Pharmacotherapy for Major Neurocognitive Disorder

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Summary

No drugs have been developed that can ameliorate major neurocognitive disorder (MND). Some drugs can ameliorate the behavioral and psychological symptoms of dementia (BPSD), which consists of two subtypes. The first type is positive symptoms such as hallucination and irritation. The second type is negative symptoms such as apathy and depression. Because the former induces serious problems for caregivers, it should be treated as soon as possible. The latter symptoms, however, should be accepted as MND itself. Doctors generally do not prescribe drugs for negative symptoms, as such an intervention typically ends in failure. Caregivers manage to provide a comfortable life for patients with negative symptoms.

Anti-dementia drugs have no significant effect on MND itself or BPSD, but on the contrary, have many adverse effects on patients with MND. Antipsychotics are effective for positive symptoms of BPSD. Hallucination and delusion can be successfully treated with high-potency antipsychotics. On the other hand, excitation, insomnia, and anxiety can be ameliorated by low-potency antipsychotics. Because reaction to these drugs is variable in each patient, and patients with MND do not explain their condition very well, precise and frequent observation of patients is necessary.

*All disease names are adopted from DSM-5

Key words: Major Neurocognitive Disorder, Medical Therapy, Behavioral and Psychological Symptoms of Dementia (BPSD)

Introduction

Approximately 5 million people suffer from major neurocognitive disorder (MND) in Japan, and the number is increasing. Patients with MND prefer to remain living in the same place where they have lived rather than spend the rest of their life in a nursing home. Their caregivers and medical staff, including their family doctors, should provide a way for them to comfortably spend the rest of their life in their homes. Cardinal symptoms of MND include memory disturbance and executive dysfunction. Memory disturbance induces secondary symptoms, i.e., behavioral and psychological symptoms of dementia (BPSD). Patients with severe aggressive behavior may injure not only themselves but also their caregivers. Although the cause of aggressive behavior should be found and treated, sedatives have to be used in an emergency. I believe that "anti-dementia drugs" are not necessary for patients with

MND. I will review MND and discuss pharmacological therapy for MND.

1. MND

1.1. Definition of MND

The category of neurocognitive disorders (NCDs) encompasses the group of disorders in which the primary clinical deficit is in cognitive function, and is acquired rather than developmental. NCDs are those in which impaired cognition has not been present since birth or very early life, and thus represents a decline from a previously attained level of functioning. Although cognitive deficits are present in many mental disorders, only disorders whose core features are cognitive are included in the NCD category. The term "dementia" has been changed to "NCD" in the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5). NCD is classified into delirium, MND, and mild NCD. DSM-5 diagnostic criteria for delirium include disturbance of consciousness with reduced ability to focus, sustain or shift attention. An electroencephalogram is useful to identify mild consciousness disturbance such as delirium. When symptoms and diagnoses are consistent with dementia, the term "dementia" is used. The term "major" is used when the decline in mental ability is severe enough to interfere with the patient's independence and daily life. MND is diagnosed when the consciousness of a person is clear, because delirium is sometimes misdiagnosed as MND. Furthermore, MND is a risk factor for delirium. In general, MND gradually and irreversibly worsens. The term "cognitive" refers to thinking and related processes.

In DSM-5, MND is defined by a substantial cognitive decline in one or more of the domains listed below:

1) Complex attention, which includes sustained attention, divided attention, selective attention, and information processing speed
2) Executive function, which includes planning, decision making, working memory, responding to feedback, inhibition, and mental flexibility
3) Learning and memory, which includes free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, and implicit learning
4) Language, which includes object naming, word finding, fluency, grammar and syntax, and receptive language
5) Perceptual-motor function, which includes visual perception, visuo-constructional reasoning, and perceptual-motor coordination
6) Social cognition, which includes recognition of emotions, the theory of mind, and insight

In the National Institute on Aging-Alzheimer's Association working group criteria, dementia is diagnosed when the patient displays cognitive or behavioral (neuropsychiatric) symptoms (=BPSD). In ICD 10 (1993), dementia is defined as a chronic progressive disease involving disturbances in higher brain functions such as memory, cognition, and executive function.

1.2. Pharmacotherapy for MND

1.2.1. Opinions about pharmacotherapy for MND

No therapy for MND has been developed. Therefore, patients with MND can only take a medication that ameliorates clinical symptoms. One of the cardinal symptoms of MND is memory disturbance, but no drugs can ameliorate this problem. Therefore, patients with MND do not take anti-dementia drugs with the expectation of recovery of memory. Some medications are effective for treating some symptoms of BPSD, and these are justified when BPSD is apparent and requires treatment.

Doctors and caregivers have different opinions about the effect of anti-dementia drugs. Some doctors prescribe anti-dementia drugs only because they want to give something to patients, regardless of their actual usefulness for this purpose. On the other hand, caregivers anticipate that anti-dementia drugs will restore or at least ameliorate cognitive function. Caregivers notice that these drugs do not ameliorate cognitive symptoms but still believe these drugs can slow exacerbation of the disease. Anti-dementia drugs can improve memory impairment in patients with MND by only one point in the Mini-Mental State Examination. Generally, the effect of anti-dementia drugs is too weak to be noticed by their caregivers. Therefore, anti-dementia drugs are not worth prescribing.

Anti-dementia drugs sometimes induce insomnia, hallucination, delusion, excitation, and confusion, especially in patients with MND that has progressed. These symptoms listed above are the same as BPSD. Most patients with MND show BPSD during their disease course. Therefore, discriminating the adverse effects of anti-dementia drugs from BPSD is confusing. Approximately 6 weeks, which is an extended period, is needed to wear off the effect of donepezil, which is another reason that anti-dementia drugs should not be prescribed for patients with MND.

1.2.2. History of anti-dementia drugs

The first anti-dementia drug was the infamous calcium hopantenate. This drug was initially adopted for use in developmentally delayed children with low motivation. In 1983, the drug was allowed to be prescribed to patients with low motivation due to the sequelae of cerebrovascular disease (CVD). Many doctors prescribed this drug not only for patients with CVD but also for patients with MND because no drug was available for patients with MND.

Many pharmaceutical companies developed drugs similar to calcium hopantenate because they were profitable. Researchers in these pharmaceutical companies adopted calcium hopantenate as a control in statistical studies, because calcium hopantenate could significantly improve patients with MND. Companies did not adopt a placebo as a control, as is typically done, perhaps because these companies knew that no significant differences were present in the effect of their drugs when the placebo was used as a control. In 1987, a new guideline was introduced stating that a placebo is required as a control whenever new

drugs are evaluated. In 1996, the Ministry of Finance demanded that the Ministry of Health and Welfare (MHLW) require that all anti-dementia drugs be reevaluated using a placebo as a control. Reevaluation showed that most anti-dementia drugs, which were called brain metabolic stimulants or cerebral circulation activators at that time, do not affect dementia. Therefore, doctors did not use these drugs. Many neurologists had previously noticed that these drugs were useless. Many drugs have very weak effects and are not adopted in other countries except Japan. Many Japanese patients take many drugs. Doctors readily prescribe drugs to their patients, and patients want to take drugs.

On May 19, 1998, MHLW reported that idebenone, indeloxazine hydrochloride, bifemelane hydrochloride, and propentofylline do not effectively ameliorate the loss of motivation and emotional impairment caused by CVD. The government alleged that improvement in skills in a rehabilitation and nursing environment enhances the mental condition in patients with CVD. That is the reason that the four drugs mentioned above did not show significant improvement compared with the placebo. Such allegations are called "twi sting the truth and truckling to the times." The president of the Japanese medical association responded to this report and made a charge against the secretary of MHLW that patients' confidence in their doctors was severely damaged because doctors have prescribed ineffective drugs to patients.

I do not regard these drugs as useless, because they may improve alertness in some patients similar to current anti-dementia drugs.

1.2.3. Current drugs for Alzheimer's disease (AD)

At present, no disease-modifying drugs for AD are available, and thus, current treatment aims at alleviating symptoms. Cholinergic neurons in the basal nucleus whose axons extend to the cerebral cortex are severely diminished in AD. The activity of choline acetyltransferase in this region is decreased by 30-60%. Augmentation of cholinergic transmission is currently the mainstay of treatment for AD. This treatment is analogous to dopamine supplement therapy in Parkinson's disease. Acetylcholine is very rapidly broken down by cholinesterase into choline and acetate, and thus, cholinesterase inhibitors enhance cholinergic transmission. The observation that anticholinergic agents such as trihexyphenidyl induce a state of confusion resembling MND has given rise to the cholinergic hypothesis that a deficiency in acetylcholine is critical in the genesis of the symptoms of AD. In 1993, tacrine, which was the first cholinesterase inhibitor to affect the brain, was approved by the United States Food and Drug Administration, but it is hepatotoxic and has limited use. Subsequently, donepezil was approved in multiple countries in addition to Japan. The drug slightly improves cognitive functions in patients with

MND after 24 weeks of treatment, which is a typical trial period in clinical studies. However, no further improvement or some decline was observed after 6 months. The study showed a 6- to 12-month delay in the progression of cognitive dysfunctions, after which clinical deterioration resumed. Three drugs, donepezil, rivastigmine, and galantamine, are currently used as cholinesterase inhibitors for patients with AD. Their effect is generally weak, usually producing no dramatic improvement in symptoms. They induce adverse effects on the central nervous system (CNS) such as extrapyramidal symptoms and positive BPSD (excitation, irritation, insomnia, delusion, hallucination, etc.), which are difficult to distinguish from exacerbation of BPSD. Furthermore, patients treated with cholinesterase inhibitors tend to show syncope, bone fractures, accidental injuries, bradykinesia, and a higher rate of cardiac pacemaker device insertion.

Memantine is a noncompetitive antagonist of the NMDA-type glutamate receptor and is used as either an adjunct or an alternative to cholinesterase inhibitors in patients with AD. However, co-administration of cholinesterase inhibitors with memantine does not result in significant improvement compared to high-dose donepezil administration. This drug has negative effects on the CNS, e.g., epilepsy, positive symptoms of BPSD, vertigo, falling, headaches, and somnolence. Doctors and caregivers tend to misunderstand these symptoms as a part of BPSD.

These drugs are not necessary for patients with MND. The first-generation anti-dementia drugs improve apathy in some patients, and the second-generation drugs are also effective in restoring vitality in some patients. However, these drugs are effective for only a limited time. An anti-dementia drug may sedate or induce delusion in a certain person, but make another person active. What will happen to each patient is unpredictable, and thus, these drugs are not safe for patients with MND.

1.2.4. Neurotransmitters in AD

Acetylcholine is decreased in AD. The amount of acetylcholine is the lowest among all neurotransmitters. Cholinergic neurons located at the nucleus basalis of Meynert are the central neurons affected in AD. The loss of the nucleus basalis cholinergic neurons in patients with AD is severe: from about 500,000 in the healthy adult to less than 100,000 in patients displaying advanced AD. Cholinergic neuronal loss, especially in the basal forebrain, occurs not only in AD but also in Parkinson's disease, amyotrophic lateral sclerosis, Down syndrome, progressive supranuclear palsy (PSP), and olivopontocerebellar atrophy. Loss of cholinergic neurons and the consequent impairment in dopaminergic transmission could be the mechanism underlying AD-related psychiatric symptoms.

Excessive glutamate is toxic to neurons. A decrease in the glutamate transporter capacity, which increases the concentration of glutamate in the synapse, and a selective

loss of vesicular glutamate transporters, which increases the concentration of glutamate in the cytosol, have been observed in the AD brain. Moreover, excitatory amino acid transporter 2, which is primarily located in perisynaptic astrocytes, is impaired in AD and also increases the concentration of glutamate around the synapse. Glutamate transmission is enhanced when glycine is bound to the GluN1 subunit of the glutamate receptor. The role of glycine in glutamate transmission is to facilitate the recovery of glutamate receptor sensitivity. D-serine also binds to the GluN1 subunit and enhances glutamate transmission. However, excessive D-serine produced in astrocytes is also harmful to neurons. D-serine is increased in the hippocampus of patients with AD. Approximately 90% of hippocampal neurons are glutamatergic. The remaining 10% of hippocampal neurons are inhibitory, and most are GABAergic. The hippocampal GABAergic system is preserved in AD, meaning that atrophy of the hippocampus in the AD brain occurs mainly in glutamatergic neurons.

The involvement of dopamine in AD is unclear because significant differences between AD brain and age-matched control brain have not been clearly shown. The dopaminergic system gradually undergoes several changes during the physiological aging process. Decreased release of dopamine, reduced dopamine receptor expression (in particular D2 subtypes), and reduced dopamine transporter expression in the striatum, the hippocampus, and the frontal cortex are typical in the aged brain. Thus, severe degeneration of the dopaminergic system does not occur in AD. Lewy bodies and alpha synucleinopathy pathology are observed in 50% of AD patients as well as 30% of healthy aged controls, which means that degeneration of dopamine neurons tends to accompany AD. The degenerative alteration of the dopaminergic system is different between AD and Parkinson's disease. In Parkinson's disease, the dorsal striatum is predominantly affected, whereas the dorsal striatum is relatively spared, and the nucleus accumbens is profoundly affected in AD. Patients with AD, particularly in the later stage, show bradykinesia, gait disturbance, face masking, and tremor. As mentioned earlier, these extrapyramidal symptoms are not due to the failure of the dopaminergic system but extranigral systems such as the frontal cortex. The earlier the impairment of the dopaminergic system occurs, the faster the cognitive decline in healthy aging and AD. Therefore, enhancement of the dopaminergic system may improve some cognitive functions in AD.

The serotonergic system is also impaired in AD. This impairment is not inherent in the etiology of AD but is associated with non-cognitive BPSD such as mood disturbance, emotion expression, appetite, wake-sleep cycle, confusion, agitation, and depresson. The amount of serotonin, serotonergic innervation in the brain, and the number of serotonergic neurons in the raphe are reduced in the postmortem AD brain. Notwithstanding the

denervation of serotonergic systems in the brain, a decrease in serotonin receptors has been reported. A reduction in 5-HT2A receptors has been observed with positron emission tomography (PET) in AD. A reduction in 5-HT1A receptors in the temporal cortex is correlated with aggressive behavior in AD, whereas reduced binding of these receptors in the hippocampus is correlated with cognitive decline. PET imaging has shown a reduction in 5-HT1A receptor binding in the hippocampus and parahippocampus in patients with mild AD. The density of 5-HT1B/1D and 5-HT6 receptors is reduced in the frontal and temporal cortex in AD. 5-HT6 receptors are present in the cerebral cortex and are related to cognitive function.

The histamine concentration in the brain is diminished in patients with AD. The tuberomammillary nucleus, which is the only source of neuronal histamine in the brain, degenerates in patients with AD.

2. BPSD

2.1. Definition and characteristic symptoms of BPSD

The International Psychogeriatric Association defines BPSD as symptoms of disturbed perception, thought content, mood, or behavior that frequently occur in patients with MND. BPSD is classified into two types, positive symptoms and negative symptoms. Besides this classification, BPSD is also categorized into psychological symptoms and behavioral symptoms. Psychological symptoms of BPSD are revealed by asking caregivers and patients. They include delusion, false recognition, hallucination, depression, apathy, insomnia, and anxiety. Behavioral symptoms of BPSD include poriomania, aggression, resistance to caregivers, inappropriate sexual behavior, emotional stress reaction, dusk reaction, screaming, restlessness, collectionism, swearing, and following. They are revealed by observing the patient's behavior. Delirium, which is a disturbance of consciousness with excitation, is a different concept from BPSD. However, caregivers, in general, cannot distinguish delirium from BPSD. The type of BPSD symptoms depends on the circumstances where the patient lives. Caregivers may misunderstand the patient's behavior as BPSD. Doctors should ask several people caring for the patient with MND whether the behavior that the caregiver reports is considered BPSD or is a legitimate claim of the patient. Almost all drugs acting on the CNS can induce BPSD. Among non-CNS-acting drugs, H2 blockers, anti-histaminergic drugs, and an anticholinergic drug can induce BPSD.

Each type of MND has specific positive symptoms. A delusion of theft is a frequent psychological symptom, and poriomania is a frequent behavioral symptom in patients with AD. Patients with vascular NCD show unstable mood, irritability, and day and night reversal. Furthermore, these specific positive symptoms are specific to the disease stage. Delusion of theft and blaming family members are frequently seen in the early stage of AD. As the disease progresses, behavioral abnormalities

such as poriomania and resistance to caregivers appear. Patients' anxiety causes poriomania. They forget the purpose of leaving home because of memory disturbance. They do not understand where they are, which is the typical symptom of visuospatial disturbance.

In DSM-5, hallucination is defined as a perception-like experience with the clarity and impact of a real event but without external stimulation of the relevant sensory organ. Among hallucinations, visual hallucination is frequently seen in MND; on the other hand, auditory hallucination is dominant in schizophrenia. Vivid visual hallucination is a characteristic symptom in patients with NCD with Lewy bodies. Visual hallucination is also seen in approximately 20% of patients with AD. In frontotemporal NCD and vascular NCD, visual hallucination is rarely observed.

Sexual disinhibition embarrasses the patient's family members. The disinhibition of instinct is due to damage to the orbitofrontal cortex. Many subtypes of MND, e.g., frontotemporal NCD, AD, and vascular MND, involve sexual disinhibition. Antipsychotics are worth trying to dampen sexual disinhibition. When the patient is male, intensive care by male caregivers suppresses sexual disinhibition. Benzodiazepine and dopamine agonists induce and exacerbate sexual disinhibition.

In DSM-5, agitation is defined as excessive motor activity associated with a feeling of inner tension. The activity is usually nonproductive and repetitious, and consists of behaviors such as pacing, fidgeting, wringing of the hands, pulling of clothes, and the inability to sit still. Half of patients with MND show agitation. At the beginning of the disorder, patients are anxious about their loss of cognitive function, and so they are agitated. As the disease progresses, the patients feel agitation because of misunderstanding of their circumstances. Caregivers should look into the person's physical condition and whether agitation behavior comes from physical problems, which should be addressed. Antidepressants exacerbate agitation because the drugs induce serotonin syndrome and activation syndrome.

Aggression is classified into violence and rant; both are seen in the advanced stage of MND. Patients with MND express aggression when they are receiving care from caregivers with little experience with the patients. Caregivers should pay attention to patients' suicidal tendencies because the target of violence occasionally turns to the patients themselves. Physical violence occurs quite often and is a serious problem. Risk factors for aggression are male sex, body pain, constipation, low activities of daily living (ADL), advanced MND, difficulty in communication, violent character, and nervous character. Patients with MND will be angry when somebody prevents them from doing what they want to do. Hypofunction of the frontal lobe and the temporal lobe is responsible for this irritability. A premorbid characteristic such as lack of coordination or

frustration is related to the irritability.

The "desire to go home" phenomenon is frequently seen in nursing homes and happens in patients with the advanced stage of MND. This phenomenon is also seen even when patients are in their homes because some patients do not think that they are living in their own house. They go out looking for their home. When patients think that they are not in their homes, they think it is time to go home in the evening. In the evening, caregivers finish working and start to go home, stimulating the patients to try to go home. Caregivers can persuade them to remain where they are by telling the patients "Here is a hotel, and tonight you are going to stay here." Dusk reaction means exacerbation of positive symptoms of BPSD or cognitive function. This phenomenon ofen coexists with the "desire to go home" phenomenon.

Interference is not a popular word because the concept is difficult to understand. The patient with interference perpetually corrects others' behavior, not caring about others' feelings. Such a patient may hide others' cutlery during a meal, pull out all drawers and scatter items in the room, or pull off all the toilet paper on the roll. Interference can be seen in someone who once cared for someone else and persists. When caregivers try to stop this behavior, the person becomes frustrated and angry. To stop such interference, caregivers may try to distract the person and ask them to do other activities such as folding laundry.

Collectionism is the habit of collecting meaningless items. A cause of this behavior is loneliness.

Fecal smearing appears in the late stage of patients with MND. The cause of this behavior is fecal incontinence and a lack of understanding of what to do with the feces. Patients who use an adult diaper tend to show fecal smearing. Some patients enjoy the feeling of feces.

Insomnia is widespread in patients with MND. A physical problem such as back pain or gastroesophageal regurgitation disrupts sleep. Disruption of the circadian rhythm is one cause of insomnia. The best way to sleep well is to participate in activities in the daytime and to avoid a midday nap. Oversleeping in the morning can be caused by a hangover from hypnotics. Short-acting hypnotics should be used whenever a person needs these medications. When patients wake up in the middle of the night, they sometimes show night delirium. In such cases, hypnotics cannot remedy insomnia with delirium. In general, non-benzodiazepines such as zolpidem (Myslee®), zopiclone (Amoban®), and eszopiclone (Renesta®); and melatonin agonists such as ramelteon (Rozerem®) are preferable, but such weak drugs cannot induce sleep in patients with delirium. Therefore, a potent and short-acting benzodiazepine such as triazolam is used. However, triazolam induces anterograde amnesia and delusion; therefore, 0.125 mg triazolam is preferable to 0.25 mg. If patients cannot sleep with 0.125 mg triazolam, I add anti-histaminergic drugs

such as hydroxyzine and an atypical antipsychotic such as quetiapine. Single use of quetiapine is one of the best uses of this drug as a hypnotic. Recently, tandospirone was reported to be preferable for treating insomnia because it has few adverse effects. Orexin receptor antagonists such as suvorexant (Belsomra®) can be used. Rapid eye movement (REM) sleep movement disorder is sometimes misdiagnosed as night delirium. REM sleep movement occurs from midnight to early morning, but night delirium occurs in the evening.

Patients may feel anxiety and loneliness, and thus, remaining close to caregivers is helpful to ease their loneliness.

Apathy is defined as a decrease in volition and interest and is sometimes misdiagnosed as depression or refusal to communicate with others. Apathy is frequently accompanied by frontotemporal NCD, vascular NCD, and extrapyramidal disorders. Appetite loss is sometimes derived from apathy; therefore, caregivers should judge whether the person cannot eat or will not eat. Patients with apathy do not complain, but patients with depression complain about their mental disorder, which helps to discriminate between apathy and depression. Drugs that stimulate the CNS should not be used in patients with apathy, because such drugs do not work appropriately and also induce adverse effects such as positive symptoms of BPSD. Impairment of the mesocorticolimbic dopaminergic system has been consistently reported to be responsible for apathy. Hypofunction of the frontal cortex is the principal cause of apathy. Therefore, apathy is MND itself. Intensive care is the best choice for these patients. Doctors and paramedical workers should explain the status quo of the patient to the person's family and explain that apathy is a principal symptom of MND and that it should be accepted as a natural course of MND.

Depression in patients with MND is difficult to identify because the countenance of patients is often a somewhat masked face. Depression is concealed by physical complaints that accompany depression. The best treatment for depression is to utilize social support such as daycare or day service. The effect of antidepressants is equivocal, and neither selective serotonin uptake inhibitors (SSRIs) nor mirtazapine can improve depression.

Eating disorders in patients are categorized as apathy, anorexia, and food cognitive impairment. Continuous chewing without swallowing indicates dysphasia because swallowing is a vulnerable function in patients with MND. Eating meals in a common room rather than in an individual patient's room may encourage residents in nursing homes to communicate with each other. Patients with MND, however, are distracted by other residents and cannot concentrate on eating a meal. Tube feeding has no advantage for life expectancy or nutritional amelioration.

Pseudowork is meaningless work such as pulling clothes from drawers, putting them

back, and repeating this behavior endlessly. If the behavior is not harmful, it is better left unaddressed.

2.2. Assessment of BPSD

To assess the condition of patients with BPSD, both ADLs and BPSD should be evaluated. ADLs are classified into basic ADLs (BADLs) and instrumental ADLs (IADLs). IADLs are used to determine whether the person can live by him/herself. BADLs are assessed with the Nishimura ADL Scale or the Barthel Index. The Lawton IADL Scale is used to assesses IADLs.

Many scales are available to assess BPSD. The Neuropsychiatric Inventory is the most popular and is composed of 12 questionnaires (delusion, hallucination, agitation/aggression, depression/dysphoria, anxiety, elation/euphoria, apathy/indifference, disinhibition, irritability/lability, motor disturbance, night-time behavior, and appetite/eating). ADLs are assessed with the Physical Self-Maintenance Scale, which is the most popular. Six basic categories (toileting, feeding, dressing, grooming, physical ambulation, and bathing) are scored in the Physical Self-Maintenance Scale. The Clinical Dementia Rating is a widely utilized clinical tool for grading the relative severity of MND, by which caregivers evaluate memory, orientation, judgment, problem solving, community affairs, home and hobby, and personal care.

2.3. Places where patients with MND should live

The Japanese government recommends that patients with MND live in their homes using general support systems (New Orange Plan 2015 by the Ministry of Health, Labor and Welfare). Because BPSD is a significant cause of hospitalization, caregivers in their homes must take care not to induce BPSD in patients with MND. When patients with MND show BPSD, a manual about how to manage BPSD is an essential tool for caregivers. Not all MND patients show BPSD. BPSD is sometimes caused by stress due to people around the patients, because patients may feel anxious when they cannot satisfy their psychological needs. Patients may go astray and show BPSD.

Caregivers sometimes experience burnout and may abuse their patients. Therefore, caregivers should visit a hospital when their nursing home patients display BPSD. Doctors will explain to the caregivers that the positive symptoms of BPSD of the patients will disappear soon, and caregivers may feel relieved.

Financial problems are associated with coping with BPSD, according to Section 2 Long-Term Care Health Facilities (so-called Rohken in Japanese). The fee for a doctor's visit and the costs of drugs in Section 2 Long-Term Care Health Facilities are not included in Rohken. Therefore, seeing a doctor frequently is an extra expense.

When a patient with BPSD is too violent to cope with in his or her home, the patient should be compulsorily hospitalized in a psychiatric hospital in accordance with the law of hospitalization for medical care and protection.

The guidelines of the American Psychiatric Association state that patients with AD should remain in a simple living situation with no environmental changes.

2.4. Pharmacotherapy for BPSD

2.4.1. Perspective

Although non-pharmacological approaches to the treatment of BPSD should be considered first, they are often ineffective. Whenever caregivers are exhausted by dealing with BPSD, they should go to the hospital to obtain medications prescribed by doctors. Although a variety of pharmacological options are available, none of them work very well. Both cholinesterase inhibitors and glutamatergic drugs may reduce BPSD, especially negative symptoms. Their effects are modest, however, and they do not successfully treat some of the most troublesome symptoms such as agitation. On the contrary, these drugs often worsen positive symptoms.

Among BPSD, a sudden onset type of BPSD may be due to physical reasons in the patients. Patients with severe MND cannot state their complaints properly to caregivers. Stupor condition may be the only symptom even when the patients have serious medical problems. Coping with patients with BPSD is similar to coping with severe patients in the emergency department.

Memory disturbance is not curable, but BPSD is curable with appropriate medical treatment. To treat BPSD with drugs, a precise diagnosis of MND is required, because patients with NCD with Lewy bodies should be prescribed antipsychotic drugs with caution. On the other hand, drugs for BPSD are prescribed not according to the diagnosis but the symptoms. For example, low-potent antipsychotics are used for agitation, and high-potent antipsychotics are used for hallucination. The number of drugs should be as few as possible. Whenever BPSD disappears, the amount of antipsychotics is slowly reduced and stopped.

Caregivers misunderstand that patients with positive symptoms are active. The opposite is true. Sedatives over-sedate these patients. Caregivers and doctors typically pay attention to their physical disease complications, because patients with MND, most of which are aged, often suffer from many other diseases such as chronic heart failure, diabetes, hypertension, and arteriosclerosis.

Physical, mental, and economic problems in patients with MND are variable. Characteristics of family members and caregivers are variable. Doctors ask not only patients but also their caregivers about the chief complaint. Doctors also evaluate the comprehensive ability of caregivers and the ability of caregivers to nurse their patients. Care managers and social workers are of great help in caring for these patients and families. An eager caregiver is sometimes codependent on the patient. Such caregivers do not want to sedate their patients even if the patients show violence because they feel that the patients are wrongfully treated when the patient is administered a sedative.

2.4.2. Antipsychotics for BPSD

Although no drugs for BPSD are covered by health insurance, quetiapine, haloperidol, perospirone, and risperidone are permitted for treatment of delusion, psychomotor excitation, and irritability due to MND. Antipsychotics are prescribed in approximately 20% of MND patients. In general, non-pharmacological care should be tried first for patients with BPSD. When this does not work, antipsychotics are administered. However, in an emergent patient such as one in a major depressive state or one who injures himself/herself or others, antipsychotics should be used first.

Because aged patients and patients with MND are sensitive to medications, the dose of antipsychotics should be started at one-half or one-fourth of the regular dose. Doctors should evaluate the effect of antipsychotics within a week, which is a short period for regular assessment of antipsychotics. For example, at least 2-4 weeks are typically required for antidepressants to begin to work. In the guidelines for MND 2017, atypical antipsychotics are recommended for treatment of anxiety, restlessness, delusion, and hallucination. The effect of antipsychotics on the treatment of poriomania is controversial, but I feel that antipsychotics are effective. The guidelines state that the level of evidence is C (weak) and that the grade of recommendation is 2 (weak). In other words, atypical antipsychotics can be used for BPSD, but it depends on the case.

Antipsychotics are efficacious for positive symptoms of BPSD, but their use is often limited by their adverse effects, e.g., Parkinsonism, sedation, and falling. In addition to these adverse effects, the use of atypical antipsychotics in elderly patients is associated with a higher risk of stroke and overall mortality.

For agitation, atypical antipsychotics are effective. Among antipsychotics, a low dose of risperidone is the best, and aripiprazole has the same effect as risperidone. The effect of olanzapine is equivocal, and quetiapine is not effective. Person-centered care by caregivers is required for all care of patients with MND. Person-centered care is focused on the needs of the person rather than the needs of the service judged by medical staff. Patients have views on what is best for them and on their priorities in life. Thus, health care workers should meet their needs.

Benzodiazepines can be used for occasional control of acute agitation but are not recommended for long-term management because of their adverse effects on cognition, muscle weakness, and falling. Even for anxiety and insomnia, which are generally thought to be good indications for benzodiazepines, antipsychotics can be used instead of benzodiazepines in patients with MND. Among antipsychotics, risperidone, olanzapine, and quetiapine are recommended. Haloperidol is not adequate for anxiety. Typical antipsychotics such as chlorpromazine and haloperidol may be useful for aggression,

but extrapyramidal symptoms, especially with haloperidol, limit their use to controlling acute episodes. Haloperidol is not recommended as the first-line drug for BPSD. Antipsychotic drugs prescribed for BPSD are not covered by health insurance. They are for schizophrenia. However, some drugs are permitted for use in patients with BPSD.

The Japan Consortium for Antipsychotics Treatment in AD is a large cohort in which the effect of antipsychotic treatment for BPSD on mortality was studied. No significant differences were seen between patients who received antipsychotics and patients who did not. However, the mortality rate jumped up 2.5-fold when patients were newly treated and then continued to be treated for over 11 weeks. No particular cause of death was noted in the patients newly treated with antipsychotics. They died of pneumonia or senility. Importantly, the average age at the beginning of the study was 81 years. Naturally, antipsychotics are harmful to older people. Furthermore, patients with MND who have BPSD and need antipsychotics are sensitive to nearly all drugs. Over-sedation, hypotension, falling, dysphasia, edema, and malignant syndrome are listed as adverse effects of antipsychotics. Moreover, exacerbation of glucose intolerance is evident in patients treated with olanzapine and quetiapine. The longer antipsychotics are used, the worse cognitive function becomes. To identify an extrapyramidal adverse effect early, wrist rigidity should be checked because it is an easy technique to identify Parkinsonism.

2.4.3. Anti-AD drugs for BPSD

Cholinesterase inhibitors are not useful for positive symptoms. They exacerbate irritability and fretfulness. Scientific evidence for the use of anti-dementia drugs for BPSD is not sufficient.

2.4.4. Antidepressants for BPSD

Antidepressants may be useful for patients with hypochondria who repeatedly complain about poor physical conditions. Hypo-activity should be discriminated from depression. Depressive mood and inappropriate guilt are apparent in one-fourth of patients with MND. Among all types of antidepressants, SSRIs or serotonin noradrenaline reuptake inhibitors (SNRIs) should be used first. Tricyclic antidepressants are not suitable because of their severe anticholinergic damage to the CNS (e.g., delirium) and peripheral organs (e.g., dry mouth, constipation, and urinary retention). Serotonin syndrome includes myoclonus, hyperhidrosis, and tachycardia in addition to restlessness and irritation. Besides these symptoms, hyperreflexia, myoclonus, muscle rigidity, fever, diarrhea, and flushed skin are listed as symptoms of serotonin syndrome. SSRIs and SNRIs may induce serotonin syndrome when these drugs are started or added to other drugs. When patients show such symptoms, SSRIs and SNRIs should be stopped. When patients are

still very confused after stopping these medications, chlorpromazine and benzodiazepines are administered to treat confusion. Anti-dementia drugs also cause serotonin syndrome, which may continue for more than 2-3 weeks because anti-dementia drugs such as donepezil have a longer half-life in the brain than in the blood. Trazodone may be useful for anxiety and sexually inappropriate behavior. SSRIs may exacerbate apathy, which is sometimes difficult to discriminate from depression. SSRIs also induce hyponatremia.

2.4.5. Other drugs for BPSD

Yokukansan can sedate irritable patients. This effect is mild, so it is useful for mild agitation. Although this drug does not induce any severe adverse effects on the CNS, weakness in lower extremities due to hypokalemia may occur.

Benzodiazepines are not recommended because they induce over-sedation, delusion, ataxia, cognitive impairment, and falling, especially in patients over 75 years or patients with MND. Long-acting benzodiazepines such as ethyl loflazepate (Meilax®) are worse than short-acting ones such as etizolam (Depas ®). Zolpidem (Myslee ®), zopiclone (Amoban®), and eszopiclone (Lunesta®) are recommended hypnotics.

Amantadine is an anti-Parkinson drug. Its mechanism of action is unclear but appears to involve presynaptic dopamine reuptake blockade, facilitation of dopamine release, postsynaptic dopamine agonism, and receptor modulation. It also has anticholinergic properties and blocks NMDA glutamate receptors, which may induce BPSD and exacerbate cognitive function. When administered in the morning, this drug increases awakening.

Carbamazepine is used as a mood stabilizer for manic disorder; therefore, it is also used to treat irritability. However, it induces dizziness and drowsiness even in a small dose. This drug appears to have no benefit for MND. Patients with MND are apt to show epilepsy as the disease progresses. Especially in AD, amyloid protein that has accumulated in the hippocampus becomes a focus of epilepsy. The dominant type of epilepsy in patients with MND is non-convulsive. Valproic acid is the best choice for patients with MND because it has fewer adverse effects on cognitive function and because of its effectiveness on positive BPSD such as irritability. New antiepileptics are useful for epilepsy in aged patients. Among them, lamotrigine (Lamictal ®) and levetiracetam (Ekepla ®) are covered by health insurance and can be prescribed in the early stage of AD.

3. Diseases that show MND

In DSM-5, NCD is subdivided into AD, frontotemporal NCD, NCD with Lewy bodies, vascular NCD, NCD due to traumatic brain injury, substance/medication-induced NCD, NCD due to HIV infection, NCD due to prion disease, NCD due to Parkinson's disease,

NCD due to Huntington's disease, NCD due to another medical condition, NCD due to multiple etiologies, and unspecified NCD. However, clinically, MND is classified into AD, frontotemporal NCD, NCD with Lewy bodies, Creutzfeldt-Jacob disease, and other neurodegenerative diseases, because each disease has characteristic features that require special care and attention.

3.1. AD

AD is diagnosed when it is proven pathologically. The Alzheimer's type of NCD is diagnosed when clinical features are similar to pathologically proven AD. Most studies have been performed in clinically diagnosed AD. Approximately 30-40 years ago, the term "senile dementia of AD" was only used in living patients. However, nowadays, the word "AD" is often used to describe living patients.

Diagnostic criteria for AD in DSM-5 include gradually progressive MND in more than a couple functional disabilities. In DSM-5, neurocognitive functions are classified into six domains: 1) complex attention, 2) executive function and planning, 3) learning and memory, 4) language, 5) perceptual-motor function, and 6) social cognition. Social cognition is often preserved until the late stage of the disease. In the early stage, depressive state and apathy are common. In the middle stage, psychiatric symptoms are apparent. Moreover, in the end stage, neurological symptoms such as dysphasia, incontinence, myoclonus, and epilepsy may be apparent. Until the 1980s, vascular NCD was over-diagnosed. AD is, however, over-diagnosed at present.

Patients with AD are generally gentle and friendly to doctors. Even when they resist their caregivers, they are gentle in front of doctors. Caregivers should not react emotionally against patients with AD, because the patient's feelings are not impaired. Patients with AD who quarrel with their caregivers at home become very quiet and smile in front of doctors. Doctors and caregivers understand this symptom. Even when such patients refuse a suggestion from their caregivers, the doctor may be able to persuade them.

The cardinal and initial symptom of AD is the disturbance of episodic memory. Episodic memory is memory of autobiographical events (times, places, associated emotions, and other contextual knowledge related to who, what, when, where, and why) that can be explicitly stated or conjured. It is the collection of past personal experiences that occurred at a particular time and place. To identify memory disturbance in patients with AD, the delayed recall examination is the most sensitive. Patients cannot recall when a hint is given. Time orientation is the first symptom among all orientation disturbances. Then, place and person in that order. Executive dysfunction appears relatively early in the disease and hinders working in the office and at home. Then, aphasia and social cognitive dysfunction such as visuospatial dysfunction and personality changes appear.

Aphasia is initially amnesic then sensory. Frequency and repetition are relatively conserved. Patients who suffer from visuospatial dysfunction may go astray even around their house and cannot copy figures. IADLs are impaired early in the disease, but ADLs can be preserved.

As the disease progresses, 80% of patients show BPSD. Depression and apathy are common in the beginning. Irritability, confusion, refusal, hallucination (auditory), delusion (especially thief delusion), delirium, insomnia, and poriomania may be apparent in the middle stage. Myoclonus and convulsion indicate the terminal stage of the disease.

3.2. Frontotemporal NCD

The disease concept of frontotemporal NCD is complex. Frontotemporal NCD is a clinical entity that is based on topography, which is classified into a behavioral variant of frontotemporal NCD, semantic NCD, and progressive non-fluent aphasia. Even though frontotemporal NCD is classified into three types, they show the same symptoms when they progress. Although frontotemporal lobar degeneration is a pathological entity, the name is adopted in the Japan Intractable Disease Center. In DSM-5, frontotemporal NCD is divided into two subgroups, the behavioral type and the language disorder type.

Frontotemporal lobar degeneration (FTLD) is classified into FTLD-tau, FTLD-TDP43 (TAR DNA-binding Protein of 43kDa), and FTLD-FUS (fused in sarcoma) according to characteristic proteins in abnormal inclusions. Beside FTLD, abnormal tau also exists in AD, PSP, and corticobasal degeneration (CBD). Tauopathy is classified into two types: three-repeat tauopathy and four-repeat tauopathy. Frontotemporal NCD is classified into three-repeat tauopathy. PSP, argyrophilic grain disease, and CBD are classified into four-repeat tauopathy. Both types of tau are present in the brain of AD. An excessively phosphorylated, ubiquitinated, and cleaved form of TDP43 and mutation in FUS also exist in amyotrophic lateral sclerosis. More than 50% of behavioral variants of frontotemporal NCD, 80% of semantic NCD, and 70% of progressive non-fluent aphasia are FTLD-TDP variants.

In frontotemporal NCD, BPSD is apparent before memory disturbance. BPSD listed in frontotemporal NCD as diagnostic symptoms are as follows:

1) Socially disinhibited behavior (socially inappropriate behavior; lack of courtesy and manners; impulsive, indiscriminate, and casual action)
2) Indifference or apathy
3) Lack of empathy (lack of reaction to other people's desires and feelings; reduction or loss of social interest; interaction with others or human warmth)
4) Adherence/stereotypy (repetition of primitive movements, e.g., tapping a table repeatedly; compulsive ritual behavior, e.g., going to the toilet without micturition)

5) Oral tendency (pica) and changes in eating habits (alteration of taste, e.g., sweets lover; bulimia; an increase in drinking and smoking) Among them, apathy and stereotypy are often the first symptoms.

These symptoms are difficult to treat. Only SSRIs are weakly recommended in the literature. I believe antipsychotics should be used to sedate patients with frontotemporal NCD who show problematic symptoms. When the disease progresses, disinhibition becomes inconspicuous. Abnormal eating behavior may be treated with Yokukansan or aripiprazole. Cholinesterase inhibitors exacerbate these symptoms.

3.3. NCD with Lewy bodies

The prevalence of pathologically proven NCD with Lewy bodies is 20% of all MND. However, the MHLW Group Research stated that the prevalence is only 4.5%. Cardinal diagnostic criteria include:

1) Fluctuating impairment of cognition with attention and arousal levels

2) Appearance of concrete delusion

3) Parkinsonism

Haunted hallucinations may be misdiagnosed as delirium. A low dose of cholinesterase inhibitors may be useful for not only cognitive function but also hallucination. Clinical features of NCD with Lewy bodies include a vivid visual hallucination, REM sleep movement disorder, hypotension, and excessive reactions to drugs. Among them, visual hallucination with anosodiaphoria should be treated with antipsychotics. Quetiapine, olanzapine, and risperidone are useful, but exacerbation of Parkinsonism is inevitable. These medications should be tried carefully, because patients with NCD with Lewy bodies are sensitive to antipsychotics, especially their sedative effect, which prevents them from staying awake. Furthermore, these patients are prone to falling asleep. Their blood pressure markedly decreases when they stand up and increases when they lay down. All atypical antipsychotics that have a similar structure as chlorpromazine, e.g., quetiapine and olanzapine, have α-blocking activity, which induces orthostatic hypotension. All antipsychotics more or less worsen Parkinsonism in these patients. Among all antipsychotics, quetiapine has a low effect on worsening of Parkinsonism. Although haloperidol and serotonin-dopamine antagonists such as risperidone do not induce hypotension and excess sedation, they induce Parkinsonism more than chlorpromazine-like antipsychotics and aripiprazole. As the disease progresses, the amount of antipsychotics and antiparkinsonian drugs should be varied. For example, a small dose of levodopa with dopa decarboxylase inhibitor, such as 100 mg/day, exacerbates hallucination at the beginning of the disease, but 600 mg/day does not induce hallucination when the disease progresses.

Donepezil is the only drug that is covered by health insurance for NCD with Lewy bodies, because the activity of cholinergic neurons is more damaged than

that in AD. Although a randomized controlled trial of donepezil suggested that BPSD, as well as cognitive function, were significantly improved by the drug, I do not think that donepezil is worth prescribing, because donepezil is too weak to address BPSD. Moreover, in general, antipsychotics are required to sedate patients. Furthermore, donepezil exacerbates positive symptoms in BPSD and induces epilepsy when the physical condition of patients is not good. A low dose of donepezil such as 1-3 mg is effective for apathy as well as hallucination and may function like a placebo. Parkinson's disease is one of the most placebo-effective diseases. Memantine is harmful because it worsens hallucination and delusion, as well as apathy.

Parkinsonism in NCD with Lewy bodies is treated with levodopa, but the dose should be as low as possible because levodopa easily induces hypotension and hallucination in NCD with Lewy bodies more than in Parkinson's disease.

3.4. Vascular NCD

According to the National Institute of Neurological Disorders and Stroke-Association Internationale pour la Recherche et l'Enseignement en Neurosciences criteria, vascular NCD is diagnosed when CVD causes NCD. The most important thing is the time course. When cognitive impairment is apparent within 3 months after a CVD episode, or impairment fluctuates or shows stepwise progression following a recognized stroke, cognitive impairment is considered to be caused by CVD. The volume of infarction is correlated with the severity of cognitive impairment. Strategic single-infarct NCD is caused by cerebral infarction of important brain regions that are responsible for higher-order brain function. The symptoms include memory disturbance, low motivation, abulia, delirium, and cognitive impairment.

In DSM-5, vascular NCD is defined as the onset of MND that is chronologically related to the onset of CVD, when CVD is proven with neuroimaging tests. MND has characteristic features of intricate attention as well as executive function disorder related to frontal lobe dysfunction. Vascular etiology may range from a large vessel stroke to microvascular disease; the presentation is therefore very heterogeneous, stemming from the types of vascular lesions and their extent and location. The lesions may be focal, multifocal, or diffuse and occur in various combinations. The cognitive deficits in these cases can be attributed to the disruption of cortical-subcortical circuits. Complex attention, particularly the speed of information processing and executive ability, are likely to be affected.

No drugs are approved for the treatment of vascular NCD by health insurance, although many so-called brain metabolic stimulants or cerebral circulation activators once were used. Drugs for AD are not recommended.

3.5. Other diseases that are clinically diagnosed as AD

Clinically, argyrophilic grain disease is diagnosed when MND is mild even though atrophy of the frontal and temporal lobes is severe. The z scores of AD and argyrophilic grain disease quantified with the voxel-based specific regional analysis system for AD are 2.1 and 4.1, respectively. Argyrophilic grain disease is sometimes misdiagnosed as AD. Among aged people, the prevalence of argyrophilic grain disease is 5-9%. Not all patients with argyrophilic grain disease show MND. Senile NCD of the neurofibrillary tangle (NFT) type is defined as senile NCD with many NFTs in the hippocampus and few senile plaques in the brain. Clinical features of the disease are severe memory disturbance and other mild cognitive disturbances. Both argyrophilic grain disease and senile NCD of the NFT type are classified into primary age-related tauopathy. BPSD is more apparent in both diseases than in AD. Atrophy of the medial temporal lobe in argyrophilic grain disease is not symmetrical, although it is symmetrical in AD.

3.6. PSP and CBD

PSP is the second most frequent disease that shows Parkinsonism. MND in PSP has received attention, although psychological symptoms such as cognitive disorder, character alteration, emotional disorders, or memory disturbance are initial symptoms in half of patients with PSP. The prevalence of PSP was previously reported to be 5 in 100,000. However, recent reports have shown that the prevalence is approximately 5-20 in 100,000, due to population aging and the clinical variance of PSP. Pathological PSP is subdivided into Richardson syndrome, PSP-Parkinsonism, PSP-pure akinesia with gait freezing, PSP-corticobasal syndrome, PSP-non-fluent aphasia, and PSP-cerebellar ataxia. Cardinal symptoms of BPSD in PSP include attention deficit, indifference, and a lack of concern about personal space. Features of BPSD in PSP used to be called subcortical NCD, but the feature is almost the same as frontotemporal NCD. In addition to the symptoms mentioned above, patients with PSP show slowness of thought, amnesia, apathy, lack of vocabulary, depression, and perseveration.

CBD is a disease with frontal and parietal lobe atrophy and basal ganglion degeneration. Typical clinical symptoms of CBD are unilateral apraxia and muscle rigidity. Both PSP and CBD are four-repeat tauopathies. During the disease, 70% of patients with CBD show MND.

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認知症の薬物療法について思うこと

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認知症に対し４種類の薬物の保険適用が認められているが，それらは疾患自体を治療しないし，進行の抑制もしない。たちが悪いことに，興奮や不眠など介護を難しくする症状を発現させたり，痙攣のような生命に関わる有害作用を生じさせたりする。認知症患者は他の疾患も併発している場合も多く，そのため多剤服用しているので，服用薬の種類をそれ以上増やさないためにも抗認知症薬は服用すべきではない。1980年に脳代謝賦活薬，脳循環改善薬というものがあった。プラセボと同じ効果しか認められず，再審査後にほとんどすべて市場から消えた。現在の抗認知症薬の処方状況はデジャヴュに他ならない。

しかし，認知症に伴う行動心理症状（BPSD）は患者のQOLや尊厳を損なうので積極的に介入すべきである。その場合，安易に薬物に頼るべきではない。認知症患者はコミュニケーション障害があるが，その原因を探索し，それに対して可能な限りケアの工夫などで対処すべきである。非薬物的対応が奏功しない場合は薬物を少量，短期間投与する。長期に渡らざる得ない場合は中止可能かどうか定期的にチェックすべきである。

キーワード：認知症，薬物療法，行動心理症状（BPSD）