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Review Article

Taiwan Dementia Treatment Guideline

Li-Kai Huang [a,c,d,e,f], Pai-Yi Chiu [r], Yi-Chun Yeh [g,h], Ya-Ting Chang [l], Kai-Ming Jhang [n], Cheng-Sheng Chen [g,h], Shu-Ping Chao [a,c], Chia-Pei Lin [b,c], Wei-Hung Chang [o], Wei-Pin Hong [p], Mei-Feng Huang [g,h], Ching-Hua Lu [q], Yao-Tung Lee [b,c], Chao-Hsien Hung [v], Ching-Kuan Liu [i,j,k], Wei Lin [v], Chiung-Chih Chang [l,m], Chau-Jong Hu [a,c], Ming-Chyi Pai [s,t,u] *

[a] *Department of Neurology, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan,* [b] *Department of Psychiatry, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan,* [c] *Dementia Center, Shuang Ho Hospital, Taipei Medical University, New Taipei City, Taiwan,* [d] *Graduate Institute of Humanities in Medicine, Taipei Medical University, Taipei, Taiwan,* [e] *Taipei Neuroscience Institute, Taipei Medical University, Taipei, Taiwan,* [f] *PhD Program for Neural Regenerative Medicine, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan,* [g] *Department of Psychiatry, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan,* [h] *Department of Psychiatry, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [i] *Department of Neurology, Kaohsiung Medical University Hospital, Kaohsiung Medical University, Kaohsiung, Taiwan,* [j] *Department of Neurology, Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [k] *Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan,* [l] *Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan,* [m] *Department of General Neurology, Institute for Translational Research in Biomedicine, Chang Gung Memorial Hospital-Kaohsiung Medical Center and Chang Gung University College of Medicine, Kaohsiung, Taiwan,* [n] *Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan,* [o] *Department of Psychiatry, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan,* [p] *Department of Neurology, National Cheng Kung University Hospital, National Cheng Kung University, Tainan, Taiwan,* [q] *Department of Neurology, School of Medicine, China Medical University and Hospital, Taichung, Taiwan,* [r] *Department of Neurology, Show Chwan Memorial Hospital, Changhua, Taiwan,* [s] *Division of Behavioral Neurology, Department of Neurology, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan,* [t] *Alzheimer's Disease Research Center, National Cheng Kung University Hospital, Tainan, Taiwan,* [u] *Institute of Gerontology, College of Medicine, National Cheng Kung University, Tainan, Taiwan,* [v] *Department of Neurology, Chang Bing Show Chwan Memorial Hospital, Changhua, Taiwan*

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SUMMARY

This guideline covers treatment for people with dementia, including pharmacological treatment focusing on cognitive function and behavioral and psychological symptoms of dementia.
This guideline covers updated evidence-based discussion of how nonpharmacological treatments are beneficial, including exercise, occupational therapy, multidimensional intervention, cognitive behavioral therapy, and dietary recommendations.

1. Introduction

This guideline was developed by a working group established by the Taiwan Dementia Society and consisted of neurologists and psychiatrists. According to World Alzheimer Report 2015 published by Alzheimer's Disease International, 46.8 million people worldwide were living with dementia in 2015. This number will almost double every 20 years.[1] During the coronavirus disease 2019 (COVID-19) pandemic, the majority of deaths occurred in the older population.[2] These deaths might change the population age structure and dementia prevalence worldwide. A nationwide population-based cross-sectional survey conducted in all 19 Taiwan counties between December 2011 and March 2013 indicated that the age-adjusted prevalence of all-cause dementia was 8.04%, which is expected to increase due to the rapid aging of society,[3,4] thus considerably affecting economy and human rights. From the perspective of integrated care for dementia in Taiwan, the New Dementia Prevention and Care Policy-Action Plan 2.0 was implemented in 2018 by the Ministry of Health and Welfare. From the perspective of medical care for dementia in Taiwan, the coverage of the National Health Insurance (NHI) reached 92% after its launch; by the end of 2014, the NHI covered 99.9% of the Taiwanese population.[5] The pharmacological treatments approved by the United States Food and Drug Administration (USFDA) for improving cognitive function in patients with Alzheimer's dementia and Parkinson's disease dementia (PDD), including cholinesterase inhibitors (ChEIs) and N-methyl-D-aspartate (NMDA) receptor antagonists, have been covered by the NHI since two decades. New clinical trials and cohort studies have reported that the reduction of modifiable risk factors can be effective for dementia prevention.[6] The health literacy of caregivers and general practitioners who care for people with dementia should be enhanced.[7] The main focus of this treatment guideline is to provide updated, evidence-based recommendations for supporting these areas of practice.

2. Pharmacological treatment for improving cognitive ability (Table 1)

2.1. Donepezil for the treatment of Alzheimer's disease

Regardless of severity, the use of 5 or 10 mg of donepezil for de-

* Corresponding author. Division of Behavioral Neurology, Department of Neurology, National Cheng Kung University Hospital, No. 138, Sheng Li Road, Tainan, North District, Tainan 704, Taiwan.
E-mail address: pair@mail.ncku.edu.tw (M.-C. Pai)

Table 1
Pharmacological treatment for cognition enhancement.

	ChEIs			NMDA antagonist
Generic name	Donepezil	Rivastigmine	Galantamine	Memantine
Indications	Mild to severe	Mild to moderate	Mild to moderate	Moderate to severe
Dose (Taiwan listed)	Oral 5 g and 10 mg	Oral 1.5, 3.0, 4.5, 6.0 mg, Patch 4.6 mg and 9.5 mg, Solution 2 mg/ml	Oral 8 mg and 16 mg	Oral 10 mg, Solution 10 mg/ml
Recommended maintenance dose	Daily dose 5–10 mg	Daily dose 4.6–12 mg	Daily dose 8–16 mg	Daily dose 5–20 mg
Common side effects	Oral medications include nausea, vomiting, diarrhea, insomnia, infection, burnout, muscle spasms, anorexia, headache, dizziness, weight loss, fainting, and weakness. Redness and itching of the skin are also found in the patch.			Dizziness, headache, diarrhea, constipation, allergies, hallucinations, confusion, etc.

ChEIs: cholinesterase inhibitors; NMDA: N-methyl-D-aspartate.

mentia due to Alzheimer's disease (AD) can improve cognitive function, overall performance, and daily function and even ameliorate psychobehavioral symptoms in moderate and severe cases. Although a dose of 10 mg/day is slightly more effective in improving cognitive function compared with a dose of 5 mg/day, it might lead to more side effects. Some studies have reported that the early and long-term use of donepezil can be beneficial for cognitive function.[8–18]

2.2. Donepezil for the treatment of non-Alzheimer's disease

In patients with vascular cognitive impairment (VCI), donepezil can slightly improve cognitive function. In people with PDD/dementia with Lewy bodies (DLB), donepezil can improve cognitive function and overall performance. However, donepezil is not recommended for frontotemporal dementia (FTD).[19–29]

2.3. Rivastigmine for the treatment of Alzheimer's disease

The oral administration of 6–12 mg/day of rivastigmine or the use of a 9.5-cm rivastigmine patch for 24 h can improve cognitive function, daily living, and overall assessment in patients with mild and moderate AD. In addition, the long-term use (26 weeks) of low-dose oral capsules (1–4 mg) is beneficial. Patches have the same effect as oral capsules but result in fewer adverse drug reactions. High-dose patches can be used in patients with severe AD, with the same risk of side effects as low-doses patches. Care should be taken to prevent adverse drug reactions during the dose adjustment period, especially gastrointestinal symptoms.[30–32]

2.4. Rivastigmine for the treatment of non-Alzheimer's disease

The use of rivastigmine in patients with PDD can improve executive function and daily function. Patients with VCI receiving rivastigmine may exhibit a slight improvement in cognitive function but no substantial benefits in daily life and overall function. Adequate evidence indicating that rivastigmine can improve cognitive function in patients with less common cognitive disorders, such as FTD, Huntington's disease, traumatic brain injury, and multiple sclerosis, is not yet available. In addition, valid evidence supporting the use of rivastigmine in patients with mild cognitive impairment (MCI) is absent.[33–36]

2.5. Galantamine for dementia or mild cognitive impairment

Continuous use of 16–24 mg of galantamine for more than 6 months can significantly improve the cognitive and daily function of patients with mild and moderate AD. The safety of galantamine is similar to that of other ChEIs. Patients with MCI using galantamine should be aware of the increased mortality risk. No study has yet demonstrated the effectiveness of galantamine in preventing progression to dementia. Galantamine may improve cognitive performance in patients with VCI.[37–40]

2.6. Memantine for the treatment of Alzheimer's disease

Memantine can improve overall performance, cognitive function, daily function, and behavior in patients with moderate to severe AD. In patients with mild AD, treatment with memantine for 6–7 months is not effective. Clinical trials should examine the efficacy of memantine use for a long period in patients with mild AD to determine whether memantine should be used early and whether it exerts long-term therapeutic effects. Memantine exhibited low effectiveness in treating other types of disorders. Additional clinical trials should be conducted for further analysis.[41–45]

2.7. Cholinesterase inhibitors in combination with memantine for the treatment of Alzheimer's disease

The combination of ChEIs and memantine is frequently used to treat patients with moderate to severe AD in clinical practice in Taiwan despite not being approved by the Bureau of National Health Insurance for adaptation. Several clinical studies have reported that combined therapy can more effectively improve cognitive and overall function compared with monotherapy; however, some disputes and different opinions still exist due to inconsistent findings.[46–49] ChEIs are still the first choice for treatment and should be used early after the diagnosis of dementia due to AD.[50] Moreover, ChEIs should be used in combination with memantine if brain deterioration continues after treatment.[51]

The effectiveness of monoclonal antibodies remains to be confirmed; therefore, they are not yet available in the market.[52–54] The inhibition of Aβ42 production and the condensation of oligomers are the focus of current drug development for AD, and combination therapy remains a possible treatment option for the future.[55,56]

3. Pharmacological treatment for behavioral and psychological symptoms of dementia

People with dementia experience various mood or behavioral problems or psychotic symptoms, which are termed as "behavioral and psychological symptoms of dementia (BPSD)." BPSD includes delusion, misidentification, hallucination, agitation, aggression, apathy, depression, anxiety, irritability, sleep problems, eating problems, elation/euphoria, disinhibition, and aberrant behavior. Patients may falsely believe that someone is stealing something from them (theft

delusion), that their spouse has an affair with the caregiver (jealous delusion), and that the food is poisoned and thus not eat it (persecution delusion). In addition, they may see nonexistent individuals, animals, or insects (hallucination); steal at shops (disinhibition); and wake up at night with walking around, yelling, or disorganized speech (parasomnia). These symptoms exert considerable physical or psychological burden on caregivers. Patients with different types of dementia exhibit different types of BPSD. For example, delusions and hallucinations, especially visual hallucinations, are most commonly observed in patients with Lewy body dementia. Although delusions and hallucinations may also occur in patients with vascular dementia or dementia due to AD, their occurrence is less common than in those with Lewy body dementia. Compared with the core cognitive symptoms of dementia, such as memory impairment, executive dysfunction, and language impairment, BPSD causes higher financial or caregiver burden and more considerably reduces the quality of life of caregivers.

Medication is not the first option to manage BPSD. Other factors related to the patient, caregiver, or environment should be examined first. For example, whether patients' mood or behavioral problems are caused by their pain or physical discomfort, caregivers' poor communication skills, or environmental factors (e.g., increased noise or insufficient light) should be examined. After improving the aforementioned factors, patients' mood and behavioral problems may improve. If the symptoms still do not improve or become severe, medication can be considered. However, many challenges are encountered while using medication for BPSD. Drugs with favorable efficacy often have safety concerns. Taking antipsychotics as an example, the USFDA has issued safety warnings, highlighting the risk associated with using second-generation antipsychotics for dementia. In addition, other drugs used for treating BPSD, including antidepressants and antiepileptic drugs, have risk considerations. However, pharmacotherapy is still one of the most commonly used treatments in the medical field and the most efficient treatment under emergency conditions. This section summarizes principles and clinical considerations that should be followed when prescribing psychotropic drugs for treating BPSD.

3.1. Antipsychotics

Compared with first-generation antipsychotics, second-generation antipsychotics have fewer side effects, exert a weaker deteriorating effect on cognitive function, and lead to higher quality of life. Physicians should pay attention to adverse effects such as drowsiness and dizziness. Some drugs may cause cardiovascular diseases, weight gain, abnormal blood sugar levels, hyperlipidemia, increased appetite, dry mouth, and even agranulocytosis. Antipsychotics are the most effective drugs for treating agitation/aggression and psychotic symptoms in dementia. A study conducted by the National Institute of Mental Health (NIMH Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease Study) compared the efficacy of risperidone, olanzapine, and quetiapine for dementia due to AD. The results revealed that all the three antipsychotics were effective in alleviating agitation, and risperidone and olanzapine were effective in alleviating suspiciousness, delusion, and hostility;[57] among them, risperidone exhibited the highest efficacy. The time to treatment discontinuation for any reason did not significantly differ among the three antipsychotics; the average continuous use time was 5.3–8.1 weeks.[58] Other meta-analyses have indicated the effect of risperidone on delusion, aggression, and irritability in dementia.[59–61] Although aripiprazole is an emerging drug, meta-analyses have reported its efficacy in improving irritability and psychotic symptoms.[59,61] Inconsistent results have been demonstrated for olanzapine. Moreover, studies have failed to prove the efficacy of quetiapine.

The USFDA issued a warning in 2005 that second-generation antipsychotic drugs used for treating dementia can increase the mortality rate by 1.6–1.7 times. The number needed to harm for second-generation antipsychotic drugs is 1/100. The cause of death is mostly heart disease or lung infection. The risk associated with first-generation antipsychotics is even higher than that associated with second-generation antipsychotics.[62] Thus, clinicians must pay attention to the side effects and safety of drugs during drug treatment.

A study reported that the discontinuation of antipsychotic drugs could increase the recurrence of agitation/psychotic symptoms.[63] In 2018, the Cochrane Library indicated that the quality of existing studies still needs to be improved. According to the current evidence, the discontinuation of antipsychotics exerts no or little effect on BPSD; however, for patients with severe symptoms, continuation of antipsychotic treatment can be more beneficial.[64]

When administering antipsychotics to treat agitation/aggression or psychotic symptoms in people with dementia, the use of a low starting dose, slow titration, and the lowest effective dose is crucial. The recommended therapeutic doses are lower than those for general adults. Taking several commonly used antipsychotics as examples, the recommended starting dose and therapeutic dose are listed in Table 2. Based on clinical experience, the relative starting and therapeutic doses for Chinese patients may be lower due to ethnic and physical differences.[65] In the National Institute for Health and Care Excellence (NICE) dementia treatment guidelines issued in June 2018, several key points for treating the neuropsychiatric symptoms of dementia are listed:[66] (1) antipsychotics should only be used when there is a risk of patients harming themselves or others or when these symptoms cause high distress; (2) before administering antipsychotics, the benefits and risks of treatment should be discussed with the patient and caregivers; (3) the lowest effective dose and shortest duration possible should be used; and (4) the need to continue antipsychotics should be evaluated every 6 weeks.

3.2. Antidepressants

According to the pharmacological mechanism, antidepressants can be divided into selective serotonin reuptake inhibitors, selective serotonin and norepinephrine reuptake inhibitors, norepinephrine and dopamine reuptake inhibitors, monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), and norepinephrine and serotonin receptor modulators. Some antidepressants, such as TCAs, exert anticholinergic effects that can deteriorate cognitive function, which is not recommended for dementia. Most meta-analysis studies have not supported the effectiveness of antidepressants on the depressive symptoms of dementia.[67] However, in a subgroup analysis, antidepressants still appeared to be effective for more severe depressive symptoms.[68] Although citalopram is effective for agitation,[69] its use

Table 2
Recommended dose of antipsychotic drugs for people with dementia (Southern Health NHS Foundation Trust, 2015).

Drug	Initial dose	Therapeutic dose
Risperidone	0.25 mg bid	0.5 mg bid
Olanzapine	2.5 mg qd	5–10 mg qd
Quetiapine	25 mg qd	25–150 mg daily
Aripiprazole	5 mg qd	10 mg qd

is limited to nonsevere types of agitation.[70] However, clinicians should pay attention to the possible side effects of citalopram, including QT prolongation, falls, and hyponatremia.

The NICE guideline published in 2018 indicates that antidepressants should not be regularly administered to people with dementia with mild-to-moderate depressive symptoms.[66]

3.3. Anticonvulsants

A meta-analysis including 72 people with dementia reported that carbamazepine improved the overall psychotic symptoms of dementia.[71] Two review articles including case series reports, retrospective medical record surveys, open trials, and double-blinded randomized controlled trials have indicated that valproate is not beneficial for treating BPSD.[72,73] The NICE guideline published in 2018 does not promote the use of anticonvulsants for dementia, especially valproate, which is not recommended due to its lack of efficacy.[66]

3.4. Benzodiazepines

Insomnia is the most common sleep problem in people with dementia, followed by hypersomnia and parasomnia (such as rapid eye movement sleep behavior disorder [RBD]). Nonpharmacological treatments, such as improved sleep hygiene and cognitive behavioral therapy, are recommended. In terms of pharmacological treatments, clinical trials on melatonin, ramelteon, trazodone, benzodiazepines (BZDs), and non-BZDs (Z-drug) have been conducted. In 2016, a Cochrane review of randomized controlled trial reported that melatonin and ramelteon exhibited no benefit, and that low-dose trazodone (50 mg) exerted some minor effects on sleep problems in people with dementia.[74] No randomized controlled trial on BZDs has yet been performed. Several observational studies have indicated the risk of dementia in patients using BZDs.[75,76] BZDs might be involved in AD pathogenesis;[77,78] however, the detailed mechanism remains to be clarified. Therefore, BZDs should be cautiously used in people with dementia.

Recently, the USFDA approved two drugs with new pharmacological mechanisms for sleep disorders. Suvorexant and Lemborexant are orexin receptor antagonists. Preliminary results indicated that the drugs could increase 28 minutes of sleep time in patients with AD.[79]

RBD is especially related with DLB or dementia due to Parkinson's disease. Although USFDA–approved drug treatment is currently not available, melatonin (6–18 mg) or clonazepam (0.5–1 mg) can be considered for treatment and should be prescribed from a lower dose. The 2018 NICE guidelines do not recommend using melatonin to treat insomnia in people with dementia.[66] The guidelines recommend improving sleep by using multimodal treatments such as sleep hygiene education, increased sunlight exposure, exercise, and individualized activities.

4. Nonpharmacological treatment

No consistent evidence has indicated that (1) exercise, (2) occupational therapy, (3) multidimensional intervention, or (4) cognitive behavioral therapy can delay the deterioration of the daily function of people with dementia. In people with dementia, individual intervention is more effective than group intervention. Customized interventions of exercise, activity planning, cognitive rehabilitation, or environment therapy can be beneficial. Combined group intervention (people with dementia and caregivers) care has been observed to be the most effective. Compared with occupational and psychological intervention, exercise is a more economical and effective intervention.[80] Sensory intervention (aroma, massage, and light intervention), psychosocial intervention (those involving nostalgia, music, and pets), and structuralized nursing care (bathing, oral care, and healthy diet) are suggested to stabilize the daily functions of people with dementia. In patients undergoing mild dementia–centered cognitive training, understanding their difficulties and life needs at home is the first step. Based on the first step, setting goals for training can increase the satisfaction of patients and family members and can improve cognitive function.[81] Participating in 1 hour of Go game per day could improve the depression index of patients with Alzheimer's dementia.[82] Older individuals engaging in leisure activities more than twice per week had a lower risk of dementia compared with those engaging in leisure activities less than once per week in a 4-year longitudinal follow-up study.[83] However, no study has indicated that board games can improve the cognitive function of people with dementia. For individuals without dementia, daily mental exercises (reading newspapers and magazines and playing board games, cards, and mahjong) for 3 years could reduce the risk of dementia in 4–6 years.[84]

Occupational therapy includes (1) environmental assessment to meet the needs of people with dementia, (2) training the problem-solving skills of people with dementia, (3) caregiver educating and training, and (4) interactive caregiver education and training. Occupational therapy can improve the independence and quality of life of people with dementia.[85] Overall, music intervention could improve the social behavior of people with dementia. More than five times of music intervention for more than 30 minutes during each intervention alleviated depression and anxiety in people with dementia residing in nursing centers; live music could improve apathy symptoms and was more effective than prerecorded music.[86] Interactive music can alleviate anxiety, reduce stress, and improve the emotional state of people with severe dementia. Moreover, interactive music can effectively improve interpersonal relationships in people with dementia.[87] Using a musical instrument twice a week, whether for 2 hours or 30 minutes, could temporarily improve the mood of people with severe dementia.[88,89] Inhaling the scent of lavender could alleviate the irritability of individuals with dementia.[90] Using lavender essential oil combined with massage (acupoint acupressure for 2 minutes combined with 2.5% lavender essential oil and 5minutes of warmup exercise) could more effectively alleviate the agitation of people with dementia compared with simply inhaling the scent of lavender.[91] For mood problems, using a lavender essential oil diffuser for at least 1 hour during sleep could improve restlessness, aggression, irritability, and abnormal behavior at night. The efficacy of lavender essential oil is higher than that of sunflower essential oil.[90] Professional massage intervention on the shoulders, neck, back, hands, and feet of people with dementia could significantly lower irritability, aggression, anxiety, and depression.[92–94] Exercise intervention could improve the performance of activities of daily living in people with dementia and reduce the risk of falls. However, evidence regarding the effect of exercise intervention on cognitive or mental behavioral symptoms is not consistent. Recent studies have demonstrated that exercise could improve cognitive performance in people with AD.[95–97] Setting individualized exercise goals and performing these exercises appropriately can be beneficial: twice a week, one hour each time, with endurance (cycling), balance (walking in straight lines and climbing ladders) and executive function (correctly throwing balls) exercises. Customized home-based exercises are more effective in improving overall function than group-based exercise activities.[98] Exercise can delay the decline in ADL and the deteri-

oration of emotional problems. For people with MCI, aerobic exercise and resistance training were more effective in improving executive function than stretching and balance training.[99] A study conducted in Taiwan reported that in individuals with MCI, steps walked per day were more strongly correlated with cognition compared with calories burned per day.[100] Longer walking time could ameliorate sundown syndrome.[101] In addition, compared with resistance exercise, aerobic exercise exhibited a stronger correlation with increased neuroprotective factors,[102] whereas resistance and aerobic exercises exerted the same effect on the reduction of the inflammatory responses of individuals with MCI.[103]

Cognitive training for approximately 30–60 minutes, including time, place, and people information, could improve cognitive function;[104] however, the intervention of orientation did not reduce behavioral problems or depression symptoms. Reality-oriented intervention is a repetitive and meaningful time, place, and people information stimulus that can help people with dementia to have a better understanding of the surrounding environment. In addition, more than 10 hours of reality-oriented therapy can be regarded as an appropriate dose for improving cognitive function in people with dementia.[104] Light intervention was effective for alleviating agitation, depression, and sleep disorders in some people with dementia; however, further research is required.[92,105] Ten weeks of intervention, from Monday to Friday with 1 hour of light intervention per day in the day time, could reduce restlessness and problems such as depression, abnormal behavior, and changes in appetite.[106]

The daily intake of 30 kcal/kg of body weight and appropriate nutrition for people with dementia in combination with a high-protein diet (20% of the total calories) are beneficial for wound healing. Dehydration can lead to the acute confusion state and can even increase mortality. Individuals with dementia experience challenges to maintain adequate hydration, including difficulties in getting up to get the drink and swallowing, decreased thirst sensation, and refusal to drink. Regular audit of hydration practices at home is necessary. Policies, procedures, and guidelines can help caregivers manage hydration in their routine practice.[107–109]

Adding various vitamins and dietary minerals to the diet can be beneficial for the nutritional status of people with dementia residing in the nursing center. However, for patients with mild-to-moderate Alzheimer's dementia, excessive vitamin B intake is not beneficial. Folic acid supplementation can improve global cognition. Vitamin C and E are not beneficial for overall cognition. Omega-3 fatty acids can delay the decline in overall cognitive function in patients with MCI and mild dementia. For individuals with mild dementia with the ApoE 4 gene, anxiety can be improved using omega-3 fatty acids. For those with mild dementia without the ApoE 4 gene, using omega-3 fatty acids may improve depression. Various nutritional formulas or phospholipids only have a transient effect on cognitive improvement or exert no effect.[110–112] Dietary recommendations for preventing or reducing dementia areas follows: (1) high, but not moderate, adherence to the Mediterranean diet (MeDi) can reduce the risks of cognitive impairment and dementia in healthy individuals and can delay the progression of AD, and (2) MeDi combined with antihypertensive diet (Mediterranean plus Dietary Approaches to Stop Hypertension diet) involving eating more foods that are beneficial for the brain (vegetables, nuts, berries, beans, whole grains, seafood, poultry, olives oil, and wine) and eating less unhealthy foods (red meat, butter and margarine, cheese, pastries and sweets, and fried foods/fast foods) was significantly positively correlated with the delay of cognitive decline and could reduce the risk of AD.[113–115] Twenty-one classes of acupuncture class every 2 days for 6 weeks with each acupuncture class lasting for approximately 30 minutes could improve cognitive function and daily life function in patients with mild vascular dementia.[116] In patients with mild to moderate Alzheimer's dementia, acupuncture for 12 weeks three times per week could improve the Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-cog).[117]

5. Discussion

The scope of the guideline focuses on dementia treatment in general practice. The guideline addresses dementia caused by common diseases including AD, vascular dementia, PDD, DLB, and FTD without covering other rare diseases such as prion diseases, HIV infection, progressive supranuclear palsy, corticobasal degeneration, multisystem atrophy, and Huntington's disease with dementia. The treatment plan for these rare diseases should be tailored according to each patient's diagnosis and staging as well as by referring to the latest treatment development in the field. Novel research criteria for dementia diagnosis are dependent on fluid and imaging biomarkers. For instance, the National Instituteon Aging-Alzheimer's Association published a research criterion for AD diagnosis in 2018 that emphasizes the biological definition through the extensive use of biomarkers. In addition, pathological studies have indicated that the mismatch of clinical diagnosis to pathological findings can be a concern.[118–120] Furthermore, mixed pathology in the aged population is not uncommon,[121] thus increasing complexity in defining the pathological contribution to clinical phenomenology. This guideline follows clinical diagnosis criteria for the aforementioned dementia diseases but does not overemphasize biomarkers.

For the past 20 years, substantial progress has not been made for novel pharmacological treatment for dementia. Although many studies have targeted amyloid beta while developing new therapies, no new successful treatment has been proven to be effective for dementia due to AD or other subtypes of dementia. Currently, donepezil, rivastigmine, galantamine, and memantine are the only four drugs that are widely used for symptom relief, but they do not modify the disease progression of AD; these drugs have been used for more than 20 years. Because no better treatment is available, optimal treatment strategies for dementia due to AD include starting treatment in the earlier stages of dementia (not the MCI stage), titrating to higher doses as soon as possible, and titrating to a higher dose when deterioration is observed.[122] ChEIs in combination with memantine are often used clinically for the treatment of patients with moderate-to-severe AD in Taiwan despite not being licensed by the Bureau of National Health Insurance. ChEIs, which are still the first choice for the treatment of dementia due to AD, should be used early after the diagnosis of dementia due to AD and should be added to memantine if deterioration continues after treatment. For dementia with non-AD causes, rivastigmine is approved for the treatment of dementia due to PD (PDD). Rivastigmine is superior to the control drug in the combined analysis of neuropsychiatric symptoms (NPI-10), cognition (ADAS-Cog or MMSE), and daily function (ADAS-ADL). The American Heart Association and the Stroke Society (AHA/ASA) recommend that donepezil should be used in VCI cases. Donepezil was also found to be effective in patients with DLB;[123] therefore, donepezil is approved in Japan and some Asian countries. However, for dementia due to FTLD or other brain disorders, neither ChEIs nor memantine has been suggested.

Neuropsychiatric symptoms in dementia are common and distressing problems. Up to 97% of people with dementia have ever experienced neuropsychiatric symptoms.[124] These neuropsychiatric symptoms may not only increase the burden of caregivers and accelerate early institutionalization but also increase social costs.[125]

Until now, pharmacological treatment with both high efficacy and safety is lacking. Thus, nonpharmacological treatment should be used first. However, these strategies have largely not been translated into real-world clinical management and standard care.[126] In clinical situations, pharmacotherapy is still one of the most commonly used treatments and the most efficient treatment under emergency conditions. Among pharmacological treatment, antipsychotics have shown the highest efficacy, especially for alleviating agitation, aggression, and psychosis. However, the USFDA has warned about the risks of cerebrovascular events and mortality associated with the use of antipsychotics. Clinical trials of antipsychotics are limited within 12 weeks; thus, the long-term benefit remains uncertain. Potential pharmacological alternatives to antipsychotics with high efficacy and safety still need to be explored. Although recommendations for the nonpharmaceutical management of dementia often lack consistency or a consensus, studies generally suggest that individual interventions are more effective than group interventions, and tailormade interventions of exercise, activity planning, cognitive rehabilitation, or the environment therapy is more effective.[127] Exercise is a more economical and effective intervention compared with occupational intervention and psychological intervention.[80] To improve the ADL functions of people with dementia, sensory intervention, psychosocial intervention, and structuralized nursing care are suggested to stabilize the ADL functions of people with dementia;[128] occupational therapy has been shown to improve the independence and quality of life of people with dementia;[85] and setting goals for training can increase the satisfaction of patients and family members.[81] With regard to setting goals, tailormade exercises at home are effective in improving overall function.[98] Moreover, reality-oriented intervention enables people with dementia to have a better understanding of the surrounding environment, and it significantly improves cognitive function.[104]

Regarding mood instability, inhaling the scent of lavender could improve the irritability of people with dementia.[90] Moreover, using lavender essential oil combined with massage could alleviate agitation in people with dementia.[91] Taken together, the results revealed that using a lavender essential oil diffuser can improve restlessness, aggression, irritability, and abnormal behavior at night,[90] and professional massage interventions on the shoulders, neck, back, hands, or feet can significantly decrease irritability, aggression, anxiety, and depression.[92–94] In addition, exercise delays the deterioration of emotional problems,[99] using a musical instrument can temporarily improve the mood of patients with severe dementia,[88,89] and light intervention is effective for agitation, depression, or sleep disorders in some people with dementia.[92,105] In Taiwan, a study showed that steps walked per day was correlated with cognition in patients with MCI,[100] longer walking time could improve sunset syndrome,[101] and aerobic exercise could increase neuroprotective factors.[102] Lastly, diet and nutrition are critical in people with dementia. The daily intake of 30 kcal/kg of bodyweight and appropriate nutrition are beneficial for wound healing, and folic acid supplementation could improve global cognition. Omega-3 fatty acids can delay the decline of overall cognitive function in patients with MCI and mild dementia, and the effect of omega-3 fatty acids is affected by the presence of ApoE4 gene.[110–112] Long-term drinking active and stable liquid water could delay or improve AD in animal experiments.[129] MeDi combined with a antihypertensive diet was significantly positively correlated with delaying cognitive decline and could reduce the risk of AD.[113,114,130] For patients with mild to moderate Alzheimer's dementia, acupuncture for 12 weeks three times per week could improve ADAS-cog.[117] This guideline uses an evidence-based medicine approach to summarize current scientific and clinical information in response to unmet treatment needs. From the perspective of clinical practice, infrastructure construction differs by regions, and the information does not account for individual variations. The information should not be considered inclusive of all proper treatments or a substitute for the independent professional judgment of the treating provider.

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