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**Special Feature Article**

# Treatment Strategy for Refractory Symptoms: For Behavioral and Psychological Symptoms of Dementia

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## Abstract

Patients with dementia including Alzheimer's disease sometimes present irritability, agitation, delusions, so called as BPSD (behavioral and psychological symptoms of dementia), which can be problematic in clinical settings. Antipsychotics have been often used for the management of challenging BPSD. However, in 2005, a meta-analysis reported that the mortality rate of the group receiving atypical antipsychotics increased 1.6 to 1.7 times, and the FDA issued a warning for these drugs. The 2016 APA guidelines state that it should be used after careful consideration of risks and benefits. In Japan, there are no strong regulations against antipsychotics to patients with dementia. One study reported that the use of typical antipsychotics drugs are decreasing, but the use of atypical antipsychotics are increasing in Japan. A large-scale cohort study in Japan reported that a newly antipsychotic administered group have 2.5 times risk of death after 11 weeks. Therefore, the 2017 Guidelines for dementia also give priority to non-pharmacological management for BPSD. Non-pharmacological management prior to pharmacological invention is considered to be a consensus, but there is no non-pharmacological management with sufficient evidence for BPSD. It is important to review subject's symptoms, reconsider the diagnosis, and consider other physical conditions and psychosocial factors that can affect behaviors when physicians encounter refractory BPSD. The authors did some researches to find the predictors of to antipsychotic

administration, that can determine whether antipsychotic are effective before treatment. The authors are also trying to collect knowledge of non-pharmacological management for BPSD. These efforts are important in the future prevention and treatment of BPSD.

**Keywords**: dementia, BPSD, pharmacological management, antipsychotics, non-pharmacological management

## Introduction.

Behavioral and psychological symptoms of dementia (BPSD) such as irritability, agitation, delusions, and nighttime behaviors appear during the course of the disease among subjects with dementia. These symptoms decrease the quality of life of patients, increase the burden of caregivers, and may lead to early hospitalization or institutionalization. Psychiatrists are often called upon to deal with them in clinical situations. Especially for symptoms such as irritability and agitation, antipsychotic drugs are often used as pharmacotherapy. In clinical practice, atypical antipsychotics with relatively few side effects, such as extrapyramidal symptoms, tend to be used. In a questionnaire survey conducted by Homma in the 2000s, 62% of psychiatrists working in psychiatric hospitals in Japan treat BPSD in their patients with dementia, 93% of whom received medication, and 81% of whom used antipsychotics.

## I. Warning against the use of antipsychotic drugs

In this context, it has been questioned whether antipsychotics are effective in treating BPSD in dementia. A large, double-blind, placebo-controlled trial of atypical antipsychotics, CATIE-AD, was conducted in North America. 421 patients with Alzheimer's disease (AD) with psychiatric symptoms were randomized to olanzapine, quetiapine, risperidone, or placebo. The dosage was adjusted as needed and the patients were observed for 36 weeks. They concluded that the side effects offset the benefits of atypical antipsychotics for psychotic symptoms, aggression, or agitation in AD patients.

At the same time, in 2005, a meta-analysis of 15 randomized, blinded trials was published, which reported that atypical antipsychotics increased

the risk of death by 1.6 to 1.7 times compared with placebo 17) . Because of that, the U.S. Food and Drug Administration (FDA) warned of the risks of atypical antipsychotics, such as olanzapine, quetiapine, and risperidone, when used to the elderly. However, there was no warning for typical antipsychotics. Then, a report comparing atypical antipsychotics and typical antipsychotics reported that the mortality rate of the elderly was higher with typical antipsychotics than with atypical antipsychotics 19). In response, the FDA issued a similar warning for typical antipsychotics in 2008.

A meta-analysis of 16 double-blind, placebo-controlled trials evaluated 3,343 patients in the antipsychotic group and 1,707 patients in the placebo group and found that although atypical antipsychotics were more effective than placebo on all measures, including the BPRS, CMAI, NPI, CGI-C, and CGI-S in 2014. However, somnolence [odds ratio: (OR)=2.95], extrapyramidal symptoms (1.74), cerebrovascular disease (2.50), urinary tract infection (1.35), edema (1.80), gait disturbance (3.35), and death (1.52) were more frequent. They concluded that the efficacy, safety, and tolerability should be carefully considered clinically.

On the other hand, in a longitudinal follow-up study of nursing home patients using conventional antipsychotics (n=138) and atypical antipsychotics (n=95), the effect of antipsychotics on the difference in mortality was reported to disappear when the effect of various confounding factors (especially the intensity of psychiatric symptoms) was excluded. It should be noted that such different results have also been reported 8).

In any case, these reports have made the use of antipsychotics for BPSD in dementia patients more difficult than in the past. The 2016 American Psychiatric Association (APA) guidelines for antipsychotic treatment of patients with dementia recommend (1) antipsychotic treatment of less urgent cases only when agitation and psychiatric symptoms are severe, dangerous, or cause significant distress, (2) a thorough evaluation of whether nonpharmacologic treatment is effective prior to treatment, (3) assess the potential benefits and risks and discuss them with the patient and the patient's representative before treatment, (4) start at a low dose and titrate upward until the lowest effective dose is reached, (5) in the event of side effects, consider the risks and benefits before deciding

whether the drug should be discontinued, (6) if no effect is seen after 4 weeks of treatment, discontinue the drug after tapering. (7) if a satisfactory effect is obtained, try tapering or discontinuing the drug within 4 months of the start of treatment, (8) continue follow-up at least once a month for 4 months after discontinuation of treatment.

## II. Changes in Japan

How has this trend changed the use of antipsychotics for BPSD in dementia patients in Japan? Okumura, Y., et al. investigated longitudinal changes in the use of antipsychotics for elderly patients with dementia in a secondary analysis of data from the Social Medical Practices Survey, which randomly sampled receipts. 21.3% of all patients were treated with antipsychotics from 2008 to 2010. Between 2002-2004 and 2008-2010, the use of second-generation antipsychotics increased from 4.9% to 11.2%, and the use of first-generation antipsychotics decreased from 17.4% to 12.1%. They also reported a 1.1-fold increase in the use of antipsychotics after adjusting for the overall prevalence of antipsychotic use 15). In In other words, the use of atypical antipsychotics increased while the use of typical antipsychotics decreased, resulting in a slight increase in overall use.

Arai, H. et al. conducted a prospective study of 10,079 Japanese patients with AD to assess the risk of death from antipsychotic medications 1). The study was conducted at 357 medical institutions, 69% of which were female and the mean age was 81 years. At the time of enrollment, 63.7% of the patients had been using antipsychotics for at least 6 months, and the most commonly used atypical antipsychotics were quetiapine, risperidone, and olanzapine. Notably, the mortality rate in the new medication group was 9.4% in the first 11 to 24 weeks of treatment, 2.5 times higher than that in the non-treatment group, even after adjusting for factors such as age, sex, and weight.

Based on these results, the Ministry of Health, Labour and Welfare (MHLW) published the first edition of the "Guidelines for the Use of Psychotropic Drugs for BPSD for Family Physicians" in 2013 and the second edition in 2016, regarding the use of antipsychotics for BPSD in Japan 6). In this guideline, it is emphasized that non-pharmacological interventions should be given the highest priority, physical conditions should be checked, and medications should be selected according to the symptoms.

The "Guidelines for the Treatment of Dementia Diseases 2017" also states that in the presence of BPSD, the cause should first be assessed, non-pharmacological interventions should be prioritized if there is no urgency, and even if there is urgency, the initiation of non-pharmacological treatment should be considered at the same time as pharmacological treatment 13) (Figure 1).

## III. The Melancholy of Non-Pharmacological Therapy

As described above, the current consensus is that non-pharmacological treatment should be considered before using antipsychotics for BPSD. On the other hand, in clinical practice, it is difficult to answer the question of how to provide non-pharmacological treatment when a patient with BPSD such as agitation or agitation that requires urgent treatment is in front of us. In the first place, non-pharmacological therapies are difficult to intervene systematically, and evidence is difficult to collect, so there are few guidelines on how they should be administered in practice. A systematic review of the effectiveness of 33 non-pharmacological therapies for agitation in dementia found that caregivers could benefit from learning person-centered care and learning the skills to talk appropriately with patients 7). However, neither of these non-pharmacological therapies can be practically used by clinicians in urgent situations. However, none of these are non-drug therapies that clinicians can realistically use in urgent situations. Others, such as group activities, music therapy programs, tactile ® care, and massage, have also been mentioned, but they are not practical for physicians to use immediately in a clinical setting. It can be said that clinicians are in such a dichotomous situation.

## IV. Importance of reviewing the diagnosis

At this point, it is necessary to return to the point that the term BPSD includes a variety of conditions and is not a single condition. The term BPSD is useful in explaining that dementia includes symptoms other than amnesia and cognitive dysfunction. The term BPSD is useful in explaining that dementia includes symptoms other than amnesia and cognitive dysfunction, and was proposed by the International Association of Geriatric Psychiatry in 1996 to replace the misleading term "problem behavior. On the other hand, the term BPSD may lead to a generalization of a wide variety of

symptoms.

The types of BPSD vary greatly depending on the diagnosis. Hirono, N. et al. in Japan compared BPSD in AD, dementia with Lewy bodies (DLB), and frontotemporal dementia (FTD) using the Neuropsychiatric Inventory. For example, hallucinations and delusions are prominent in DLB, but hardly noticeable in FTD, indicating that the type of BPSD differs greatly depending on the type of disease 4) (Fig. 2).

Different diagnoses mean different neurological underpinnings and different treatments. For example, antipsychotic drugs should not be used for DLB visual hallucinations because of the risk of side effects. On the other hand, cholinesterase inhibitors have been reported to be effective in the treatment of visual hallucinations in DLB 10). The treatment strategy varies greatly depending on the diagnosis. Also, there are some reports that SSRIs are effective for behavioral symptoms such as stereotypic behaviors in FTD, although the level of evidence is not high.

## V. Factors influencing the appearance of BPSD

In addition, the importance of understanding the psychosocial background and adjusting environmental factors has already been mentioned in many articles, and it goes without saying that various other factors also have a significant impact on the appearance of BPSD. For example, even if we focus on AD as the causative disease, a wide variety of factors influence the appearance of BPSD, including biological factors (genetic background), intermediate factors (cognitive function, age, ADL, physical condition, cognitive function, medications), and psychosocial factors (original personality, residential status, marital status, caregiver burden, etc.) (Fig. 3). Paradoxically saying, when conventional pharmacotherapy fails, it is important to reexamine the symptoms, consider various factors such as drugs and physical conditions, and reconsider the diagnosis.

## VI. New Challenges

Under such circumstances, the authors have made several new attempts to treat BPSD. First of all, we are attempting to identify predictors of response to pharmacotherapy for BPSD using the large-scale CATIE-AD data described above. For example, we reported that diabetes mellitus, cognitive function, physical function, and severity of

early psychotic symptoms predicted the response to antipsychotic medication for psychotic symptoms and anger in AD patients after 8 weeks of treatment 11). Similarly, we reported that cognitive function preservation contributed to the improvement of symptoms such as psychotic symptoms and irritability in AD patients after 36 weeks. Such information can be of great help in actual pharmacotherapy.

We are also trying to find non-pharmacological interventions that are actually useful. For example, in books, there are suggestions such as "If the patient resists assistance, tell them verbally what you are going to do" or "If the patient stands up, guide them by talking to them instead of stopping them. However, the effectiveness of these methods has not been confirmed, and it has not been clarified whether they are actually effective or with what probability of response they are effective. On the other hand, it is impractical to test the efficacy of various treatment methods for various BPSD one by one in a randomized controlled trial. Therefore, the authors are constructing a system that utilizes "collective knowledge" for the purpose of clarifying the effectiveness in actual clinical situations, using a website called "Dementia Chienowa Net.) We believe that these efforts will be important in the prevention and treatment of BPSD in the future.

## Conclusion

While there is a recent trend toward non-pharmacological interventions prior to pharmacotherapy for BPSD in dementia, there is a lack of non-pharmacological therapies that can be used by clinicians in urgent situations. In Japan, there are no strong restrictions on the administration of antipsychotics to patients with dementia, although there are some insurance coverage issues. As a result, antipsychotic treatment as pharmacotherapy for BPSD has been used for a long time. For this reason, we believe that the time when pharmacotherapy has reached an impasse is a good opportunity to reconsider the diagnosis and to reexamine the physical conditions and psychosocial factors that influence BPSD.

There are no conflicts of interest to be disclosed in relation to this paper.

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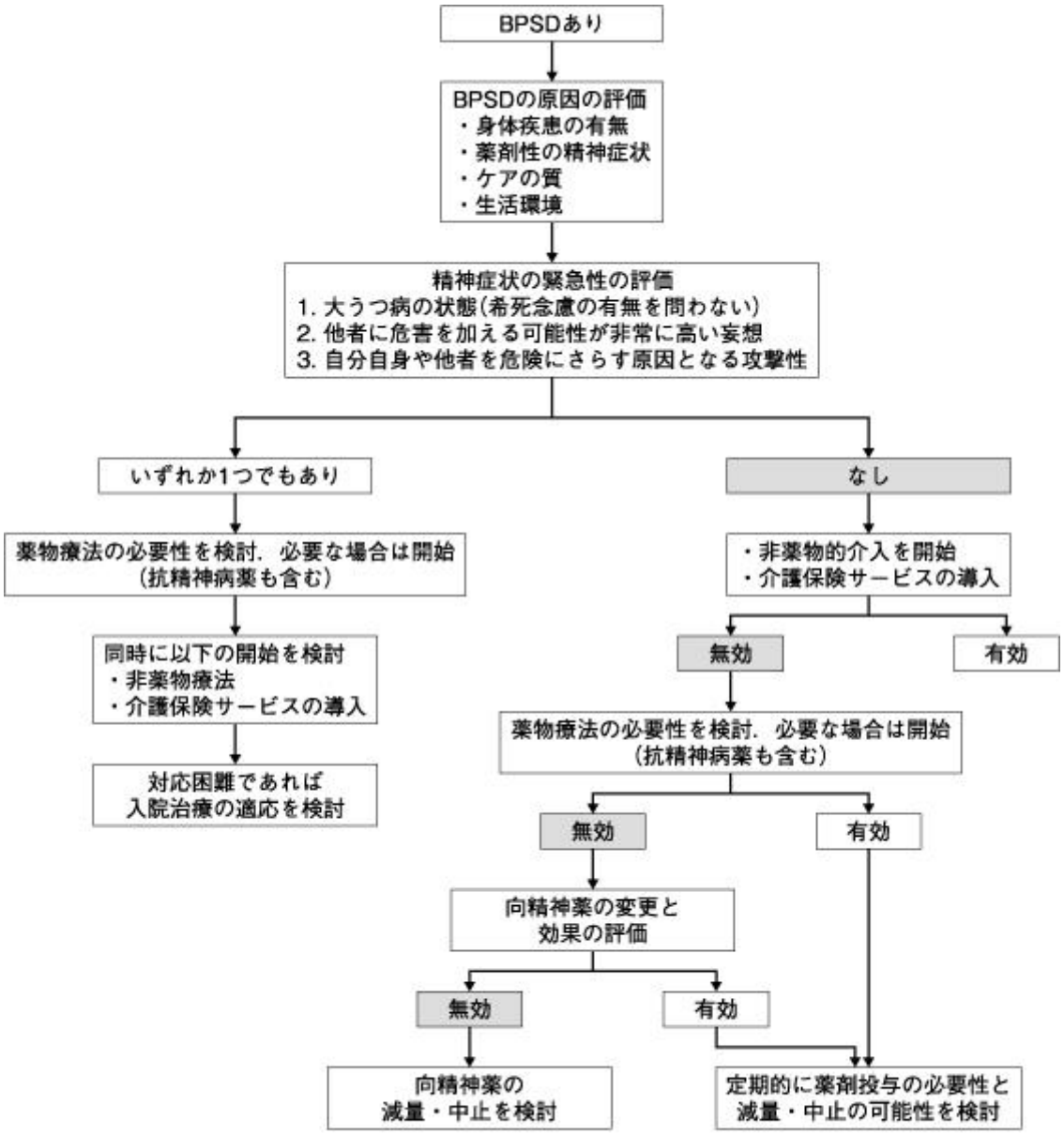


図1　認知症疾患診療ガイドライン2017における BPSD の治療アルゴリズム
(文献 13 より引用)

Figure 1

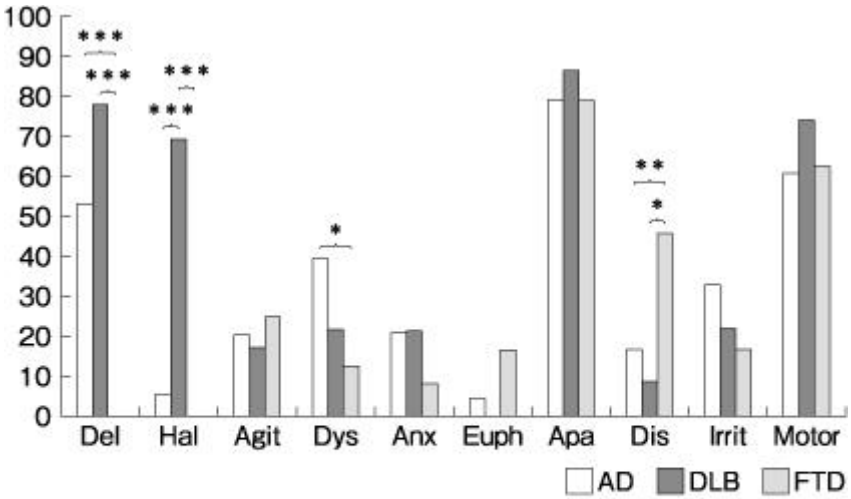


図2　認知症の種類による BPSD の差異
AD：Alzheimer's disease, DLB：dementia with Lewy bodies,
FTD：frontotemporal dementia
（文献 4 より引用）

Figure 2

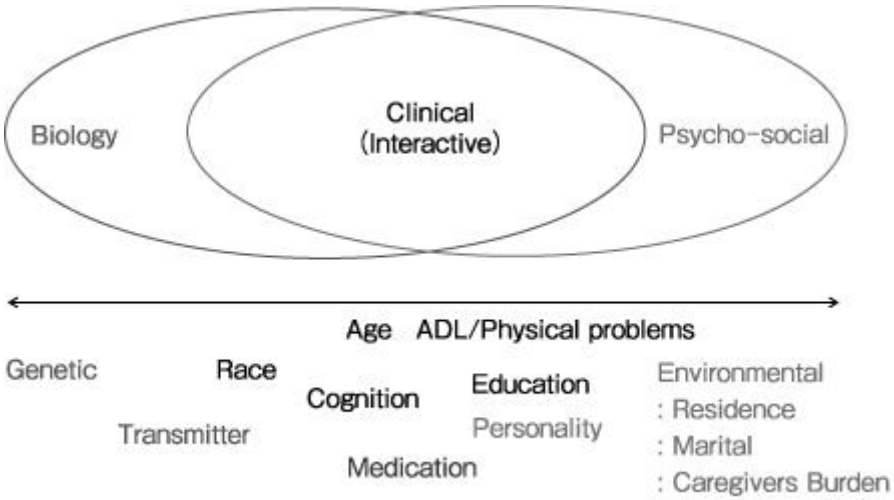


図3　BPSD の出現に影響を与える因子

Figure 3