and less pain. (Arnold LM, 2006)

There is a need to educate primary care physicians and physicians about the underlying role of sleep in chronic disorders.

Hyperarousal throughout the entire 24 hour cycle is one possible definition of insomnia. (Bastien CH et al, 2008) Chronic insomnia in children indicates risk of adult onset anxiety disorders; insomnia is one of the signs of both depression and anxiety. Like insomnia, depression often goes undiagnosed in primary care settings, so screening for insomnia may also increase the likelihood of detecting depression. (Ani C et al, 2008; Neckelmann D, et al, 2006) Depression and anxiety are associated with increased stress response, which involves the central nervous system, which is responsive to adequate SWS, leading (as outlined above) to increased incidence of, among other conditions, cognitive disorders, diabetes, stroke, and heart disease, as well as increased pain response. (Academic Highlights 2008)

There is an opportunity for primary care physicians and psychiatrists to use insomnia as a diagnostic tool in assessing both the physical and psychological contributors to disease

Sleep architecture changes with age, promoting fragmented as opposed to consolidated sleep. Elderly people tend to wake frequently at night, or very early in the morning. As many then nap the next day they generally are getting adequate hours of sleep within a 24-hour period. But fragmented sleep does not engender the biological and mental processes required for alertness and wellbeing, as the links between sleep deprivation and common age-associated disorders such as the loss of memory and onset of diabetes described above, or the sleep-loss secondary to being a caregiver to persons with dementia (such caregivers are an estimated population

of over 10 million adults). (McCurry SM et al, 2007) Cognition in patients with both Alzheimer's disease and sleep apnea has been improved when continuous positive airway pressure improved total sleep time. (Frincu-Mallos C, 2008) Patients with Parkinson's disease and REM sleep behavior disorder have a higher likelihood of cognitive deficits than patients with Parkinson's disease alone. (Vendette M, et al, 2007) Sleep complaints, when linked to both age-related declines in physiology and age-related increases in disease, can be described as a "geriatric syndrome" that includes loss of health, physical function, and social status. (Avidan AY, 2005; Vaz Fragoso CA, Gill TM, 2007)

Depression and anxiety drugs, along with sedative-hypnotics, are the three medications most often prescribed for ambulatory geriatric patients. In addition, many elderly people self-medicate for insomnia with alcohol or over-the-counter antihistamines. Medication can contribute to the loss of physical and cognitive function in the elderly, especially if it causes confusion, somnolence, or dizziness, all common side effects of benzodiazepines. (Wolkove N, et al, 2007) Use of benzodiazepines has been correlated with an increased risk of falling. Excessive dosing, rather than drug half-life, seems to be an underlying factor in the higher serum concentrations found in patients who fall. Falling contributes to frailty and increased likelihood of being institutionalized in the elderly, with concomitant social and actual costs. (McCall WV, 2003) Recent pharmacological research provides options that may avoid the more severe dependence and side effect risks in an elderly population. (Lieberman JA, 2006; Walsh JK, et al, 2006; Roth T, 2007) This in turn may provide longer-term cost-relief to both patients, their families, and insurers. (Botteman MF et al, 2007; Balkrishnan R et al, 2007)

There is a need to educate primary care physicians and psychiatrists about the special treatment needs and options associated with the elderly.

There is a need to educate insurers about the relative cost-benefits of coverage for long-term treatment.

### **Educational Objectives**

The following educational objectives for a "Chronic Insomnia in Primary Care" program were developed to address the educational needs identified in this report.

Upon completion of the suggested educational activity, participants should be able to:

- Understand the potential clinical significance of primary or co-morbid insomnia and incorporate appropriate questions and self-assessment tools into their clinical practice
- Be aware of the current range of insomnia treatment options
- Incorporate knowledge of the importance of factors such as age and gender into assessment and treatment of chronic insomnia
- Be ready to refer patients to specialists to insure proper treatment of medical and mental co-morbidities
- Be proactive in educating insurers and in requesting long-term coverage for sleep medications shown to have no tolerance or withdrawal effects

## References

- Academic Highlights: treating depression and anxiety in primary care. *Prim Care Companion J Clin Psychiatry* 2008;10(2):145-152.
- Ancoli-Israel S, Krystal A, Durrence H et al. Consistency of symptom improvement in elderly adults with chronic insomnia treated with doxepin 1, 3 and 6 mg. *SLEEP* 2008; 31:A257 Abstract
- Ani C, Bazargan M, Hindman D, Bell D, et al. Depression symptomatology and diagnosis: discordance between patients and physicians in primary care settings. *BMC Fam Pract* 2008; 9:1 Abstract.
- Arnold LM. New therapies in fibromyalgia. *Arthritis Research & Therapy* 2006; 8:212
- Avidan AY. Insomnia and Sleep Health Expert Column: Epidemiology, assessment, and treatment of insomnia in the elderly patient. *Medscape Neurology & Neurosurgery* 2005;7(2)
- Balkrishnan R, Joish VN, Bhosle MJ, et al. Prior authorization of newer insomnia medications in managed care: is it cost saving? *J Clin Sleep Med* 2007;3(4):393-398.
- Basner M, Fomberstein KM, Razai FM, et al. American time use survey: sleep time and its relationship to waking activities. *SLEEP* 2007 Sept; 30(9):1085-1095. Abstract
- Banks S, Dinges DF. Behavioral and physiological consequences of sleep restriction. *J Clin Sleep Med* 2007;3(5):519-528.
- Basta M, Chrousos GP, Vela-Bueno A, Vgontzas AN. Chronic insomnia and stress system. *Sleep Med Clin* 2007 June;2(2):279-291.
- Bastien CH; St-Jean G; Morin CM; Turcotte I; Carrier J. Chronic psychophysiological insomnia: hyperarousal and/or inhibition deficits? An ERPs investigation. *SLEEP* 2008;31(6):887-898 Abstract.
- Blackman MR, Muniyappa R, Wilson M, et al. Diurnal secretion of growth hormone, cortisol, and dehydroepiandrosterone in pre- and perimenopausal women with active rheumatoid arthritis: a pilot case-control study *Arthritis Res Ther* 2007;9(4):R73. Abstract
- Botteman MF, Ozminkowski RJ, Wang S, et al. Cost effectiveness of long-term treatment with eszopiclone for primary insomnia in adults: a decision analytical model. *CNS Drugs* 2007;21(4):319-334. Abstract.
- Busner J, Targum SD. The Clinical Global Impressions Scale: applying a research tool in clinical practice. Accessed online at [www.psychiatrymmc.com/the-clinical-global-impressions-scale-applying-a-research-tool-in-clinical-practice/](http://www.psychiatrymmc.com/the-clinical-global-impressions-scale-applying-a-research-tool-in-clinical-practice/) July 30, 2008.
- Datta S, MacLean RR. Neurobiological mechanisms for the regulation of mammalian sleep-wake behavior: reinterpretation of historical evidence and inclusion of contemporary cellular and molecular evidence. *Neurosci Biobehav Rev* 2007;31(5):775-824. Abstract
- Dijk DJ. Slow-wave sleep, diabetes, and the sympathetic nervous system. *PNAS* 2008; 105(4):1107-1108.
- Doghramji K. The epidemiology and diagnosis of insomnia. *Am J Manag Care* 2006;12:S214-S220.
- Erman M, Seiden D, Zammit G, Saiati S, Zhang J. An efficacy, safety, and dose response study of ramelteon in patients with chronic primary insomnia. *Sleep Med* 2006;7:17-24.
- Ferrie JE, Shipley MJ, Cappuccio FP, et al. A prospective study of change in sleep duration: associations with mortality in the Whitehall II cohort. *SLEEP* 2007 December;30(12):1659-1666. Abstract.
- Fogel J. Behavioral treatments for insomnia in primary care settings. Accessed August 4, 2008 at [www.medscape.com/viewarticle/462938](http://www.medscape.com/viewarticle/462938).
- Frincu-Mallos, C. CPAP improves cognition in patients with AD and OSA by increasing total sleep time. Accessed August 4, 2008 at [www.medscape.com/viewarticle/576149](http://www.medscape.com/viewarticle/576149).
- Gais S, Born J. Declarative memory consolidation: mechanisms acting during human sleep. *Learning & Memory* 2004;11:679-685.

Hajak G, Bandelow B, Zulley J, Pittrow D. "As needed" pharmacotherapy combined with stimulus control treatment in chronic insomnia—assessment of a novel intervention strategy in a primary care setting. *Ann Clin Psychiatry* 2002 Mar;14(1):1-7. Abstract.

Hervas A, Garcia de Jaon E. Cognitive state as a conditioner of frailty in the elderly. Perspective from a health centre. *An Sist Sanit Navar* 2005 Jan-Mar;28(1):35-47. Abstract (trans. From Spanish)

Kavey N, Quattrucci B, Kavey M, Beckmann D. Low dose doxepin in the treatment of chronic insomnia. *Sleep Research* 1997; 26:387 Abstract

Krystal A, Lankford A, Durrence H et al. Efficacy of doxepin 3 and 6 mg on early morning awakenings in adults with primary insomnia. *SLEEP* 2008; 31:A257 Abstract

Knutson KL, Spiegel K, Penev P, and Cauter E. The metabolic consequences of sleep deprivation. *Sleep Med Rev* 2007 June; 11(3):163-178.

Lankford A, Krystal A, Durrence H, et al. Doxepin 3 and 6 mg in a 53-day trial of adults with primary insomnia: effects following discontinuation. *SLEEP* 2008; 31:A256 Abstract

Lankford A, Segal S, Borders J et al. Efficacy and safety of doxepin 6mg in a 4-week outpatient trial of elderly adults with primary insomnia. *SLEEP* 2008; 31:A256 Abstract

Lieberman JA. Update on the safety considerations in the management of insomnia with hypnotics: incorporating the modified-release formulations into primary care. *Prim Care Companion J Clin Psychiatry* 2007;9(1):25-31. Abstract.

McCall WV. Sleep in the elderly: burden, diagnosis, and treatment. *Prim Care Companion J Clin Psychiatry* 2004;6:9-20.

McCurry SM, Logsdon RG, Teri L, Vitiello MV. Sleep disturbances in caregivers of persons with dementia: contributing factors and treatment implications. *Sleep Med Rev* 2007 April; 11(2):142-153. Abstract.

Morin CM, Vallieres A, Ivers H. Dysfunctional beliefs and attitudes about sleep (DBAS): validation of a brief version (DBAS-16). *SLEEP* 2007;30(11):1547-1554.

Neckelmann D, Mykletun A, Dahl AA. Chronic insomnia as a risk factor for developing anxiety and depression. *SLEEP* 2007;30(7):873-880.

Overland S, Glozier N, Sivertsen B, et al. A comparison of insomnia and depression as predictors of disability pension: the HUNT Study. *SLEEP* 2008; 31(6):875-880. Abstract.

Pollack M, Kinrys G, Krystal A, et al. Eszopiclone coadministered with escitalopram in patients with insomnia and comorbid generalized anxiety disorder. *Arch Gen Psych* 2008; 65(5):551-562 Abstract.

Reeder CE, Franklin M, Bramley TJ. Current landscape of insomnia in managed care. *Am J Manag Care* 2007; 13(5 Supp):S112-6 Abstract.

Rosenthal LD, Dolan DC, Taylor DJ, Briesef E. Long-term follow-up of patients with insomnia. *Proc (Bayl Univ Med Cent)* 2008 July; 21(3):264-265.

Roth T. Insomnia: definition, prevalence, etiology, and consequences. *J Clin Sleep Med* 2007;3(5 Supp);S7-S10.

Roth T. Sleep therapy: new generation pharmacologic agents for managing insomnia. *J Clin Sleep Med* 2007; 3(5 Supp);S5-S6.

Roth T, Durrence H, Gotfried M et al. Efficacy and safety of doxepin 1 and 3 mg in a 3-month trial of elderly adults with chronic primary insomnia. *SLEEP* 2008; 31:A230 Abstract

Roth T, Jaeger S, Jin R, Kalsekar A, Stang PE, Kessler RC. Sleep problems, comorbid mental disorders, and role functioning the National Comorbidity Survey Replication (NCS-R). *Biol Psychiatry*. 2006; 60(12):1364-1371.

Roth T, Zammit GK, Shcarf MB, Farber R. Efficacy and safety of as-needed, post bedtime dosing with indiplon in insomnia patients with chronic difficulty maintaining sleep. *SLEEP* 2007 December;30(12):1731-1738 Abstract

Sinton CM, Fitch TE, Gershenfeld HK. The effects of leptin on REM sleep and slow wave delta in rats are reversed by food deprivation. *J Sleep Res* 1999;8:197-203.

Tasali E, Leproult R, Ehrmann DA, Van Cauter E. Slow-wave sleep and the risk of type 2 diabetes in humans. *Proc Natl Acad Sci USA* 2008 January 22;105(3):1044-1049. Abstract.

Vaz Fragoso CA, Gill TM. Sleep complaints in community-living older persons: a multifactorial geriatric syndrome. *J Am Geriatr Soc* 2007 Nov; 55(11):1882-1883. Abstract.

Wallender MA; Johansson S; Ruigomez A; Rodriguez LAG; Jones R. Morbidity associated with sleep disorders in primary care: a longitudinal cohort study. *Prim Care Companion J Clin Psych* 2007;9(5):338-345.

Walsh JK; Krystal AD; Amato DA; Rubens R; Caron J; Wessel TC; Schaefer K; Roach J; Wallenstein G; Roth T. Nightly treatment of primary insomnia with eszopiclone for six months: Effect on sleep, quality of life, and work limitations. *SLEEP* 2007;30(8):959-968.

Wolkove N, Elkholy O, Baltzan M, Palyew M. Sleep and aging: 2. Management of sleep disorders in older people. *CMAJ* 2007 May 8;176(10):1449-1454. Abstract.

Univ. of Pennsylvania School of Medicine news release. Searching for Shut eye: Penn study identifies possible sleep gene. Accessed July 30, 2008 at [www.uphs.upenn.edu/news/News\\_Releases/2008/07/sleepless-fly-gene-print.html](http://www.uphs.upenn.edu/news/News_Releases/2008/07/sleepless-fly-gene-print.html).

Vendette M, Gagnon J-F, Massicotte-Marquez J. REM sleep behavior disorder predicts cognitive impairment in Parkinson disease without dementia. *Neurology* 2007;69:1843-1849 Abstract

Zemlan FP; Mulchahey JJ; Scharf MB; Mayleben DW; Rosenberg R; Lankford A. The efficacy and safety of the melatonin agonist beta-mehtyl-6-chloromelatonin in primary insomnia: a randomized, placebo-controlled, crossover clinical trial. *J Clin Psychiatry* 2005; 66:384-390.