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Insomnia and dementia: is agomelatine treatment helpful? Case report and review of the literature

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***Abstract*:** The treatment of sleep disorders in Alzheimer's disease (AD) may be quite challenging in elderly patients because of drug side effects or interactions and comorbid local or systemic diseases. Here, we report a patient with AD, who was suffering from severe insomnia and depression. We ordered agomelatine for the treatment of insomnia in this patient, and it was quite helpful not only for insomnia but also for depression and for the cognitive symptoms related with dementia. Our aim was to share these observations for similar patients.

Keywords: agomelatine, Alzheimer's disease, dementia, sleep

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Introduction

Insomnia, as a disease or as a symptom of other diseases, occurs in 25% of adult populations [Lichstein *et al.* 2004; Wolkove *et al.* 2007; Fortier-Brochu *et al.* 2012]. Changes in sleep architecture occur in the aging process, but dementia itself causes more changes, which lead to further deterioration of this architecture during the course of the disease [Bliwise, 1993; Peter-Derex *et al.* 2015]. In fact, dementia and sleep architecture changes can affect each other. Among the types of dementia, Alzheimer's disease (AD) is the commonest one [Brookmeyer *et al.* 2007], and it is quite sensitive to sleep-related disturbances. Any kind of sleep disturbance results in deficiency of the sleep-dependent memory consolidation process, and this leads to decreased quality of life and decreased functional abilities. All cognitive functions (language, motor skills, attention, emotional reactivity and executive functions) can be affected [Peter-Derex *et al.* 2015]. Moreover, sleep disturbances may also lead to increased daytime irritability, aggressiveness, aberrant motor behaviors, and disinhibitions [Moran *et al.* 2005; García-Alberca *et al.* 2013; Rauchs *et al.* 2010; Shin *et al.* 2014; Cipriani *et al.* 2015].

There is growing evidence that circadian rhythm and sleep disorders are risk factors for the development of AD [Ballard *et al.* 2011; Yaffe *et al.* 2011; Slats *et al.* 2013]. Bidirectional association has been suggested between sleep–wake cycle abnormalities, sleep deprivation and amyloid-β accumulation in patients. One direction is that sleep disturbances (e.g. sleep deprivation, reduced quality of sleep) increase the amyloid-β depositions, and the other direction is that increased amyloid-β accumulation causes increased wakefulness and altered sleep patterns [Kang *et al.* 2009; Spira *et al.* 2013; Ju *et al.* 2013]. An animal study revealed one of these associations in mice, where sleep deprivation led to increased amyloid-β accumulation [Kang *et al.* 2009].

Acetylcholine has functions in both memory consolidation and maintaining normal sleep, and is found in low concentrations in AD [Yaffe *et al.* 2014]. In sleep, acetylcholine plays a prominent role in the activation of rapid eye movement (REM) sleep and in the reciprocal interactions in between the cholinergic system and REM facilitatory-inhibitory neurons [De Jesus Cabeza *et al.* 1994; Cipriani *et al.* 2015]. Systemic administration of an acetylcholinesterase inhibitor in studies also supported its role in sleep, leading to increased REM sleep bout durations and greater intensity of phasic REM phenomena [Jouvet, 1962; Grace and Horner, 2015].

Circadian rhythm is regulated by melatonin, which interacts with MT1 and MT2 receptors.

The MT1 receptor is expressed in the suprachiasmatic nucleus (SCN), the hippocampus, the retina and basal ganglia region. The MT2 receptor is expressed mostly in the hippocampus, the SCN and the retina. In addition to these areas, pineal gland, thalamic, cortical and cerebellar neurons and glial cells have these receptors [Srinivasan *et al.* 2012; De Berardis *et al.* 2013b]. Stimulation of MT1 and MT2 receptors by agomelatine, which is a potent melatonin receptor agonist, enhanced cognitive functions in rats [Conboy *et al.* 2009; Bertaina-Anglade *et al.* 2011].

The hippocampus is the most important region for learning and memory in humans. Degeneration of the hippocampus might also be a contributive factor for sleep-related pattern disturbances [Zhu *et al.* 2012; Meerlo *et al.* 2009]. The hippocampus has a different aspect from other brain regions, and it contains stem cells which give rise to new neurons in the brain, even in adulthood. This plasticity might make it sensitive to sleep deprivation [Kreutzmann *et al.* 2015]. Animal studies have revealed that restriction of sleep to 4 hours per day for a month caused reduced neurogenesis, morphological changes, and 10% volume loss in the brains of adult rats [Mueller *et al.* 2008; Kreutzmann *et al.* 2015; Novati *et al.* 2011]. The treatment of sleep disorders in AD may be quite challenging in elderly patients because of drug side effects or interactions and comorbid local or systemic diseases.

Here, we report a patient with AD, who was suffering from severe insomnia and depression. We ordered agomelatine for the treatment of insomnia in this patient, and it was quite helpful not only for insomnia but also for depression and for the cognitive symptoms related with dementia. Our aim is to share these observations for similar patients.

Case report

A 91-year-old woman was admitted to the outpatient clinic with severe insomnia. Difficulty in falling asleep, repetitive sleep fragmentations and awakenings, and short durations of night sleep (4 hours/night) were reported for the previous 1 year period. She had been diagnosed with AD 2.5 years before, and she had been taking memantine (20 mg/day).

Her medical history revealed that she had been hospitalized one year before because of hyponatremia-related delirium. She had only been taking mianserin (10 mg/day) at that time for insomnia. Insomnia duration was 20 years and during that time she had no history of depression. No other reasons were found for hyponatremia and it resolved after the mianserin treatment was stopped. Delirium also improved when the treatment was stopped, but chronic insomnia recurred and lorazepam was ordered (1.25 mg/day).

In the follow-up period, difficulty in falling asleep and fragmentations of night sleep were partly improved. Increased daytime sleepiness was a side effect of this treatment, and also depressive mood was observed at the end of the period. Anhedonia, crying episodes, and death thoughts were observed (she had no suicide plans but she continuously wanted to be dead). In her examination, orientation to person, time, and place were normal. Protected abstract thinking, protected judgment, depressed mood, thoughts of death and anhedonia, declined associations, and decreased speech at a low volume were found, but perception was normal and no delusions or hallucinations were found. Her mini mental state examination test (MMSE) score was 19. The magnetic resonance imaging scan was compatible with dementia (moderate cortical atrophy and enlargement of the cerebral ventricles and sulci). The electroencephalogram revealed no abnormality. Agomelatine 25 mg/day was started for depression and insomnia, and lorazepam was stopped. With agomelatine treatment, insomnia began to improve. Besides the improvement of insomnia, self-care (first week) and depressive symptoms (second week) also improved. At 1 month, psychiatric examination revealed improved depressive symptoms, improved cognition, improved daily functioning, decreased sleep fragmentations and decreased daytime sleepiness. Her repeated MMSE test score was 23. During the treatment period, liver functions were analyzed according to the product sheet recommendations and no adverse effects were observed.

Discussion

The diagnosis and treatment of dementia require more expertise and cooperation with other specialties. Structural changes affect the whole brain and these changes lead to functional deficits not only in memory but also in other cortical functions. Depression and insomnia are generally seen in the course of the disease, sometimes at the beginning, and sometimes in the middle or in the later part. Similarly, sleep-related abnormalities

(sleep deficiencies or abnormal sleep patterns) are also seen in the course of AD, and these also aggravate the amnestic disease symptoms [Rauchs *et al.* 2010; Peter-Derex *et al.* 2015]. Normally, a proper sleep process has a critical role in memory consolidation. Depression is another cause of both disrupted sleep patterns and cognitive decline in AD [Maglione *et al.* 2012; Baglioni *et al.* 2011; Byers and Yaffe, 2011]. Sleep disturbances are a predictive factor for depressive symptoms, and studies have also revealed that there is an association between apathy and sleep problems in AD [Arbus *et al.* 2011; Mulin *et al.* 2011]. In our case, insomnia was a leading complaint and we observed some improvements in the cognitive functions after it was restored. Because the insomnia was of a chronic nature and arose before the depression, we did not associate cognitive function defects with depression. Our case emphasized to us the importance of sleep not only for cognition but also for mood, especially in patients with AD.

Hypnotic drugs are the usual choices in insomnia treatment, but both benzodiazepine and non-benzodiazepine hypnotics have some side effects especially in elderly people (e.g. hangover, anterograde amnesia, cognitive decline, paradoxical and rebound effects) [Rudolph and Knoflach, 2011; Cipriani *et al.* 2015]. At the beginning, we used lorazepam for the treatment of insomnia. Although it was helpful at first, it failed in the long term. Excessive daytime sleepiness further aggravated the deterioration of cognition and the deterioration of self-care. Also, lorazepam did not prevent the occurrence of the depressive symptoms.

Melatonin is another drug that is used for the treatment of insomnia in humans. In fact, it is naturally synthesized in the pineal gland, and has an effect on increased sleep propensity and synchronization of the circadian clock as well as having a cytoprotective, antioxidant and even anti-amyloid effect [Pandi-Perumal *et al.* 2005; Cardinali *et al.* 2005; Lin *et al.* 2013]. Neuroprotective properties of melatonin have been shown in animal models [Stefanova *et al.* 2015], and levels of melatonin are found to be low in AD patients compared to controls [Uchida *et al.* 1996; Mahlberg *et al.* 2008]. The possible role of melatonin for preventing the progress of AD is suggested in animal models, but the hopeful findings have not been correlated in human studies [Peng *et al.* 2013]. Clinical trials that related the effect of melatonin to AD have given conflicting results [Serfaty *et al.* 2001; Singer *et al.* 2003; Gehrman *et al.* 2009; Jansen *et al.* 2006; Xu *et al.* 2015]. The short half-life of melatonin ($T_{1/2}$ is 45 min), poor oral bioavailability (approximately 15%), and the ubiquitous action of melatonin might be the cause of these different results [Carocci *et al.* 2014; Harpsøe *et al.* 2015].

Agomelatine is a receptor agonist that affects both MT1 and MT2 melatonin receptors and an antagonist that affects 5-hydroxytyriptamine 5HT 2C receptors. It acts on the SCN, hippocampus, frontal cortex and striatum which leads to improvement of sleep duration, restoration of the circadian rhythm, improvement of sleep physiology (MT1 receptor, REM sleep and MT2 receptor, non-REM sleep), and improvement in mood [Dubovsky and Warren 2009; Bonakis *et al.* 2012; Quera Salva *et al.* 2007; Comai *et al.* 2013; Plesničar, 2014]. Agomelatine also has positive effects on anxiety and depressive symptoms, but has no adverse effects on cognition during the treatment of patients, especially the elderly [Heun *et al.* 2013; Laudon and Frydman-Marom, 2014].

In our case, first restoration of insomnia and then also improvement of cognitive functions may be the consequence of both the increase in sleep duration and also the change of sleep architecture (the increase in the REM period). We know that aging changes the sleep architecture and that these changes may be one of the reasons for changed learning abilities. In recent studies, the relations were defined between sleep architecture modifications and learning capability changes [Peter-Derex *et al.* 2015]. The decreased levels of acetylcholine in patients with AD may be the common pathway for these conditions [Rasch *et al.* 2009; Hornung *et al.* 2007; Peter-Derex *et al.* 2015]. Increasing the REM period with agolematine treatment may have potential advantages for patients with insomnia, depression and cognitive defects when compared to other REM period-suppressant drugs such as antidepressants [tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), mirtazapine, and trazadone] [Mayers and Baldwin, 2005]. In addition, animal studies have revealed increased hippocampal and prefrontal cortex neogenesis, increased expression of brain-derived neurotrophic factor levels, and increased cellular signaling enzyme levels with agomelatine treatment [Pompili *et al.* 2013]. Agomelatine is also

helpful in other neurodegenerative diseases such as Parkinson's disease. It has been used for depression in Parkinson's disease and was found helpful not only for depression, but also for sleep and motor dysfunctions [De Berardis *et al.* 2013a; Avila *et al.* 2015].

Proper management of sleep problems in AD patients is important for both cognitive functions and behavioral problems [Shin *et al.* 2014]. In our patient, we observed a good clinical response with agomelatine treatment during the treatment of insomnia and depression. We also observed good clinical outcomes for cognition. To the best of the authors' knowledge, this is the first case report demonstrating that agomelatine is highly effective in the treatment of insomnia and depression, with also a positive effect on the cognitive functions of an AD patient. Agomelatine, which has a good side effect profile in the elderly, may be an option in AD patients who also have insomnia.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

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