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Original Research Reports

Cognitive Dysfunction in Patients With Late-Life Somatic Symptom Disorder: A Comparison According to Disease Severity

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Background: *Late-life somatic symptom disorder (SSD) is characterized by various aging-associated factors, such as a functional decline, psychosocial problems, and cognitive dysfunction. However, the details of the cognitive dysfunction that occur in late-life SSD are still unknown.* **Objective:** *The aims of this study were to reveal the cognitive profile of patients with late-life SSD and to evaluate how cognitive dysfunction affects disease severity.* **Methods:** *We compared the cognitive profiles of patients with late-life SSD (n = 40) with those of normal control subjects (n = 21). In addition, we divided the patients with late-life SSD into mild-to-moderate (n = 24) and severe (n = 16) groups and compared the cognitive profiles of the 3 groups.* **Results:** *Patients with late-life SSD exhibited a lower Mini-Mental State Examination total score and attention decline. In the 3-group comparison, the severe group had a lower Mini-Mental State Examination score and Frontal Assessment Battery score than the normal control group, whereas no significant difference was seen between the mild-to-moderate and the normal control groups.* **Conclusions:** *Our data suggest that different cognitive patterns may exist depending on disease severity, possibly indicating differences in pathogenesis.*

(Psychosomatics 2015; ■:■■■–■■■)

INTRODUCTION

Somatic symptom disorder (SSD) is a psychiatric disorder that is commonly observed in primary health care, as these patients tend to visit medical facilities to elucidate their pathogenesis and to receive treatment.[1] According to current diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders (fifth edition) (DSM-5), SSD is characterized by somatic symptoms that either are very distressing or result in a significant disruption of functioning, as well as excessive and disproportionate thoughts, feelings, and behaviors regarding those symptoms.[2] The diagnosis of SSD requires both criterion A, the somatic symptoms, and criterion B, which covers excessive thoughts, feelings, and behaviors related to these somatic symptoms or associated health concerns. At least one of the following must be present: (1) disproportionate and persistent thoughts about the seriousness of one's symptoms, (2) a persistently high

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level of anxiety about health or symptoms, and (3) excessive time and energy devoted to these symptoms or health concerns.

Among elderly people, somatic complaints now appear to be as common as they are among young people.[3] Furthermore, the prevalence of somatoform disorders (as diagnosed according to the former DSM-IV text revision diagnostic criteria) is relatively high among the elderly.[4]

SSD exhibits high levels of comorbidity with other anxiety-related disorders or major depressive disorders or both.[6] Therefore, few studies have focused on SSD, especially in the elderly population, and the disease mechanism of late-life SSD remains unclear. In view of this situation, we focused on elderly patients with SSD without any psychiatric comorbidity.

Somatic complaints in the elderly tend to be related to various factors characterized by the aging process[5] and cognitive dysfunction.[6] Moreover, the severity of somatic complaints in late-life influences the patients' quality of life and their disabilities.[3]

From cognitive viewpoints, several studies showed that the presence or severity of anxiety is associated with a lower cognitive performance in the elderly.[7] In a previous study, we observed correlations between disease severity and cognitive dysfunction in patients with late-life somatoform disorders (as diagnosed according to the former DSM-IV text revision diagnostic criteria).[6] We suspected that the cognitive profiles influencing the appearance of symptoms and the symptomatic severity might differ.

No other previous studies comparing the cognitive profiles of normal control (NC) subjects and patients with late-life SSD have been reported. We hypothesized that the representation of distinct characteristics in patients with intractable somatic symptoms occurred as a result of cognitive dysfunction. Thus, it may be necessary to compare cognitive function in patients with late-life SSD according to disease severity.

Based on previous findings regarding the effect of cognitive dysfunction on late-life SSD, the aim of the present study was to examine how cognitive deficits influence the presence of late-life SSD using age-matched NCs.

Furthermore, we confirmed the influence of cognitive profiles on the severity of late-life SSD. We classified the patients into a mild-to-moderate SSD group and a severe SSD group according to the DSM-5 criteria. The cognitive profiles of these groups were then compared with those of NCs. Severity was evaluated as follows:

Mild: Only one of the symptoms specified in criterion B was fulfilled.
Moderate: Two or more of the symptoms specified in criterion B criteria were fulfilled.
Severe: Two or more of the symptoms specified in criterion B were fulfilled, plus there were multiple somatic complaints.

METHODS

Participants

From October 2012 to June 2013, 89 consecutive outpatients aged 65 years old or older who met the criteria for SSD according to the DSM-5 and who had been referred to The Jikei University Kashiwa Hospital outpatient clinic were assessed. All the patients were referred by general physicians, and the absence of any physical disease capable of explaining the somatic symptom was confirmed. All the patients were diagnosed as having SSD according to the DSM-5 diagnostic criteria by 2 expert geriatric psychiatrists (K. I. and T. N.).

The study exclusion criteria were as follows: (1) the presence of severe physical illness, (2) the presence of neurocognitive disorders according to the DSM-5 diagnostic criteria, (3) the presence of atrophy of cortical lesion on magnetic resonance imaging findings (an expert radiologist measured the atrophy of the cerebral cortex using a technique that has been validated via histologic[8] as well as manual measurements),[9] (4) the presence of mild cognitive impairment (MCI) according to the diagnostic criteria for amnestic MCI,[10] (5) the presence of major depressive disorder or a Hamilton Depression Scale score >14 (this number is a valid cutoff score for the Hamilton Depression Scale for patients with dysphasia, compared with the standard cutoff score[11,12]), (6) a diagnosis of another significant psychiatric disorder (e.g., another anxiety-related disorder, hypochondriasis, illness anxiety disorder, pain disorder, or conversion disorder), and (7) a history of major depression or another anxiety-related disorder during the last 5 years. In total, 40 patients with SSD were eligible for inclusion in the present study.

In total, 21 age-matched NC subjects were also recruited for this study. None of these NC subjects had any psychiatric disorder, neurologic illness, history of substance abuse, or history of a psychiatric disorder.

The present study was approved by the Ethics Committee of the Jikei University School of Medicine. A written informed consent was obtained from the subjects or their designated representatives.

Psychologic Assessment

The Short Health Anxiety Inventory

The Short Health Anxiety Inventory (SHAI) was created to measure health anxiety in a manner that would be applicable in medical contexts.[13] In patients with somatic complaints, health anxiety is one of the factors that can amplify somatic perception.[14] We used the SHAI to evaluate the excessive fears or beliefs of patients that led to their misinterpretation of bodily sensations or symptoms.

The Hamilton Anxiety Scale

The Hamilton Anxiety Scale (HAMA) is a rating scale for evaluating the severity of anxiety-related disorders.[15] The HAMA consists of 2 subscores, psychic anxiety (HAMA-PSY; ranging from 0–28 points) and somatic anxiety (HAMA-SOM; ranging from 0–28 points). HAMA-SOM consists of the following items: muscular symptoms, sensory symptoms, cardiovascular symptoms, respiratory symptoms, gastrointestinal symptoms, genitourinary symptoms, and autonomic symptoms (ranging from 0–4 points). The HAMA test and its subscores are reliable and valid for anxiety-related disorders,[15] and the HAMA total and HAMA-SOM have proven to be sensitive measures for evaluating the severity of somatic symptoms.[16–19]

Cognitive Assessment

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) is a well-known and widely used test for screening cognitive impairment. Possible scores range from 0–30. A score of 28 is the median for normal octogenarians with more than 12 years of education.[20] Patients with an MMSE score <24 were regarded as possibly having dementia and were excluded from the present study.

Frontal Assessment Battery

The Frontal Assessment Battery (FAB) was recently introduced as a short screening test for exploring various functions of the frontal lobes and for evaluating executive functions.[21] The Japanese FAB version consists of 6 subtests: (1) similarities, (2) lexical fluency, (3) motor series, (4) conflicting instructions, (5) go/no go, and (6) prehension behavior. Each subtest is rated from 0–3, with the total score ranging from 0–18.

Japanese Version of the Neurobehavioral Cognitive Examination

The Japanese version of the Neurobehavioral Cognitive Examination (J-COGNISTAT) is a comprehensive cognitive test that consists of 10 subtests designed to convert raw scores for each subtest into age-matched standardized scores, which are distributed with a mean of 10 and a standard deviation of 1. The cutoff point for each standardized score is set between 8 and 9. If a subject's score is not more than 8, the score is considered to indicate an impaired level.[22]

Assessment of Other Factors

Some previous studies have reported an increased risk of cognitive impairment among benzodiazepine and antidepressant users. Thus, we examined whether the benzodiazepine and antidepressant dosage confounded the effects of cognitive functions. Evaluations of the correlations between the benzodiazepine/antidepressant dosages and cognitive functions were based on an equivalent conversion table for anxiolytic drugs.[23]

STATISTICAL METHODS

SPSS 19.0 J (SPSS Japan Inc.) was used for all the statistical analyses. To compare differences between NC subjects and patients with late-life SSD, we used the Welch *t*-test for demographic characteristics, including age, education, duration of illness, SHAI score, HAMA-SOM score, HAMA-PSY score, and HAMA total score. The sex ratio was assessed using the chi-square test. To investigate group differences in

the neuropsychologic assessments, we also used the Welch *t*-test. To compare differences among the 3 groups, we used a one-way analysis of variance with Tukey *post hoc* testing. As an exploratory study was intended, the *p* values were not initially corrected for multiple tests so that the data trends would be apparent. However, the Bonferroni-corrected *p* value requirements (MMSE subtest scores: $p = 0.05/11$, FAB subtest scores: $p = 0.05/6$, and J-COGNISTAT subtest scores: $p = 0.05/10$) were reported, and the effects of the correlations were noted. If significant differences were found within the cognitive subtests, we evaluated the correlation of each subtest and the correlation between the benzodiazepine/antidepressant dosage and the test scores using the Spearman rho test in patients with late-life SSD.

RESULTS

Demographics of NC Subjects and Patients With Late-Life SSD

Table 1 shows the characteristics of the NC subjects and the patients with late-life SSD. The patients with late-life SSD had relatively high average SHAI scores ($p < 0.01$), HAMA-SOM scores ($p < 0.001$), HAMA-PSY scores ($p < 0.001$), and HAMA total scores ($p < 0.001$).

Comparison of Cognitive Profiles Between NC Subjects and Patients With Late-Life SSD

Comparison of cognitive profiles in 2 groups is summarized in Table 2. The patients with late-life SSD had significantly lower MMSE total score ($p = 0.03$) and J-COGNISTAT subtest score for attention ($p < 0.001$) than the NC subjects did.

Demographics of NC Subjects, Patients With Mild-to-Moderate Late-Life SSD, and Patients With Severe Late-Life SSD

The characteristics of the 3 groups are summarized in Table 3. The dosages of the benzodiazepine agents ($p < 0.001$) and antidepressant agents ($p = 0.004$) in the 3 groups differed significantly. The SHAI ($p < 0.001$), HAMA-SOM ($p < 0.001$), HAMA-PSY ($p < 0.001$), and HAMA total scores ($p < 0.001$) of the 3 groups also differed significantly.

Comparison of Cognitive Profiles Among NC Subjects, Patients With Mild-to-Moderate Late-Life SSD, and Patients With Severe Late-Life SSD

Cognitive profiles in 3 groups are summarized in Tables 4 and 5. The patients with severe late-life SSD had significantly lower MMSE total scores than the NC subjects did ($p = 0.01$). This group also showed lower FAB total scores ($p = 0.009$), conflicting

TABLE 1. Comparison of Demographic Data for Normal Control (NC) Subjects vs Patients With Late-Life Somatic Symptom Disorders (Late-Life SSD)

	NC subjects ($n = 21$) (mean ± SD)	Patients with late-life SSD ($n = 40$) (mean ± SD)	χ^2 score	*p* Value
Sex (male/female)	9/12	8/32	3.58	0.06
Age	74.9 ± 5.9	74.6 ± 5.2		0.85
Education (y)	11.9 ± 1.9	11.8 ± 2.1		0.84
Duration of illness (y)	–	7.0 ± 6.9		NA
Onset age	–	67.4 ± 7.7		NA
Benzodiazepine dosage (mg/d)	–	4.7 ± 4.1		NA
Antidepressant dosage (mg/d)	–	16.9 ± 25.1		NA
SHAI score	10.9 ± 8.1	23.0 ± 9.1		<0.01*
HAMA-SOM score	0.2 ± 0.5	7.9 ± 4.3		<0.001†
HAMA-PSY score	1.1 ± 1.0	7.2 ± 4.2		<0.001†
HAMA total score	1.4 ± 1.2	15.2 ± 7.4		<0.001†

NA = not available; NC = normal control; HAMA = the Hamilton Anxiety Scale; HAMA-PSY = the Hamilton Anxiety Scale, psychic score; HAMA-SOM = the Hamilton Anxiety Scale, somatic subscore; SHAI = the Short Health Anxiety Inventory; SD = standard deviation; SSD = somatic symptom disorder.

*$p < 0.05$.

†$p < 0.01$.

TABLE 2. Comparison of Cognitive Profiles for Normal Control (NC) Subjects vs Patients With Late-Life Somatic Symptom Disorders (Late-Life SSD)

	NC subjects ($n = 21$) (mean ± SD)	Patients with late-life SSD ($n = 40$) (mean ± SD)	p Value
MMSE total score	28.5 ± 1.4	27.4 ± 2.0	0.03*
FAB total score	16.1 ± 1.4	15.7 ± 1.6	0.31
J-COGNISTAT subscores			
Orientation	9.5 ± 0.9	9.6 ± 0.9	0.77
Attention	9.2 ± 1.2	6.2 ± 3.1	<0.001†
Comprehension	9.2 ± 1.6	8.3 ± 2.0	0.14
Repetition	10.3 ± 0.7	9.8 ± 1.4	0.12
Naming	9.6 ± 0.8	9.8 ± 0.7	0.50
Constructive ability	8.8 ± 1.2	7.9 ± 1.4	0.02
Memory	9.2 ± 0.7	9.5 ± 0.7	0.27
Calculation	9.7 ± 0.6	8.9 ± 1.4	0.006
Similarities	9.9 ± 0.8	10.2 ± 0.8	0.17
Judgment	10.1 ± 1.0	10.6 ± 1.0	0.28

FAB = frontal assessment battery; J-COGNISTAT = the Japanese version of the Neurobehavioral Cognitive Examination; MMSE = Mini-Mental State Examination; NC = normal control; SD = standard deviation; SSD = somatic symptom disorder.

*$p < 0.05$.

†Bonferroni-corrected $p < 0.05/10 = 0.005$.

TABLE 3. Comparison of Demographic Data for 3 Groups: Normal Control (NC) Subjects, Patients With Mild-to-Moderate Late-Life Somatic Symptom Disorders (Late-Life SSD), and Patients With Severe Late-Life SSD

	NC subjects ($n = 21$) (mean ± SD)	Mild-to-moderate late-life SSD ($n = 24$) (mean ± SD)	Severe late-life SSD ($n = 16$) (mean ± SD)	χ^2 or F score	p Value	*Post hoc**
Sex (male/female)	9/12	6/18	2/14	4.32†	0.12	
Age	74.9 ± 5.9	75.5 ± 5.5	73.3 ± 4.8	0.79	0.46	
Education (y)	11.9 ± 1.9	12.3 ± 2.0	11.1 ± 2.0	1.59	0.21	
Duration of illness (y)	–	7.9 ± 6.9	5.7 ± 6.8	1.00	0.32	
Onset age	–	67.3 ± 7.3	67.5 ± 8.4	0.02	0.90	
Benzodiazepine dosage (mg/d)	0.0 ± 0.0	4.2 ± 4.2	5.6 ± 3.9	13.4	<0.001‡	Control < mild-to-moderate, Control < severe
Antidepressant dosage (mg/d)	0.0 ± 0.0	13.1 ± 19.1	23.8 ± 33.3	6.00	0.004‡	Control < severe
SHAI score	10.9 ± 8.1	19.6 ± 7.8	28.1 ± 9.0	17.62	<0.001‡	Control < mild-to-moderate < severe
HAMA-SOM score	0.2 ± 0.5	5.7 ± 2.9	11.2 ± 3.9	57.41	<0.001‡	Control < mild-to-moderate < severe
HAMA-PSY score	1.3 ± 1.2	4.7 ± 2.9	10.8 ± 3.0	54.44	<0.001‡	Control < mild-to-moderate < severe
HAMA total score	1.4 ± 1.2	10.6 ± 4.2	22.1 ± 5.7	95.66	<0.001‡	Control < mild-to-moderate < severe

NC = normal control; HAMA = the Hamilton Anxiety Scale; HAMA-PSY = the Hamilton Anxiety Scale, psychic score; HAMA-SOM = the Hamilton Anxiety Scale, somatic subscore; SHAI = the Short Health Anxiety Inventory; SD = standard deviation; SSD = somatic symptom disorder.

*Significant *post hoc* comparisons ($\alpha < 0.05$) using Tukey-HSD test. Sex ratio was analyzed using the chi-square test.

†The chi-square score.

‡$p < 0.01$.

TABLE 4. Comparison of Cognitive Profiles for Normal Control (NC) Subjects, Patients With Mild-to-Moderate Late-Life Somatic Symptom Disorders (Late-Life SSD), and Patients With Severe Late-Life SSD

	NC subjects ($n = 21$) (mean ± SD)	Mild-to-moderate late-life SSD ($n = 24$) (mean ± SD)	Severe late-life SSD ($n = 16$) (mean ± SD)	*F* score	*p* Value	*Post hoc*[*]
MMSE total score	28.5 ± 1.4	28.0 ± 2.0	26.8 ± 1.8	4.73	0.01[§]	Control > severe
FAB total score	16.1 ± 1.4	16.3 ± 1.2	14.8 ± 1.7	5.16	0.009[†]	Control > severe, mild-to-moderate > severe
FAB subtest scores						
Similarities	2.8 ± 0.7	3.0 ± 0.0	2.6 ± 0.7	3.09	0.05	
Lexical fluency	2.1 ± 0.8	2.3 ± 0.7	2.1 ± 0.6	0.19	0.82	
Motor series	2.9 ± 0.3	2.9 ± 0.4	2.6 ± 0.8	2.24	0.12	
Conflicting instructions	2.9 ± 0.2	2.9 ± 0.2	2.5 ± 0.6	7.36	0.001[‡]	Control > severe, mild-to-moderate > severe
Go/no go	2.3 ± 0.7	2.2 ± 0.7	2.0 ± 0.8	0.58	0.56	
Prehension behavior	3.0 ± 0.0	3.0 ± 0.0	3.0 ± 0.0	NA	NA	

FAB = frontal assessment battery; MMSE = Mini-Mental State Examination; NA = not available; NC = normal control; SD = standard deviation; SSD = somatic symptom disorder.

[*]Significant *post hoc* comparisons ($\alpha < 0.05$) using Tukey-HSD test.

[†]$p < 0.01$.

[‡]Bonferroni-corrected $p < 0.05/6 = 0.008$.

[§]$p < 0.05$.

instructions among the FAB subtests ($p = 0.001$), and J-COGNISTAT subtest scores for calculation ($p < 0.001$) than the NC subjects and the patients with mild-to-moderate late-life SSD did. J-COGNISTAT subtest scores for attention were significantly lower in both the patients with mild and the patients with severe late-life SSD than in the NC subjects ($p < 0.001$).

Correlations Between Benzodiazepine/ Antidepressant Dosages and Cognitive Subscores in Patients With Late-Life SSD

Only the J-COGNISTAT subtest for calculation was correlated with the benzodiazepine dosage in patients with late-life SSD ($\rho = -0.33$, $p = 0.04$). No other subtests were correlated with either the benzodiazepine or the antidepressant dosages.

DISCUSSION

In this study, we found that the patients with late-life SSD had a lower MMSE total score and a lower attention score for the J-COGNISTAT subtest, compared with the NC subjects. In a 3-group comparison, the severe late-life SSD group had a lower MMSE total score than the NC subjects did. This group also had a lower FAB total score, a lower "conflicting instructions" FAB subtest score, and a lower calculation score for the J-COGNISTAT subtest, compared with the other groups. The attention score for the J-COGNISTAT subtest was lower in both the mild-to-moderate and severe late-life SSD groups than in the NC subjects. The benzodiazepine dosage for the mild-to-moderate and severe SSD groups was significantly higher than that for the NC subjects. The antidepressant dosage in the severe SSD group was significantly higher than that for the NC subjects.

In previous studies investigating cognitive decline in patients with late-life anxiety disorders, reductions in general cognitive functioning and attention function were reported.[7] In the present study of patients with late-life SSD, we also found an attention defect and a decline in general cognitive functioning.

In a comparison of the 3 groups, the severe late-life SSD group had a lower executive function score. However, the mild-to-moderate late-life SSD group showed no decline in executive functions. Thus, these cognitive test results appeared to differ according to disease severity among patients with late-life SSD. The FAB score assessing executive function may be an indicator of disease severity.[6]

TABLE 5. Comparison of J-COGNISTAT Subtests for Normal Control (NC) Subjects, Patients With Mild-to-Moderate Late-Life Somatic Symptom Disorders (Late-Life SSD), and Patients With Severe Late-Life SSD

	NC subjects ($n = 21$) (mean ± SD)	Mild-to-moderate late-life SSD ($n = 24$) (mean ± SD)	Severe late-life SSD ($n = 16$) (mean ± SD)	*F* score	*p* Value	*Post hoc*[*]
J-COGNISTAT subscores						
Orientation	9.5 ± 0.9	9.6 ± 0.9	9.6 ± 1.1	0.06	0.94	
Attention	9.2 ± 1.2	5.8 ± 3.2	6.9 ± 2.8	10.21	<0.001[†]	Control > mild-to-moderate, control > severe
Comprehension	9.2 ± 1.6	8.7 ± 2.2	7.9 ± 1.8	2.00	0.14	
Repetition	10.3 ± 0.7	10.0 ± 0.4	9.5 ± 1.4	2.26	0.11	
Naming	9.6 ± 0.8	9.7 ± 0.8	9.8 ± 0.5	0.33	0.72	
Constructive ability	8.8 ± 1.2	7.9 ± 1.5	7.9 ± 1.3	3.02	0.06	
Memory	9.2 ± 0.7	9.6 ± 0.6	9.4 ± 0.9	1.02	0.36	
Calculation	9.7 ± 0.6	9.3 ± 1.2	8.2 ± 1.4	8.80	<0.001[†]	Control > severe, mild-to-moderate > severe
Similarities	9.9 ± 0.8	10.3 ± 0.3	10.0 ± 0.9	1.77	0.18	
Judgment	10.1 ± 1.0	10.7 ± 1.0	10.7 ± 1.0	0.58	0.56	

J-COGNISTAT = the Japanese version of the Neurobehavioral Cognitive Examination; NC = normal control; SD = standard deviation; SSD = somatic symptom disorder.

[*]Significant *post hoc* comparisons ($\alpha < 0.05$) using Tukey-HSD test.

[†]Bonferroni-corrected $p < 0.05/10 = 0.005$.

Several possibilities may explain this result. Firstly, this difference might have contributed to the difference in the FAB score between the mild-to-moderate and the severe late-life SSD groups. "Conflicting instructions" resembles the Stroop test task and requires the ability to perform a contrary reaction to each of the 2 pattern directions effectively.[21] In patients with mild-to-moderate late-life SSD, the acquirement of such self-correction in executive functions might influence their ability to access corrective information necessary to modify their irrational beliefs.[24]

A second possibility may be explained by coping strategies. Poor coping strategies can lead to such somatic symptoms. Coping strategies are associated with attention, working memory, and executive functions.[6] Patients with mild-to-moderate late-life SSD may have a greater ability to cope through such reciprocal balancing of cognitive functions, compared with patients with severe late-life SSD. The collapse of such balance may lead to the poorer prognosis for patients with late-life SSD.

There is still a possibility that severe late-life SSDs are a prodromal stage of neurodegenerative diseases, such as dementia with Lewy bodies or Parkinson disease with dementia. A previous report has mentioned that somatic complaints were observed more frequently among patients with dementia with Lewy bodies or Parkinson disease with dementia than among patients with other types of dementia.[25] Although we excluded patients with amnestic MCI or dementia using cognitive assessments and a brain magnetic resonance imaging examination in the present study, patients with a prodromal stage of dementia with Lewy bodies or Parkinson disease with dementia are difficult to identify. The severe group may overlap with the nonamnesic type of MCI presentation.

A possible correlation between medication effects and disease severity must be considered because the severe SSD group received a relatively high dose of anxiolytic drugs. The dosages of anxiolytic drugs differed significantly among the 3 groups. Two possibilities may explain this result. First, the medication might influence the disease severity. Second, the severe group might have exhibited resistance to the treatment. In the present study, all the patients were medicated after confirmation of a diagnosis of SSD. Furthermore, the disease severity was classified according to the DSM-5 at the same time. Thus, we believe that the latter possibility is more likely. The disease severity of patients with SSD, as diagnosed according to the DSM-5 criteria, is probably not influenced by the effects of medication.

The HAMA-PSY score differed significantly among the 3 groups. We evaluated whether psychic anxiety in patients with late-life SSD may affect cognitive function. This problem can be explained from a psychopathologic viewpoint. Rief and Barsky suggested the applicability of a signal-filtering model in patients with somatic complaints.[14] This model mentions that somatic symptoms can be amplified by a reduction in filtering activity. Under this pathogenesis model, filtering activity is decreased by several factors (e.g., anxiety for health, depressive mood, and lack of distraction), and somatic symptoms occur because of a reduction in the filter system. Therefore, the HAMA-PSY score may reflect filtering activity. The HAMA-PSY score is just one factor in the appearance of somatic complaints, whereas the HAMA-SOM score reflects the severity of SSD precisely. Therefore, we believe that cognitive dysfunction in patients with late-life SSD is not influenced by the HAMA-PSY score directly. Additionally, we excluded patients with other anxiety-related disorders. For these reasons, cognitive dysfunction in patients with severe SSD does not appear as an anxiety effect, but results from the severity of SSD.

An attention decrement was found in both the mild and the severe late-life SSD groups. This result may indicate that an attention decrement may be a surrogate marker for disease specificity, rather than disease severity. A lower calculation skill in patients with severe late-life SSD reflects a defect in working memory. However, the effect of the benzodiazepine must be considered, as the calculation score was correlated with the benzodiazepine dosage.

This study had some limitations. First, the sample size was comparatively small. The reason for this is that we sampled the participants strictly and excluded patients with any possibility of a different diagnosis. Second, we evaluated executive functions using the FAB test, which has a ceiling effect. Patients with MCI or dementia were excluded from our sample in the present study, and there is a limitation to examining the details of executive functions using the FAB test. Third, our investigation used a cross-sectional research approach. To confirm our hypothesis, further longitudinal study is needed.

CONCLUSION

We elucidated the cognitive profiles of patients with late-life SSD and concluded that the cognitive profiles influenced the severity of late-life SSD. We found differences in the cognitive profiles among NC subjects, patients with mild-to-moderate late-life SSD, and patients with severe late-life SSD. Therefore, differences in pathogenesis might result in a subgroup of patients with severe late-life SSD among patients with late-life SSD. The further development of treatment strategies targeting prognostic subgroups, rather than late-life SSD itself, is required.

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Non-Pharmacological Management for Patients with Frontotemporal Dementia: A Systematic Review

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Abstract. Frontotemporal dementia (FTD) is a neurodegenerative disorder characterized by changes in behavior and language caused by focal degeneration of the frontal and anterior temporal lobes. The behavioral symptoms are distressing to patients and their caregivers. Non-pharmacological management is important as no disease-specific pharmacological treatment for FTD is currently available. The primary objective is to review the literature on non-pharmacological management for FTD and to propose directions for future research, with reference to findings. A search was performed using PubMed, MEDLINE, and EMBASE. Search terms included "frontotemporal dementia", and words related to non-pharmacological management, and it identified a total of 858 articles. Results revealed that very few randomized controlled trials exist on non-pharmacological management interventions for FTD. These interventions have been proposed by literature based on clinical experience. A small number of studies have supported behavioral management techniques that exploit disease-specific behaviors and preserved functions in patients with FTD, along with the management of caregivers' distress. These limitations warrant well-designed large-scale research to examine effects of non-pharmacological interventions on behavioral symptoms of FTD.

Keywords: Behavioral management, caregiver support, environmental strategies, non-pharmacological interventions in frontotemporal dementia

INTRODUCTION

Frontotemporal dementia (FTD) is a neurodegenerative disorder, caused by focal degeneration of the frontal and anterior temporal lobes, and characterized by progressive changes in behavior, emotion, and personality [1]. The disease begins insidiously and progresses gradually; core clinical criteria include early behavioral disinhibition, early apathy, early loss of sympathy or empathy, impulsive stereotypic behavior, and dietary changes [2]. FTD is a common cause of early-onset dementia, and has a similar incidence and prevalence to Alzheimer's disease (AD) among early-onset dementia cohorts [3]. FTD can be classified into three clinical syndromes based on the early and predominant symptoms, behavior variant FTD (bvFTD)

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and two forms of primary progressive aphasia (PPA) syndromes such as semantic variant PPA (svPPA), and non-fluent variant PPA (nfvPPA).

Behavioral symptoms of FTD affect patients' lives and have profound implications for their caregivers [4]. This condition is relatively less known for most caregivers; they do not expect their family to develop FTD. Furthermore, as most patients develop FTD at a young age, financial problems often exist for both patients and their family caregivers. Additionally, lack of general information also results in delayed initial diagnosis and intervention, which worsens the situation [5]. Burden and stress are higher in FTD caregivers than in caregivers of patients with AD or other dementias [6–10].

To date, there is no disease specific pharmacological treatment for FTD. Medications for AD and psychiatric disorders are frequently used as off-label treatments for FTD [11]. Current pharmacological studies on FTD mainly focus on treating behavioral symptoms, using various kinds of psychotropics, including acetylcholinesterase inhibitors, antidepressants, atypical antipsychotics, and NMDA glutamate receptor antagonists [12–17]. However, the effects of these medications are insufficient, and adverse effects often limit the pharmacological treatment of FTD [18]. Specifically, an important concern is the increased susceptibility to extrapyramidal symptoms induced by antipsychotics in patients with FTD [19].

That being said, non-pharmacological interventions or managements are important in managing and caring for both patients with FTD and their caregivers. Non-pharmacological interventions may offer significant benefit to the quality of life of the patients [20]. A combination of pharmacological treatment with non-pharmacological approach is also necessary for the appropriate management of patients with FTD [21]. However, as disease symptoms and problematic behaviors differ largely between AD and FTD, standard non-pharmacological techniques established for patients with typical AD, including cognitive training and cognitive rehabilitation, are sometimes ineffective for patients with FTD [22, 23].

To the best of our knowledge, there is few systematic review article focused on non-pharmacological interventions for patients with FTD [24]. In this article, we reviewed existing literature on non-pharmacological interventions for patients with FTD, including behavioral management, environmental strategies, and caregiver support. Behavioral management is a technique that aims to control and mitigate socially disruptive behaviors of patients, whereas environmental modification is a way to manage patients' environment and circumstances to avoid unfortunate results of these behaviors. On the other hand, support of caregivers can help family caregivers to cope with the impact of their illness. Although there are very few clinical trials exploring behavioral and environmental interventions in FTD, several reports suggest that non-pharmacological interventions could be effective for patients with FTD. The present review also discusses the limitations of previous studies, addressing the reasons explaining the few clinical trials. Finally, based on the results of non-pharmacological intervention studies, we propose future directions for the development and establishment of clinical research on non-pharmacological interventions for patients with FTD.

METHOD

PubMed, Medline, EMBASE, and references from relevant studies, review articles, and books were searched using the terms dementia and ("frontal lobe" or frontotemporal or early-onset or young-onset) and (management or intervention or therapy or treatment or nonpharmacologic* or environment* or care). Only publications pertaining to non-pharmacological management in FTD were selected and no time span was specified for date of publication. Cross-referencing of the identified publications was also performed. The results were searched for relevance, and the bibliographies of articles were additionally screened. We selected clinical trials on non-pharmacological management for behavioral symptoms in FTD. As such, studies on language training for semantic variant patients were excluded and thus, we excluded search terms such as "language training" and "speech therapy" for patients with PPA. We also excluded management for patients with amyotrophic lateral sclerosis or motor neuron disease from our review. The literature search was conducted independently by two of the authors (S.S. and S.N.). To enhance the quality of reporting in the present systematic review, we followed standardized guidelines [25]. The last search was conducted on September 20, 2014, and in total yielded 9 articles (4 clinical trials and 5 case reports) from 858 articles, which formed the empirical basis of this review. As the number of the articles we found was limited, we referred to researches related to non-pharmacological management, reviews, and expert opinions in order to facilitate discussion on common interventions, which were not included in them.

Table 1
Clinical trials on non-pharmacological management for patients with frontotemporal dementia

Study	Design	*n*	Intervention	Follow-up duration	Primary outcome measure	Results
Behavioral management						
Ikeda et al., 1995 [27]	open-label trial	$n=6$	preserved procedural memory method (old hobbies and habits)	not controlled	clinical observation of behaviors	those methods were helpful for reducing social misconduct and disinhibition
Environmental strategies						
No systematic study						
Caregiver support						
Mioshi et al., 2013 [34]	15-week open-label non-randomized controlled trial	intervention, $n=9$; control, $n=12$	cognitive appraisal and coping strategies program	12 month	Zarit Burden Inventory, Cambridge Behavioral Inventory Revised	greater reductions in both caregivers' burden and reactions to patients' challenging behaviors in intervention group
McKinnon et al., 2013 [51]	15-week open-label non-randomized controlled trial	intervention, $n=9$; control, $n=12$	cognitive appraisal and coping strategies program	15 weeks	problem-solving scenario	improved functioning in the problem-solving task in the intervention group (63%), compared with the control group (13%)
Community health services and institutional care						
No systematic study						
Other interventions						
Kimura and Takamatsu, 2013 [73]	8-week open-label trial	$n=20$	lavender aroma therapy	8-week	Neuropsychiatric Inventory	decrease in NPI total score and NPI subscale score "apathy/indifference"

Case reports, expert opinion reviews, and retrospective studies are not included in this table.

RESULTS

Clinical trials on non-pharmacological management for patients with frontotemporal dementia are summarized in Table 1 (case reports, expert opinion reviews, and retrospective studies are not included).

Behavioral management

Non-pharmacological behavioral management strategies are based largely on narrative and clinical experience rather than evidence from clinical studies [26]. There are several reports that suggest that some behaviors are amenable to interventions. Behavioral management techniques can target socially disruptive behaviors, such as inappropriate commentary or touching, as well as stereotypic behaviors, such as walking around in the same location.

Ikeda et al. reported that troublesome behavioral symptoms were managed by reintroducing old hobbies and favorite games in six patients with FTD. They also reported that those methods were helpful for reducing social misconduct and disinhibition [27]. They aimed at utilizing presumably preserved procedural memory to take control of troublesome behavioral symptoms in patients with FTD. The same group also reported upon a few cases treated with a behavioral therapy called "routinizing therapy", in which stimulus-bound and stereotypic behaviors are replaced with appropriate behaviors. This therapy was reported to help manage troublesome behaviors and contribute to a stable routine [28].

Another strategy is to redirect behaviors using the antecedent-behavior-consequence model, although no systematic study has been conducted to examine its effectiveness [21]. In this model, an antecedent is an event or factor that initiates or contributes to the occurrence of behavior, the behavior is a specific behavioral symptom, and consequences are all the reactions and responses to the behavior. Merrilees and colleagues reported that this model can be helpful for caregivers to understand the behavior and help to manage behavioral symptoms in patients with FTD [21].

It may be also useful for patients with FTD to use rehabilitation techniques or to retrain through preserved memory [29]. The learning and memory system corresponding to either declarative/explicit or procedural/implicit systems provides a theoretical framework

for behavior-based treatment strategies. These strategies, which enhance basic attention functions (i.e., repetitive rehearsal) and utilize procedural/ implicit learning, are the most relevant when applying rehabilitation interventions.

No study has examined the effectiveness of cognitive training, cognitive rehabilitation, or cognitive enhancement therapy in patients with FTD. These strategies are suggested to be effective in patients with AD whose memory and visuospatial abilities are damaged and may be a treatment target for non-pharmacological interventions [22]. However, memory and visuospatial abilities are relatively preserved in patients with FTD [30]. These different patterns of preserved ability between the disease groups may play an important role in designing non-pharmacological interventions. Cognitive training may be less effective than behavioral management considering improving patients' quality of live. Furthermore, educational level was considered to affect cognitive abilities, supporting the idea that cognitive reserve constitutes one of the major factors to cope with pathology in patients with AD [31, 32]. Borroni et al. investigated the role of educational level and other modifiable and non-modifiable factors in 117 patients with FTD, as compared to those with AD and other neurodegenerative disorders [33]. They found that those with FTD were more educated when modifiable factors were considered. The result indicates that patients with FTD may present behavioral symptoms even though they are highly educated, which demonstrates that education or cognitive reserve may not confer a protective role for the development of behavioral symptoms in patients with FTD. Thus, cognitive enhancement therapies are thought to be ineffective in patients with FTD.

Overall, behavioral management techniques that target disease specific behaviors and preserved functions seem to be more effective than cognitive training in patients with FTD.

Environmental strategies

Many review articles have addressed the importance of environmental strategies, which may be employed to minimize the unfortunate results of behaviors [8, 16, 17, 20, 26, 34–43]. As each patient faces different situations, it is difficult to conduct clinical studies of these environmental strategies. As such, most are mainly based on narrative and clinical experience and no clinical studies that provide evidence on these environmental strategies exist. In this section, we summarized expert opinions.

Safety issues

First, clinicians and care staff should evaluate FTD behaviors in terms of their threat to safety, as well as their frequency and duration of altered behaviors [44]. Physical safety around the home (e.g., in the kitchen, bathroom, and pool) and in public (e.g., whenever inappropriate behaviors may trigger a dispute) should be considered. Most patients benefit from a stable and structured environment [28]. For example, it is recommended that patients keep the same daily routine and that objects or furniture are kept in the same position around them. In addition, caregivers may change their schedule to accommodate a patient's relatively harmless rituals, or a family may choose restaurants that the patient already knows in order to minimize disruptions.

The disease stage should also be taken into consideration for safety and risk management, as it may affect diverse aspects of patients' daily life. In the earlier course of FTD, decisions about safety and competence may be particularly challenging. This is best achieved with the assistance of a multidisciplinary team, including input from patients' family, nurses, speech therapists, and social workers [45]. Specifically, clinicians should be aware of self-harmful events [46]. Despite its importance, there is no epidemiological data about the prevalence of self-harmful events in FTD compared with other forms of dementia, and thus, further research is needed.

Hyperorality and swallowing

Alterations in eating habits such as hyperorality, binge eating, and food preference are common in patients with FTD [47]. These symptoms requires caregivers to provide dietary oversight to prevent excessive weight gain and dangerous placement of inedible objects into patients' mouth [16]. Further, dietary restrictions and supervisions are difficult to conduct and may possibly induce emotional reactions of patients. However, to date, no clinical trials have been conducted on interventions with these symptoms. In addition to hyperorality and overeating, dysphagia may develop during the late stages of FTD [48]. Langmore et al. examined swallowing function in 21 patients with FTD and PPA using fiberoptic endoscopy [49], which revealed moderate swallowing abnormalities in 12 of them. Only four caretakers reported swallowing difficulties. These abnormalities could not be explained in the context of compulsive eating behaviors, but seemed to reflect deficits in cortical and subcortical pathways connecting to the brainstem swallowing center. Therefore, caregivers should also be careful for prevent choking and aspiration.

Financial issues

Severe financial problem is common in the early stages of FTD [50]. As patients with FTD are usually younger than other cause of dementia, patients with FTD tend to be working and have dependent children at home [51–55]. Thus, FTD can bring about an unexpected loss or reduction in income, which results in abrupt financial distress in their family. Furthermore, financial trouble may occur in accordance with their behavioral changes such as neglecting bills, impulsive spending, compulsions, and poor judgment, as well as costs associated with providing care [12, 56]. Some patients with FTD face a serious dilemma before their diagnosis, as they lose their job due to poor work performance, which subsequently results in the loss of health insurance. All patients and families should be recommended to be careful to protect their finances.

Driving issues

In the early stage of FTD, memory and visuospatial functions are relatively preserved [6]. Patients may still be capable of operating a vehicle in this stage. Driving problems in FTD typically arise from FTD-specific poor judgments and antisocial behavioral problems, including speeding, impulsive acts, and disregard for traffic rules [12], and thus, cognitive tests may not be appropriate to identify patients who should not drive. It may be important to examine their driving behavior as well as driving capacity with a driving assessment program that includes road testing. To make decisions relying on such procedure can help demonstrate an objective process for patients with FTD. The decision to recommend termination of driving should be made carefully. If the decision was made prematurely, it can threaten patients' independence and life participation. It also causes unnecessary conflict between patients and their families or their physicians since patients do not have insight regarding their dangerous driving and may refuse to stop driving.

As a whole, despite a paucity of evidence in support of these environmental strategies, they may be employed to minimize unfortunate results from behaviors associated with FTD, including clinically relevant issues on safety, eating behaviors, finance, and driving.

Caregiver support

There is relatively more evidence for the management of caregivers' distress than for environmental strategies in patients with FTD. It is critically important to address the physical, emotional, and financial problems of the caregivers. As such, some interventions may be effective to reduce this distress.

Caregiver distress

As FTD affects one's personal identity from early stage, feelings of isolation are often sources of profound distress for a caregiver [7, 8, 10, 57]. As most patients develop FTD at a young age, physically active patients also bother caregivers. Caregivers for patients with FTD reported that the delay to proper diagnosis was the most frustrating aspects of their experience [8, 15]. Difficulties in caring for patients with FTD include: 1) the assumption that dementia is an illness in the elderly and the limited advocacy in professional societies; 2) high rates of misdiagnosis with other neuropsychiatric diseases, resulting in inadequate care; 3) lack of knowledge and training on how to deal with behavioral symptoms among caring staff; and 4) insufficient funding for treatment programs [50, 58, 59]. Many studies found the overall caregiver burden to be greater in patients with FTD than in those with AD [7, 10, 35, 57]. Both depression and stress are more common in caregivers of FTD patients than in those with AD [8, 17, 60]. Also, caregivers of patients with FTD were not satisfied with the information about the disease, as well as counseling and follow-up advice [58].

Early, accurate diagnosis offers the best prospect for effective management of patients with FTD. Explaining to caregivers that the behavioral features have a certain neurological basis is important [35, 61]. Understanding the anatomical underpinnings of these altered personality characteristics and behaviors can help caregivers accept and adjust to the patients' behavior. This can also help them shift their focus to applying behavioral management strategies. On the other hand, as FTD progresses, patients usually display increasing apathy and fewer intrusive behaviors, such as disinhibition and stereotypical behaviors, which may result in easier behavioral management and decreased caregiver stress [17, 39, 60]. Thus, obtaining accurate and up-to-date information about the disease provides a sense of understanding and heightened control [34, 51, 58].

Intervention for caregivers

Social support for caregivers is important and includes support from family and friends as well as from health professionals, including physicians, nurses, and home health aides. A multidisciplinary team should pay attention to signs of burnout and

depression in caregivers [61]. Caregivers benefit from support from health care providers and possibly even more from other caregivers experiencing similar issues. Thus, support groups with other caregivers of patients with FTD can be very helpful. Support for caregivers includes genetic counseling for at-risk family members, which should always be undertaken cautiously.

The development of strategies to maintain emotional and physical safety was shown to minimize caregiver burden [39]. Moreover, it is crucial for caregivers to recognize the limit of their capacity and to know when to ask others for help. Mioshi et al. conducted a caregiver intervention program for caregivers of patients with FTD, which was comprised of two main components: cognitive appraisal and coping strategies [34, 51]. Caregivers learned to appraise a stressful situation and identify the type of stressor based on its modifiable and non-modifiable characteristics. Mioshi et al. compared an intervention program group ($n=9$) and a control group ($n=12$) in order to assess the utility of the intervention [34]. The intervention group showed greater reductions in both their burden and their reactions to patient's challenging behaviors, with a greater increase in the use of humor as a coping mechanism, in comparison with the control group. Greater rates of those who showed improved functioning in the problem-solving task in the intervention group (63%) than the control group (13%) [51]. They speculated that these changes may be maintained over time to provide lasting benefits to caregivers. Riedijk et al. examined changes in caregivers' burden and partner relations in 63 patients with FTD during a 2-year follow up [53]. They found that the patients reached maximum dementia severity with stable Neuropsychiatric Inventory (NPI) levels after 2 years. Contrary to their expectations, caregivers' burden decreased, while psychological well-being remained stable. Coping style and social support changed unfavorably. Relationship closeness was preserved, whereas communication and sharing viewpoint on life were dramatically reduced. They suggested that caregivers of patients with FTD need support to cope with an increasingly hopeless situation. Bristow and colleagues compared stress level, psychological assessments of perceived stress, psychological well-being, coping and social support between 25 caregivers of patients with FTD and 36 non-caregivers [62]. Caregivers as a group reported greater stress and poorer psychological well-being, but there was considerable variation, with some caregivers reporting better psychological functioning than non-caregivers.

Community health services and institutional care

Few systematic studies investigating the effects of community health services and institutional care in patients with FTD have been conducted. Thus, most available evidence is based on clinical expert opinions [12, 23, 63–65].

Community care service

When patients are disabled as a result of FTD, their caregivers should assist them by applying for long-term care service or other types of insurance, such as disability support, although systems may differ between countries. However, getting approval may be particularly challenging in patients that show atypical presentation of the dementia. Morhardt et al. indicated that the frustrations that patients and their families report in their attempt to access community-based and long-term care services are consistent. These frustrations included: 1) difficulty of obtaining a diagnosis; 2) financial concerns due to loss of employment and income; 3) the arduous process of accessing social security disability insurance; and 4) few community-based and long-term care services are equipped to adequately respond to their care needs for the symptoms of FTD [63]. Shnall and collaborators reported upon an interventions service that was developed with the involvement of stakeholders in FTD care to deal with gaps in services in a sustainable way, including internet-based videoconferencing support group for spouses, a website that provides support and counseling for children and their parents, and an adult day program designed for FTD patients [66].

Nursing home

In a nursing home or group home care, patients with FTD often experience conflicts with other residents as a result of their behavioral symptoms. Yokota et al. reported beneficial effects of home-like physical and social environments on their behavioral symptoms and quality of life ($n=8$). Such an environment also led to the reduction of psychotropic drug dosage in those with FTD living in a nursing home [67]. Home-like physical and social environments should be valued greater to optimize a combination of pharmacological and non-pharmacological interventions in diverse care settings for patients with FTD.

Hospital care

A prospective nationwide hospital-based clinico-epidemiologic study in Germany revealed that behavioral disturbances were the predominant reason

for hospital admission among 58 patients with frontotemporal lobar degeneration including FTD [68]. The authors also reported that a large number of patients with FTD were admitted to psychiatric hospitals. Furthermore, in another study, more than half of the patients with FTD were likely to be misdiagnosed with psychiatric disorders [69]. Therefore, caution should be paid to misdiagnosis, resulting in long-term hospitalization in patients with FTD.

Other interventions

In addition to the aforementioned methods, there are several interventional attempts to prevent disease progression and to reduce behavioral symptoms. As the disease progresses, maintaining physical and cognitive activities becomes increasingly important. Exercise was shown to benefit mood, cognition, and overall health in patients with dementia, yet this was not specific to patients with FTD [70]. Several epidemiological association studies and randomized clinical trials demonstrated that regular aerobic exercise may enhance neuronal connectivity networks, provide neuroprotection, and attenuate cognitive decline in neurodegenerative diseases [71]. The benefit of increased physical activity has been mainly demonstrated for the prevention of AD and vascular dementia, yet less so for FTD [72]. However, given this growing body of evidence, exercise should be incorporated into a multi-faceted treatment strategy for patients with FTD. Physical therapy might also be helpful in patients with mobility problems, such as parkinsonism related to FTD, possibly reducing the risk of falls. Further, Kimura and Takamatsu conducted a 8-week open-label trial with lavender aroma therapy for 20 subjects with FTD and found significant decrease in NPI total score and NPI subscale score "apathy/indifference" [73]. There are many reports that nutrition and diet may prevent the development of AD and other causes of dementia [66, 74, 75]. However, there are currently no reports on diet or nutrition for FTD patients.

DISCUSSION

In summary, despite the significance of behavioral changes in FTD and its burden on caregivers in clinical settings, there are no systematic randomized trials on non-pharmacological management interventions for FTD. These interventions have been proposed by reports based on clinical experience [26]. A small number of studies have supported behavioral management techniques that exploit disease-specific behaviors and preserved functions in patients with FTD, along with the management of caregivers' distress. Experience-based expert opinions have supported environmental strategies. In addition, there are several case intervention studies not described above such as an ecological approach with focus on everyday activities using preserved episodic memory [76], hospital environmental controls for restoring sleep–wake cycles [77], administration of a lollipop to control vocally disruptive behavior [78], and music therapy to reduce behavioral changes [79].

The paucity of evidence for non-pharmacological management interventions for FTD is surprising, taking into account that behavioral symptoms of FTD drastically affect patients' lives and have profound implications for their caregivers; currently, there is no clear evidence supporting the usage of pharmacological treatments.

Some reasons may be considered for the small amount of evidence based on clinical trials [80]. First, although FTD is a common cause of early-onset dementia, this condition is less common in the elderly population and the total number of patients with the disease is smaller than the number with AD. Second, disease knowledge in the general population is lacking, and the diagnosis of FTD can be difficult for non-specialists, resulting in misdiagnosis as AD or other conditions such as late-onset psychosis. Third, it is difficult to measure outcomes of non-pharmacological interventions in patients with FTD. For example, the NPI, which is commonly used to measure behavioral symptoms of dementia, is not sensitive to behavioral symptoms specific to FTD, such as stereotypic behavior or loss of sympathy and empathy. Lack of FTD-specific clinical rating scales makes it difficult to conduct interventional research on FTD. Thus, it is crucial to develop appropriate measurement tools in order to identify target symptoms and assess intervention effects for patients with FTD [81]. There are several newly developed FTD-specific outcome measures such as the FTD modified Clinical Dementia Rating [81], the Frontotemporal Dementia Rating Scale [82], stereotypy rating inventory [83], and the appetite & food preference questionnaire [47]. These measures can be useful for assessment of intervention effects for patients with FTD. Fourth, it is challenging to control for confounding factors, such as environmental factors, caregiving circumstances, and relationship with caregivers, which should be considered in order to conduct optimal non-pharmacological intervention research.

In order to conduct non-pharmacological intervention research with a larger sample of patients, focus should be placed on target symptoms, and validity of measured outcomes should be improved. Furthermore, collaboration between researchers is required, potentially to facilitate a multicenter research study. Using the information obtained from these non-pharmacological interventions, researchers can help nurses and family members work together to create targeted strategies for behavioral management and to provide family support.

LIMITATIONS

This review has to be considered in light of its limitations. First, as mentioned in the discussion, the limitation of the literature is the paucity of large-scale well-designed studies on non-pharmacological interventions for FTD and a lack of applicable rating scales specific to FTD. Further, no study has compared effectiveness of pharmacological and non-pharmacological interventions for FTD.

Non-invasive stimulation, such as transcranial magnetic stimulation, has gathered attention as a treatment for cognitive impairment in dementia, in particular, AD and vascular dementia [84, 85]. However, although there is an attempt to use this technique to patients with FTD [86], no study has examined effects of transcranial magnetic stimulation on behavioral symptoms in dementia. Further research is needed to target behavioral changes in FTD.

CONCLUSION

In conclusion, we provided an overview of non-pharmacological approaches for FTD, including behavioral management, environmental strategies, caregiver support, and community services. However, no systematic research using large cohorts has been conducted. Some of these behavioral management methods appear to be effective and thus need to be investigated with larger-scale double-blind randomized clinical trials. These non-pharmacological interventions may facilitate optimal quality of life for individuals with FTD and their families. It is clearly expected that medical providers become more familiar with this knowledge, while individuals with FTD and their caregivers can learn novel ways to utilize non-pharmacological interventions.

DISCLOSURE STATEMENT

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