

## Disinhibition Associated with Long-term Use of Donepezil

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### Abstract

Neuropsychiatric adverse events related to the long-term use of donepezil are not well known. Herein we report on two very elderly patients with Alzheimer's disease in whom Disinhibition occurred after at least 5 years of oral donepezil.

Neither of the two patients (one an 88-year-old woman and the other a 98-year-old woman) had a history of pre-existing psychiatric disorder, and no adverse events had been noted after starting donepezil prior to the development of Disinhibition. After discontinuation of donepezil, Disinhibition resolved within 1-2 months, during which time there were no physical, environmental, or other prescription changes.

A causal relationship between donepezil and Disinhibition was considered to be present. There have been no reports of Disinhibition associated with donepezil use in patients with Alzheimer's disease. As we enter into a super-aging society, further studies are needed to determine how long donepezil should be administered.

**Keywords:** Donepezil; Disinhibition; Alzheimer's disease; Long term; Adverse event

### Introduction

Donepezil, a drug used worldwide in the treatment of dementia, effectively improves cognitive function in patients with dementia with Lewy bodies and Alzheimer's disease. The most commonly reported adverse events related to donepezil include nausea and/or diarrhea, insomnia, and dizziness. Most studies evaluating the effects of donepezil have been conducted over periods ranging from 6 months to a few years [1-5]. To the best of our knowledge, there have been no reports in which patients have been followed-up for more than 5 years; that is, the adverse events related to the long-term use of donepezil are not well known. One study followed-up patients treated with donepezil for 4.9 years and observed neuropsychiatric adverse events such as agitation, insomnia, and confusion [6]. However, the authors of that study speculated that many of the adverse events that occurred were related to symptoms of Alzheimer's disease [6]. In fact, the longer donepezil is used, the harder it becomes to determine causal relationships between adverse events and the drug.

Herein we report on two very elderly patients with Alzheimer's disease in whom Disinhibition occurred after they had been taking donepezil orally for at least 5 years and who recovered from Disinhibition soon after discontinuation of this medication.

### Case Report

#### Case 1

The first patient, an 88-year-old woman, was originally an introverted person with no history of mental illness. She had visited a neurology department with a chief complaint of forgetfulness 9 years earlier. At that time, the patient's Hasegawa Dementia Scale-Revised (HDS-R) [7] score was 23; a diagnosis of Alzheimer's disease was made and the patient was started on donepezil. Thereafter, donepezil 5 mg/day was prescribed by the patient's family doctor in accordance with the neurologist's instructions. The patient's course was uneventful, with no particular adverse reactions. However, the dementia gradually progressed and the patient had started receiving day care services 2 years earlier because she was unable to remember where the bathroom was located at home. In the summer of 2012, the patient was noted to be talking in a harsh tone and in a loud voice. In addition, she was

easily angered about trivial matters and repeatedly banged on the table when she needed something. At home, the patient developed sleeplessness, walking around the house during the night. While receiving day care services, the patient sang loudly and continuously songs that she remembered from her childhood, thereby annoying others. She presented to our hospital in November 2012. While in the waiting room, the patient sang songs loudly. She greeted us in high spirits and told us her name in answer to our questions, but would not answer questions relevant to the HDS-R and Mini-Mental State Examination (MMSE), saying only "I don't know" and continuing to sing songs. Computed tomography (CT) showed medial temporal atrophy of the brain. Medical assessments performed by the patient's family doctor had identified no physical conditions that could have contributed to the onset of behavioral symptoms. According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), the patient was diagnosed with Alzheimer's disease. Donepezil 5 mg, the only oral medication the patient was taking, was discontinued and the patient's condition was followed-up. Three weeks after donepezil discontinuation, the patient's continuous singing had decreased, as had the hyper kinesis at night. Seven weeks after donepezil discontinuation, the patient was able to sleep well. She remained mildly irritated and occasionally sang songs, but was very much calmer compared with her state at the time of her first visit. Eleven weeks after donepezil discontinuation, the patient's mental status had improved to a state of calmness and she no longer sang songs continuously. The patient could communicate with others, showing no decrease in activities of daily living (ADL). Her family told us that she had returned to her former state and so hospital treatment was considered to be complete.

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## Case 2

The second patient, a 98-year-old woman, was originally a mild-mannered person with no history of mental illness. Forgetfulness was becoming more noticeable with aging, although it was not certain when the forgetfulness had appeared initially. According to the patient's family doctor's records, her HDS-R score, which had been assessed 7 years earlier, was 19. The patient had been started on donepezil by the family doctor 5 years earlier because of severe forgetfulness. Her HDS-R score at that time was 18. Dementia gradually progressed and the patient's HDS-R score 3 years prior to her presentation was 10, showing a declining trajectory. Hypobulia was noted because the patient appeared to be mentally inactive. Thus, she started receiving day care services. One year earlier, the patient was no longer able to recognize her own house or family. The dose of donepezil was therefore increased to 10 mg. However, because of decreased initiative, the patient was unwilling to do anything and simply lay in bed at home. Late in November 2015, the patient started to talk continuously during the day care service and did not eat lunch because of excitement. Physical examination and blood biochemistry suggested that there were no physical conditions that could have contributed to the behavioral change. Considering a possible effect of the medication, the patient's family doctor reduced the dose of donepezil to 5 mg, but there was no change in the patient's behavior. The patient continued talking at home and tried to go out on her own, saying "I'm going to meet my sister". The patient appeared to have developed Disinhibition and was brought to our hospital in December 2015.

At the time of the first visit, the patient had an HDS-R score of 8 and an MMSE score of 8, consistent with severe dementia. CT showed diffuse brain atrophy, but no space-occupying lesion. According to the DSM-IV, the patient was diagnosed with Alzheimer's disease. The patient was smiling and in high spirits, but had difficulty communicating with others because of hearing impairment. The patient's prescriptions at that time were an antihypertensive (one tablet) and donepezil 5 mg. The donepezil was discontinued and follow-up examinations were performed. Five weeks after donepezil discontinuation, irritability was alleviated and the patient no longer talked continuously. Ten weeks after donepezil discontinuation, the patient's mental state had reverted to her former condition, with no changes noted in her ADL, and so hospital treatment was considered to be complete.

## Discussion

Both patients in this report had used donepezil for at least 5 years. No adverse events had been noted prior to the development of the symptoms described herein, for which the families of both patients sought treatment. Accordingly, donepezil was considered to have been appropriately administered to these patients for several years after the initiation of treatment. Disinhibition completely resolved within 1-2 months after discontinuation of donepezil, during which time there were no physical changes in the patients and no environmental changes. Therefore, a possible causal relationship between donepezil and Disinhibition was considered to be present. Considering that donepezil has a long half-life in the blood (approximately 90 h), it is not unreasonable to speculate that the symptoms of Disinhibition resolved following the discontinuation of this medication.

It has been reported that 11% of patients with Alzheimer's disease exhibited Disinhibition during follow-up over 4 years [8]. However, there have been no reports on Disinhibition potentially associated with the use of donepezil. The occurrence of "donepezil-induced mania" has occasionally been reported in patients with a history of mood disorder

in their youth who developed a manic state within several weeks of starting donepezil treatment [9]. These cases differ from the patients reported herein in that neither of our two patients had a past history of mental illness and the duration of donepezil use was long, suggesting a different mechanism of symptom onset from that of previously reported cases.

Patients with Alzheimer's disease first manifest disorders of the posterior association areas, such as the temporal and parietal lobes, and then develop disorders of the anterior association areas as the disease progresses [10]. Because approximately 10 years had passed since Alzheimer's disease had developed in our two patients, the development of Disinhibition in these patients may have been associated with decreased frontal lobe function due to the progression of dementia. It may also have been associated with the fact that both women were very elderly. It is common for very elderly patients with Alzheimer's disease to also have argyrophilic grain dementia. Thus, brain pathologies other than Alzheimer's disease may have been involved in the events that occurred in the two patients described herein.

Nearly 20 years have passed since donepezil was launched on the market and it is certain that this drug is effective for Alzheimer's disease. However, there are limited studies focusing on the long-term use of donepezil considering factors such as treatment duration, the upper limit of the age range of patients for whom this drug can be used, and the severity of dementia for which it would be appropriately indicated [11-15]. Particularly in Japan, there is a tendency for drugs, once they have been started for dementia, not to be readily discontinued. This could be due to medical professionals not being able to determine when to discontinue dementia drugs and patients' families strongly desiring the continuous use of these drugs. In terms of the safety of pharmacological treatment and reducing medical costs in a super-aging society, we come to a stage where we need to re-evaluate the use of donepezil in this context.

## Conclusion

We have presented case reports of two very elderly patients with Alzheimer's disease in whom Disinhibition occurred after the long-term use of donepezil. As we enter into a super-aging society, these cases raise the question as to how long donepezil should be administered. Further investigations of this issue are needed.

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