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CASE SERIES

Use of Methylphenidate in Excessive Daytime Sleepiness in Alzheimer's Patients Treated with Donepezil: Case Series

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Abstract: Sleep disorders, inversion of sleep rhythm, excessive daytime sleepiness, and sleeplessness at night are common in Alzheimer's disease (AD). Sleep disorders in AD have a diverse pathogenesis and their incidence increases as the disease progresses. Some publications indicate possible beneficial effects of methylphenidate on sleep. We presented two cases of patients with diagnosed AD accompanied by sleep disorders which had a significant impact on their functioning. The pathogenesis of sleep disorders was different in those two cases. In both case studies, the use of methylphenidate brought an immediate clinical effect, improving sleep at night and functioning during the day.

Keywords: sleep disorders, Alzheimer's disease, treatment, methylphenidate

Biological rhythm disorders, especially sleep disorders in Alzheimer's disease (AD), are significantly more common than in the rest of the population. Their incidence increases as the disease progresses. They significantly worsen the patient's functioning by exacerbating neuropsychiatric symptoms and cognitive disorders.[1–3] They are also a major burden for carers.[4] Sleep disorders in AD have multiple causes. Progressive degenerative changes, especially in areas where melatonin and hypocretin (orexin) are secreted, seem to be of key importance.[4] Typical sleep disorders in AD include disturbances in the sleep–wake cycle with activity at night and sometimes excessive daytime sleepiness.[5,6] Increased daytime sleepiness often turns into narcolepsy.[7]

The accompanying treatment may be another cause of sleep disorders. During treatment with donepezil, insomnia and nightmares are observed,[8] especially when the medication is administered in the evening.[9] Studies indicate a relation between the use of donepezil and changes in sleep architecture. These include extension of the REM stage, which may be accompanied by nightmares experienced by the patients.[10,11]

Treatment with acetylcholinesterase inhibitors, including donepezil, may also be associated with other side effects. One of them is severe salivation. Animal models have shown the possibility of inducing salivation with Cholinesterase inhibitors (IAChE). This is a peripheral effect.[12]

In the presented cases, methylphenidate was used to reduce the increased excessive daytime sleepiness in patients with AD.

The research project was reviewed and approved by the Ethical Committee (decision no. 21/2019) at the Institute of Psychology at the University of Gdansk, Poland.

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Both patients provided written informed consent for the case details to be published.

Case 1

The patient, aged 73, was diagnosed with dementia in Alzheimer's disease based on ICD-10 criteria and after neuroimaging (head CT with contrast). At the time of diagnosis, the assessment of dementia according to MMSE scale (corrected by Mungas et al)[13] was 20 points. The patient had no accompanying diseases and did not take other drugs. Donepezil was administered, initially at a dose of 5 mg, which was tolerated well. The dose was increased after 6 weeks to 10 mg/day evening. At the follow-up visit after 4 weeks, the carer reported that the patient started to wake up at night with nocturnal terror and agitation and then fell asleep with difficulty. The amount of night's sleep was reduced. At the same time, the carer observed significantly increased daytime sleepiness. The patient fell asleep many times during the day, actually every time she was left alone. Moreover, increased salivation occurred. It appeared about 10–12 days after the increased dose was administered and occurred continuously. The clinical assessment revealed that the patient's mental condition seemed to deteriorate compared to the baseline study, which was confirmed by the MMSE assessment (17 points). It was recommended to change the time of donepezil administration from evening to morning, but as a result, although sleep disturbances partially improved, nausea occurred, which significantly reduced the appetite. In that situation, after subsequent 3 weeks, it was decided to maintain the current donepezil dosage (10 mg) administered again in the evening, and to add methylphenidate in the initial dose of 5 mg in the morning, and after 7 days, 10 mg in the morning (extended-release tablets CR).

During the following examination after 4 weeks, remission of the daytime sleepiness was observed and the amount of night's sleep was significantly increased. The patient's night sleep was deepened, there were no more incidents of sudden awakenings combined with anxiety. Although there were still awakening incidents, they were not accompanied by significant anxiety. After waking up, the patient was falling asleep again quickly. Her daytime responsiveness and functioning improved. In addition, salivation was significantly reduced. Follow-up MMSE assessment 19 points. After the following 2 months methylphenidate was discontinued, nevertheless during the next 6 months of observation no clear daytime sleepiness or increased salivation recurred. Stabilisation of the dementia process was observed. Laboratory test and electrocardiogram revealed no significant deviations.

Case 2

A 69-year-old man treated for Alzheimer's disease. He was taking donepezil for three years, initially for the period of a few weeks, 5 mg a day, then 10 mg a day in the evening. No symptoms indicating improper drug tolerance have been reported. He was referred for medical consultation due to sleep disturbances which had been intensifying for about four months. The amount of his night's sleep was decreased as he was waking up frequently at night, which was accompanied by increased daytime sleepiness. The patient fell asleep many times during the day, actually every time he was left alone. Excessive sleepiness and slightly increased irritability were observed also during the examination. It was noted that the patient was taking short naps even when the examiner was trying to talk to him and during the physical and psychometric examination. The patient demonstrated the sleep attacks which were similar to those seen in narcolepsy.

The severity of cognitive dysfunction was assessed as moderate. The patient scored 16.87 points in the MMSE scale (corrected by Mungas et al)[13] and 32 points in the ADAS-cog scale. Basic biochemical tests, blood cell count and electrocardiogram did not reveal any clinically significant abnormalities. The MRI scan revealed no focal signs apart from the generalised cortical atrophy located mainly in temporal lobes. Initially, only the time of donepezil administration was changed from evening to morning; however, during the four-week follow-up period, no differences were observed with respect to the presented sleep disorders. During the following examination, methylphenidate was added in the initial dosage of 5 mg in the morning (extended-release tablets CR). As the carer reported, after the following four weeks the daytime sleepiness decreased, but it was still observed. The medical history was confirmed by observation, which revealed that the patient presented a much lower degree of sleepiness that during previous examinations. No symptoms indicating improper drug tolerance have been reported. It was decided to increase dosage to 10 mg (extended-release tablet CR), administered in the morning. The subsequent examination revealed a significant improvement. The daytime sleepiness was radically reduced (the patient happened to take 1–2 short naps a day), the night's sleep was consolidated and prolonged and the patient's responsiveness was improved. The increased irritability observed before did not occur again. The drugs were tolerated well. The patient was taking10 mg donepezil in the evening and 10 mg methylphenidate (CR) in the morning for another

seven weeks during which previously reported sleep disturbances were not observed. However, a repeated attempt to reduce the dosage to 5 mg/day was unsuccessful, because it resulted in increased daytime sleepiness almost immediately. Eventually, the drug was discontinued due to the enhances irritability/impulsiveness of the patient. After discontinuation of treatment, daytime sleepiness increased significantly again and the night's sleep worsened due to frequent awakenings. The assessment of cognitive functions revealed a gradual progression of dementia (MMSE 16.87 points, ADAS-cog scale: 35 points). No significant abnormalities were found in the additional tests and physical examination.

Discussion

Two cases of patients with diagnosed Alzheimer's disease, accompanied by sleep disorders having significant impact on functioning, were presented. Sleep disorders in the course of Alzheimer's disease occur typically, worsen as dementia increases and are probably related to cholinergic deficit.[7] However, they are caused by many factors.[4] Their pathogenesis seems to be diverse also in the described cases. In the first case, there seems to be a clear connection with the use of donepezil. Nightmares were described in the course of donepezil treatment.[8] Especially when the drug was administered in the evening.[9] This may be related to the activation of cholinergic fibres.[14] Reducing the amount of the night's sleep has an effect on increased daytime sleepiness, which may have been the case with the first patient. In the second case, it was rather the progressive degenerative process that caused increased daytime sleepiness, leading to narcolepsy-like states. In both cases, the administration of methylphenidate at a relatively low dose proved beneficial. It seems that its activating effect, reducing daytime sleepiness, was crucial. Lower amount of sleep during the day was probably associated with greater demand for the night's sleep and thus its prolongation and deepening. This had an overall positive clinical effect, even though methylphenidate may also be associated with the night's sleep disorders.[15]

Although in the described cases the dosage took place in the morning, these were the CR medications, and in the elderly, the metabolism of drugs may be prolonged. On the other hand, some publications indicate possible beneficial effects of methylphenidate on sleep.[16,17] Another problem that occurred earlier during therapy and most probably was related to increased levels of donepezil, was salivation. The symptom also depends on the peripheral effect on cholinergic fibres and is unlikely to have much to do with the severity of the dementia process itself.[12] In the case of a significantly exacerbated symptom, the problem is that most agents reducing salivation have cholinolytic effects, ie, potentially adverse impact on cognitive functions. In this case, methylphenidate may prove to be an acceptable agent.[18]

In both of the cases described, methylphenidate was discontinued after quite a short time. In the first case, some adaptation to donepezil probably occurred, which caused nightmares to disappear. The continued use of methylphenidate was not justified in that case. The second patient developed irritability and impulsive behaviour. Although they had already been reported earlier and were initially eliminated with the reduction of daily sleepiness, they may accompany the use of methylphenidate.[19] That was why it was decided to discontinue the drug.

Sleep disorders, reversal of the daily rhythm, excessive daytime sleepiness and sleeplessness at night are common in AD.[20] Alterations in the suprachiasmatic nucleus and melatonin secretion are the major factors linked with the cause of Circadian Rhythm Disturbances in AD.[21] Circadian Rhythm Disturbances are among the most common reasons for institutionalisation of individuals with AD.[22] Excessive daytime sleepiness is one of the clinical manifestations with which they present. There have been previous attempts to treat it with methylphenidate.[21] In the presented two cases, the use of methylphenidate has brought an immediate clinical effect, improving the night's sleep and the daytime functioning. The choice of this agent was determined, on the one hand, by its earlier use in the cases of excessive daytime sleepiness[23] and, on the other hand, by reports of use in AD patients.[24–27]

In the AD group, methylphenidate was used to reduce the symptoms of apathy with encouraging results.[24,25,27,28] Moreover, a positive trend was noted in the assessment of overall cognitive functioning[22,27] and attention.[28] Previous research indicates that methylphenidate is relatively safe to use in this clinical population.[25–27] However, the use of methylphenidate was accompanied by close monitoring of its safety profile. At present, indications for methylphenidate use include diagnostic categories other than dementia and different age groups. There are extremely few studies conducted on elderly people, especially those with dementia, hence it is necessary to maintain great caution in the use of methylphenidate.

Disclosure

The authors report no conflicts of interest for this work.

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