A REVIEW ON ANTIDEPRESSANTS EFFECT ON HUMAN CIRCADIAN RHYTHM

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ABSTRACT

The natural body clock, or circadian rhythm, often gets disrupted in people with major depressive disorder (MDD), particularly affecting sleep patterns. This disruption is closely linked to depression, as sleep issues are not only a symptom but also a diagnostic criterion for MDD. Insomnia often appears before mood symptoms, indicating its importance in the development of depression. When sleep cycles are disturbed, it can hinder recovery and prevent a full return to well-being.

Recognizing and treating sleep disturbances early on could be crucial for both managing current depression and preventing future episodes. Research highlights that certain receptors in the brain, particularly melatonergic (MT1 and MT2) and 5-HT2C serotonin receptors, play a key role in regulating circadian rhythms.

Agomelatine is a new type of antidepressant that works by stimulating melatonin receptors while also blocking some serotonin receptors. This medication not only helps improve mood but also enhances sleep quality without many of the side effects associated with traditional antidepressants, such as weight gain or sexual dysfunction. These benefits make agomelatine a promising option for treating depression and supporting a full recovery.

Keywords

agomelatine; circadian rhythm disturbances; major depressive disorder; recovery; remission; residual symptoms.

Introduction

There's growing interest in how biological rhythms, particularly circadian rhythms, relate to major depressive disorder (MDD). Research shows that disruptions in these natural rhythms, like changes in sleep patterns, can significantly affect mood. Sleep disturbances are a well-recognized factor in depression and are even included as a diagnostic criterion for major depressive episodes in the DSM-IV.

Insomnia often occurs before other symptoms of depression emerge, and sleep problems can predict future episodes of depression. This suggests that identifying and treating sleep issues early could be key to managing and preventing recurrent depression.

In this article, we'll explore how disturbances in circadian rhythms are connected to depression, discuss challenges related to remission and relapse in MDD, and look at strategies for achieving better recovery for those affected by this condition.

Circadian rhythms are our body's natural cycles that typically follow a 24-hour pattern, influencing when we feel awake and when we feel sleepy. As people age, these rhythms often start to deteriorate, leading to poorer sleep quality and cognitive issues. In conditions like Alzheimer's Disease (AD), this deterioration can become even more pronounced, affecting a significant number of patients at various stages of their illness.

Research shows that people with vascular cognitive disorders experience more sleep disturbances than those with Alzheimer's. Additionally, disruptions in circadian rhythms can impact recovery in patients who have suffered a stroke.

In Alzheimer's patients, common behavioural changes include daytime restlessness, nighttime insomnia, and increased agitation. Nocturnal sleep disturbances often lead to daytime napping, which can be closely linked to the severity of dementia

Circadian rhythm disturbances in Alzheimer's can be quite severe and are major factors leading to patients being placed in care facilities. These disturbances can also result in shorter life expectancy for residents in long-term care and create significant emotional and physical challenges for caregivers.

Circadian Rhythm

We inhibit the rhythmic world, where the earth's rotation on its axis or its orbit around the sun create predictable patterns. These movements give rise to daily and seasonal rhythms that influence light intensity, ambient temperature, humidity, and host of other environmental factor.

Pharmacology of agomelatine and circadian function:

Agomelatine is an innovative antidepressant that acts uniquely on the brain's melatonin and serotonin systems. It works primarily as an agonist for melatonin receptors MT1 and MT2 and also blocks the 5-HT2C serotonin receptors. This combination of actions gives it a distinctive role in regulating mood and biological rhythms.

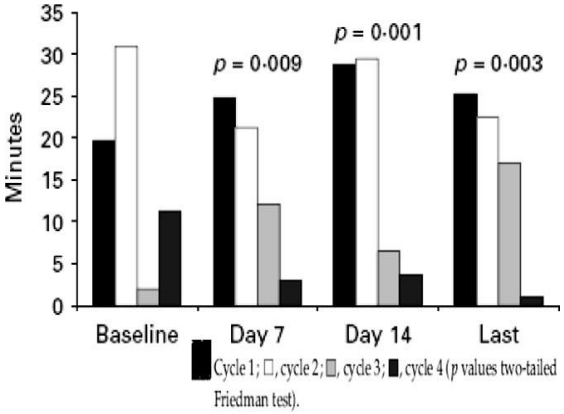
The suprachiasmatic nucleus (SCN), the brain's primary circadian clock, has a high concentration of melatonin and serotonin receptors. Research indicates that the expression of MT1 receptors varies throughout the day, influenced by light and the body's internal clock. Similarly, the 5-HT2C receptors show a circadian rhythm in their expression, although this rhythmicity is not observed for all serotonin receptors.

Quality of Remission with the Melatonergic Antidepressant Agomelatine:

Agomelatine has shown a strong affinity for the MT1, MT2, and 5-HT2C receptors in humans. Animal studies indicate that it can effectively reset disrupted circadian rhythms, suggesting that it may help restore balance in individuals with mood disorders associated with circadian rhythm disturbances. Overall, agomelatine's ability to target these receptors positions it as a promising treatment for depression, particularly in patients with circadian rhythm disruptions.

Agomelatine is a melatonergic antidepressant that has shown efficacy in treating major depressive disorder (MDD) through several clinical trials. Studies demonstrate that a standard dose of 25 mg/day significantly reduces Hamilton Depression Rating Scale (HAMD) scores compared to placebo over 6-8 weeks. In particular, a stringent measure of remission (HAMD $\leq$ 6) revealed that 30.4% of patients on agomelatine achieved remission, compared to 15.4% on placebo. An increased dose of 50 mg/day offered

additional benefits for those with insufficient response.



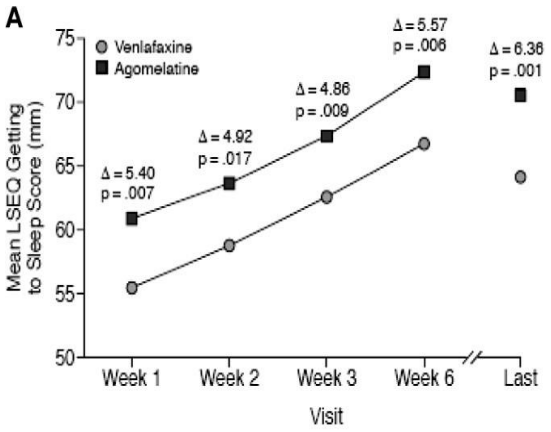
Agomelatine's performance is comparable to traditional antidepressants, showing similar efficacy to the SNRI venlafaxine and the SSRI paroxetine. In a trial, remission rates after 12 weeks were reported as 73% for agomelatine versus 66.9% for venlafaxine.

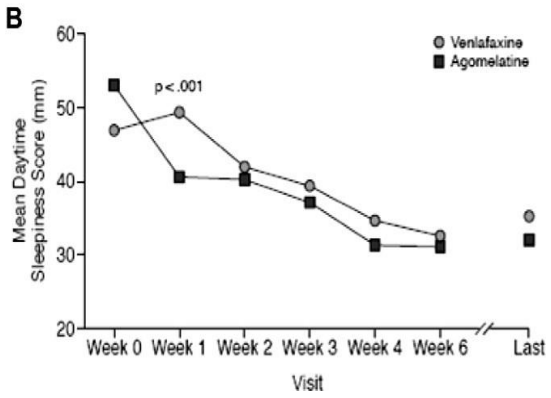
For patients with severe depression (HAMD ≥ 25), agomelatine demonstrated notable effectiveness, with a greater treatment effect observed as baseline depression severity increased. This aligns with findings for other antidepressants like escitalopram and venlafaxine at higher doses.

Additionally, agomelatine offers unique benefits related to sleep regulation. As a melatonergic agonist and 5-HT2C antagonist, it improves sleep quality without sedative effects, enhancing both sleep architecture and daytime alertness. Studies have shown that patients treated with agomelatine experience better sleep continuity and improved overall quality of life.

Polysomnography research further supports these findings, indicating that agomelatine normalizes non-rapid eye movement (NREM) sleep patterns in patients with MDD, correlating with subjective reports of improved mood and sleep quality.

Overall, agomelatine appears to provide high-quality remission in MDD, with particular advantages in sleep regulation and daytime functioning compared to traditional antidepressants. Further studies are ongoing to explore its full potential.





Common AD Symptoms Related to CRDs:

In Alzheimer's disease (AD), common symptoms related to circadian rhythm disturbances (CRDs) include insomnia, changes in nighttime behavior, and excessive daytime sleepiness, often stemming from disrupted sleep at night. One specific issue that can occur is REM behaviour disorder, where patients may act out their dreams.

Insomnia:

Insomnia in AD patients can arise from various causes. While it is often linked to neurodegenerative changes affecting circadian rhythms, it's important to consider other factors that might contribute to sleep problems. For instance, sleep apnea—where breathing stops and starts during sleep—can lead to confusion and awakenings. In some cases, using a continuous positive airway pressure (CPAP) machine has been found to improve both insomnia and cognitive function in affected individuals.

In Alzheimer's disease (AD) patients, circadian rhythm disturbances can be further complicated by other factors. Psychiatric issues, particularly depression and anxiety, are significant contributors to insomnia. Addressing these mental health conditions may help improve sleep in individuals with AD.

Additionally, excessive consumption of stimulants like coffee, tea, and caffeinated soft drinks can worsen sleep problems. Theophylline, a medication often used for respiratory conditions, can also lead to insomnia. Moreover, cholinesterase inhibitors, such as donepezil, which are commonly prescribed for AD, may occasionally cause sleep disturbances.

Hypersomnia

Excessive daytime sleepiness, known as hypersomnia, can be related to changes in different sleep stages. Conditions like idiopathic hypersomnia affect NREM sleep, while narcolepsy affects REM sleep. Narcolepsy, which is characterized by sudden urges to sleep, can be accompanied by symptoms like cataplexy (a sudden loss of muscle tone), vivid hallucinations, and brief periods of paralysis. It's generally uncommon in older adults, including those with Alzheimer's disease (AD).

In the elderly, hypersomnia is more frequently seen in conditions like Parkinson's disease (PD), Lewy body dementia (DLB), or Parkinson's disease dementia (PDD) rather than in AD. A newly discovered neuropeptide in the hypothalamus called hypocretin-1 may play a role in maintaining wakefulness. Lower levels of hypocretin-1 could contribute to sleep fragmentation in AD, leading to increased daytime sleepiness. Targeting the hypocretin system could potentially help improve wakefulness and sleep quality in AD patients.

For those with AD, treatments for insomnia or medications for nighttime agitation often contribute to excessive daytime sleepiness. Additionally, certain drugs, like anticonvulsants and those with strong anticholinergic effects (such as some antihistamines), can cause sedation and increase sleepiness during the day.

A lack of engaging activities can also lead to boredom and contribute to daytime sleepiness. Sometimes, caregivers may encourage daytime sleeping to make their caregiving easier, which can disrupt nighttime sleep and further worsen circadian rhythm disturbances.

Sundowning

Sundowning refers to a state of increased agitation or confusion that often occurs in the late afternoon or evening, typically between 4 PM and 11 PM. During this time, individuals with Alzheimer's disease (AD) may exhibit behaviors such as loud vocalizations, wandering, physical aggression, and general restlessness.

Interestingly, some studies suggest that the peak time for these behaviors might even be as early as 2:30 PM.

The prevalence of sundowning in AD patients ranges from about 12% to 25%. This phenomenon likely indicates changes in the body's ability to regulate sleep and wakefulness, which can affect how patients experience time and reality.

Several factors can contribute to sundowning. For example, fatigue, decreased lighting, and increased shadows can create confusion, making it difficult for individuals to distinguish between dreams and reality. Changes in environment, like moving to a new nursing home or shifts in caregivers, can also exacerbate agitation. Sundowning often peaks during the middle stages of Alzheimer's disease but may lessen as the disease progresses.

REM Sleep Behaviour Disorder (RBD)

REM Sleep Behaviour Disorder (RBD) can be classified as either idiopathic or secondary to identifiable causes, with most cases linked to neurodegenerative diseases. For instance, people with narcolepsy may experience RBD due to the degeneration of neurons that produce hypocretin. Certain medications, including sedative hypnotics, tricyclic antidepressants, anticholinergics, and selective serotonin reuptake inhibitors, can also induce RBD. There have even been reports of RBD occurring in Alzheimer's patients taking rivastigmine, a cholinesterase inhibitor.

RBD is characterized by violent physical activity during dreaming, resulting from the loss of muscle paralysis that normally occurs during REM sleep. This leads to increased muscle activity, which can be measured through electromyographic (EMG) recordings from the face and limbs during sleep. Patients with RBD may injure themselves or their bed partners, often in response to vivid dreams.

It's important to differentiate RBD from nocturnal paroxysmal dystonia (NPD), which involves abnormal movements during the night, such as trunk and head movements and limb flexing. NPD is usually linked to nocturnal frontal lobe epilepsy and occurs primarily during NREM sleep, while RBD occurs during REM sleep. NPD is typically treated with anticonvulsants like carbamazepine, whereas RBD is often managed with clonazepam.

Treatment Approaches

There is solid evidence that behavioural and environmental strategies can help alleviate sleep problems and nighttime disturbances in patients with Alzheimer's disease (AD). For example, creating a calming bedtime routine, ensuring a comfortable sleep environment, and engaging patients in regular daytime activities can improve sleep quality.

Pharmacological options are also available to treat symptoms related to circadian rhythm disturbances. However, it's important to be cautious with certain medications, such as benzodiazepines, which can worsen cognitive decline and potentially exacerbate conditions like obstructive sleep apnoea, commonly seen in AD patients. Additionally, some medications may cause daytime drowsiness, which can interfere with nighttime sleep.

Overall, a combination of behavioural interventions and careful medication

management is often the best approach to address sleep issues in individuals with AD.

Behavioural and Environmental Approaches:

There are several simple and effective interventions that can help manage circadian rhythm disturbances (CRDs) in Alzheimer's disease (AD) patients. Here are some strategies to consider:

1**. Regular Activity Schedule**: Keeping a consistent daily routine, such as serving dinner early, can help regulate sleep patterns.

2. **Bedtime Routines**: Establishing calming bedtime rituals can signal to the body that it's time to wind down.

3. **Minimize Noise and Light**: Reducing noise levels and limiting exposure to bright lights at night can create a more restful environment.

4. **Limit Stimulants**: Reducing caffeine and alcohol intake can improve sleep quality.

Many AD patients, especially those in long-term care, may spend excessive time in bed and not enough time engaging in physical activities, which can disrupt circadian rhythms. Incorporating mental, physical, and social activities can help combat boredom and reduce daytime napping.

Research has shown that a lack of bright light exposure is common among long-term care residents, contributing to circadian dysregulation. Light exposure is a powerful cue for regulating sleep-wake cycles, so increasing daily light exposure can be beneficial.

In one study, community-dwelling AD patients who engaged in daily exercise combined with 60 minutes of bright light therapy experienced significant improvements. They had fewer nighttime awakenings, less total wakefulness at night, and decreased depression after two months. These positive effects were maintained for six months, highlighting the effectiveness of combining physical activity with light therapy in improving sleep and overall well-being.

Table1: Dosing Schedule of Medications Used in Circadian Rhythm Disturbances (CRD)

Table 1: Dosing schedule of medications used in CRD.

Symptom	Medication	Initial Dose	Titrating Schedule	Maximum Daily Dose
Insomnia	Trazodone	25mg hs	25mg increments q 3–5 days	50–100 mg
	Zolpidem	5mg hs	5mg increments q 3-4 days	5–10mg
	Mirtazapine	15mg hs	15mg q week	15–30mg
	Quetiapine	25mg hs	25mg increments q 3-5 days	25–100 mg
	Chloral hydrate	250mg hs	250mg increments q 5–7 days	250–1000 mg
Behavioural Dyscontrol	Memantine	5mg am	5mg increments q week	20mg
	Donepezil	5mg am	5mg increments in 4 weeks	5–10mg
	Rivastigmine Transdermal	4.6mg od	9.5mg 4 weeks later	9.5mg
	Galantamine ER	8mg od	8mg increments q 4 weeks	16–24mg
	Risperidone	0.25mg hs	0.25mg increments q week	0.5–1.5 mg
	Olanzapine	2.5mg hs	2.5mg increments q week	5–10mg
	Carbamazepine (check level)	100mg hs	100mg increments q 3-5 days bid or tid	600mg
	Oxcarbazepine	300mg hs	300mg increments q week	2400mg
	Divalproex ER (check level)	125mg hs	125mg increments q 3-4 days	1500mg
Excessive Daytime Sleepiness	Methylphenidate	2.5mg am	2.5mg increments am and early pm	20mg
	Modafinil	100mg am	100mg increments q week	200mg
REM Sleep Behaviour Disorder	Clonazepam	0.25mg hs	0.25mg increment q week	1mg
	Melatonin	3mg hs	Add 3mg if needed	6mg

Bright light therapy has shown several benefits for people with Alzheimer's disease, particularly in improving sleep and activity patterns. A two-week study using actigraphy (which measures movement) found positive changes in activity levels. Additionally, a long-term study in the Netherlands involving nearly 200 residents at care facilities indicated that bright light therapy could help with both cognitive and non-cognitive symptoms of dementia, although the effects were less pronounced when combined with melatonin.

In summary, regular exposure to bright light can be effective for managing issues related to day-night cycles. For patients with REM Sleep Behaviour Disorder (RBD), ensuring safety by removing hazardous items from the bedroom and placing a soft mattress next to the bed can be beneficial.

Furthermore, clinical observations suggest that some Alzheimer's patients with obstructive sleep apnoea, who are treated with continuous positive airway pressure (CPAP) therapy, may experience improved sleep quality. It's generally recommended to try behavioural and environmental strategies first before considering medication option

Pharmacological Approaches

There are several medications available to help manage issues like insomnia, behavioral disturbances, nighttime agitation or wandering, excessive daytime sleepiness, REM Sleep Behaviour Disorder, and restless legs syndrome. However, it's important to combine these medications with environmental and behavioural changes for the best results.

When selecting a medication, it's crucial to tailor the choice and dosing to each

individual patient. This personalized approach ensures that treatment is effective and takes into account the unique needs and circumstances of each person.

It's the clinician's responsibility to carefully consider any potential side effects and drug interactions when prescribing medications. This means they need to be aware of how different drugs can affect each other and how they might impact the patient's overall health. By doing so, clinicians can help ensure that treatments are safe and effective for each individual patient.

Insomnia is a common issue for people with Alzheimer's disease, and if it's not properly treated, it can worsen both cognitive and non-cognitive symptoms. Medications that are often used to help with sleep include trazodone, zolpidem, sedating antidepressants like mirtazapine, and sometimes low doses of sedating atypical antipsychotics such as quetiapine and chloral hydrate.

When considering antipsychotics for Alzheimer's patients, it's important to keep in mind the FDA warnings about potential risks, including increased chances of mortality, stroke, and related events. Benzodiazepines should generally be avoided because they can impair cognitive function, affect balance, and increase the risk of falls.

For issues like nocturnal agitation, wandering, aggression, and hallucinations, medication can be considered after checking for other medical problems and trying behavioral strategies. Effective options may include atypical antipsychotics, anticonvulsants, short-acting benzodiazepines like lorazepam, longer-acting ones like clonazepam, and trazodone. Always refer to the dosing guidelines for these medications to ensure safe and effective use.

While higher doses of medications like methylphenidate or modafinil can pose cardiovascular risks for older adults, lower doses may be helpful for managing excessive daytime sleepiness. It's important to weigh the benefits and risks of these medications and have a discussion with the patient and their family before starting treatment. Keep in mind that stimulants might also aggravate symptoms of "sundowning," such as hallucinations.

Restless legs syndrome is another common issue in Alzheimer's patients that can complicate sleep problems. Medications like pramipexole (0.25 mg) or ropinirole (0.5 mg), taken at bedtime, are often prescribed for this condition. However, the stimulating effects of these drugs can sometimes worsen sleep disturbances for some patients.

REFERENCES

1. *Addressing circadian rhythm, Journal of Psychopharmacology disturbances in depressed patients 22(7) Supplement (2008) 13–18 for Psychopharmacology ISSN 0269-8811SAGE Publications Ltd, Los Angeles, London, RW Lam Division of Clinical Neuroscience, Department of Psychiatry, University of British Columbia, Vancouver, BC, Canada. New Delhi and Singapore10.1177/0269881108092591*
2. *Audinot, V, Mailliet, F, Lahaye-Brasseur, C, Bonnaud, A, Le Gall, A, Amossé, C, et al. (2003) New selective ligands of human cloned melatonin MT1 and MT2 receptors. Naunyn Schmiedebergs Arch Pharmacol 367: 553–561.*
3. *Holmes, MC, French, KL, Seckl, JR (1995) Modulation of serotonin and corticosteroid receptor gene expression in the rat hippocampus with circadian rhythm and stress. Brain Res Mol Brain Res 28: 186–192.*
4. *Kennedy, SH, Guilleminault, C (2006) Antidepressant efficacy of agomelatine 25–50 mg versus venlafaxine 75–150 mg: two randomized, double blind studies.*

[abstract]Eur Neuropsychopharmacol 16 (Suppl. 4): 319–320.

5. *Masana, MI, Benloucif, S, Dubocovich, ML (2000) Circadian rhythm of MT_1 melatonin receptor expression in the suprachiasmatic nucleus of the C3H/HeN mouse. J Pineal Res 28: 185–192.*
6. *Montgomery, SA, Kasper, S (2007) Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. Int Clin Psychopharmacol 22: 283–291.*
7. *Pickard, GE, Rea, MA (1997) Serotonergic innervation of the hypothalamic suprachiasmatic nucleus and photic regulation of circadian rhythms. Biol Cell 89: 513–523.*
8. *D. L. Bliwise, "Sleep apnea, APOE4 and Alzheimer's disease 20 years and counting?" Journal of Psychosomatic Research, vol. 53, no. 1, pp. 539–546, 2002.*
9. *S. T. O'Keeffe, K. Gavin, and J. N. Lavan, "Iron status and restless legs syndrome in the elderly," Age and Ageing, vol. 23, no. 3, pp. 200–203, 1994.*
10. *T. Shochat, J. Loredo, and S. Ancoli-Israel, "Sleep disorders in elderly," Current Treatment Options in Neurology, vol. 3, pp. 19–36, 2001.*
11. *S. K. Inouye, S. T. Bogardus Jr., P. A. Charpentier et al., "A multicomponent intervention to prevent delirium in hospitalized older patients," New England Journal of Medicine, vol. 340, no. 9, pp. 669–676, 1999.*
12. *W. C. Bailey, J. M. Richards Jr., B. A. Manzella, M. Brooks, R. A. Windsor, and S.-J. Soong, "Characteristics and correlates of asthma in a university clinic population," Chest, vol. 98, no. 4, pp. 821–828, 1990.*
13. *S. L. Rogers, R. S. Doody, R. C. Mohs, and L. T. Friedhoff, "Donepezil improves cognition and global function in Alzheimer disease: a 15-week, double-blind, placebocontrolled study," Archives of Internal Medicine, vol. 158, no. 9, pp. 1021–1031, 1998.*
14. *Burns, M. Rossor, J. Hecker et al., "The effects of donepezil in Alzheimer's disease—results from a multinational trial," Dementia and Geriatric Cognitive Disorders, vol. 10, no. 3, pp. 237–244, 1999.*
15. *R. J. Wurtman, "Narcolepsy and the hypocretins," Metabolism, vol. 55, no. 2, pp. S36–S39, 2006.*
16. *L. F. Friedman, J. M. Zeitzer, L. Lin et al., "In Alzheimer disease, increased wake fragmentation found in those with lower hypocretin-1," Neurology, vol. 68, no. 10, pp. 793–794, 2007.*
17. National Sleep Foundation, Sleep in America Poll, WB and A Market Research, Washington, DC, USA, 2003.
18. *K. Meguro, M. Ueda, I. Kobayashi et al., "Sleep disturbance in elderly patients with cognitive impairment, decreased daily activity and periventricular white matter lesions," Sleep, vol. 18, no. 2, pp. 109–114, 1995.*
19. *D. L. Bliwise, J. S. Carroll, and W. C. Dement, "Predictors of observed sleep/wakefulness in residents in long-term care," Journals of Gerontology, vol. 45, no. 4, pp. M126–M130, 1990.*
20. *S. R. Allen, W. O. Seiler, H. B. Stahelin, and R. Spiegel, "Seventy-two hour polygraphic and behavioral recordings of wakefulness and sleep in a hospital geriatric unit: comparison between demented and nondemented patients," Sleep, vol. 10, no. 2, pp. 143–159, 1987.*
21. *D. L. Algase, "Wandering in dementia," Annual Review of Nursing Research, vol. 17, pp. 185–217, 1999.*
22. *P. A. O'Leary, W. E. Haley, and P. B. Paul, "Behavioral assessment in Alzheimer's disease: use of a 24-hr log," Psychology and Aging, vol. 8, no. 2, pp. 139–143, 1993.*
23. *J. Martin, M. Marler, T. Shochat, and S. Ancoli-Israel, "Circadian rhythms of agitation in institutionalized patients with Alzheimer's disease," Chronobiology International, vol. 17, no. 3, pp. 405–418, 2000.*
24. *M. H. Kryger, T. Roth, and W. C. Dement, Principles and Practice of Sleep Medicine, W. B. Saunders, Philadelphia, Pa, USA, 3rd edition, 2000.*
25. *F. W. Myron and M. L. Anne, Textbook of Alzheimer's Disease and Other Dementias, vol. 8, American Psychiatric , 2009.*

26. J. G. Ouslander, B. R. Connell, D. L. Bliwise, Y. Endeshaw, P. Griffiths, and J. F. Schnelle, "A nonpharmacological intervention to improve sleep in nursing home patients: results of a controlled clinical trial," Journal of the American Geriatrics Society, vol. 54, no. 1, pp. 38–47, 2006.

27. S. S. Carvalho-Bos, R. F. Riemersma-van Der Lek, J. Waterhouse, T. Reilly, and E. J. W. Van Someren, "Strong association of the rest-activity rhythm with well-being in demented elderly women," American Journal of Geriatric Psychiatry, vol. 15, no. 2, pp. 92–100, 2007.

28. S. S. Campbell, D. F. Kripke, J. C. Gillin, and J. C. Hrubovcak, "Exposure to light in healthy elderly subjects and Alzheimer's patients," Physiology and Behavior, vol. 42, no. 2, pp. 141–144, 1988.

29. S. Ancoli-Israel, J. L. Martin, D. F. Kripke, M. Marler, and M. R. Klauber, "Effect of light treatment on sleep and circadian rhythms in demented nursing home patients," Journal of the American Geriatrics Society, vol. 50, no. 2, pp. 282–289, 2002.

30. S. M. McCurry, L. E. Gibbons, R. G. Logsdon, M. V. Vitiello, and L. Teri, "Nighttime insomnia treatment and education for Alzheimer's disease: a randomized, controlled trial," Journal of the American Geriatrics Society, vol. 53, no. 5, pp. 793–802, 2005.

31. J. K. Gammack, "Light therapy for insomnia in older adults," Clinics in Geriatric Medicine, vol. 24, no. 1, pp. 139–149, 2008.

32. A. Fetveit and B. Bjorvatn, "Bright-light treatment reduces actigraphic-measured daytime sleep in nursing home patients with dementia: a pilot study," American Journal of Geriatric Psychiatry, vol. 13, no. 5, pp. 420–423, 2005.

33. K. Mishima, M. Okawa, Y. Hishikawa, S. Hozumi, H. Hori, and K. Takahashi, "Morning bright light therapy for sleep and behavior disorders in elderly patients with dementia," Acta Psychiatrica Scandinavica, vol. 89, no. 1, pp. 1–7, 1994.

34. S. Ancoli-Israel, P. Gehrman, J. L. Martin et al., "Increased light exposure consolidates sleep and strengthens circadian rhythms in severe Alzheimer's disease patients," Behavioral Sleep Medicine, vol. 1, no. 1, pp. 22–36, 2003.

35. S. Ancoli-Israel, J. L. Martin, P. Gehrman et al., "Effect of light on agitation in institutionalized patients with severe Alzheimer disease," American Journal of Geriatric Psychiatry, vol. 11, no. 2, pp. 194–203, 2003.

36. S. Ancoli-Israel, D. W. Jones, M. A. Hanger, et al., "Sleep in the nursing home," in Sleep and Respiration in Aging Adults, pp. 77–84, Elsevier, New York, NY, USA, 1991.

37. R. F. Riemersma-van Der Lek, D. F. Swaab, J. Twisk, E. M. Hol, W. J. G. Hoogendijk, and E. J. W. Van Someren, "Effect of bright light and melatonin on cognitive and noncognitive function in elderly residents of group care facilities: a randomized controlled trial," Journal of the American Medical Association, vol. 299, no. 22, pp. 2642–2655, 2008.

38. K. Asayama, H. Yamadera, T. Ito, H. Suzuki, Y. Kudo, and S. Endo, "Double blind study of melatonin effects on the sleep-wake rhythm, cognitive and non-cognitive functions in Alzheimer type dementia," Journal of Nippon Medical School, vol. 70, no. 4, pp. 334–341, 2003.

39. C. G. Lyketsos, L. L. Veiel, A. Baker, and C. Steele, "A randomized, controlled trial of bright light therapy for agitated behaviors in dementia patients residing in long-term care," International Journal of Geriatric Psychiatry, vol. 14, no. 7, pp. 520–525, 1999.

40. E. J. W. Van Someren, A. Kessler, M. Mirmiran, and D. F. Swaab, "Indirect bright light improves circadian restactivity rhythm disturbances in demented patients," Biological Psychiatry, vol. 41, no. 9, pp. 955–963, 1997.

41. A. Fetveit and B. Bjorvatn, "Bright-light treatment reduces actigraphic-measured daytime sleep in nursing home patients with dementia: a pilot study," American Journal of Geriatric Psychiatry, vol. 13, no. 5, pp. 420–423, 2005.

42. B. Naegele, J.-L. Pepin, P. Levy, C. Bonnet, J. Pellat, and C. Feuerstein, "Cognitive executive dysfunction in patients with obstructive sleep apnea syndrome (OSAS)

after CPAP treatment," Sleep, vol. 21, no. 4, pp. 392–397, 1998.

43. *H. M. Engleman, S. E. Martin, I. J. Deary, and N. J. Douglas, "Effect of continuous positive airway pressure treatment on daytime function in sleep apnoea/hypopnoea syndrome," Lancet, vol. 343, no. 8897, pp. 572–575, 1994.*

44. *J. S. Street, W. S. Clark, K. S. Gannon et al., "Olanzapine treatment of psychotic and behavioral symptoms in patients with Alzheimer disease in nursing care facilities: a doubleblind, randomized, placebo-controlled trial," Archives of General Psychiatry, vol. 57, no. 10, pp. 968–976, 2000.*

45. *D. Q. McManus, L. A. Arvanitis, and B. B. Kowalcyk, "Quetiapine, a novel antipsychotic: experience in elderly patients with psychotic disorders," Journal of Clinical Psychiatry, vol. 60, no. 5, pp. 292–298, 1999.*

46. *I. R. Katz, D. V. Jeste, J. E. Mintzer, C. Clyde, J. Napolitano, and M. Brecher, "Comparison of risperidone and placebo for psychosis and behavioral disturbances associated with dementia: a randomized, double-blind trial," Journal of Clinical Psychiatry, vol. 60, no. 2, pp. 107–115, 1999.*

47. *S. M. Stahl, J. S. Markowitz, E. M. Gutterman, and G. Papadopoulos, "Co-use of donepezil and hypnotics among Alzheimer's disease patients living in the community," Journal of Clinical Psychiatry, vol. 64, no. 4, pp. 466–472, 2003.*

48. *L. E. Maclean, C. C. Collins, and E. J. Byrne, "Dementia with Lewy bodies treated with rivastigmine: effects on cognition, neuropsychiatric symptoms, and sleep," International Psychogeriatrics, vol. 13, no. 3, pp. 277–288, 2001.*

49. *M. Schredl, B. Weber, M.-L. Leins, and I. Heuser, "Donepezilinduced REM sleep augmentation enhances memory performance in elderly, healthy persons," Experimental Gerontology, vol. 36, no. 2, pp. 353–361, 2001.*

50. *E. Holsboer-Trachsler, M. Hatzinger, R. Stohler et al., "Effects of the novel acetylcholinesterase inhibitor SDZ ENA 713 on sleep in man," Neuropsychopharmacology, vol. 8, no. 1, pp. 87– 92, 1993.*

51. *G. A. Yorston and R. Gray, "Hypnopompic hallucinations with donepezil," Journal of Psychopharmacology, vol. 14, no. 3, pp. 303–304, 2000.*

52. *J. S. Ross and J. R. Shua-Haim, "Aricept-induced nightmares in Alzheimer's disease: 2 case reports," Journal of the American Geriatrics Society, vol. 46, no. 1, pp. 119–120, 1998.*

53. *G. T. Grossberg, V. Pejovic, M. L. Miller, and S. M. Graham,′ "Memantine therapy of behavioral symptoms in communitydwelling patients with moderate to severe Alzheimer's disease," Dementia and Geriatric Cognitive Disorders, vol. 27, no. 2, pp. 164–172, 2009.*

54. *D. Kunz and F. Bes, "Melatonin as a therapy in REM sleep behavior disorder patients: an open-labeled pilot study on the possible influence of melatonin on REM-sleep regulation," Movement Disorders, vol. 14, no. 3, pp. 507–511, 1999.*

55. *B. F. Boeve, M. H. Silber, and T. J. Ferman, "Melatonin for treatment of REM sleep behavior disorder in neurologic disorders: results in 14 patients," Sleep Medicine, vol. 4, no. 4, pp. 281–284, 2003.*

56. *M. L. Fantini, J.-F. Gagnon, D. Filipini, and J. Montplaisir, "The effects of pramipexole in REM sleep behavior disorder," Neurology, vol. 61, no. 10, pp. 1418–1420, 2003.*