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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本邦におけるFTDに対するoff-label処方の実態について

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原著

本邦におけるFTDに対するoff-label処方の実態について

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要　旨

全国4施設の専門外来をFTD圏の診断名で紹介された連続例87例の背景因子，紹介医の診療科および認知症症状に対する処方の内容などを調査した．紹介医は精神科医が6割で，ほか神経内科医，一般内科医，脳神経外科医などであった．約半数の例に認知症症状に対する薬剤が用いられ，コリンエステラーゼ阻害剤は様々な診療科から2割の患者に処方されていた．向精神薬は精神科医によって1/3以上の患者に処方され，抗うつ薬，抗精神病薬の処方が多かった．前頭側頭葉変性症や運動ニューロン疾患と診断されていた例には処方はなされていなかった．他の背景因子は薬剤使用には影響を与えなかった．FTDへの薬物療法ガイドラインの作成が望まれる．

キーワード：前頭側頭型認知症，off-label処方，コリンエステラーゼ阻害剤，向精神薬，薬物療法

1．はじめに

前頭側頭型認知症（frontotemporal dementia：FTD）は前頭葉や側頭葉前方部に変性の中心がある変性性認知症群であり，初老期に発症する変性性認知症の中では，アルツハイマー病（Alzheimer's disease：AD）に次いで多いとされる（Ratnavalli et al., 2002）．FTDの患者は病初期から前頭葉機能の障害に伴う社会行動の変化や人格の変化を呈することが特徴であり，臨床診断基準においても，脱抑制や無為，共感性の欠如，常同行動，食行動異常といった行動変化が主要な項目として述べられている（Rascovsky et al., 2011）．これらの特徴的な行動変化から病初期から介護者の負担が大きく（Mioshi et al., 2013），一方で精神疾患や他の認知症性疾患に誤診されていることも多いため（Woolley et al., 2011），医療現場においても対象に苦慮することが多い疾患群である．

現時点では，本邦においても，また主要な欧米諸

Off-label medication for frontotemporal dementia in Japan

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国においてもFTDに保険適応のある薬剤はない（Boxer et al., 2012b）．アルツハイマー病（Alzheimer's disease：AD）に対して用いられるコリンエステラーゼ阻害剤（Cholinesterase inhibitor：ChEI）がFTDに用いられている例も臨床場面ではみとめられるが，これらの薬剤はFTDの行動障害を悪化させることが報告されている（Mendez et al., 2007）．また行動障害を抑える目的で抗精神病薬が用いられることも多いが，FTDの患者は抗精神病薬に対して錐体外路症状などの危険性が高いことも報告されている（Kerssens et al., 2008）．このような疾患であるFTDに対して，本邦における適応外処方の実態はこれまで明らかになっていない．

本研究の目的は専門医以外によってFTDと診断を受けた場合，1）どのような処方がなされるのか，2）処方の内容に影響を与えるような因子があるのか，を明らかにすることである．

2. 対象と方法

2008年1月から2010年12月の期間に全国4施設（公益財団法人浅香山病院，愛媛大学医学部附属病院精神科神経科，熊本大学医学部附属病院神経精神科，東京慈恵大学医学部附属病院精神神経科）の認知症専門外来を受診した連続例から，紹介医でFTDないしはそれに類する診断名（ピック病，疑い病名を含む）で紹介された患者を抽出した．そのうえで，それらの患者の年齢，性別，教育歴，罹病期間，Mini mental state examination：MMSE得点（Folstein et al., 1975）といった背景因子，前医の診療科，前医における認知症症状に対する処方（ChEI，他の認知機能障害に対する薬剤，抗精神病薬，抗うつ薬，抗不安薬，気分調整薬，漢方薬など）の有無とその内容，介護保険取得状況，専門医の最終診断などを各施設の認知症データベースより調査した．ただし，本報告は2010年末までの集計であり，ChEIとして処方されたのはDonepezilのみである．診療科別の処方割合や紹介医の診断別の処方割合についてはχ^2検定およびFisherの正確検定にて検定を行い，薬剤の使用に影響を与える背景因子を検討するための2群比較においては，t検定あるいはχ^2検定およびFisherの正確検定にて検討を行った．

専門医の最終診断にあたっては，各施設に認知症学会及び老年精神医学会の専門医がおり，画像診断および共通した認知機能バッテリーを用いて，血液検査などで共通のプロトコールに則って除外診断を行い，各疾患の診断基準に基づいて診断を行っている．

本研究はデータベースを用いた調査であり介入研究ではない．患者の匿名性に関しては十分な配慮がなされており，データベースを用いる研究を行うことに関しては，各施設の倫理委員会の承認を各々得ている．

3. 結　果

3.1. 患者および紹介医の背景

今回対象となった患者87例の背景を表1に示す．男女比はほぼ同等で，平均年齢が66.9歳，平均の初診時MMSE得点は18.4であった．

紹介医の診断はFTDおよび疑い，前頭側頭葉変性症（Frontotemporal lobar degeneration：FTLD）および疑い，側頭葉優位型圏内，ピック病および疑い，運動ニューロン疾患（Frontotemporal dementia with motor neuron disease：FTD-MND）圏内などであり，FTDの診断が6割以上を占めた．紹介医の属性は精神科，神経内科，内科，脳神経外科，その他であり，精神科が6割以上を占めた．

3.2. 認知症に対する薬剤を使用していた例

87例のうち，何らかの認知症に対する薬剤の使用を用いていた例はほぼ半数の49.4%（43例）であった．認知機能に対する薬剤を用いていたのは23%（20例）であり，ChEIは20.7%（18例）に用いられていた．脳代謝改善薬は2.3%（2例）に用いられていた．一方で精神症状に対する薬剤（以下向精神薬とする：抗精神病薬，抗うつ薬，抗不安薬，気分調整薬，特定の漢方薬を含む）は35.6%（31例）に用いられていた（ChEIとの重複や，向精神薬同士での重複を含む）．抗うつ薬が16.1%（14例）に，漢方薬（全て抑肝散）が11.5%（10例）に，抗精

表 1. demographic data of patients and referring physicians

Sex (Male : Female)	42 : 45
Age	66.9 (11.6)
education (year)	11.3 (2.9)
disease duration (year)	3.0 (2.1)
MMSE score	18.4 (9.5)
Referring physicians' diagnosis (FTD/FTLD/temporal variant/Pick's disease/FTD-MND)	55/5/9/11/7
Referring physicians' background (psychiatrist/neurologist/general physician/neurosurgeon/others)	53/17/9/6/2

MMSE : Mini-Mental State Examination
FTD : Frontotemporal dementia
FTLD : Frontotemporal Lobar Degeneration
FTD-MND : FTD with motor neuron disease
mean (SD) for Age, education, disease duration, and MMSE score

神病薬が 10.3% (9 例) に，抗不安薬が 9.2% (8 例) に，気分調整薬が 1.1% (1 例) に用いられていた．

3.3. 診療科別の処方

診療科によって処方の傾向が異なるかどうかも検討した．まず ChEI の診療科別の処方率であるが，精神科では 13/53 (24.5%)，神経内科では 2/17 (11.8%)，内科では 2/9 (22.2%)，その他は 1/8 (12.5%) であった．χ^2 検定 (Fisher の正確検定) にて有意差は認められなかった．一方で向精神薬は精神科では 26/53 (49.1%) に処方されていたのに対し，神経内科では 1/17 (5.9%)，内科では 2/9 (22.2%)，その他は 2/8 (25.0%) と χ^2 検定 (Fisher の正確検定) にて有意 (P=0.003) に精神科で多く処方されていた．抗精神病薬が処方されていた 9 例のうち 8 例は精神科での処方であり，抗うつ薬は 14 例全例が精神科での処方であった．漢方薬 (抑肝散) は 10 例中 8 例が精神科での処方であった．向精神薬については，どの種類の薬剤でも精神科での処方が多いという結果であった．

3.4. 紹介医の診断別の処方

紹介医の診断名による処方割合についても検討した．まず，ChEI が処方されていた 18 例では FTD および疑いという診断が 11 例 (61.1%) で最も多く，FTLD および疑い，FTD-MND 圏内と診断された例には ChEI は処方されていなかった．向精神薬が処方されていた 31 例でも FTD および疑いが 21 例 (67.7%) ともっと多く，FTLD および疑い，FTD-MND 圏内と診断された例には向精神薬は処方されていたなかった．

3.5. 専門医の診断と紹介医の処方

専門医の診断は必ずしも紹介医の診断と一致しない．紹介医の過小診断や過剰診断に基づく処方も問題になりうる．そこで，専門医の診断と紹介医の処方割合についても検討した．ChEI が処方されていた 18 例のうち，専門医によって FTD と診断された例は 4 例 (28.6%) であったが，ChEI が処方されていなかった 69 例のうち，専門医によって FTD と診断された例は 20 例 (29.0%) であった．ほぼ類似した値であり，χ^2 検定と Fisher の正確検定によって有意差は認められなかった．向精神薬が処方されていた 31 例のうち，専門医によって FTD と診断された例は 5 例 (16.1%) であった．一方で向精神薬が処方されていなかった 56 例のうち，専門医によって FTD と診断された例は 19 例 (33.9%) であり，向精神薬が処方されていなかった例の方が専門医によって FTD と診断される割合が高い傾向にあった．しかし χ^2 検定と Fisher の正確検定によって有意差は認められなかった．

3.6. 薬剤の使用に影響を与える背景因子

ChEI の使用に影響を与えるような背景因子があるかどうか，ChEI の使用の有無によって 2 群に分け，比較を行った (表 2)．しかしながら，性別，

表 2. Factors associated with ChEI use

	No ChEI use (n=69)	ChEI use (n=18)	
Sex (Male : Female)	33 : 36	9 : 9	n.s
Age	65.7 (12.1)	71.4 (8.0)	n.s
education (year)	11.3 (3.0)	11.5 (2.8)	n.s
disease duration (year)	2.8 (2.1)	3.7 (1.8)	n.s
MMSE score	19.0 (9.5)	16.0 (9.2)	n.s
care insurance use (yes : no)	20 : 49	5 : 13	n.s

ChEI : Cholinesterase Inhibitor
MMSE : Mini-Mental State Examination
mean (standard deviation) for Age, education, disease duration, and MMSE score

表 3. Factors associated with psychotropic drug use

	No psychotropic drug use (n=56)	psychotropic drug use (n=31)	
Sex (Male : Female)	26 : 30	16 : 15	n.s
Age	67.6 (11.4)	65.7 (12.0)	n.s
education (year)	11.5 (2.8)	11.1 (3.2)	n.s
disease duration (year)	2.9 (2.1)	3.0 (2.2)	n.s
MMSE score	17.7 (9.2)	19.6 (10.0)	n.s
care insurance use (yes : no)	19 : 37	6 : 25	n.s

MMSE : Mini-Mental State Examination
mean (standard deviation) for Age, education, disease duration, and MMSE score

年齢，教育年数，罹病期間，MMSE 得点，介護保険の取得状況などいずれも 2 群間の有意差はなかった．

同様に，向精神薬の使用に影響を与えるような背景因子があるかどうか，向精神薬の使用の有無によって 2 群に分け，比較を行った（表 3）．しかしながら，性別，年齢，教育年数，罹病期間，MMSE 得点，介護保険の取得状況などいずれも 2 群間の有意差はなかった．

4. 考　察

本検討は本邦で最初の FTD に対する off-label 処方の実態調査である．その結果，約半数の例に何らかの認知症症状に対する薬剤が用いられ，ChEI は 2 割の例に処方されていることが明らかになった．向精神薬は 1/3 以上に処方されており，中では抗うつ薬の処方が多かった．ChEI はさまざまな診療科の医師に処方されていが，向精神薬は主に精神科医によって処方されていた．

FTD に対する不適切な治療に関してはいくつかの問題がある．まず，FTD が他の疾患に誤診され，間違った治療を受けている可能性である．FTD は精神疾患や他の認知症性疾患に誤診されることも多く（Woolley et al., 2011），そのために不適切な治療を受ける可能性がある．しかしながら，今回の対象は，紹介医によって FTD 及び類する疾患の診断がなされている例である．その例に対して 2 割に ChEI が，1/3 以上に向精神薬が処方されていた．

この本報告の ChEI の処方率の 2 割という割合を多いと判断するか，少ないと判断するかは，意見の分かれる点と思われる．例えば，他の変性疾患によ

る認知症の例では，レビー小体型認知症（Dementia with Lewy bodies：DLB）に対してのChEIの使用は数多くの論文で有用性が示され，本邦のMoriらの多施設共同RCTにおいても，認知機能，全般機能，そして精神症状も改善したと報告された（Mori et al., 2012）．実臨床においても，ChEIは多くの例に用いられていると推測される．

その一方でFTDに対するChEIの投与の報告は多くはない（Kertesz et al., 2008；Mendez et al., 2007）．そしてほとんどで，有効性は認められなかったと報告され，また脱抑制と衝動性の悪化が認められたとの報告もある（Mendez et al., 2007）．筆者らもFTDの精神症状がChEIで悪化した例を報告している（品川ら，2009）．本報告でChEIが処方された2割のFTD例は，他に選択肢がなくChEIを使用していると推測されるが，これはなるべく避けるべきであり，今後さらなる啓発が必要と思われる．

ChEIが処方されていた18例においても，ChEIが処方されていなかった69例においても，専門医によってFTDと診断された例は3割弱であった．これはつまり，例えば行動・心理症状（Behavioral and psychological symptoms of dementia：BPSD）を伴うADのような例が紹介医によって多くFTDと誤診され，ChEIが処方されているわけではないことを意味する．さらにChEIが用いられている対象と，そうでない対象との間には背景因子に有意差のある項目はなく，ChEIが用いられる対象の一定の傾向は認められなかった．

本報告は2010年末までの集計であり，2011年に本邦で発売された，GalantamineやRivastagmine，Memantineは今回の検討には含まれていない．Memantineは認知機能改善目的以外にもBPSDに対して有用との報告があり（Gauthier et al., 2008），BPSDのある対象に比較的多く用いられ，Memantineが今回の調査の対象に含まれていたならば，その頻度は高かったかもしれない．しかしながら，Memantineは近年米国において大規模な無作為化試験が行われたが，プラセボに比して有意な結果を得ることはできなかった（Boxer et al., 2012a）．実際にはMemantineの投与も有用でない可能性が高い．

一方で35%という向精神薬の処方割合についてはどう考えるべきであろうか？ 2012年の「かかりつけ医による認知症者に対する向精神薬の使用実態調査に関する研究事業報告書」によれば，認知症患者に対する向精神薬の服用は95%とかなり高率であった（認知症ケア学会，2012）．ただしこの数字は医師が複数の患者に対してひとりでも向精神薬を使用している割合であり，単純な比較はできない．また2006年の報告で，精神科医が診ている認知症患者の62%にBPSDが認められ，そのうち93%が薬物療法を受け，そのうち81%に抗精神病薬が用いられていた（すなわち，精神科医が診ている認知症患者の47%に抗精神病薬が用いられていた）という報告もある（本間，2006）．それらに比べると本報告の数字は低い．他の疾患より行動症状が目立ち，それに伴う介護負担も大きいはずのFTDにおいて，何故向精神薬の処方割合が低いのであろうか？ これにはいくつかの理由があると考えられる．まず，他の認知症と異なり，FTDと診断された場合，不用意に向精神薬を処方せず，専門医への紹介を優先させている可能性がある．また，本研究の例は入院例を含まない外来例であることや，処方医の診療科の比率が前述の調査と異なるため，それが処方割合に影響している可能性もある．いずれにせよ，安易な向精神薬の処方を行っていないという点では，好ましいことと思われる．

向精神薬のなかで，抗うつ薬の使用が最も頻度が高かったのは興味深い．選択的セロトニン再取り込み阻害薬（selective serotonin reuptake inhibitor：SSRI）の強迫性障害や神経性大食症に対する有効性を背景として，最初にSwartzらがFTD患者に対するSSRIの使用を報告して以降（Swartz et al., 1997），フルボキサミンやパロキセチン，セルトラリンの有用性の報告がなされている（Ikeda et al., 2003；Mendez et al., 2005；Moretti et al., 2002）．SSRIではないが，間接的セロトニン再取り込み阻害薬であるトラドゾンを用い，興奮，焦燥，うつなどの症状に改善がみられたという報告もあり（Lebert et al., 2004），抗うつ薬はFTDの常同行動や食行動異常に対して有用である可能性が高い．その抗うつ薬が抗

精神病薬や抗不安薬より多く用いられているということは，これらの知識が普及しているということを意味する．前述の厚生労働省の統計では，認知症全般に対して最も多く用いられる向精神薬は抗精神病薬という結果であり，それに比べて好ましい結果であると言える．

抗うつ薬に比して頻度が低いとはいえ，抗精神病薬も約 1 割に対して用いられていた．行動障害に対して用いられている可能性があり，この数字はある程度やむを得ないと言えるかもしれない．しかし他の認知症における BPSD 同様に，FTD においても過鎮静や錐体外路症状などの問題がある（Kerssens et al., 2008）．FTLD と診断された 100 例のうち 61 例に重篤な BPSD があり，24 例に抗精神病薬が投与されたが，8 例（33%）に錐体外路症状が認められたとの報告もある（Pijnenburg et al., 2003）．さらに抗精神病薬の使用には注意を喚起していく必要がある．

漢方薬（抑肝散）は，や抗うつ薬に次いで多く処方されていた．抗精神病薬に比べ比較的安全に使用できる点が評価されているものと考えられた．FTD に対する漢方薬の知見は少なく，本邦の木村らの 5 例のケースシリーズがある程度である（Kimura et al., 2009）．今後さらなる多数例での検討が求められる．

向精神薬が処方されていた 31 例と，向精神薬が処方されていなかった 56 例では，専門医によって FTD と診断された割合は 16.1%（前者）と 33.9%（後者）で，向精神薬が処方されていなかった例の方が高い傾向にあったが，有意差は認められなかった．そのため断言はできないが，向精神薬が処方されている例の方が，過剰診断されやすい傾向にあると考えられた．その他の背景因子に有意差のある項目はなく，向精神薬が用いられる対象の一定の傾向は認められなかった．

FTLD，FTD-MND といった診断名がついていた場合，ChEI も向精神薬も用いられていなかった点は興味深い．これらの診断名がつけられた場合，典型的な行動症状ではなく，言語症状や運動症状などの非定型的な症状が存在する可能性がある．そういった例に対しては ChEI も向精神薬使用せずに，専門医への紹介を優先させるという対応をとると考えられた．

本研究の限界点について述べる．まず本研究では 4 施設という限られた施設への紹介例を対象としており，いずれも精神科の認知症専門外来への紹介であり，自然と精神科からの紹介が多く，一方で FTD-MND のような例は比較的少ない．このようなサンプリングバイアスが結果に影響を与えた可能性はある．

その一方で専門外来受診例であり，重度な行動障害を有し，在宅での生活が困難で入院しているような例は含まれていない．このような患者を含めると off-label 処方の割合が変わる可能性がある．また，なお各施設の専門医の診断にあたっては，画像診断および認知機能バッテリーを用い，診断基準に基づいて診断を行っている．しかしながら全例が病理診断を受けているわけではなく，病理学的な最終診断が FTD ではない可能性は否定できない．また，各患者がどのような症状を有しており，紹介医がどの症状に対して処方をしたかに関しては，各施設の受診時には既に処方がなされた以降であり，症状が変化した可能性があるので，評価できない．今後は紹介医がどのような症状に対して処方をしたかという調査も必要である．

5. まとめ

本研究は，本邦ではじめてなされた FTD に対する off-label 処方の現状調査である．ChEI や抗精神病薬などが用いられている現状が明らかとなり，今後は薬剤使用に対する啓発や，非薬物療法を含めた FTD への治療ガイドラインの整備が望まれる．

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Off-label medication for frontotemporal dementia in Japan

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In order to clearly the situation of off-label medication in Japan, we investigated the medication and demographic data of consecutive 87 subjects those were referred with the diagnosis of Frontotemporal dementia (FTD) syndrome. 60% of referring physicians were psychiatrists, followed by were neurologists, general physician, neurosurgeon, and other physicians. Half of the subjects were treated with some kind of medications for dementia. Cholinesterase inhibitor is prescribed for 20% of all subjects by various physicians, while psychotropic drugs were prescribed for 35% of all subjects mainly by psychiatrists. Antidepressant and antipsychotics are most common among them. Other background factors such as age, sex, duration, and MMSE scores are not associated with medication use. We need to establish guideline of pharmacological treatment for patients with FTD.

Key wards : Frontotemporal dementia, off-label medication, cholinesterase inhibitor, psychotropic drugs, pharmacological treatment

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特集：アセチルコリンと神経疾患 ― 100 年目の現在地

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