

5-HT_{1A} Partial Agonist Tansospirone for Behavioral and Psychological Symptoms in Oldest-old Patients with Dementia at a Special Elderly Nursing Home

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Objective: To investigate the efficacy of tandospirone, an azapirone anxiolytic similar to buspirone that is used in Japan, for behavioral and psychological symptoms of dementia (BPSD), especially in oldest-old patients.

Methods: This was an open-label observational study involving residents with BPSD in a special elderly nursing home between August 2013 and August 2018. The severity of dementia was assessed using the Clinical Dementia Rating (CDR) scale; as the main outcomes, the severity of BPSD was assessed using the Clinical Global Impressions-Severity scale (CGI-S) and Neuropsychiatric Inventory-12 (NPI-12) at baseline and 4 weeks after the maintenance dose of tandospirone was reached. The administration of tandospirone started at 30 mg, divided into three doses per day. Two weeks later, if the efficacy was sufficient based on the clinical nursing record, that dose was continued; if the efficacy was insufficient, the daily dose was increased from 40 mg/day to a maximum dose of 60 mg/day.

Results: Thirty-three participants (25 females [76%], mean age 87.1 ± 5.4 years) completed the study. Twenty-three participants (70%) were oldest-old (18 females [78%], mean age 89.9 ± 3.4 years). The mean CDR score was 2.9 ± 0.3 in all participants. Tandospirone treatment showed few or no obvious adverse effects and significantly improved CGI-S scores, as well as total scores and many subscale scores on the NPI-12, in both the sample at large and the oldest-old participants.

Conclusion: This study demonstrated the efficacy and safety of tandospirone for BPSD in oldest-old participants.

KEY WORDS: Behavioral and psychological symptoms of dementia; Dementia; Aged, 80 and over; Observational study; Serotonin receptor agonists; Tandospirone.

INTRODUCTION

Globally, over 40 million patients are diagnosed with dementia, and the number is thought to have doubled in the last 20 years [1]. The number of people over 85 years of age (oldest-old) and the prevalence of dementia in that age range are also increasing every year. Behavioral and psychological symptoms of dementia (BPSD), such as hallucinations, delusions, agitation, depression, and anxiety, often decrease patients' quality of life and cause distress in family members and caregivers [2-4].

Non-psychopharmacological interventions for BPSD, such as supportive, environmental, and psychosocial interventions, are needed as first-line treatments [5,6], and a meta-analysis of these interventions reported that they were useful [7]. If non-psychopharmacological interventions are insufficient, psychopharmacological interventions for BPSD may be needed. However, antipsychotic medications may increase mortality in elderly persons [8-10], and a meta-analysis showed that benzodiazepine medications also increase the risk of severe adverse effects, such as hip fractures, in elderly persons [11]. Cholinesterase inhibitors such as donepezil have shown inconsistent effects on BPSD, sometimes improving and sometimes worsening patients' condition [12]. Therefore, safer psychopharmacological treatment for BPSD should be considered in elderly persons, especially oldest-old persons. However, to the best of our knowledge, there is little evi-

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dence on pharmacological interventions for BPSD in oldest-old patients.

Tandospirone, an azapirone anxiolytic similar to buspirone that is used in Japan, is a partial agonist of the 5-hydroxytryptamine (5-HT)_{1A} receptor and is reported to have a lower risk of sedative effects, cognitive impairment, and withdrawal symptoms than benzodiazepines [13,14]. However, only a few previous studies have reported the efficacy of azapirone derivatives for BPSD [15-17]. Furthermore, there has been no previous study involving oldest-old persons except for our previous case report [18]. In the present study, the efficacy of tandospirone for BPSD, especially for oldest-old patients, was investigated.

METHODS

Study Design

This was an open-label observational study. The participants were residents in a special elderly nursing home who presented with BPSD; subjects with or without a history of psychotropic medication use were included. If they had a serious physical illness; a history of intellectual disability; or a history of psychiatric disorders, such as schizophrenia, schizoaffective disorder or bipolar disorder, they were excluded from the study. If other psychotropic medications were being taken at baseline, no other psychotropic medications except tandospirone were added or changed until assessment of the main outcomes in this intervention. First, the physician performed physical and laboratory examinations to exclude mental states related to several illnesses that could be treated medically. Second, nonpharmacological interventions such as environmental coordination were examined for at least 1 month. Third, we assessed the severity of BPSD at baseline and began to administer tandospirone. All patients or their legal guardians signed written informed consent forms approved by the institutional ethics committees of Nursing Home Galilee, which conformed to the provisions of the Declaration of Helsinki. We calculated the sample size based on Matsuda's study [16] and Sato's study [17]. In order to detect significance with a power of 0.80 at $\alpha = 0.05$ at an effect size of $d = 0.8$, 15 participants were needed. Participants moved into the nursing home between August 2013 and August 2018. All patients diagnosed with dementia had Alzheimer's disease (AD), vascular dementia (VD), AD with comorbid VD, or dementia

with Lewy bodies (DLB), according to the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association diagnostic criteria [19], the National Institute of Neurological Disorders and Stroke-Association International pour la Recherche et l'Enseignement en Neurosciences criteria [20], or the Consortium on DLB International Workshop 2005 or 2017 criteria [21,22]. The severity of dementia was assessed using the Clinical Dementia Rating (CDR) [23]; as the main outcomes, the severity of BPSD was assessed using the Clinical Global Impressions-Severity scale (CGI-S) [24] and Neuropsychiatric Inventory-12 (NPI-12) [25] at baseline and 4 weeks after the maintenance dose of tandospirone was reached. In order to evaluate participants fairly, one nurse consistently assessed the CGI-S and NPI-12 scores based on the reports of caregivers and nurses. The administration of tandospirone started at 30 mg, divided into three doses per day. Two weeks later, if the efficacy was sufficient based on the clinical nursing record, that dose was continued; if the efficacy was insufficient, the daily dose was increased from 40 mg/day to a maximum dose of 60 mg/day. CGI-S and NPI-12 scores were assessed once the participants had been stable for at least four weeks after the establishment of the maintenance dose.

For safety, staff members measured vital signs every day, and after the study, physicians performed physical and laboratory examinations again.

After assessment of the main outcomes of tandospirone intervention, antipsychotic and benzodiazepine doses were decreased. The mean doses of antipsychotics and benzodiazepines at baseline were converted to chlorpromazine and diazepam equivalents, respectively.

Statistical Analysis

We calculated the sample size using G*Power 3 based on the results of previous studies [26]. Other statistical analyses were performed with SPSS 22.0 (IBM Co., Armonk, NY, USA). The CGI-S scores, NPI-12 scores, chlorpromazine equivalent doses, and diazepam equivalent doses were recorded and tested for normality using the Shapiro-Wilk test. Then, the changes in all participants, including oldest-old participants, were analyzed using the Wilcoxon signed-rank test. Descriptive statistics are expressed as the means \pm standard deviation. Significance was defined at the 95% level (p value < 0.05).

Table 1. Patient characteristics

Variable	All participants	Only participants over 85 years old
Sex (female:male)	25:8	18:5
Age (yr)	87.1 ± 5.4 (73–96)	89.9 ± 3.4 (85–96)
Diagnosis of dementia		
Alzheimer's disease (AD)	15	11
Vascular dementia (VD)	12	10
AD + VD	2	2
Dementia with Lewy bodies	4	0
Durations of dementia (yr)	6.8 ± 4.4 (1–17)	6.9 ± 4.4 (1–17)
Clinical dementia rating	2.9 ± 0.3	2.9 ± 0.3
Prescribed antedementia drugs	4	1
Prescribed antihypertensive drugs	19	13
Prescribed anticoagulants	11	8
Prescribed hypoglycemic drugs or insulin	2	2
Prescribed hypolipidemic drugs	7	4
Prescribed antipsychotics	10	8
Mean dose of antipsychotics (mg/day)	75.0 ± 41.2	82.8 ± 42.8
Prescribed benzodiazepines	6	4
Mean dose of benzodiazepines (mg/day)	4.9 ± 3.4	5.5 ± 4.1
Mean dose of tandospirone (mg/day)	48.2 ± 15.1	47.0 ± 15.5

Values are presented as number only or mean ± standard deviation (range).

Mean doses of antipsychotics are given in chlorpromazine equivalents. Mean doses of benzodiazepines are given in diazepam equivalents.

RESULTS

Thirty-five participants joined this study, and two participants dropped out because of early nausea or vomiting; thus, 33 participants completed the study. The characteristics of the participants are shown in Table 1. The mean age was 87.1 ± 5.4 (73–96) years, and 25 participants (76%) were female. Twenty-three participants (70%) were oldest-old. Their mean age was 89.9 ± 3.4 (85–96) years, and 18 participants were female (78%). AD was the most common diagnosis in both groups. The duration of dementia was 6.8 ± 4.4 (1–17) years. The mean CDR score was 2.9 ± 0.3 in all participants. At baseline, four participants were receiving antedementia medications (1 receiving donepezil only, 1 receiving rivastigmine only, 1 receiving memantine only, 1 receiving both donepezil and memantine), nineteen were receiving antihypertensive medications, eleven were receiving anticoagulant medications, two were receiving hypoglycemic medications or insulin, seven were receiving hypolipidemic medications, ten were receiving antipsychotic medications, and six were receiving benzodiazepines. Among the oldest-old participants, one was receiving donepezil, eight were receiving antipsychotics, and four were receiving benzodiazepines at baseline. The changes in the

CGI-S and NPI-12 scores of all participants are shown in Table 2, and the changes specifically in the oldest-old participants are shown in Table 3. After 4 weeks of fixed-dose treatment, the mean dose of tandospirone was 48.2 ± 15.1 mg/day in all participants and 47.0 ± 15.5 mg/day in oldest-old participants. CGI-S scores were significantly improved in both all participants ($p < 0.001$) and oldest-old participants ($p < 0.001$), and NPI-12 total scores were significantly improved both in the overall group of participants ($p < 0.001$) and in the oldest-old participants ($p < 0.001$). In the overall sample, there were significant improvements on the following nine subscales of the NPI-12: delusions ($p = 0.028$); agitation/aggression ($p = 0.005$); depression/dysphoria ($p = 0.005$); anxiety ($p = 0.001$); apathy/indifference ($p = 0.026$); disinhibition ($p = 0.018$); irritability/lability ($p = 0.002$); nighttime behavioral disturbances ($p = 0.017$); and appetite and eating abnormalities ($p = 0.027$). Eight subscales of the NPI-12 were significantly improved in oldest-old participants, as follows: agitation/aggression ($p = 0.018$); depression/dysphoria ($p = 0.012$); anxiety ($p = 0.003$); apathy/indifference ($p = 0.039$); disinhibition ($p = 0.042$); irritability/lability ($p = 0.012$); nighttime behavioral disturbances ($p = 0.042$); and appetite and eating abnormalities ($p = 0.042$). Concerning safety, tandospirone was decreased to 20 mg/day

Table 2. Changes in CGI-S and NPI-12 scores from baseline after tandospirone initiation in all participants

Measure	Before administration	After 4 weeks at a fixed dose	<i>p</i> value
CGI-S	4.2 ± 1.0	3.1 ± 1.2	< 0.001***
NPI-12			
Total	28.4 ± 12.1	15.2 ± 13.6	< 0.001***
Delusions	2.8 ± 4.8	1.8 ± 3.7	0.028*
Hallucinations	1.7 ± 4.8	1.2 ± 3.3	0.18
Agitation/aggression	4.6 ± 4.4	3.3 ± 4.0	0.005**
Depression/dysphoria	2.5 ± 3.7	0.8 ± 1.8	0.005**
Anxiety	4.6 ± 4.9	1.9 ± 2.5	0.001**
Euphoria/elation	0	0	1
Apathy/indifference	0.8 ± 1.9	0.1 ± 0.5	0.026*
Disinhibition	1.8 ± 3.5	0.7 ± 1.7	0.018*
Irritability/lability	4.2 ± 4.6	2.7 ± 3.9	0.002**
Aberrant motor behavior	1.2 ± 2.7	0.8 ± 1.8	0.18
Nighttime behavioral disturbances	2.1 ± 2.5	1.2 ± 1.5	0.017*
Appetite and eating abnormalities	2.1 ± 4.2	0.8 ± 2.5	0.027*

Values are presented as mean ± standard deviation.

CGI-S, Clinical Global Impressions-Severity scale; NPI-12, Neuropsychiatric Inventory-12.

p* < 0.05, *p* < 0.01, ****p* < 0.001.

Table 3. Changes in CGI-S and NPI-12 scores from baseline after tandospirone initiation in participants > 85 years old

Measure	Before administration	After 4 weeks at a fixed dose	<i>p</i> value
CGI-S	4.0 ± 1.0	2.9 ± 1.1	< 0.001***
NPI-12			
Total	30.5 ± 12.9	15.8 ± 14.4	< 0.001***
Delusion	2.7 ± 5.0	1.5 ± 3.6	0.068
Hallucination	1.6 ± 4.1	0.9 ± 2.8	0.18
Agitation/aggression	4.6 ± 4.4	3.3 ± 4.0	0.018*
Depression/dysphoria	3.1 ± 4.1	1.0 ± 2.0	0.012*
Anxiety	5.2 ± 4.8	2.3 ± 2.8	0.003**
Euphoria/elation	0	0	1
Apathy/indifference	1.0 ± 2.1	0.1 ± 0.6	0.039*
Disinhibition	1.7 ± 3.4	0.7 ± 1.8	0.042*
Irritability/lability	4.3 ± 4.6	2.9 ± 3.9	0.012*
Aberrant motor behavior	1.5 ± 3.1	0.9 ± 2.0	0.18
Nighttime behavioral disturbances	2.2 ± 2.7	1.2 ± 1.4	0.042*
Appetite and eating abnormalities	2.7 ± 4.7	1.1 ± 3.0	0.042*

Values are presented as mean ± standard deviation.

CGI-S, Clinical Global Impressions-Severity scale; NPI-12, Neuropsychiatric Inventory-12.

p* < 0.05, *p* < 0.01, ****p* < 0.001.

in one participant because of sedation, which then improved. The others had no obvious adverse effects, including physical effects, during the study.

The mean dose of antipsychotics was significantly decreased after tandospirone intervention both in the general sample (75.0 ± 41.2 mg/day to 21.3 ± 52.1 mg/day, *p* = 0.011) and in the oldest-old participants (82.8 ± 42.8 mg/day to 20.3 ± 57.5 mg/day, *p* = 0.017). The mean dose of benzodiazepines tended to decrease, but not significantly, in both groups: all participants (4.9 ± 3.4 mg/day

to 1.3 ± 2.1 mg/day, *p* = 0.068) and the oldest-old participants (5.5 ± 4.1 mg/day to 0.6 ± 1.3 mg/day, *p* = 0.11).

DISCUSSION

This study's aim was to investigate the efficacy and safety of tandospirone for patients with BPSD for whom non-pharmacological interventions were ineffective. The results showed that the tandospirone treatment showed few or no obvious adverse effects and significantly improved

CGI-S scores, as well as total scores many subscale scores on the NPI-12, both in the overall group of participants and in the oldest-old participants. Furthermore, the mean dose of antipsychotics used at baseline was significantly decreased both in the overall group of participants and in the oldest-old participants after tandospirone intervention.

We performed this study in a nursing home. Nursing homes features less medical intervention than an in-patient environment and may therefore be closer to a real-world clinical environment, which would improve the applicability of these results to daily clinical situations.

Only a few previous studies have shown the efficacy of 5-HT_{1A} agonists for BPSD [15-17]. To the best of our knowledge, this is the first study of tandospirone for BPSD in oldest-old patients other than our previous case report [18]. The density of 5-HT_{1A} receptors in the temporal cortex is reported to be inversely correlated with aggression and dementia severity in AD patients [27], and the loss of 5-HT_{1A} receptors in the hippocampus is specifically correlated with depressive symptoms in AD patients [28]. 5-HT_{1A} receptors are associated with the late stages of AD pathology, such as Braak stages V-VI, and studies in post-mortem brains of AD patients showed a decreased density of 5-HT_{1A} receptors but not other receptors [29]. It has been reported that there is an association between BPSD and 5-HT_{1A} receptors. Rivastigmine, an inhibitor of acetylcholinesterase and butyrylcholinesterase, improves depression-like behaviors in mice, but 5-HT_{1A} antagonists block these improvements [30]. On the other hand, the administration of 5-HT_{1A} antagonists and 5-HT_{2A} receptor agonists reduced the loss of hippocampal neuronal cells and improved cognitive functions in AD model rats [31,32]. Therefore, 5-HT_{1A} receptors could play important roles in the pathogenesis of BPSD in patients with severe dementia regardless of cognitive function.

Compared to the previous study [16,17], the present study used a higher mean dose of tandospirone and found equal or better efficacy. We previously reported the dose-dependent efficacy of tandospirone for BPSD in an oldest-old patient [18], but to the best of our knowledge, no study has examined the appropriate dose of tandospirone for BPSD. For patients with anxiety disorders, 60 mg/day tandospirone had more significant anxiolytic effects than 30 mg/day, without significant adverse effects [33]. In a meta-analysis of 5-HT_{1A} agonists in augmentation therapy for schizophrenia, including four randomized, placebo-

controlled trials (RCTs) of buspirone, the higher dose of buspirone was significantly more effective than placebo [34]. As indicated by this study, a higher dose of a 5-HT_{1A} agonist may lead to better efficacy for BPSD even in oldest-old patients. Furthermore, in a rodent study, the anxiolytic effect of tandospirone was positively correlated with its plasma and brain concentrations [35], and tandospirone acted through the prefrontal cortex to induce dose-dependent suppression of the lactate increase caused by foot-shock stress [36]. A high dose of tandospirone may improve BPSD not only via 5-HT_{1A} receptors but also via these mechanisms, as lactate levels in the cerebrospinal fluid of AD patients were reported to be increased, and this increase was associated with a reduction in glucose consumption in the brain [37].

In psychopharmacological interventions for BPSD, antipsychotics and benzodiazepines are generally used, but several adverse effects, such as increased mortality and hip fractures, can occur. Therefore, clinicians must be careful of adverse effects. In this study, there were few obvious adverse effects even with the highest doses of tandospirone. However, two participants dropped out because of early nausea or vomiting, and one participant experienced mild sedation. When they stopped or decreased tandospirone, they improved. When tandospirone is used for BPSD, starting at a low dose and increasing the amount slowly could be the safest option. The weak point of tandospirone is its short half-life, which necessitates 2–3 doses per day, but this frequency is at least feasible in a nursing home.

This study has several limitations. First, the severity of dementia was not investigated in the participants because of their severe cognitive impairments. Second, this study had a relatively small sample size, and the number of males was particularly small because of the sex difference in life expectancy in Japan. According to the data from the Japanese Ministry of Health, Labor and Welfare, the average Japanese life expectancy was 81.25 years for males and 87.32 years for females in 2018 [38]. Third, this study was an open-label observational study, not an RCT. One nurse independently assessed the clinical evaluations based on the reports of caregivers and nurses to avoid bias, but selection and measurement biases could not be completely avoided. Fourth, in this study, we measured the scores beginning 2 weeks after tandospirone administration; we did not measure the effects at earlier time-

points, such as 1 week after tandospirone. Therefore, we cannot exclude any naturalistic improvement independent of the effect of tandospirone. Fifth, this study demonstrated the efficacy and safety of treatment in the short term only. Finally, although we confirmed the good efficacy and safety of tandospirone for BPSD in this open-label study, confirmatory statements should be made only after prospective or randomized controlled studies. Further studies are needed to determine the efficacy of 5-HT_{1A} agonists for BPSD.

In conclusion, this study demonstrated the significant efficacy and safety of tandospirone for BPSD in oldest-old participants. A relatively high dose of 5-HT_{1A} agonists appears to be safe and is able to improve BPSD even in oldest-old patients.

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■ Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

■ Author Contributions

Conceptualization: Shinichiro Ochi. Data acquisition: Shinichiro Ochi. Formal analysis: Shinichiro Ochi, Takaaki Mori, Shu-ichi Ueno. Supervision: Takaaki Mori, Jun-ichi Iga, Shu-ichi Ueno. Writing—original draft: Shinichiro Ochi. Writing—review & editing: Takaaki Mori, Jun-ichi Iga, Shu-ichi Ueno.

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