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Mini Review: Pharmacotherapy for Behavioral and Psychological Symptoms in Alzheimer's Disease

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Abstract

Object: To show the clinical implications for pharmacotherapy for Behavioral and Psychological Symptoms of Dementia (BPSD) in Alzheimer's Disease (AD).

Background: In Japan, no medicine is permitted for BPSD in AD. On the contrary, atypical antipsychotics are inhibited because mortality rate increases when these medicines are prescribed for elderly demented patients

Methods and results: We reviewed our previous articles those reported the effects of aging and disease progress on BPSD and showed that effects of aging and disease progress caused the connections of the mood cluster (anxieties and affective disturbances) with the psychiatric cluster (delusions and hallucinations) and aggressiveness.

Conclusion: BPSD in AD was similar with bipolar features of mixed type or psychotic depression. We might prescribe medications for augmentation of depression to BPSD in AD.

Keywords: Behavioral and Psychological Symptoms of Dementia (BPSD); Alzheimer's Disease (AD); Pharmacotherapy; Augmentation

Introduction

In Japan, no medicine is permitted for behavioral and psychological symptoms of dementia (BPSD) in Alzheimer's disease (AD). On the contrary, atypical antipsychotics are inhibited because mortality rate increases when these medicines are prescribed for elderly demented patients [1]. However, antipsychotics are prescribed for BPSD such as delusions, hallucinations, agitations or aggressions with permission of proxies of AD patients. Therefore in this article, we showed and reviewed our previous articles those reported the effects of aging and disease progress on BPSD [2,3] and we recommended the clinical implication of the pharmacotherapy for BPSD in AD.

Effects of Aging and Disease Progression on Behavioral Symptoms in Alzheimer's Disease

In order to evaluate the effects of aging and disease progress on BPSD in AD, eligible subjects consecutively referred AD [4] patients because of their BPSD were evaluate. We evaluated demographic data (sex difference, educational level, age at dementia onset, the age at the time of test and severity of dementia), cognitive function and BPSD at the study entry. The severity of dementia was evaluated using Functional Assessment Staging (FAST) [5]. Cognitive function was evaluated using the Mini-Mental State Examination (MMSE) [6], and BPSD were assessed by the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) [7]. First, according to the age at the time of test, whole AD patients (n=79, WAD) group were divided into two groups, a relative older group in the WAD (with age the time of test were 81 and over, n=40, OG) and a relative younger group in WAD (with age the time of test were below 81, n=39, YG) [2]. Then the factor analysis were conducted and showed that although in YG mood cluster (anxiety and phobia, affective disturbances), Psychotic cluster (delusions, hallucination), and behavioral cluster (inappropriate behaviors, aggressiveness, diurnal rhythm disturbance) were separated distinctively, in OG the psychotic cluster (delusions, hallucination) and anxiety and phobia constituted same factor. Moreover, aggressive behaviors and affective disturbances also constituted same factor in OG [2].

Secondary according to MMSE scores, WAD (n=79) were divided into two groups, a relative higher performance group in the WAD (MMSE score of 12 or higher, n=40, HPG) and a relative lower performance group in the WAD (MMSE cores was below 12, n=39, LPG) [2,3]. We conducted the same procedures again. Although in HPG mood cluster (anxiety and phobia, affective disturbances), Psychotic cluster (delusions, hallucination), and behavioral cluster (inappropriate behaviors, aggressiveness, diurnal rhythm disturbance) were separated distinctively, in LPG the psychotic cluster (delusions, hallucination), and mood cluster (anxiety and phobia, affective disturbance) and aggressiveness constituted same factor [3].

Discussion

From these results, we considered that the mood cluster becomes connected to the psychiatric cluster and aggressiveness according

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to that the patients with AD become older and AD progresses. Generally speaking, depressive syndrome (anxieties, phobias, and affective disturbances) are thought to be diminished according to aging and the progression of dementia [8]. However, we consider that depressive symptoms are not disappeared but connected with psychotic symptoms, i.e., depressive symptoms turn up as psychotic symptoms. We refer this phenomenon "implicit depression and explicit psychosis" [3]. Moreover, this feature is also related with mixed states of depression and mania because manic symptoms (aggressiveness, delusion, hallucination) were connected with depressive symptoms (anxiety, affective disturbance) [9,10]. In fact Ng et al. reported that there were several commonalities in pathophysiological processes of bipolar disorders and dementia [9]. In fact Dorey et al. reported that some BPSD could be the consequence of both dementia and an undiagnosed comorbid bipolar disorder, or pre-existing bipolar diathesis pathoplastically altering the clinical expression of dementia [10].

We will place the suggestion on treatment of AD from our clinical implications in our two reports. In case of patients who show psychotic symptoms at relative severe stage of AD or with relative older age, it is better to prescribe for depression but not for psychosis. Moreover, aging and the progression of AD are irreversible processes. Therefore, the connections of mood cluster and psychotic cluster might be better generalized. We might prescribe "augmentation" medications for BPSD. In Japan some anticonvulsants (sodium valproate, lamotrigine), some antipsychotic agents (olanzapine, aripiprazole) and lithium carbonate are allowed for treatment of bipolar spectrum, i.e., augmentation for depression. Therefore, because depressive state is related not with monopolar depression but with bipolar spectrum or bipolar depression, we should prescribe not the antidepressants but augumentations. Therefore, if so, not antidepressant but atypical antipsychotics should be prescribed for augmentation for depressive patients. Moreover, atypical antipsychotics should be prescribed as for augmentation for depression [11,12]. Of course, these medications must have no or little anticholinergic activity; those induce cognitive dysfunctions [13] and BPSD [14] in AD patients. We refer this that antipsychotic should be prescribe not for psychosis but for depression.

However, FDA issued a warning about prescription of antipsychotic agents to demented elderly patients, because of increasing the mortality of the patients [1] therefore, we should not prescribe antipsychotic agents at first. Therefore we should prescribe antidepressants, Yokukansan (Japanese herbal medicine) and anticonvulsants or antipsychotic agents for augmentation for depression. However, if there were no effects with antidepressants, Yokukansan and anticonvulsants, we might prescribe antipsychotics as augmentation for depression. In fact, there are many reports that antidepressants ameliorate cognitive function in mice [15] as well as BPSD in human [16-19]. For example, Burke et al. reported selective serotonin reuptake inhibitor was effective to reduce psychotic symptoms in depression and psychosis complicated with dementia those were not responded to neuroleptics [15]. The effect of Yokukansan is also reported to ameliorate BPSD such as delusion and hallucination [20,21]. Perhaps, serotonergic modulation might bring the amelioration of BPSD in AD [22].

There are several limitations in the present study these two reports were without control subjects, not observing longitudinal course of cognitive dysfunctions but only cross-sectional. Moreover, these two studies didn't include "bipolarity" as predictive values. Further investigations should be required to delineate relationship between bipolarity and the features of BPSD in AD in order to better medications for BPSD in AD. We are now conducting observations in a larger patient cohort to evaluate the relationship between bipolarity and the features of BPSD in AD.

Conflicts of Interest

Koji Hori received lecture fees from Eisai Co., Ltd., Pfizer Japan Inc., Novartis Pharma K.K., Daiichi Sankyo Inc., Ono Pharmacuetical Co., Ltd., Janssen Pharmaceutical K.K., Yoshitomi Yakuhin Co., and Mitsubishi Tanabe Pharma Co. Mitsugu Hachisu received funding from Astellas Pharma Inc., Meiji Seika Pharma Co., Ltd., Dainippon Sumitomo Pharm Co., Ltd., Eli Lilly Japan K.K., and Shionogi & Co., Ltd., and received lecture fees from Meiji Seika Pharma Co., Ltd. and Mitsubishi Tanabe Pharma Co.

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