18
Sleep and Quality of Life in Alzheimer's Disease and the Dementias

Doug Neef and David Larson

Summary Sleep changes are inherent to dementia but difficult to define or measure. As the sleep changes in dementia are probably related to neuronal changes in the brain, the location and severity of these changes, manifested as different clinical dementias, affects the presentation of sleep pathology. In the case of most dementias, including Alzheimer's dementia, the sleep problems affect both the patient and the caregiver. Treatment involves a multifaceted approach, including identification of treatable medical problems, correction of sleep hygiene, and identification and treatment of the particular form of dementia. Cholinesterase inhibitors seem to be emerging as the drug of choice for sleep problems in dementia.

Keywords Dementia · Alzheimer's disease · dementia with Lewy bodies · cholinesterase inhibitors · suprachiasmatic nucleus (SCN) · normal aging

Learning objectives:

- Sleep changes are frequently seen in dementia but are difficult to define and measure in this population.
- Sleep changes in dementia are probably related to specific neuronal changes in the brain. The location and severity of these changes, manifested as different clinical dementias, affect the presentation of sleep pathology.
- Treatment of sleep disturbance in dementia involves a multifaceted approach—identifying treatable medical problems and correction of sleep hygiene, as well as the identification and treatment of the specific form of dementia.

Introduction

Sleep problems are sometimes hard to define even in healthy patients, but when you add dementia and aging, these problems become even harder to define and harder to measure. For example,

1. How does one define a sleep problem in a demented patient?
2. How does the clinician measure a sleep problem in a demented patient?
3. Does the sleep problem bother the patient or the caregiver?
4. Is it a sleep problem if it bothers the caregiver but not the patient?
5. Who does the reporting, the patient or the caregiver?
6. Are caregiver reports adequate substitutes for patient reports in patients with dementia?
7. Can dementia patients accurately report a sleep problem?
8. What type of dementia is it?
9. How severe is the dementia?
10. What role do other factors (besides the dementia) play in the sleep problem?

Numerous other questions could be asked, and all would illustrate the problems associated with current research involved with sleep in dementia. Investigational studies must not only define the type of dementia, but also quantify it, as different dementias in different stages affect sleep differently. Similarly, methods must be developed to both identify and quantify sleep problems in the different forms of dementia. A useful first step is identifying the several causes of sleep disruption in the elderly and the demented which include: (i) physiological changes associated with "normal" aging; (ii) sleep problems associated with physical or mental health problems ("disease") and their treatment; (iii) primary sleep disorders; (iv) poor "sleep hygiene," that is, poor sleep-related practices and habits; and (v) some combination of the above (1). Sleep changes in dementia are likely related to the degenerative

From: J. C. Verster et al. (eds.): *Sleep and Quality of Life in Clinical Medicine*
© 2008 Humana Press, Totowa, NJ

neuronal changes in the brain associated with the different clinical dementia syndromes. The location and severity of those changes, manifested as different clinical dementias, affects the presentation of both the disease and the sleep pathology. Treatment involves a multifaceted approach: identifying treatable medical problems, correcting sleep hygiene, as well as treating the particular form of dementia. In this chapter, we will concentrate on the sleep changes associated with Alzheimer's disease (AD) but also briefly look at sleep problems in other types of dementia such as dementia with Lewy bodies (DLB) and frontotemporal dementia (FTD), realizing that recognition of the sleep problem could even provide a helpful key in the differential diagnosis of dementia.

Sleep disturbances associated with early or mild dementia seem to be an exacerbation of the changes in "normal" aging. On EEG, aged normal subjects had less stage 3 and stage 4 sleep, less rapid eye movement (REM) sleep, and more wakefulness than normally found in young adults. Patients with AD had even less stage 3 sleep, no stage 4 sleep, very little REM sleep, and experienced fragmentation of their sleep, with frequent awakenings (2). This decrease in slow wave sleep (SWS) and REM sleep is manifested as the duration and frequency of awakenings and more daytime napping increases (1, 2), and although the sleep disturbance seems to worsen with increasing severity of the AD (a linear relationship), there is a possible inverted U-shaped profile in which patients with moderate dementia have more sleep impairment than persons in the early or advanced stages of disease (3). This highlights again the difficulty characterizing sleep problems in dementia, as problems can vary with both the type and severity of dementia.

The clinical changes in sleep associated with dementia are likely related to damage to the neuronal pathways that initiate and maintain sleep, starting with the SCN of the hypothalamus. As outlined by Vitiello and Borson, the SCN is believed to be the "internal" clock that generates circadian rhythms. It does this independently of environmental cues but uses light and physical activity, and perhaps social interaction and food, to synchronize these internal rhythms with our 24-h day (1). The SCN has input pathways that link it to the retina, limbic forebrain, other hypothalamic nuclei, the raphe nuclei, and reticular formation, and it also responds to various hormones. The output pathways through which the SCN controls circadian rhythms are not as well understood but seem to project to other areas of the brain controlling sleep, wakefulness, and arousal. The SCN also regulates the production of the "sleep hormone" melatonin, through connections to the sympathetic superior cervical ganglion and, in turn, to the pineal gland (1, 4). There are also subcortical pathways that regulate arousal and sleep–wake cycles, including cholinergic pathways (basal forebrain nuclei), serotonergic pathways (raphe nuclei), dopaminergic pathways (nigrostriatal and pallidostriatal), and noradrenergic pathways (locus coeruleus). Part of the pathophysiology of dementia is felt to be due to neurodegeneration of these different pathways, both at a pathologic and biochemical level, with different lesions manifesting as different forms of dementia. Thus, different aspects of sleep and wakefulness can be affected depending on the type and severity of dementia and the neurons and biochemical transmitters involved. However, there is also overlap between the structures and neurotransmitters affected. Ultimately, dementia pathology affects not only the cognitive functions of the cortex but also deeper portions of the brain that control such functions as memory and arousal. It is the damage to these deeper neuronal pathways that initiate and maintain sleep that is the probable cause of the acceleration of the normal age-related sleep changes found in dementia (1).

Thus, how and when sleep problems manifest themselves can depend on the type of dementia involved as well as the stage of the dementia although these differences in sleep pattern presentation show more variation during the initial stages of dementias than they do during the later stages of those same diseases. A helpful categorization of dementias is outlined by Boeve and Saper (5), who have divided the dementias into three groups based on the protein lesion involved. AD is primarily an amyloidopathy, with pathological changes caused by deposition of the β-amyloid protein. Pick disease, corticobasal degeneration, and progressive supranuclear palsy (PSP) are tauopathies, with changes to the tau protein. Finally, in Parkinson's disease (PD), PD with dementia (PDD), DLB, and multiple system atrophy (MSA), lesions are composed of intracellular α-synuclein and are thus termed synucleinopathies. Although there is often a mixture of more than one pathology (i.e., mixed dementia) and there can be an overlap of symptoms, especially later in the disease process, this distinction seems helpful in understanding the dementias in regards to their typical presentation. Although sleep problems differ somewhat with the different dementias, they tend to be similar within a pathologic class. Therefore, it is important to clarify both the type and degree of dementia as both can affect the sleep presentation. Research into the area of sleep and dementia is complex because it requires differentiation of the different dementia types as well as assessment of different sleep symptoms. Although most studies have been performed on AD patients, studies on patients with other dementias are starting to appear.

Sleep Disturbance in Alzheimer's Disease

Sleep disturbances in patients with dementia have been described for several decades in the medical literature (6, 7). The reported incidence of sleep disturbance in AD has been reported to range from 27 to 40% depending on the level of cognitive disturbance in the population being studied (8, 9). Sleep disturbance in patients with AD is often multifactorial in etiology. Individuals with AD may have disordered sleep due to co-morbid conditions such as obstructive sleep apnea, arthritis, heart failure, GERD, and nocturia. Additional factors including medication side effects, depression, anxiety, and

delirium can all contribute to sleep problems in AD (1). Those who care for individuals with AD may also suffer from disordered sleep. This may have a detrimental effect on quality of life measures for these individuals as well.

Description of Sleep Disturbance in AD

There is growing evidence that the neuropathologies of AD disrupt the circadian clock's output and result in sleep disturbance for many individuals affected by this disease. A recent study examining brain tissue from individuals with AD noted differential expression of the genes involved with rhythmic production of melatonin in the pineal glands of individuals with only histologic evidence of AD as well as those with clinical evidence of AD. It is believed that these changes are caused by uncoupling of the pineal gland from SCN control. Individuals with a more advanced stage of AD had more pronounced changes (4). These changes at the molecular level appear to manifest as characteristic alterations in the sleep behavior of affected patients. Individuals with AD are more likely than the non-demented elderly (NDE) to report sleep problems (8). When compared to the NDE, individuals with AD are noted to spend an increased amount of time in bed taking naps during the day, spend more overall time in bed at night, and have more fragmented nighttime sleep (10, 11). Sundowning or nocturnal delirium is another entity frequently referred to within this population in association with sleep disturbances. Although this concept has no consensus definition in the literature, it has been conventionally used to describe behavioral changes that occur in patients with dementia around the daily onset of darkness or that follow a diurnal pattern (12).

In 2003, a group of experts in the study of sleep changes and dementia proposed a set of criteria for diagnosing disturbances in the sleep–wake cycles of AD patients. A brief summary of their proposed criteria follows. First, a complaint regarding insomnia or increased daytime sleepiness is expressed by the patient or is observed by the caregiver. Second, polysomnography, actigraphy, or sleep log observations demonstrate two of the following four:

1. Episodes of wakefulness after sleep onset long enough or frequent enough to affect the daily functioning or well-being of either the patient or caregiver.
2. A decrease in total sleep time that is equal to one-fourth of the patient's total premorbid nighttime sleep or a pattern of sleeping less than 6 h between 9:00 p.m. and 6:00 a.m. if the premorbid sleep pattern is unknown.
3. Poor daytime wakefulness as evidenced by daytime napping increased in duration and/or frequency compared to the individual's premorbid state.
4. Disrupted sleep–wake rhythm evidenced by an altered ratio of day–night sleep.

The above changes are noted in association with a diagnosis of probable AD, are not present prior to the beginning of the dementia and evolve over the course of the disease. Finally, the sleep disturbance is not fully accounted for by comorbid general medical conditions, other sleep disorders, or parasomnias. These guidelines were put forth in an effort to facilitate the study of sleep disorders in the population affected by AD (13).

Implications of Sleep Disturbance for Patient and Family Members

Sleep disorders can diminish the patient's quality of life and become a specific challenge to caregivers. AD patients who engaged in nighttime behaviors such as eating, drinking, wandering, and waking up to talk were more likely to be institutionalized at 1 year when compared to AD patients who had no reported sleep disturbance at baseline. Sleep problems have been noted to correlate with increased aggression that is often a proximal cause for institutionalization in this patient population (9, 14). Caregivers report that being awakened at night is the sleep-related symptom they find most disturbing (15). Among individuals with AD, increased time spent in bed is associated with worsened mini-mental status exam (MMSE) scores. Disordered sleep appears to be a marker for more rapid progression of cognitive and functional deficits in individuals with AD. As the neuronal "hardware" responsible for cognition and daily function is damaged by the progression of AD, sleep seems to decay in parallel (8, 16–18).

Family caregivers of the disabled elderly have been noted to have an increased risk for psychiatric morbidity due to the strain associated with caregiving. In addition, caregivers experiencing emotional or mental strain in conjunction with their caregiving role have been reported to have an increased risk of mortality when compared with non-caregiving controls (19). Poor sleep among caregivers of AD patients is associated with increased serum levels of interleukin-6 and fibrin D-dimer, which have proinflammatory and procoagulant effects. It seems plausible that disturbed caregiver sleep may place the caregiver at an increased risk for cardiovascular morbidity (20).

Treatment Strategies

There are several approaches to the treatment of the sleep disturbances characteristic of AD. These strategies consist of therapy for any comorbid conditions that may be exacerbating sleep problems, non-pharmacologic therapy targeted at sleep pathology, and pharmacologic interventions. As an example of the importance of treating comorbid conditions that compromise sleep, recently published papers have demonstrated that treating obstructive sleep apnea (OSA) with continuous positive airway pressure (CPAP) is both feasible and beneficial for patients with dementia. The presence of dementia should not discourage clinicians from treating AD patients who suffer from OSA with CPAP (21, 22). Despite

these promising findings, there is a paucity of patient-oriented evidence regarding the value of many therapies currently used for sleep problems in the population affected by AD (1).

Non-Pharmacologic Strategies

Experts in the field of sleep disturbance and dementia have recommended multifaceted behavioral strategies for improving sleep in patients with dementia. Many of these strategies involve improvement of the sleep–wake cycle through modulators of the circadian rhythm (23). The so-called sleep hygiene practices to improve sleep include establishing consistent daily times for going to bed and arising from bed, establishing a bedtime routine, and limiting napping to a brief time in the morning or early afternoon. It may also be helpful to add daytime activities such as exercise or group interaction to the patient's routine in lieu of daytime naps. Efforts should be made to optimize the patient's exposure to natural outdoor light as well as bright light in the daytime living quarters. The use of alcohol and caffeine should be minimized. A light bedtime snack may decrease nocturnal awakenings related to hunger. Finally, the individual's sleeping area should be as quiet and dark as possible (24, 25).

Light therapy has also attracted interest as a potential treatment for sleep disturbance. The goal of light therapy is to expose the patient to increased amounts of natural or artificial light. This added light exposure may provide input to the SCN that will facilitate entrainment of the individual's circadian clock to the 24-h day. This may be especially important in institutionalized patients who receive suboptimal light exposure from their environment. Studies examining the efficacy of light therapy have had mixed results. An intervention that included caregiver education about sleep hygiene, daily walking, and light exposure from an artificial light source appeared to provide a benefit in terms of decreased number of nighttime awakenings, decreased total time awake at night, and decreased daytime sleepiness (26, 27). It seems that behavioral interventions pose a minimal risk of adverse side effects to patients and should be considered the first line of therapy for sleep disturbance in AD.

Pharmacologic Interventions

Data describing the safety and efficacy of medications for sleep problems in the population affected by dementia are scarce. Recent, small trials have examined the effects of cholinesterase inhibitors on sleep in patients with AD. These studies used actigraphy and polysomnography to measure patient response to treatment. In both studies, there appeared to be significant trends toward improvement in sleep-related parameters as measured by EEG and actigraphy (28, 29). It remains to be seen whether or not treatment with this class of medications will have a benefit for these patients as demonstrated by improvements in meaningful quality of life measures.

Typical and atypical neuroleptic agents are often prescribed for individuals with dementia to treat symptoms such as aggression, agitation and psychosis. The neuroleptics appear to be useful for the short-term treatment of these symptoms. Although it makes intuitive sense that the treatment of psychiatric symptoms would improve sleep, the usefulness of this class of medication for sleep in dementia is not known (1). The adverse effects of neuroleptics in the population of patients with AD have been well described. These adverse effects include extrapyramidal symptoms, drowsiness, and possibly excess mortality. Antipsychotic agents should be used judiciously, if at all, in this population (30–32).

Benzodiazepines and the non-benzodiazepine hypnotics such as zolpidem and zaleplon are frequently prescribed as short-term sleep aids in the general population. They have not been well-studied in individuals with dementia, and it is difficult to comment on their safety or efficacy in this population. Sleep aids with anticholinergic activity such as the tricyclic antidepressants and the sedating antihistamines may exacerbate the cholinergic abnormalities inherent to AD and should be avoided (1).

In light of the disturbance in melatonin production that has been described with AD, there has been considerable interest in melatonin and melatonin receptor agonists as a treatment for disordered sleep in AD. Studies of melatonin replacement have had mixed results (33, 34). Ramelteon, a melatonin receptor agonist, has recently been brought to market. Although this represents a promising possibility for the treatment of disturbed sleep in AD (35), further research is needed to determine the role this class of drugs will play in the treatment of sleep disturbances related to AD.

Other Dementias

Dementia with Lewy Bodies

Sleep disturbances in DLB, one of the synucleinopathies, are being increasingly studied and differ somewhat from AD. Core features of DLB include fluctuating cognition (delirium), recurrent visual hallucinations, and Parkinsonism. Suggestive features include REM sleep behavior disorder, severe neuroleptic sensitivity, and low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET imaging (36). When compared with AD, sleep profiles in DLB are also different. Both groups suffer from sleep problems, but DLB patients seem to suffer from more overall sleep disturbance. DLB patients have a greater tendency to fall asleep at inappropriate times during the day and to also have more nighttime sleep disturbance (37). They are more likely to suffer from periodic limb movements, confusion on awakening, and bad dreams (38). A recent study suggested four differentiating characteristics between patients with DLB and AD: (i) daytime drowsiness and lethargy, (ii) daytime sleep of 2 or more hours, (iii) staring into space for long periods, and (iv) episodes of disorganized speech. Three or four of

these features were seen in 63% of DLB patients as compared with 12% of patients with AD (39). Patients with DLB also may respond to rivastigmine better than those with AD (38). Finally, patients with DLB can have a severe sensitivity to neuroleptics, and these medications should be strictly avoided in patients with DLB (36, 40). These findings illustrate the importance of distinguishing between the various dementias and how sleep patterns can aid in that distinction.

Frontotemporal Dementias

Research into the tauopathies, as represented by FTD (or Pick's disease), suggests that they differ from both AD and DLB. FTD and AD patients have been found to show different circadian abnormalities. The expression of an entrained circadian rhythm as an organized pattern of rest-activity is compromised in FTD, while a normal core-body temperature rhythm is maintained (41). Thus, in AD, both the central pacemaker (core body temperature rhythm) and behavioral expression are altered, whereas in FTD only the behavioral expression is altered. This suggests that chronobiological treatments such as light therapy may be ineffective in patients with FTD as their central circadian pacemaker "clock," as measured by core body temperature, seem to be functioning, and the behavioral problems are emerging "downstream" from the SCN (41).

Issues that need to be addressed by future research:

- Prospective investigations to more clearly elucidate the progression of sleep changes over the course of the various dementias.
- Establishment of validated criteria for the diagnosis of sleep disturbance in dementia.
- Studies to more clearly describe the efficacy of strategies for treating the sleep disturbances associated with the dementias.

References

1. Vitiello MV, Borson S. Sleep disturbances in patients with Alzheimer's disease: epidemiology, pathophysiology and treatment. *CNS Drugs*. 2001;15(10):777–96.
2. Prinz PN, Peskind ER, Vitaliano PP, Raskind MA, Eisdorfer C, Zemcuznikov N, et al. Changes in the sleep and waking EEGs of nondemented and demented elderly subjects. *J Am Geriatr Soc*. 1982;30(2):86–93.
3. van Someren EJ, Hagebeuk EE, Lijzenga C, Scheltens P, de Rooij SE, Jonker C, et al. Circadian rest-activity rhythm disturbances in Alzheimer's disease. *Biol Psychiatry*. 1996;40(4): 259–70.
4. Wu YH, Fischer DF, Kalsbeek A, Garidou-Boof ML, van der Vliet J, van Heijningen C, et al. Pineal clock gene oscillation is disturbed in Alzheimer's disease, due to functional disconnection from the "master clock". *Faseb J*. 2006;20(11):1874–6.
5. Boeve BF, Saper CB. REM sleep behavior disorder: a possible early marker for synucleinopathies. *Neurology*. 2006;66(6): 796–7.
6. Cameron D. Studies in senile nocturnal deliruim. *Psychiatry Quarterly*. 1941;15:47–53.
7. Strejilevich SM. The nocturnal restlessness of the elderly psychotic. *Encephale*. 1962;51:238–62.
8. Tractenberg RE, Singer CM, Kaye JA. Symptoms of sleep disturbance in persons with Alzheimer's disease and normal elderly. *J Sleep Res*. 2005;14(2):177–85.
9. Moran M, Lynch CA, Walsh C, Coen R, Coakley D, Lawlor BA. Sleep disturbance in mild to moderate Alzheimer's disease. *Sleep Med*. 2005;6(4):347–52.
10. Tractenberg RE, Singer CM, Kaye JA. Characterizing sleep problems in persons with Alzheimer's disease and normal elderly. *J Sleep Res*. 2006;15(1):97–103.
11. Ancoli-Israel S, Klauber MR, Gillin JC, Campbell SS, Hofstetter CR. Sleep in non-institutionalized Alzheimer's disease patients. *Aging (Milano)*. 1994;6(6):451–8.
12. Bachman D, Rabins P. "Sundowning" and other temporally associated agitation states in dementia patients. *Annu Rev Med*. 2006;57:499–511.
13. Yesavage JA, Friedman L, Ancoli-Israel S, Bliwise D, Singer C, Vitiello MV, et al. Development of diagnostic criteria for defining sleep disturbance in Alzheimer's disease. *J Geriatr Psychiatry Neurol*. 2003;16(3):131–9.
14. Hope T, Keene J, Gedling K, Fairburn CG, Jacoby R. Predictors of institutionalization for people with dementia living at home with a carer. *Int J Geriatr Psychiatry*. 1998;13(10):682–90.
15. McCurry SM, Logsdon RG, Teri L, Gibbons LE, Kukull WA, Bowen JD, et al. Characteristics of sleep disturbance in community-dwelling Alzheimer's disease patients. *J Geriatr Psychiatry Neurol*. 1999 Summer;12(2):53–9.
16. Moe KE, Vitiello MV, Larsen LH, Prinz PN. Symposium: cognitive processes and sleep disturbances: sleep/wake patterns in Alzheimer's disease: relationships with cognition and function. *J Sleep Res*. 1995;4(1):15–20.
17. Mortimer JA, Ebbitt B, Jun SP, Finch MD. Predictors of cognitive and functional progression in patients with probable Alzheimer's disease. *Neurology*. 1992;42(9):1689–96.
18. Witting W, Kwa IH, Eikelenboom P, Mirmiran M, Swaab DF. Alterations in the circadian rest-activity rhythm in aging and Alzheimer's disease. *Biol Psychiatry*. 1990 Mar 15;27(6): 563–72.
19. Schulz R, Beach SR. Caregiving as a risk factor for mortality: the Caregiver Health Effects Study. *JAMA*. 1999;282(23):2215–9.
20. von Kanel R, Dimsdale JE, Ancoli-Israel S, Mills PJ, Patterson TL, McKibbin CL, et al. Poor sleep is associated with higher plasma proinflammatory cytokine interleukin-6 and procoagulant marker fibrin D-dimer in older caregivers of people with Alzheimer's disease. *J Am Geriatr Soc*. 2006;54(3):431–7.
21. Chong MS, Ayalon L, Marler M, Loredo JS, Corey-Bloom J, Palmer BW, et al. Continuous positive airway pressure reduces subjective daytime sleepiness in patients with mild to moderate Alzheimer's disease with sleep disordered breathing. *J Am Geriatr Soc*. 2006;54(5):777–81.
22. Ayalon L, Ancoli-Israel S, Stepnowsky C, Marler M, Palmer BW, Liu L, et al. Adherence to continuous positive airway pressure treatment in patients with Alzheimer's disease and obstructive sleep apnea. *Am J Geriatr Psychiatry*. 2006;14(2):176–80.

23. Van Someren EJ. Circadian rhythms and sleep in human aging. *Chronobiol Int*. 2000;17(3):233–43.
24. McCurry SM, Logsdon RG, Vitiello MV, Teri L. Treatment of sleep and nighttime disturbances in Alzheimer's disease: a behavior management approach. *Sleep Med*. 2004;5(4):373–7.
25. Teri L, Logsdon RG, McCurry SM. Nonpharmacologic treatment of behavioral disturbance in dementia. *Med Clin North Am*. 2002;86(3):641–56, viii.
26. McCurry SM, Gibbons LE, Logsdon RG, Vitiello MV, Teri L. Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial. *J Am Geriatr Soc*. 2005;53(5):793–802.
27. Dowling GA, Mastick J, Hubbard EM, Luxenberg JS, Burr RL. Effect of timed bright light treatment for rest-activity disruption in institutionalized patients with Alzheimer's disease. *Int J Geriatr Psychiatry*. 2005;20(8):738–43.
28. Moraes Wdos S, Poyares DR, Guilleminault C, Ramos LR, Bertolucci PH, Tufik S. The effect of donepezil on sleep and REM sleep EEG in patients with Alzheimer disease: a double-blind placebo-controlled study. *Sleep*. 2006;29(2):199–205.
29. Ancoli-Israel S, Amatniek J, Ascher S, Sadik K, Ramaswamy K. Effects of galantamine versus donepezil on sleep in patients with mild to moderate Alzheimer disease and their caregivers: a double-blind, head-to-head, randomized pilot study. *Alzheimer Dis Assoc Disord*. 2005;19(4):240–5.
30. Schneider LS, Tariot PN, Dagerman KS, Davis SM, Hsiao JK, Ismail MS, et al. Effectiveness of atypical antipsychotic drugs in patients with Alzheimer's disease. *N Engl J Med*. 2006;355(15):1525–38.
31. Ballard C, Howard R. Neuroleptic drugs in dementia: benefits and harm. *Nat Rev Neurosci*. 2006;7(6):492–500.
32. Schneider LS, Dagerman KS, Insel P. Risk of death with atypical antipsychotic drug treatment for dementia: meta-analysis of randomized placebo-controlled trials. *JAMA*. 2005;294(15):1934–43.
33. Singer C, Tractenberg RE, Kaye J, Schafer K, Gamst A, Grundman M, et al. A multicenter, placebo-controlled trial of melatonin for sleep disturbance in Alzheimer's disease. *Sleep*. 2003;26(7):893–901.
34. Asayama K, Yamadera H, Ito T, Suzuki H, Kudo Y, Endo S. Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia. *J Nippon Med Sch*. 2003;70(4):334–41.
35. Pandi-Perumal SR, Zisapel N, Srinivasan V, Cardinali DP. Melatonin and sleep in aging population. *Exp Gerontol*. 2005;40(12):911–25.
36. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, Feldman H, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurology*. 2005;65(12):1863–72.
37. Boddy F, Rowan EN, Lett D, O'Brien JT, McKeith IG, Burn DJ. Subjectively reported sleep quality and excessive daytime somnolence in Parkinson's disease with and without dementia, dementia with Lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2007;22(6):529–35.
38. Grace JB, Walker MP, McKeith IG. A comparison of sleep profiles in patients with dementia with lewy bodies and Alzheimer's disease. *Int J Geriatr Psychiatry*. 2000;15(11): 1028–33.
39. Ferman TJ, Smith GE, Boeve BF, Ivnik RJ, Petersen RC, Knopman D, et al. DLB fluctuations: specific features that reliably differentiate DLB from AD and normal aging. *Neurology*. 2004;62(2):181–7.
40. McKeith I, Fairbairn A, Perry R, Thompson P, Perry E. Neuroleptic sensitivity in patients with senile dementia of Lewy body type. *BMJ* 1992;305(6855):673–8.
41. Harper DG, Stopa EG, McKee AC, Satlin A, Harlan PC, Goldstein R, et al. Differential circadian rhythm disturbances in men with Alzheimer disease and frontotemporal degeneration. *Arch Gen Psychiatry*. 2001;58(4):353–60.