Received: 28 January 2022 | Revised: 19 March 2022 | Accepted: 23 March 2022

DOI: 10.1002/pcn5.14

CASE REPORT

PCN Reports
Psychiatry and Clinical Neurosciences
Open Access

Guanfacine for irritability, impulsivity, and agitation in elderly patients: A report of two cases

Takafumi Miyoshi MD[1] | Yayoi Noborio[2] | Chang Hoonhwa[3] | Yuki Ishimori[4]

[1]Department of Psychiatry, Itami City Hospital, Itami-shi, Hyogo, Japan

[2]Department of Nursing, Itami City Hospital, Itami-shi, Hyogo, Japan

[3]Department of Psychology, Itami City Hospital, Itami-shi, Hyogo, Japan

[4]Department of Pharmacy, Itami City Hospital, Itami-shi, Hyogo, Japan

Correspondence
Takafumi Miyoshi, MD, Department of Psychiatry, Itami City Hospital, 1-100 Koyaike, Itami-shi, Hyogo 664-8540, Japan.
Email: taka-344@hotmail.co.jp

Funding information
None

Abstract

Background: Irritability, impulsivity, and agitation in elderly patients with dementia are highly prevalent and extremely burdening for patients, caregivers, and medical staff. In general hospitals, they have been one of the major problems that develop and disturb care and treatment. However, the mechanisms underlying these symptoms remain unclear, and there is no established treatment. In actual clinical practice, antipsychotic drugs and mood stabilizers have been mainly used as pharmacotherapies for these symptoms, but adverse effects of these drugs have often been problematic.

Case Presentation: We report two valuable cases of elderly patients who were admitted to our hospital due to physical disorders and developed irritability, impulsivity, and agitation, which were effectively treated with guanfacine at very low doses and in a short period.

Conclusion: The present cases suggest that guanfacine may be a therapeutic option for treating irritability, impulsivity, and agitation in elderly patients.

KEYWORDS
agitation, elderly patients, guanfacine, impulsivity, irritability

BACKGROUND

Irritability, impulsivity, and agitation (including rough behavior) in elderly patients with dementia are highly prevalent and extremely burdening for patients, caregivers, and medical staff.[1,2] In general hospitals, they have been one of the major problems that develop and disturb care and treatment and, furthermore, can lead to injury to nurses. Finkel et al. defined these symptoms as behavioral and psychological symptoms of dementia (BPSD).[3] Antipsychotic drugs and mood stabilizers have been mainly used as pharmacotherapies for BPSD, but their adverse events have often been problematic.[4,5]

We present valuable cases of elderly patients who were admitted to our general hospital due to physical disorders and developed irritability, impulsivity, and agitation, which were effectively treated with guanfacine.

CASE PRESENTATION

Case 1

Five years before the first visit, a 77-year-old man had undergone hematoma-removal surgery for chronic subdural hematoma at

Hospital A. Approximately 4 years before the first visit, he had begun to show signs of memory loss, and 3 years prior to the first visit, he had visited the outpatient memory clinic at Hospital B. At that time, he was diagnosed with Alzheimer's disease (AD) based on his symptoms and his cognitive test results of Mini Mental State Examination 22/30 and Alzheimer's Disease Assessment Scale 13/70. A head MRI showed cerebral atrophy mainly in the bilateral hippocampus, and single photon emission computed tomography showed decreased blood flow in the bilateral posterior cingulate gyrus and precuneus. In August of the year of his first visit to our hospital, he was admitted to Hospital C for perforated peritonitis and underwent surgery. He was diagnosed with rectal cancer and peritoneal dissemination and was transferred to our surgical department in October of the same year. From the time of admission, the patient showed significant agitation, shouting, frequent toilet requests, verbal abuse, kicking the table, refusal of care, and so forth. He was referred to the department of psychiatry the day after being admitted.

Regarding the symptoms present at the time of initial examination, his consciousness was clear, and his eyes were sharp and stern. He was very irritable and unable to hold a conversation, so his cognitive function was unclear. No apparent focal neurological findings were noted. Psychiatric findings included irritability, impulsivity, and agitation (including rough behavior). There were no psychotic symptoms, such as hallucinations and delusions, and no depressive symptoms, such as depressed mood or decreased motivation. There was nothing to be noted in his vital signs and laboratory data. He needed assistance for activities of daily living (ADLs). His history of physical disorders included hypertension, chronic subdural hematoma, left shoulder fracture, and pneumonia; on the other hand, there was a psychiatric disorder history of alcohol abuse. The main medications he had been taking at the time of the first visit to our department were risperidone 1 mg, carbocisteine 150 mg, vonoprazan fumarate 20 mg, and magnesium oxide 990 mg. According to his developmental and life history, he had been short-tempered and often shouted at home. He had been a heavy alcohol drinker, who often fell and hit his head. He had been sober for 3 years before the first visit.

There were no findings suggestive of delirium, such as altered levels of consciousness and a fluctuating course. No obvious discomfort was observed, such as pain or itching, that could account for the behavioral disorders. We considered the above psychiatric symptoms to be BPSD associated with AD. We judged that nonpharmacological intervention would be difficult due to the severity of the symptoms, and we initiated pharmacotherapy. We discontinued administration of risperidone. Various psychotropic drugs, such as quetiapine 50 mg, tiapride 150 mg, and olanzapine 5 mg, were subsequently administered from Days 1 to 35, but no significant effects were seen. On Day 36, we started guanfacine 1 mg. His irritability and impulsivity began to decrease on Day 38. After that, irritability and impulsivity gradually improved, and then agitation markedly decreased. Smiles were occasionally seen, civility was observed, and conversation became slightly more feasible. However, because the shouting continued, we increased guanfacine to 2 mg on Day 43. After that, his shouting decreased, and by Day 48, his psychiatric symptoms improved to the extent that he was only sometimes agitated and shouting, and he was able to hold a conversation. The patient was discharged home on Day 60. There were no adverse events caused by guanfacine during the course of treatment. Prescriptions at discharge from our hospital were guanfacine 2 mg, olanzapine 5 mg, memantine 20 mg, lemborexant 5 mg, vonoprazan fumarate 20 mg, and magnesium oxide 990 mg.

Case 2

Approximately 10 years before the first visit, a 78-year-old man, who had begun to show signs of memory loss and violent behavior toward his wife, had visited a nearby doctor and was diagnosed with dementia; however, the details were unclear. Then, his forgetfulness progressed, and he often became confused about how to eat or use the bathroom. He had been living with his wife, but due to the increased burden of care, including violent behavior, he had been staying in a group home. In June of the year of his first visit, he was admitted to the department of surgery in our hospital for an appendectomy for his cecal cancer. He was referred to the department of psychiatry on the same day of his admission because of his refusal and resistance to care and his rough behavior toward nurses.

Regarding his symptoms present at the time of the initial examination, his consciousness was clear, and conversation was possible, but communication was superficial. His facial expression was calm. We attempted a cognitive function test, but it could not be performed. We also could not perform brain-imaging studies due to the patient's inability to maintain rest. On examination, the patient's cognitive deficits were marked, especially in recent memory, orientation, and attention. No focal neurological findings were noted. Psychiatric findings included irritability, impulsivity, and agitation. Rough behavior was often seen as impulsive behavior, especially during care and treatment, such as diaper changes, and when trying to stop the patient from leaving the ward. Wandering behavior was also observed. There were no psychotic symptoms or depressive symptoms. There was nothing to be noted in his vital signs and laboratory data. He was walking unaided but needed assistance for ADLs. His history of physical disorders included hypertension and prostate enlargement. On the other hand, delirium was the only psychiatric disorder, and there was no history of substance abuse. We could not determine his developmental history. The main medications at the time of the first visit to our department were quetiapine 25 mg, trazodone 25 mg, lemborexant 5 mg, and sodium ferrous citrate 100 mg.

There were no findings suggestive of delirium and no obvious discomfort. We considered the above psychiatric symptoms to be BPSD. We thought that AD was the most likely cause, but we could not clearly diagnose which type of dementia it was. For the same reasons as in Case 1, we determined that pharmacotherapy was the

best option. On Day 2 of hospitalization, laparoscopic tumor removal was performed. As the patient continued to show irritability, impulsiveness, and rough behavior, we started guanfacine 1 mg for these symptoms on Day 7. His irritability and impulsivity began to improve on Day 9 and continued to gradually improve thereafter. On Day 12, there was no more rough behavior. The patient was discharged on Day 17. Delirium was not observed during the course of the disease, including after the surgery. There were no adverse events with guanfacine. Prescriptions at discharge from our hospital were guanfacine 1 mg, quetiapine 25 mg, trazodone 25 mg, lemborexant 5 mg, and sodium ferrous citrate 100 mg. One limitation was that no change was observed in his wandering behavior.

DISCUSSION

The neural basis and underlying mechanisms of irritability, impulsivity, and agitation in elderly patients with dementia remain to be clearly elucidated. Although there are few reports on these symptoms, it has been pointed out that they are linked to the prefrontal cortex, insula, amygdala, cingulate gyrus, and hippocampus.[6–8] The prefrontal cortex, especially the dorsolateral prefrontal cortex (dlPFC), has been reported to be involved in disinhibition, aggression, attentional dysfunction, and hypoactive working memory.[9–11]

Guanfacine, a therapeutic agent for attention-deficit/hyperactivity disorder (ADHD), is a selective α2A agonist that stimulates α2A receptors in the prefrontal cortex and enhances the function of the dlPFC. Then, the dlPFC provides top-down regulation of the sympathetic nervous system, which consists of the amygdala, basal ganglia, and brainstem, resulting in augmented working memory, attention, and impulse control.[12–16] In addition, guanfacine directly reduces tonic firing of locus coeruleus neurons, resulting in arousal control and regulation of the interpretations of and behavioral responses to sensory stimuli in coordination with the cerebral cortex.

We assume that guanfacine administration may have enhanced dlPFC function and reduced excessive tonic firing of locus coeruleus neurons, resulting in improvements in irritability, impulsivity, and agitation in these patients. There were no adverse events, and guanfacine was well tolerated. In the present cases, it was characterized by the fact that the effects were observed at a very low dose of 1–2 mg and that the onset of the effects was rapid at 2–3 days compared with the optimal dose and the general onset of effects in children and young adults with ADHD. In addition, our patients' behaviors seemed as if they were reflexive and their attentional function seemed to improve as this reflexive behavior decreased. Guanfacine is a well-tolerated drug with fewer side-effects[17–21] than antipsychotics and mood stabilizers, so we consider that it is worthwhile to administer guanfacine to patients with AD with frontal lobe dysfunction[8] that results in reflexive irritability, impulsivity, and agitation.

Limitations are that we could not accurately evaluate the type of dementia in the second patient, and we could not differentiate the diagnosis between BPSD and ADHD manifesting in old age, mainly due to the difficulty of obtaining a detailed early developmental history in our patients.[22] In addition, we could not assess their frontal lobe function using, for example, the frontal assessment battery or Wisconsin Card Sorting Test, before and after guanfacine administration, because of the significant psychiatric symptoms and cognitive decline.

CONCLUSION

To the best of our knowledge, the present report is the first to demonstrate the efficacy of guanfacine in irritability, impulsivity, and agitation in elderly patients. We believe that it is important to accumulate more cases in the future.

AUTHOR CONTRIBUTIONS

All authors participated in discussing, writing this manuscript, and revisions. All read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

We would like to thank the members of the psychiatric liaison team in our hospital. We also give special thanks to the patients and their families. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

ETHICS APPROVAL STATEMENT

This study complied with the CARE guidelines for case reports. For the off-label use of guanfacine, we explained the expected effects and possible adverse events in detail to the patients and their families and obtained their consent before prescribing the drug.

PATIENT CONSENT STATEMENT

This study received written consent from the patients and their families.

ORCID

Takafumi Miyoshi http://orcid.org/0000-0003-0792-804X

REFERENCES

1. Goldberg SE, Whittamore KH, Harwood RH, Bradshaw LE, Gladman JR, Jones RG, et al. The prevalence of mental health

problems among older adults admitted as an emergency to a general hospital. Age Ageing. 2012;41(1):80–6.
2. Hallikainen I, Koivisto AM, Välimäki T. The influence of the individual neuropsychiatric symptoms of people with Alzheimer disease on family caregiver distress - a longitudinal ALSOVA study. Int J Geriatr Psychiatry. 2018;33:1207–12.
3. Finkel SI, Costa e Silva J, Cohen G. Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. Int Psychogeriatr. 1996;8(Suppl 3):497–500.
4. The Guideline Committee Under the Supervision of the Japanese Society of Neurology. Practice guideline for dementia 2017. Tokyo: Igaku-Shoin Ltd; 2017.
5. The Guideline Committee Under the Supervision of the Japan Geriatrics Society. Guidelines for medical treatment and its safety in the elderly 2015. Tokyo: Medical View Co., Ltd; 2015.
6. Trzepacz PT, Yu P, Bhamidipati PK, Willis B, Forrester T, Tabas L, et al. Frontolimbic atrophy is associated with agitation and aggression in mild cognitive impairment and Alzheimer's disease. Alzheimers Dement. 2013;9(5 Suppl):S95–104.
7. Brunoni AR, Marie-Anne Vanderhasselt MA. Working memory improvement with non-invasive brain stimulation of the dorsolateral prefrontal cortex: a systematic review and meta-analysis. Brain Cogn. 2014;86:1–9.
8. Ossenkoppele R, Singleton EH, Groot C, Dijkstra AA, Eikelboom WS, Seeley WW, et al. Research criteria for the behavioral variant of alzheimer disease: a systematic review and meta-analysis. JAMA Neurol. 2022;79(1):48–60.
9. Wu Y, Xu W, Liu X, Xu Q, Tang L, Wu S. Adjunctive treatment with high frequency repetitive transcranial magnetic stimulation for the behavioral and psychological symptoms of patients with Alzheimer's disease: a randomized, double-blind, sham-controlled study. Shanghai Arch Psychiatry. 2015;27(5):280–8.
10. Nakayama S, Suda A, Nakanishi A, Motoi Y, Hattori N. Galantamine response associates with agitation and the prefrontal cortex in patients with Alzheimer's disease. J Alzheimers Dis. 2017;57(1):267–73.
11. Alves GS, Carvalho AF, de Amorim de Carvalho L, Sudo FK, Siqueira-Neto JI, Oertel-Knochel V, et al. Neuroimaging findings related to behavioral disturbances in Alzheimer's disease: a systematic review. Curr Alzheimer Res. 2017;14(1):61–75.
12. Arnsten AF, Raskind MA, Taylor FB, Connor DF. The effects of stress exposure on prefrontal cortex: translating basic research into successful treatments for post-traumatic stress disorder. Neurobiol Stress. 2015;1:89–99.
13. Arnsten AF. Stress weakens prefrontal networks: molecular insults to higher cognition. Nat Neurosci. 2015;18(10):1376–85.
14. Jäkälä P, Riekkinen M, Sirviö J, Koivisto E, Riekkinen P Jr. Clonidine, but not guanfacine, impairs choice reaction time performance in young healthy volunteers. Neuropsychopharmacology. 1999;21(4):495–502.
15. Jäkälä P, Riekkinen M, Sirviö J, Koivisto E, Kejonen K, Vanhanen M, et al. Guanfacine, but not clonidine, improves planning and working memory performance in humans. Neuropsychopharmacology. 1999;20(5):460–70.
16. Wang M, Ramos BP, Paspalas CD, Shu Y, Simen A, Duque A, et al. Alpha2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. Cell. 2007;129(2):397–410.
17. Miyoshi T, Mizushima C, Noborio Y, Kimoto Y, Nakaharu Y, Shimamoto S. Efficacy of combination therapy with gabapentin and guanfacine for paroxysmal sympathetic hyperactivity following hypoxic encephalopathy: a case report. J Int Med Res. 2021;49(4):3000605211009721.
18. Iwanami A, Saito K, Fujiwara M, Okutsu D, Ichikawa H. Efficacy and safety of guanfacine extended-release in the treatment of attention-deficit/hyperactivity disorder in adults: results of a randomized, double-blind, placebo-controlled study. J Clin Psychiatry. 2020;81(3):19m12979.
19. Scahill L, McCracken JT, King BH, Rockhill C, Shah B, Politte L, et al. Extended-release guanfacine for hyperactivity in children with autism spectrum disorder. Am J Psychiatry. 2015;172(12):1197–206.
20. Iwanami A, Saito K, Fujiwara M, Okutsu D, Ichikawa H. Efficacy and safety of guanfacine extended-release in the treatment of attention-deficit/hyperactivity disorder in adults: results of a randomized, double blind, placebo-controlled study. J Clin Psychiatry. 2020;81(3):19m12979.
21. Jiang S, Czuma R, Cohen-Oram A, Hartney K, Stern TA. Guanfacine for hyperactive delirium: a case series. J Acad Consult Liaison. Psychiatry. 2021;62(1):83–8.
22. Sasaki H, Jono T, Fukuhara R, Yuki S, Ishikawa T, Boku S, et al. Late-onset attention-deficit/hyperactivity disorder as a differential diagnosis of dementia: a case report. BMC Psychiatry. 2020;20(1):550.

How to cite this article: Miyoshi T, Noborio Y, Hoonhwa C, Ishimori Y. Guanfacine for irritability, impulsivity, and agitation in elderly patients: A report of two cases. Psychiatry Clin. Neurosci. Rep. 2022;1:e14.
https://doi.org/10.1002/pcn5.14