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Impact of Plasma Donepezil Concentration on Behavioral and Psychological Symptoms of Dementia in Patients with Alzheimer's Disease

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Keywords
Alzheimer's disease · Behavioral and psychological symptoms of dementia · Donepezil · Pharmacokinetics · Polymorphism

Abstract
Background/Aims: The behavioral and psychological symptoms of dementia (BPSD) detract from the quality of life of not only dementia patients but also their family members and caregivers. Donepezil is used to treat Alzheimer's disease and is metabolized via cytochrome P450 (CYP) 2D6 and CYP3A4/5. It is controversial whether donepezil improves or exacerbates BPSD. This study investigated the relationships among BPSD, the pharmacokinetics of donepezil including its metabolite, 6-O-desmethyl donepezil, genetic polymorphisms of CYPs and P-glycoprotein, and patient backgrounds in 52 patients with Alzheimer's disease. ***Methods:*** BPSD were assessed using the Neuropsychiatric Inventory (NPI), with scores ≥20 points defined as severe BPSD. Plasma donepezil and 6-O-desmethyl donepezil concentrations were measured using liquid chromatography–tandem mass spectrometry. ***Results:*** Although significant relationships between NPI scores and plasma donepezil concentrations were not seen, none of the 15 patients (29%) with high plasma donepezil concentrations (≥60 ng/mL) developed severe BPSD. Polymorphisms of *CYP2D6*, *CYP3A5*, and *ABCB1* did not influence NPI scores. There were no significant relationships between NPI and patient background factors such as dosing regimen, concomitant use of other drugs, or laboratory test results. Two patients who underwent multiple blood samplings over 2 years showed an inverse correlation between plasma donepezil concentrations and NPI scores. ***Discussion/Conclusions:*** These results indicate that higher plasma concentrations of donepezil contribute to preventing or alleviating rather than developing or deteriorating BPSD.

Introduction

Alzheimer's disease (AD) is the most common type of dementia, representing 50–70% of dementia cases [1]. Dementia, including AD, encompasses both cognitive and noncognitive symptoms, referred to as the behavioral and psychological symptoms of dementia (BPSD). BPSD include agitation, aggression, apathy, wandering, and sleep disturbance [2]. Exacerbation of BPSD increases the burden of caregivers, in addition to reducing the quality of life of patients [3, 4]. Although BPSD were pre-

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viously treated using typical or atypical antipsychotics, it became clear that their efficacy was limited and that these drugs had marked adverse effects. Moreover, in 2005, the US Food and Drug Administration issued an advisory that atypical antipsychotics increase the risk of stroke when used to treat BPSD in elderly patients with dementia [5]. Some physicians in Japan use Japanese Kampo medicines, notably Yokukansan, for the treatment of BPSD [6], and there are reports that Yokukansan is effective for decreasing BPSD symptoms [7, 8]. The etiopathogenesis of BPSD is complicated and multifactorial, encompassing brain lesions and types of dementia, changes in neurotransmission and neuromodulation, physical disorders and pain, psychological and environmental perspective, personality traits, and life events [9]. Antidementia drugs, such as donepezil, are used not only for the improvement of cognitive disorders but also for the alleviation of BPSD. The effects of antidementia medicines on BPSD have, however, been controversial. Some reports showed improvements in BPSD by donepezil [10–14], while others had contrasting outcomes [15, 16].

Donepezil is metabolized by cytochrome p-450 (CYP) isoenzymes in humans, primarily by *CYP2D6* and to a lesser extent by CYP3A4/5 [17]. A major metabolite of donepezil is 6-O-desmethyldonepezil (6ODD), produced by *CYP2D6*. 6ODD is an active metabolite with potency to inhibit acetylcholinesterase comparable to that of donepezil [18]. However, based on animal studies, the transfer of 6ODD into the brain seems to be low [19]. The clinical contribution of 6ODD to the efficacy of donepezil treatment, therefore, remains unclear. The phenotypes of *CYP2D6* polymorphisms are divided into four groups (ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, and poor metabolizer), according to their enzymatic activity [20]. It was reported that a higher frequency of the *CYP2D6*10* allele, which encodes a low-activity form of the enzyme, was seen in responder Alzheimer's patients than in nonresponders [21]. This result suggests that higher blood concentrations of donepezil contribute to improved efficacy of the drug. Since the 6ODD/donepezil concentration ratio in blood correlates with the enzymatic activity of *CYP2D6* in individual patients, the ratio shows *CYP2D6* phenotype dependency [22]. The efflux of donepezil from the brain to peripheral blood is achieved via P-glycoprotein encoded by the *ABCB1* gene [23]. Patients with the T/T/T haplotype of three major *ABCB1* polymorphisms may show lower plasma donepezil concentrations and better clinical outcomes than those with other genotypes, but the differences are not significant [20]. There have been no reports on whether the genetic polymorphisms of *CYP2D6*, *CYP3A5*, and *ABCB1* influence the development of BPSD in patients receiving donepezil.

We recently reported the impact of polymorphisms of metabolic enzymes and transporters of donepezil on plasma donepezil pharmacokinetics in AD [22]. In this study, we investigated the influence of plasma concentrations of donepezil and 6ODD, polymorphisms of *CYP2D6*, *CYP3A5,* and *ABCB1*, and patient backgrounds on the development of BPSD.

Materials and Methods

Chemicals

Donepezil, 6ODD, and escitalopram were obtained from Tokyo Chemical Industry (Tokyo, Japan), Toronto Research Chemicals Inc. (North York, Canada), and R&D Systems Inc. (Minneapolis, MN, USA), respectively. All other chemicals were commercially available and of analytical grade.

Patient Selection

Fifty-two blood samples from AD patients were used. All patients received treatment with donepezil at the hospital of the Shizuoka Institute of Epilepsy and Neurological Disorders between January 2014 and July 2020. The backgrounds of the enrolled patients are shown in Table 1.

Drug Administration and Blood Sampling

Donepezil (3–10 mg/day) was administered once daily for at least 2 months before blood sampling. Blood samples were obtained on an average of 2.16 h (range 0.92–4.50) after oral administration (Table 1).

Pharmacogenetic Analysis

Genomic DNA of patients was extracted from whole blood using a MagNA Pure Compact® (Roche Molecular Diagnostics, Pleasanton, CA, USA). Polymorphisms of *CYP2D6* *1, *2, *4, *5, *10, and *2A were detected by the Luminex® 100/200 ™ xMAP® platform using the xTAG®*CYP2D6* RUO kit v3 (Luminex, Austin, TX, USA). Ultrarapid metabolizer, extensive metabolizer, intermediate metabolizer, and poor metabolizer were defined as described previously [22]. Polymorphism of *CYP3A5*3* was detected based on the PCR-RFLP method reported by Balram et al. [24] and slightly modified by our laboratory. Polymorphisms of *ABCB1 G2677T/A* and *C3435T* were also detected using the PCR-RFLP method reported by Tanabe et al. [25] and slightly modified by ourselves.

Evaluation of BPSD and Cognitive Impairment

The Neuropsychiatric Inventory (NPI), consisting of 10 items (total score: 120 points), was adopted as the instrument for evaluating symptoms of BPSD [26]. The NPI score was used to divide patients into two groups: high BPSD with NPI ≥20 and low BPSD with NPI <20 [27]. The Mini-Mental State Examination (MMSE) was implemented to assess the degrees of functional and cognitive impairment [28].

Table 1. Patient backgrounds

Characteristic	Patients	Mean	SD	Range
Sex	52		Male 20; female 32	
Age, years	52	75.3	8.52	54–90
Albumin, g/dL	27	4.03	0.37	3.1–4.5
AST, IU/L	52	23.7	7.55	13–51
ALT, IU/L	52	17.0	7.79	7–52
γ-GTP, IU/L	52	23.7	18.9	9–134
Serum creatinine, mg/dL	52	0.77	0.17	0.43–1.22
Body weight, kg	52	50.8	10.6	32.5–91.0
MMSE	25	19.0	6.3	3–28
Donepezil dose, mg/kg	52	0.124	0.0534	0.0549–0.270
Blood sampling time after administration	52	2.16	0.834	0.92–4.50
Concomitant use of psychotropics	7	Tiapride 5, sertraline 1, and flunitrazepam 1		
Concomitant use of Yokukansan	Yes 23, No 29			

Case report	Blood sampling, *n*	Sex	Age, years	Body weight, kg	Donepezil dose, mg	CYP2D6 phenotype	CYP3A5 genotype
Patient 1	5	Male	64	52	5–8	EM	*3/*3
Patient 2	6	Male	76	43	5	EM	*3/*3

SD, standard deviation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transpeptidase; MMSE, Mini-Mental State Examination.

Pharmacokinetic Analysis

Plasma donepezil and 6ODD concentrations were determined by high-performance liquid chromatography–tandem mass spectrometry, using the modified method of Pilli et al. [29] and Shah et al. [30]. Escitalopram was used as an internal standard. The minimum detection limit of both donepezil and 6ODD was 0.10 ng/mL. To compare individual pharmacokinetic data, we calculated the concentration/dose (C/D) ratio of donepezil or 6ODD as the plasma concentration (ng/mL) divided by the weight-adjusted dose (mg/kg).

Statistical Analysis

Statistical analyses were conducted using SPSS 23.0 (SPSS, Inc., Chicago, IL, USA). Linear regression analysis was performed using Pearson's product-moment correlation coefficient. The *t*-test and Mann-Whitney U-test were used when comparing data of two independent groups with normal and non-normal distributions, respectively. The Tukey's HSD test was applied when comparing data of three or more groups. $p < 0.05$ was considered to indicate a significant difference.

Results

Influence of Patient Background Factors and Concomitant Drugs on BPSD

The NPI scores as an index of the development of BPSD did not correlate with the MMSE scores, patient age, body weight, or sex (Fig. 1). We did not find any significant relationship between NPI scores and serum albumin, alanine aminotransferase, aspartate aminotransferase, γ-glutamyl transpeptidase, total bilirubin, or serum creatinine (online suppl. Fig. 1; for all online suppl. material, see www.karger.com/doi/10.1159/000516938). NPI scores did not differ between patients receiving or not receiving psychotropics, memantine, or Yokukansan (online suppl. Fig. 2).

Influence of the Plasma Concentration of Donepezil and Protein Polymorphisms on BPSD

Figure 2 shows the relationships between NPI scores, plasma donepezil (total and free), 6ODD concentrations, and the 6ODD/donepezil concentration ratio. Interestingly, patients with high plasma concentrations of donepezil (>60 ng/mL) or 6ODD (>0.4 ng/mL) did not develop severe BPSD, that is, their NPI scores did not reach or exceed 20 points. The donepezil dose (mg/day and mg/kg) and C/D ratios of donepezil and 6ODD did not directly correlate with NPI scores (online suppl. Fig. 3). However, patients with higher donepezil doses (>0.15 mg/kg) did not develop severe BPSD, reflecting the results of donepezil pharmacokinetics (online suppl. Fig. 3). Similarly, patients with higher donepezil C/D ratios that

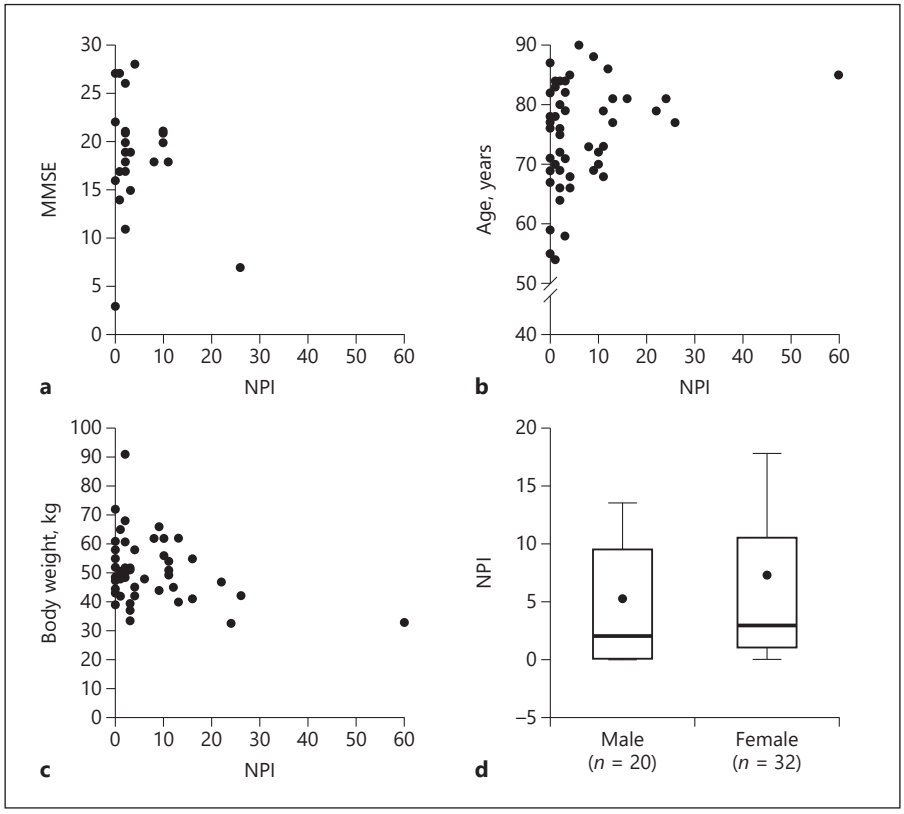

Fig. 1. Relationship between NPI scores and MMSE (**a**), age (**b**), body weight (**c**), and sex (**d**) in patients with Alzheimer's disease. The box plot presents the distribution of data based on the five-number summary. From the bottom: minimum, first quartile, median, third quartile, and maximum. NPI, Neuropsychiatric Inventory; MMSE, Mini-Mental State Examination.

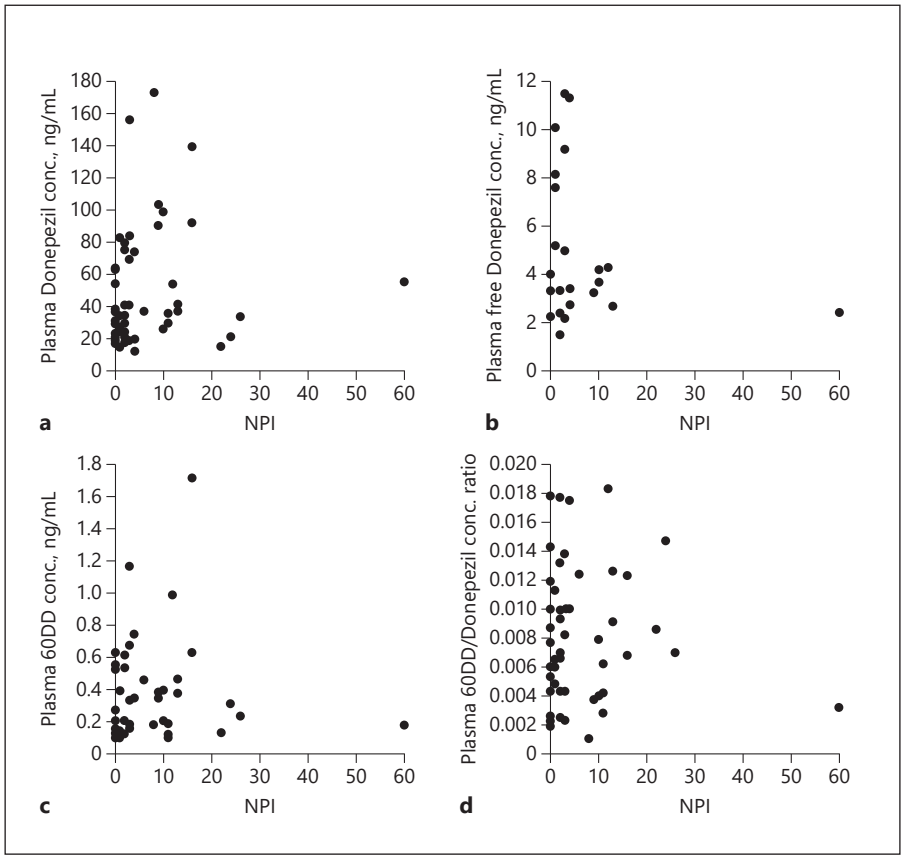

Fig. 2. Relationship between NPI scores and plasma total (**a**) and free (**b**) concentrations of donepezil, plasma total 6ODD concentrations (**c**), and the 6ODD/donepezil concentration ratio (**d**) in patients with AD. The plasma 6ODD/donepezil concentration ratio (metabolic ratio) was calculated by dividing the plasma 6ODD concentration by the plasma donepezil concentration. NPI, Neuropsychiatric Inventory; 6ODD, 6-O-desmethyl donepezil; AD, Alzheimer's disease.

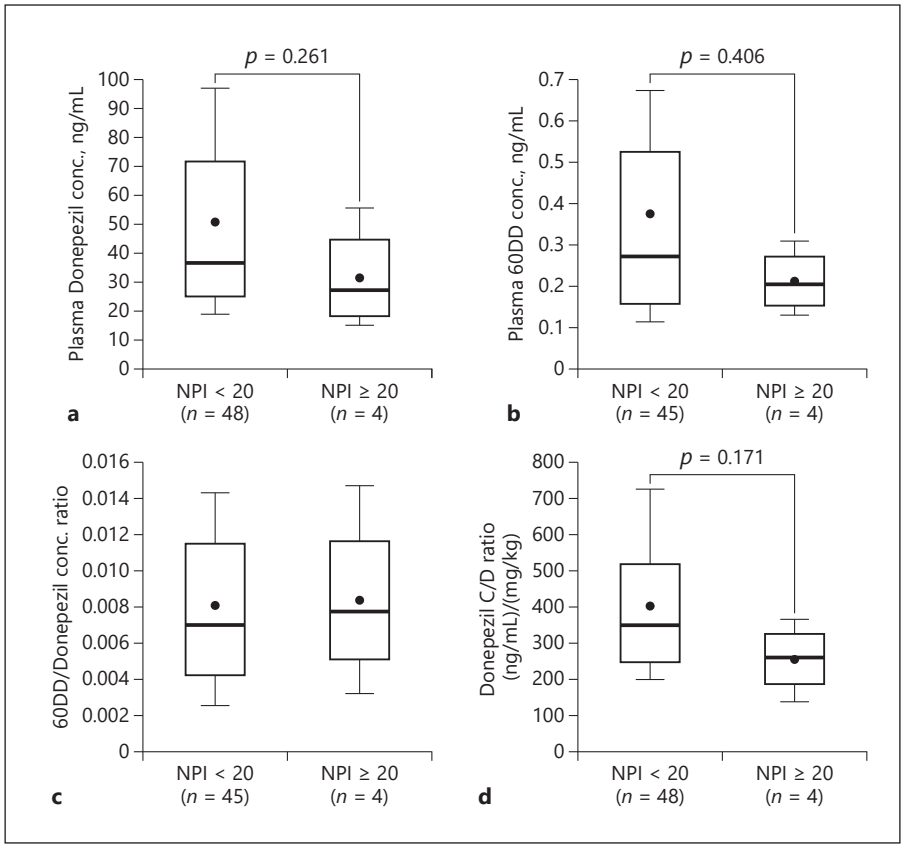

Fig. 3. Comparison of plasma donepezil (**a**), 6ODD (**b**) concentrations, 6ODD/donepezil concentration ratio (**c**), and donepezil C/D ratio (**d**) between patients with NPI < or ≥20 points. The box plot presents the distribution of data based on the five-number summary. From the bottom: minimum, first quartile, median, third quartile, and maximum. The concentration/dose (C/D) ratios of donepezil and 6ODD were calculated by dividing the plasma concentrations (ng/mL) by the weight-adjusted doses (mg/kg). The Mann-Whitney U-test was used to compare data of two independent groups. NPI, Neuropsychiatric Inventory; 60DD, 6-O-desmethyl donepezil.

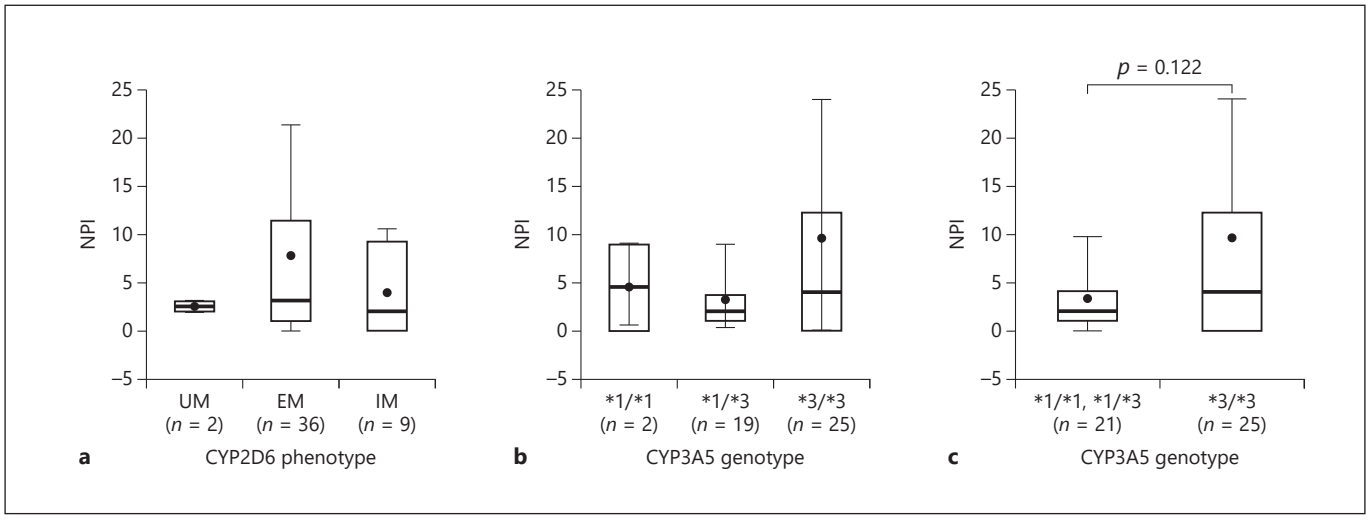

Fig. 4. Influence of *CYP2D6* phenotypes (**a**), and CYP3A5 genotypes (**b**) and phenotypes (**c**) on NPI scores in patients with AD. Patients were classified into three groups according to the *CYP2D6* genotype UM, EM, and IM. Patients were also divided into three or two groups according to the genotypes of CYP3A5. The box plot presents the distribution of data based on the five-number summary. From the bottom: minimum, first quartile, median, third quartile, and maximum. The Mann-Whitney U-test was used to compare data of 2 independent groups. NPI, Neuropsychiatric Inventory; AD, Alzheimer's disease; UM, ultrarapid metabolizer; EM, extensive metabolizer; IM, intermediate metabolizer.

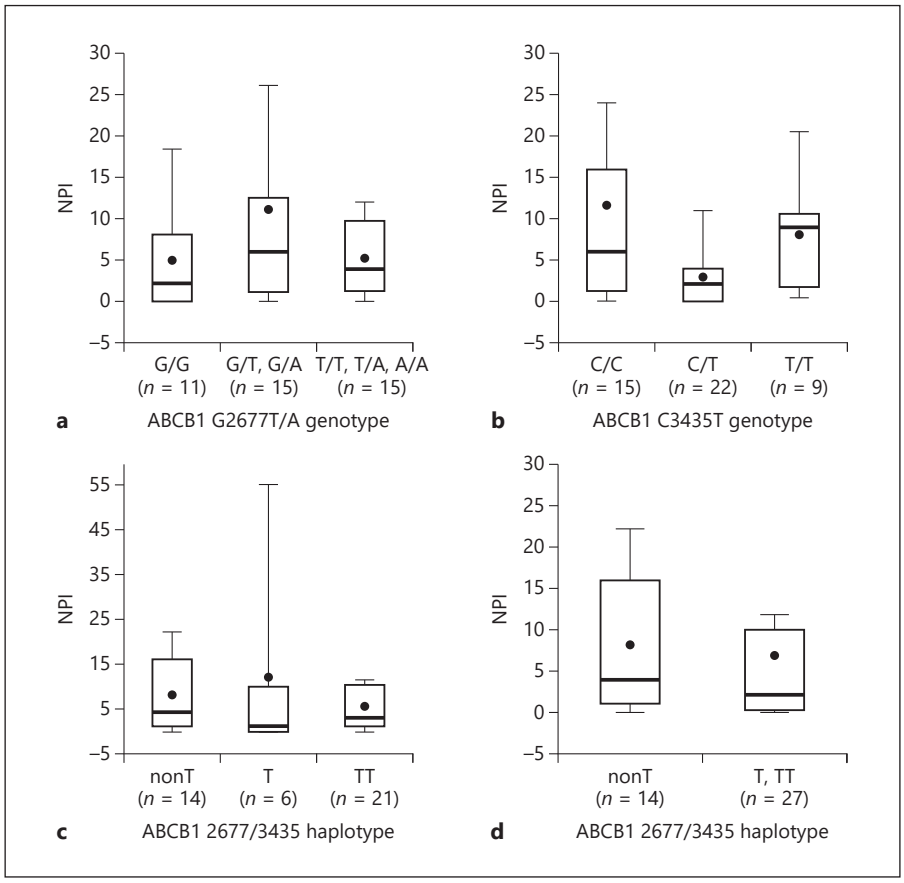

Fig. 5. Influence of *ABCB1 G2677T/A* (**a**), *C3435T* (**b**) genotypes and the presence of T alleles (**c**, **d**) on NPI scores in patients with AD. Patients were divided into three or two groups according to the *ABCB1 G2677T/A* and *C3435T* genotypes or the presence of T alleles. The box plot presents the distribution of data based on the five-number summary. From the bottom: minimum, first quartile, median, third quartile, and maximum. NPI, Neuropsychiatric Inventory; AD, Alzheimer's disease.

represented total clearance of donepezil did not develop severe BPSD. We compared plasma concentrations of donepezil and 6ODD, plasma 6ODD/donepezil concentration ratios, and donepezil C/D ratios between patients whose NPI scores were higher or lower than 20 points (Fig. 3). There were no significant differences between them, probably because of the small number of patients who developed severe BPSD. Figure 4 shows the influence of polymorphisms of *CYP2D6* and *CYP3A5* on NPI scores. There were no gene or phenotype impacts on NPI scores. Genotypes or haplotypes of *ABCB1 2677* and *3435* also did not influence NPI scores (Fig. 5).

Two Case Reports of Patients with Multiple Blood Samplings

Five or six blood samplings were obtained over 2 years from two patients whose *CYP2D6* phenotype was EM. Figure 6 shows the changes in their NPI scores. Remarkably, the changes in both patients were inversely associated with plasma donepezil concentration. The effect of concomitant use of memantine on BPSD was inconsistent between the two patients.

Discussion

As BPSD markedly lowers the quality of life of patients with dementia, their families, and caregivers, clinically effective treatments are needed for BPSD. The effects of donepezil on BPSD have been controversial [10–16]. To the best of our knowledge, this is the first attempt to clarify the relationships between the blood concentration of donepezil, 6ODD, and BPSD in patients with AD. Although this study did not find a linear relationship between plasma donepezil disposition and the development of BPSD, no patients whose plasma concentrations of donepezil exceeded 60 ng/mL developed severe BPSD. Moreover, the plasma donepezil concentrations in two patients with multiple blood samplings over 2 years showed an inverse relationship to the changes in NPI scores. Patients with high plasma donepezil concentrations did not develop any noticeable side effects. These results indicate that if a patient develops severe BPSD and the plasma donepezil concentration near the peak is <60 ng/mL, an increased dose to raise the concentration may contribute to improving severe BPSD. The optimal thera-

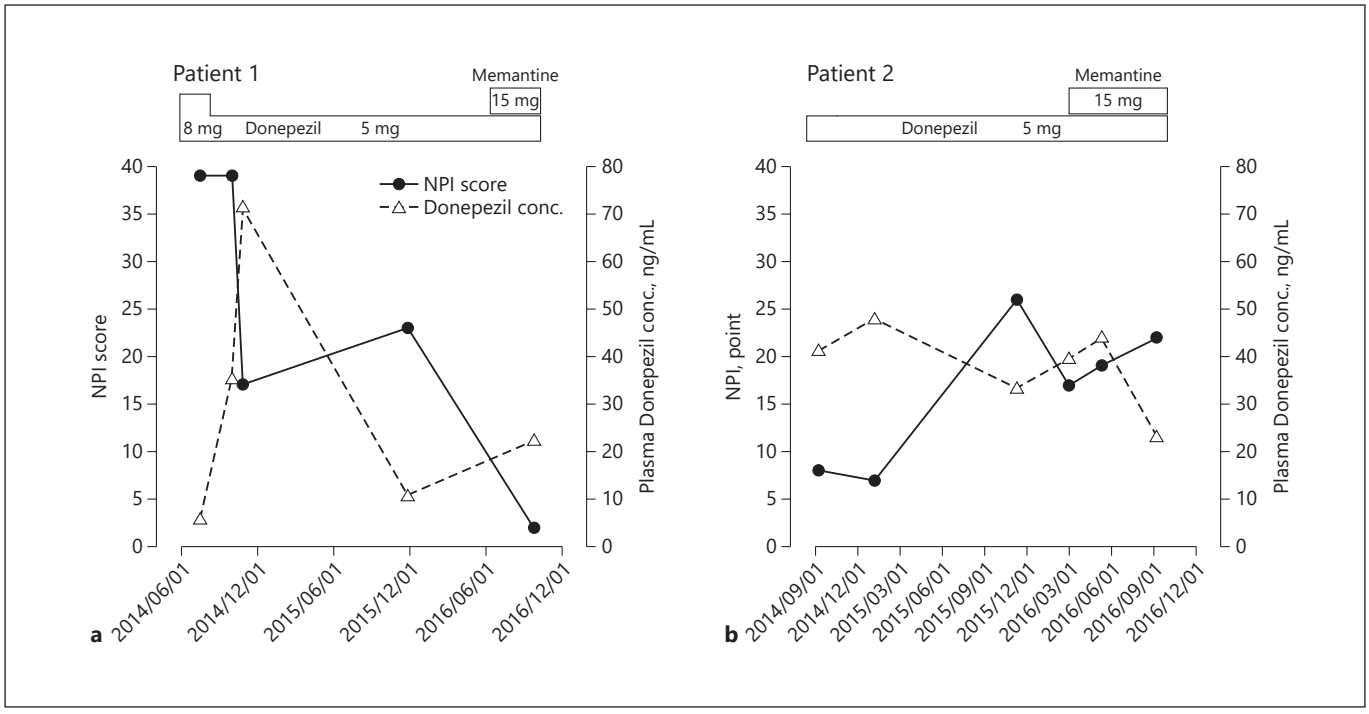

Fig. 6. Changes in NPIscores and plasma donepezil concentrations in two patients with multiple blood samplings. Two patients (patient 1, **a**; patient 2, **b**) underwent five or six blood samplings over 2 years to determine plasma donepezil concentrations and NPI scores. An inverse correlation between plasma donepezil concentrations and NPI scores was observed. NPI, Neuropsychiatric Inventory.

peutic range of donepezil is reported to be 50–75 ng/mL at the trough in plasma [31]. Noetzli et al. [32] reported that a one-compartment model describes the plasma disposition of donepezil with first-order absorption well. In EMs, trough concentrations were reported to be approximately half the plasma concentration at 2 h after oral administration, according to the pharmacokinetic parameters [32]. Hence, the plasma donepezil concentrations in patients of this study might have been below the upper level of the therapeutic range. We did not find significant differences between patients with NPI scores above or below 20 points, possibly because of the small number (four) of patients who developed severe BPSD.

CYP2D6 is a major enzymatic pathway for the degradation of donepezil, and CYP3A4/5 is the alternative pathway in men [18]. No significant gene or phenotype effects of *CYP2D6* and *CYP3A5**3 on the development of BPSD were seen. Based on the speculation that high plasma donepezil concentrations might improve BPSD, intermediate metabolizers of *CYP2D6* should have shown lower NPI scores than those of extensive metabolizers, or ultrarapid metabolizers. However, no phenotype-dependent improvement in BPSD was seen. This result was supported by the finding that plasma donepezil concentrations did not increase in a phenotype-dependent manner [22]. Since all the patients with high donepezil doses (>0.20 mg/kg) showed NPI scores below 20 points, a combined analysis of phenotypes and doses may be needed to clarify the influence of *CYP2D6* phenotypes on the development of BPSD with a larger patient cohort.

ABCB1 gene encodes P-glycoprotein, and decreased activity of P-glycoprotein due to genetic variants might cause a high donepezil concentration in the brain. We did not find a significant influence of *ABCB1* genotypes on NPI scores. Although many studies have investigated the influence of the *ABCB1 G2677T/A* and the *C3435T* genotype or haplotype on the activity of P-glycoprotein, the significance of the variant is still unclear [33–36]. Since donepezil is a substrate of the breast cancer resistance protein [37], further studies may be needed to clarify the influence of polymorphisms of the breast cancer resistance protein on the development of BPSD.

Yokukansan is a Japanese Kampo medicine that consists of crude extracts from *Atractylodes lancea* rhizome,

Poria sclerotium, Cnidium rhizome, Uncaria hook, Japanese Angelica root, Bupleurum root, and Glycyrrhiza. Yokukansan is sometimes prescribed for BPSD to Alzheimer's patients in Japan [38]. NPI scores in patients receiving Yokukansan, psychotropics, or memantine did not differ from those not receiving the drugs. Moreover, there was no significant difference in plasma donepezil concentrations between patients receiving and not receiving Yokukansan [22]. These results indicate that the effect of Yokukansan on BPSD is independent from that of donepezil.

This study had several limitations. The average blood sampling time was 2.1 h after the last administration of donepezil. We did not periodically conduct MMSE because the primary goal of this study was to investigate the relationship between the plasma donepezil concentration and development of BPSD, not cognitive function.

Conclusions

Although we did not find a direct relationship between plasma donepezil pharmacokinetics and NPI scores in Alzheimer's patients, higher plasma donepezil concentrations might be a promising factor in preventing or alleviating severe BPSD.

Statement of Ethics

The research was conducted ethically in accordance with the World Medical Association Declaration of Helsinki, Ethical Guidelines for Medical Research for Humans from the Japanese Ministry of Health, Labor and Welfare, and the Rules of the Ethics Committee of the National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders and the University of Shizuoka. This study was approved by the Institutional Review Boards at the National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders (No. 2013-33), and the University of Shizuoka (No. 27-3). All patients or their families provided written informed consent to a Statement of Ethics.

Conflict of Interest Statement

The authors declare that there are no competing interests for this work.

Funding Sources

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Author Contributions

Dr. Kagawa designed and supervised the study and wrote the manuscript. Dr. Yamamoto gathered informed consent from the patients. Dr. Kagawa, Ms. Ueno, Mr. Inomata, and Ms. Tezuka measured drug concentrations and performed gene analysis. Drs. Osawa and Yazawa designed the study and edited the manuscript. Dr. Maeda performed the gene analysis. Dr. Obi recruited patients and provided professional medical advice.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author, Y.K., upon reasonable request.

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