

Pharmacotherapies for Behavioral and Psychological Symptoms of Dementia with Alzheimer's Disease: Two Subcategories of these Symptoms

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Abstract

In this article, we reviewed our previous articles those showed that ageing process and disease progression connected affective disturbances and anxiety with delusion, hallucination and aggressiveness and those behavioral and psychological symptoms of dementia (BPSD) is related with bipolarity (BT), and we comment the pharmacotherapies for BPSD in Alzheimer's disease (AD). There are two types of BPSD with AD. One is related with the progressions of AD that is caused by the deteriorated lesions by AD pathology. Therefore, these symptoms are ameliorated by the treatment for AD, that is, cholinesterase inhibitors or N-methyl-D-aspartate receptors antagonist. The other is related with brain reserve (BR) and cognitive reserve (CR). In this pattern, the information processing system is not deteriorated. However, low BR caused by BT and low CR modulate the behaviors etwas eccentric. When lowering of brain volume caused by AD pathology is added, i.e., BR is lower than before, BPSD appears. Therefore, in this patter, SSRI, atypical antipsychotics and anticonvulsants those have the treatment option for bipolar disorders, galanatmine and SNRI are needed.

Keywords: Brain reserve; Pharmacotherapies; Psychological symptoms; Alzheimer's disease

Abbreviations: AA: Anticholinergic Activity; Ach: Acetylcholine; AD: Alzheimer's Disease; BPSD: Behavioral and Psychological Symptoms of Dementia; BR: Brain Reserve; BT: Bipolarity; CR: Cognitive Reserve; Pharmacotherapy; NMDA: N-methyl-D-Aspartate; ChEI: Cholinesterase Inhibitor; CR: Cognitive Reserve; HP: Higher Performance; HP: Lower Performance

Introduction

We previously reported that aging process [1] and disease progression of Alzheimer's disease (AD) [2] connected depressive symptoms (affective disturbance and anxiety) with psychotic symptoms such as delusion, hallucination and aggressiveness. These features are mixed state of manic state and depressive state, therefore, there might be relationship between bipolarity (BT) [3] and psychological symptoms of dementia (BPSD) in AD [4,5]. From these reports, we considered that BPSD in AD should be treated as "augmentation" (pharmacotherapy for bipolar disorder) [6]. In this previous article, we proposed the reasonability of prescribing the atypical antipsychotics for BPSD in AD. However, in Japan, there are currently no licensed medicines for the management of BPSD in AD patients although in case of oldest old patient antidepressant is useful for ameliorating BPSD in AD [7]. Moreover, although antipsychotics for BPSD are not inhibited and symptoms such as delusions, hallucinations, agitation, or aggression are prescribed with consent from the legal representatives of AD patients, there is a warning for prescription of atypical antipsychotics for demented patients because of the increased mortality rate in patients with AD [8]. Therefore, it is important to propose the other reasonability to prescribe other psychotropics than antipsychotics for BPSD in AD.

In this article, we propose this reasonability mainly based on the other our previous article that we evaluate the relationship between bipolar temperament (BT) and BPSD in AD patients [9].

Relationship between BPSD and Bipolarity in Alzheimer's Disease

We evaluate the relationship between BT and BPSD in in 65 AD patients using demographic data (sex, educational level, age at dementia onset, age at the time of test and duration of illness), BP, cognitive function, existence of BPSD. BPSD was related with BT. Lower educational level was related with BPSD among those with BT ($p < 0.05$). From these results, we considered that brain reserve (BR) and cognitive reserve (CR) were related with some kinds of BPSD in AD and treatment of BT and heightening CR might prevent some kind of BPSD in AD [9]. BR (or biological reserve) is brain volume or neuronal count that explains the individual differences of power against of inserts and

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those of real pathological structures [10]. Because certain characters were reported to be related with brain structure [11] and hyperthymic and cyclothymic temperaments were reported to be related with bipolar disorder [12], we speculated that BT might be related with BR. On the contrary, CR (neural reserve) is defined as an ability to compensate for dysfunctions caused by pathological processes in central nervous system [10]. Kartzman reported that education was one of the most important factors those attributed to CR [13]. From these points of view, we speculated that on the base of poor BR, low CR caused BPSD in AD patients because BPSD in AD was related with BT and among those with BT lower educational level was related with BPSD [9].

On the contrary, we already evaluated the BPSD in 79 consecutive AD patients in view of dementia severity using behavioral pathology of Alzheimer's disease [2]. First, we investigated the correlation between cognitive function and the severity of dementia or each symptom domain of BPSD. Then the AD patients were divided into a group with higher performance (n=40, HP group) and a group with lower performance (n=39, LP group). Subsequently, we compared BPSD between these two groups and a factor analysis of BPSD was conducted in each group. We found that disturbance of activity and disturbance of diurnal rhythm were negatively correlated with cognitive function ($p < 0.05$), while affective disturbance was positively correlated with cognitive function ($p < 0.05$). Factor analysis showed that a mood cluster (affective disturbance plus anxieties and phobias) was associated with a psychiatric cluster (paranoid and delusional ideation plus hallucinations) and with aggressiveness in the LP group. These results indicate that disease progress of AD influences the BPSD of AD patients in two ways. That is, behavioral symptoms become more severe and the mood cluster conversely becomes milder but is connected to the psychiatric cluster and aggressiveness. Moreover, there were no differences of the age at the onset of dementia or age at testing between the LP group and the HP group. This means that the duration of AD was not a determinant of the performance of our patients. At least two possible explanations for this finding can be suggested that there may be two different causes of BPSD in AD patients. There were reported the two factors those were related with BPSD in AD [14,15]. Ito et al. reported that there are two independent pathophysiological processes contributing to BPSD in AD, one of which is associated with behavioral symptoms and overlaps with cognitive dysfunction, while the other is associated with psychological symptoms and is not related to cognitive dysfunction [15].

We adopt the theory to these two studies of ours [2,9] and BPSD in AD are mainly differentiated to two subcategories. One is overlap of psychotic and behavioral factors in the LP group, in which group the factor consisted of paranoid and delusional ideation, hallucination, aggressiveness, affective disturbances, and anxieties and phobias by rapid cognitive decline. The other causing psychotic symptoms along with slow cognitive decline related with BT and low CR. The patients in LP group had worse symptoms of dementia and showed more advanced BPSD within one year of the onset of behavioral symptoms. Therefore, AD patients may develop BPSD at either the mild stage or the severe stage of cognitive dysfunction, and there is a subset of AD patients who show rapid decline of cognitive function and possibly only manifest BPSD when there is a severe decrease of their cognitive function. However, there are some overlap symptoms between in those two subcategories and it is not easy to discriminate these two subcategories clearly. Therefore, we consider that there are mainly two categories in BPSD in AD. One is related with AD pathology, i.e., downregulation of acetylcholine (ACh). The other is related with depression or bipolar pathology, i.e., downregulation of serotonin. We divide BPSD in AD into two subcategories.

We show the two patterns of BPSD in AD in Figure 1. One is related with AD pathology. When the information processing system is deteriorated, of course behavior is deteriorated. The other is related with BR and CR. In this pattern, the information processing system is not deteriorated. However, low BR and low CR modulate the behavior etwas eccentric. When downregulation of brain volume caused by AD pathology is added, i.e., BR is lower than before, BPSD appears.

A, B, C, D, E for BPSD in Alzheimer's Disease Patients

We consider that there are A, B, C, D and E in the treatment of BPSD in AD. A and D is the treatment of AD. These include cholinesterase inhibitors (ChEI) and N-methyl-D-aspartate (NMDA) receptors antagonist. These agents are effective for symptoms with cholinergic related pathology (amyloid) and progression of AD such as wandering, apathy, delusion and hallucination. In fact, combinations of these agents are effective for BPSD [16]. Moreover, we speculate that anticholinergic activity appears endogenously in AD at moderate stage, which might be related with downregulation of ACh, inflammation and upregulation of NMDA receptor activity [17,18]. When AA is burdened, BPSD such as visual hallucination, delusion and diurnal rhythm disturbance is tended to appear than cognitive dysfunction [19,20] such as memory disturbance [21-23], disorientation [24] and executive dysfunction [25]. Therefore, it is also important to prescribe ChEI and NMDA receptor antagonist for prevention of the appearance of AA and delineation of AA [26].

B is the treatment of BR. As for the BPSD in AD, Two factors are related with downregulation of BR. One is BT and the other is reduction of brain volume caused by AD pathology. Therefore, SSRI, atypical antipsychotics and anticonvulsants those have the treatment option for bipolar disorders. Needless to say the effectiveness of agents are reported [27]. Of course, ChEI are thought to be effective. However, upregulation of ACh causes depression and aggressiveness. Therefore, galantamine is better for these symptoms because allosteric nicotinic receptor modulating action causes upregulation of serotonergic, GABAergic and noradrenergic enhancing capacities [28].

C is the treatment of CR. As for the cognitive function educations, environment [10] and noradrenergic system [29] are included. Therefore, SNRI is effective for these symptoms. In fact, the effectiveness of SNRI is reported [30].

E is environment. The environmental factors are important to prevent BPSD. One is the stimulation that is processed by the system that is not deteriorated. The other is the stimulation that is heightening CR.

The Other Important Issue for BPSD in Alzheimer's Disease

As the other important issue for BPSD in AD, we comment that it is difficult for differentiation of AD form Lewy body disease (LBD). It is relatively easy to diagnose as LBD when the visual hallucination is present. However, before the appearance of visual hallucination, dysfunction of parasympathetic nerve system is present, which corresponds to the prodromal stage of LBD. Therefore, symptoms related to dysfunction of the parasympathetic nervous system occur in LBD, such as REM behavioral symptoms, syncope, and constipation [31]. Moreover, hypothalamic-pituitary-adrenal (HPA) axis hyperactivity gradually worsens at this stage caused by dysfunction of the parasympathetic nervous system [32]. Therefore, we consider that depression, which is related to HPA axis hyperactivity also develops [33]. We have already reported that anxiety and affective disturbances in AD patients are connected to delusion, hallucination, and aggressiveness by aging and

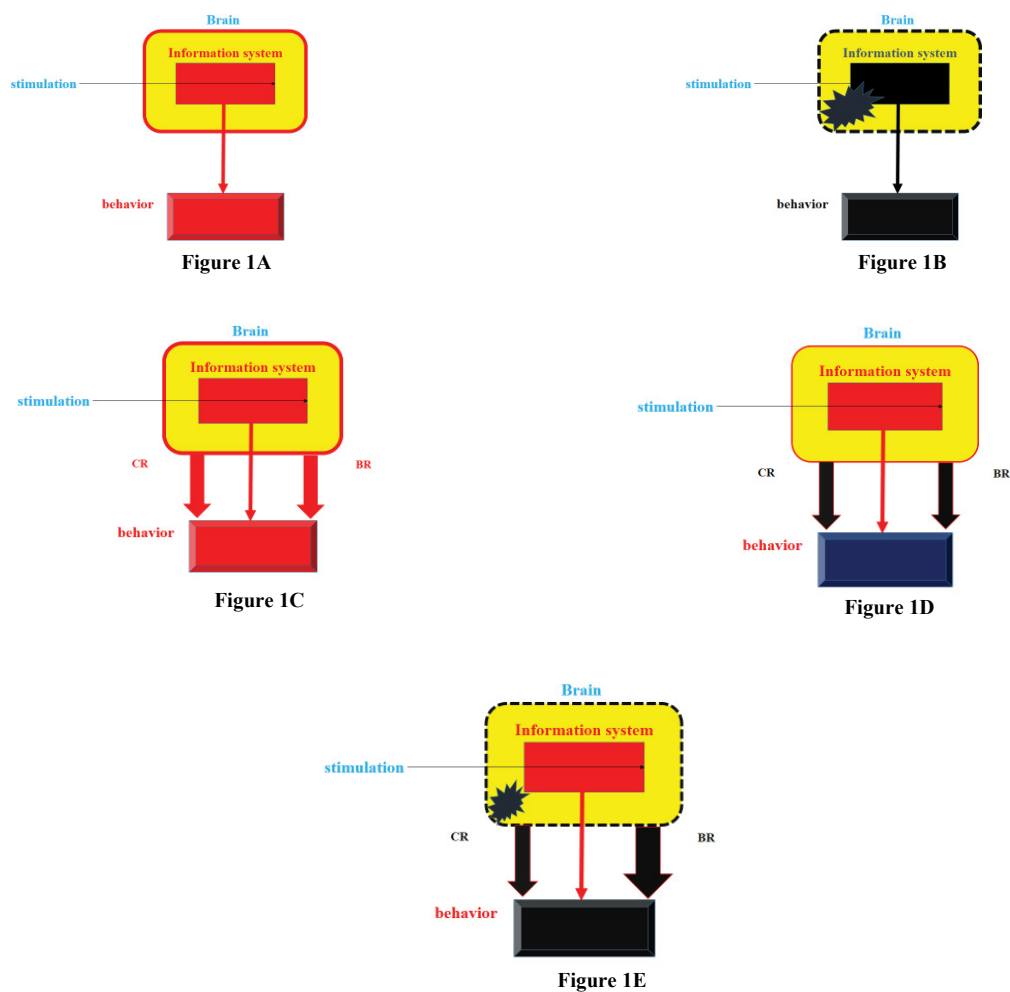


Figure 1(a-e): There are two types of BPSD with AD. One is related with the progressions of AD that is caused by the deteriorated lesions by AD pathology (Figure 1a and 1b). The other is related with brain reserve (BR) and cognitive reserve (CR). In this pattern, the information processing system is not deteriorated. However, low BR and low CR modulate the behaviors etwas eccentric. When lowering of brain volume caused by AD pathology is added, i.e., BR is lower than before, BPSD appears (Figure 1c, 1d and 1e).

the disease progress [2]. Therefore, if the degree of ACh dysfunction is relatively large, depression appears as BPSD of dementia in AD. We should keep this concept in mind. If when we treat the elder patient with depression prescribing antidepressants with or without augmentation of medicines for depression and unfavorable or not favorable effects was seen, we should consider the diagnosis of this patient as LBD and prescribe Aricept for this patient, because this medicine is only permitted for LBD patients in Japan (since September 2014).

References

- Konishi K, Hori K, Oda T, Tominaga I, Asaoka T et al. (2009) Effects of aging on behavioral symptoms in Alzheimer's disease. *Psychogeriatrics* 9: 11-16.
- Hori K, Konishi K, Tomioka H, Tani M, Minegishi G, et al. (2012) Mood symptoms are related to psychotic symptoms in severe Alzheimer's disease. *J Brain Dis Ther* S5: 002.
- Oedegaard KJ, Neckelmann D, Benazzi F, Syrstad VE, Akiskal HS, et al. (2008) Dissociative experiences differentiate bipolar-II from unipolar depressed patients: the mediating role of cyclothymia and the Type A behaviour speed and impatience subscale. *J Affect Disord* 108: 207-16.
- Ng B, Camacho A, Lara DR, Brunstein MG, Pinto OC, et al. (2008) A case series on the hypothesized connection between dementia and bipolar spectrum disorders: bipolar type VI ? *J Affect Disord* 107: 307-315.
- Dorey JM, Beauchet O, Thomas Ant erion C, Rouch I, Krolak-Salmon P, et al. (2008) Behavioral and psychological symptoms of dementia and bipolar spectrum disorders: Review of the evidence of a relationship and treatment implications. *CNS Spectr* 13: 796-803.
- Hori K, Konishi K, Tanaka H, Yokoyama S, Aoki M, et al. (2013) Pharmacotherapy for behavioral and psychological symptoms in Alzheimer's disease. *J Brain Disord Ther* 2.
- Ihara H, Arai H (2008) Ethical dilemma associated with the off-label use of antipsychotic drugs for the treatment of behavioral and psychological symptoms of dementia. *Psychogeriatrics*: 8: 32-37.
- Yokoyama S, Aoki M, Azuma K, Jimbo K, Konishi K et al. (2013) Escitalopram for Delusion in an Oldest Old Patient with Alzheimer's Disease. *J Brain Disord Ther* 2:2.
- Tanaka H, Hori K, Inamoto A (2014) Relationship with Bipolar Temperament and Behavioral and Psychological Symptoms of Dementia in Alzheimer's Disease. *J Brain Dis Ther* 3: 5.
- Mathias JL, Wheaton P (2015) Contribution of brain or biological reserve and cognitive or neural reserve to outcome after TBI: A meta-analysis (prior to 2015). *Neurosci Biobehav Rev*: 55:573-93.
- Cheetham M, H nggi J, Jancke L (2014) Identifying with fictive characters: structural brain correlates of the personality trait 'fantasy' *Soc Cogn Affect Neurosci* .

12. Gassab L, Mechri A, Bacha M, Gaddour N, Gaha L (2008) Affective temperaments in the bipolar and unipolar disorders: distinctive profiles and relationship with clinical features. *Encephale* 34: 477-482.
13. Katzman R (1993) Education and the prevalence of dementia and Alzheimer's disease. *Neurology* 43: 13-20.
14. Bidzan L, Pachalska M, Grochmal-Bach B, Bidzan M, Jastrzebowska G (2008) Behavioral and psychological symptoms of dementia of the Alzheimer type in nursing home residents. *Med Sci Monit* 14: CR559-CR567.
15. Ito T, Meguro K, Akanuma K, Meguro M, Lee E, et al. (2007) Behavioral and psychological symptoms assessed with the BEHAVE-AD-FW are differently associated with cognitive dysfunction in Alzheimer's disease. *J Clin Neurosci* 14: 850-855.
16. Hamuro A (2013) Combination therapy with galantamine and memantine improves behavioral and psychological symptoms of dementia (BPSD) in patients with early-onset Alzheimer's disease. *Aust N Z J Psychiatry* 47:583.
17. Hori K, Konishi K, Tani M, Tomioka H, Akita R, et al. (2014) Serum anticholinergic activity: A possible peripheral marker of the anticholinergic burden in the central nervous system in Alzheimer's disease. *Dis Markers* 2014: 459013.
18. Konishi K, Hori K, Tani M, Tomioka H, Kitajima Y, et al. (2015) Hypothesis of endogenous anti-cholinergic activity in Alzheimer's disease. *Neurodegener Dis*: 15: 149-56.
19. Cummings JL (2000) Cholinesterase inhibitors: a new class of psychotropic compounds. *Am J Psychiatry*: 157: 4-15.
20. Lemstra AW, Eikelenboom P, van Gool WA (2003) The cholinergic deficiency syndrome and its therapeutic implications. *Gerontology* 49: 55-60.
21. Sunderland T, Tariot PN, Cohen RM, Weingartner H, Mueller EA 3rd, Murphy DL (1987) Anticholinergic sensitivity in patients with dementia of Alzheimer type and age-matched control: A dose-response study. *Arch Gen Psychiatry* 44: 418-426.
22. Thienhaus OJ, Allen A, Bennett JA, Chopra YM, Zemlan FP (1990) Anticholinergic serum levels and cognitive performance. *Eur Arch Psychiatry Clin Neurosci* 240: 28-33.
23. Konishi K, Hori K, Uchida H, Watanabe K, Tominaga I, et al. (2010) Adverse effects of anticholinergic activity on cognitive functions in Alzheimer's disease. *Psychogeriatrics* 10: 34-38.
24. Konishi K, Hori K, Hachisu M, Tomioka H, Tani M, et al. (2015) Assessment of Cognitive Dysfunction Caused by Anticholinergic Burden in Japanese Alzheimer's Disease Patients, Using the Most Commonly Used Scales in Japan. *Nihon Shinkei Seishin Yakurigaku Zasshi* 35: 113-118.
25. Han L, Agostini JV, Allore HG (2008) Cumulative anticholinergic exposure is associated with poor memory and executive function in older men. *J Am Geriatr Soc* 56: 2203-2210.
26. Hosoi M, Hori K, Konishi K, Tani M, Tomioka H, et al. (2015) Pharmacotherapy for Neurocognitive Disorders Based on the Hypothesis of Endogenous Appearance of Anticholinergic Activity. *Neurodegener Dis*: 15: 157-61.
27. Kurita M, Sato T, Nishino S, Ohtomo K, Shirakawa H, et al. (2006) Effects of fluvoxamine on behavioral and psychological symptoms of dementia in Alzheimer's disease: a report of three cases. *Fukushima J Med Sci* 52: 143-148.
28. Hori K, Konishi K, Tomioka H, Tani M, Minegishi G, et al. (2012) Galantamine for aggressive behavior in Alzheimer's disease. *J New Rem Clin* 61: 56-57.
29. Robertson IH. (2012) A noradrenergic theory of cognitive reserve: implications for Alzheimer's disease. *Neurobiol Aging* 34: 298-308.
30. Mizukami K, Hatanaka K, Tanaka Y, Sato S, Asada T (2009) Therapeutic effects of the selective serotonin noradrenaline reuptake inhibitor milnacipran on depressive symptoms in patients with Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry* 33: 349-352.
31. McKeith IG, Dickson DW, Lowe J, Emre M, O'Brien JT, et al. (2005) Diagnosis and management of dementia with Lewy bodies: Third report of the DLB Consortium. *Neurology* 65: 1863-1872.
32. Masson GS, Nair AR, Dange RB, Silva-Soares PP, Michelini LC, et al. (2015) Toll-like receptor 4 promotes autonomic dysfunction, inflammation and microglia activation in the hypothalamic paraventricular nucleus: role of endoplasmic reticulum stress. *PLoS ONE* 10: e0122850.
33. Hori K, Konishi K, Hosoi M, Tomioka H, Tani M, et al. (2016) Anticholinergic Activity as a Behavioral Pathology of Lewy Body Disease and Proposal of the Concept of "Anticholinergic Spectrum Disorders". *Parkinson Dis*: 2016: 5380202.

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