

# A Comparison of Lamotrigine or Sodium Valproate on the Efficacy in Alzheimer's disease with Behavioral and Psychological Symptoms of Dementia: A Retrospective Open-Label Study Running Title: Efficacy of Anticonvulsants for BPSD

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## Abstract

**Aim:** We compared the clinical efficacy and subsequent changes in dosages of concomitantly used psychotropic drugs with lamotrigine and sodium valproate therapy in Alzheimer's disease (AD) with Behavioral and Psychological Symptoms on Dementia (BPSD).

**Methods:** This study was a 16-week, retrospective, open-label study. The 45 subjects were inpatients. The outcome measures assessed were BPSD and cognitive function. BPSD was assessed using the neuropsychiatric inventory (NPI) and cognitive function was assessed using the mini-mental examination (MMSE). The changes in the dosages of concomitant psychotropic drugs were also assessed.

**Results:** Although the mean changes from baseline NPI scores and the two NPI subscales (agitation and irritability) decreased both in the lamotrigine therapy group and in the sodium valproate therapy group, no significant difference was found between the two groups. The mean decrease in diazepam-equivalent dose from baseline was significantly greater in the lamotrigine therapy group than that in the sodium valproate therapy group ( $p < 0.05$ ). Furthermore, in the sodium valproate therapy group, the occurrence rates of somnolence, body tilt, and dizziness were all 30%.

**Conclusions:** The results of this study suggested that while the administration of lamotrigine or sodium valproate might be effective in patients with severe AD with BPSD, special attention is required when using sodium valproate on a daily basis.

**Keywords:** Alzheimer's disease; Behavioral and psychological symptoms on dementia; Lamotrigine; sodium valproate; Psychotropic drugs

## Introduction

In addition to core symptoms such as memory problems and disorientation, Alzheimer's disease (AD) has peripheral symptoms, which include various psychological symptoms such as hallucinations, delusions, sleep disorders, and emotional disorders, and behavioral symptoms such as hyperactivity, wandering, and physical or verbal aggression. The disease imposes a great physical and emotional burden on families and caregivers, in addition to the high costs of care and the consequent severe impairment in the quality of life (QOL) [1]. While non-pharmacological interventions such as an appropriate interference or a change in environment are the first choice for treatment, behavioral and psychological symptoms of dementia (BPSD) that is difficult and unresponsive to non-pharmacological intervention or that endangers the caregivers is suitable for drug therapy.

Elderly individuals are generally vulnerable to the development of adverse effects, as they have reduced hepatic and renal functions. Therefore, there is a possibility of a decline in activities of daily living (ADL) and QOL. In the elderly patients, the risk of drug-induced cognitive impairment increased with an increase in the number of concomitant drugs [2-4]. Therefore, efficacy of drug therapy in patients with AD accompanied by BPSD should not be the sole objective of treatment; adverse drug reactions should be kept to a minimum, and the use of concomitant drugs must be limited wherever possible.

Although the evidence of the therapeutic drug for BPSD is limited in clinical situations, antiepileptic drugs such as lamotrigine, valproate, and carbamazepine are often used. Lamotrigine is thought to stabilize nerve membranes by inhibiting voltage-dependent Na<sup>+</sup> channels and

to exert an anticonvulsant effect by inhibiting the excessive release of excitatory amino acids [5]. This compound has received attention for its possible cognitive-enhancing properties in Alzheimer's disease (AD), anti-aggressive actions in frontal lobe dementia, and antipsychotic effects in epileptic psychosis. Furthermore, several recent reports have suggested that lamotrigine may be useful in treating AD that is accompanied by BPSD [6,7]. In our previous study, we demonstrated that the administration of lamotrigine to patients with severe AD with BPSD may not only be more effective, but could also make it possible to avoid increasing the dosage of antipsychotic medications [8]. On the other hand, sodium valproate has an inhibitory action on neuronal excitability, and its effectiveness for treating psychiatric symptoms has been established. It has been suggested in some previous studies that sodium valproate is useful for the suppression of aggression, frustration, and other manic symptoms observed in AD [9]. The mechanism of action of lamotrigine and sodium valproate is the modulation of glutamate-mediated excitatory synaptic transmission and gamma-aminobutyric acid (GABA)-mediated inhibitory synaptic

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transmission. As a result, both drugs might reduce BPSD [10]. However, few reports have compared the clinical effects of lamotrigine and other antiepileptic drugs on BPSD. No other anti-epileptic drugs (e.g. gabapentine and carbamazepine) except lamotrigine or sodium valproate were administered during the study period. Based on the results of our previous study, we retrospectively investigated the clinical efficacy of lamotrigine or sodium valproate therapy in patients with AD accompanied by BPSD.

## Methods

### Subjects

Among the patients hospitalized at the Psychiatry Department of Tanzawa Hospital or admitted to homes for the elderly (Adachi Shinseien, Green Haym Arakawa, or Hadano Shojuen), this study, using a retrospective cohort design, examined the cases where lamotrigine therapy or sodium valproate therapy was initiated between January 2012 and June 2014. All subjects had been diagnosed using the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV), and the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's disease and Related Disorders Association (NINCDS/ADRDA) [11]. From medical records, inclusion criteria were as follows: 1) patients had been diagnosed AD; 2) patients were not concomitantly receiving cholinesterase inhibitors; 3) patients were not concomitantly receiving mood stabilizers; 4) patients had been treated with a stable dose of psychotropic drugs for at least 1 month; and 5) patients had not any serious internal medical comorbidity (dehydration, physical exhaustion accompanied by poor nutritional status, liver disorder, cardiovascular disorder, etc).

Furthermore, all the subjects who participated in this study were inpatients whose treatment compliance had been confirmed each time by nurse or caregiver, and whose treatment compliance was thus assured. They were required to be symptomatically stable, as judged by the treating psychiatrist, to be able to complete all the clinical measures.

### Therapy method

Subjects were administered lamotrigine or sodium valproate at an initial dose of 12.5 mg or 100 mg, respectively, in addition to their current therapeutic medications. For gradual and safe titration to an effective concentration of lamotrigine or sodium valproate, we increased the drug dose in 12.5 mg or 100 mg increments over 2 to 4 week intervals. After the dose of lamotrigine or sodium valproate was increased as necessary to optimal, psychotropic drug prescriptions were reduced wherever possible.

In order to determine psychotropic equivalents, we used the calculation table proposed by Inagaki and Inada [12,13]. When we compared baseline levels to post-lamotrigine changes in the dosages of concomitant psychotropics being administered, we calculated the subjects' daily dosages in terms of risperidone or diazepam equivalents.

### Assessment methods

The following clinical assessments were performed both at baseline and at 16 weeks. The outcome measures assessed were BPSD and cognitive function. BPSD was assessed using the NPI [14] and cognitive function was assessed using the mini-mental state examination (MMSE) [15] because our facilities did not have the Severe Impairment Battery (SIB), which is one of the best evaluation tool for cognition.

### Statistical analysis

- 1) Comparison of baseline demographics - Fisher's exact tests.
  - 2) Changes in symptoms and dosages of concomitantly used psychotropic drugs over time (within groups): paired *t*-tests. If the data did not show a normal distribution, then the Wilcoxon rank-sum test was used instead.
  - 3) Changes in symptoms and dosages of concomitantly used psychotropic drugs over time (between groups): Mann-Whitney *U* test.
- The significance level was  $p < 0.05$  in all analysis.

## Results

### Subject profiles

Of the 45 patients, 25 received lamotrigine and 20 received sodium valproate. No significant differences in baseline NPI and baseline MMSE scores were observed between the lamotrigine and the sodium valproate groups. Moreover, we observed no significant differences between the lamotrigine group and the sodium valproate group in terms of mean daily dose of previous drug treatment, duration of illness, or age. The average dose of lamotrigine or sodium valproate administered by the end of the study was  $48.0 \pm 27.6$  mg/day (25 to 100) and  $215.0 \pm 122.6$  mg/day (100 to 600), respectively (Table 1).

Most of the patients who participated in this study (71.1%) exhibited baseline MMSE scores of 10 or lower; they were all inpatients or under 24 h care. Furthermore, since these patients had advanced/severe AD, they all had difficulty communicating with staff.

Both groups in this study received concomitant psychotropic drugs: in the lamotrigine therapy group, 31.8% (7/22) received antipsychotics and 18.2% (4/22) received benzodiazepines; in the sodium valproate therapy group, 50.0% (10/20) received antipsychotics and 25.0% (5/20) received benzodiazepines.

### Efficacy

Although the mean changes from baseline NPI scores and the two NPI subscales (agitation and irritability) decreased both in the lamotrigine therapy group and in the sodium valproate therapy group, no significant difference was found between the two groups. However, the mean decrease from baseline in the NPI anxiety subscale was significantly greater in the lamotrigine therapy group than that in the sodium valproate therapy group ( $p < 0.05$ ). On the other hand, the

Characteristics	Sodium valproate therapy group (n=20)	Lamotrigine therapy group (n=25)	p-value
Age (years) (mean $\pm$ S.D.)	84.0 $\pm$ 6.2	87.3 $\pm$ 5.8	0.07
Gender (M: F)	4:16	2: 23	
Duration of illness (years) (Mean $\pm$ S.D.)	8.9 $\pm$ 4.1	10.2 $\pm$ 4.0	0.30
Risperidone equivalents dose (mg/day) (baseline) (Mean $\pm$ S.D.)	0.4 $\pm$ 0.7	0.3 $\pm$ 0.3	0.42
Diazepam equivalents dose (mg/day) (baseline) (Mean $\pm$ S.D.)	0.8 $\pm$ 1.7	2.1 $\pm$ 2.7	0.07
MMSE Score (baseline) (Mean $\pm$ S.D.)	3.2 $\pm$ 5.8	4.4 $\pm$ 6.2	0.55
NPI total score (baseline) (Mean $\pm$ S.D.)	36.6 $\pm$ 11.7	34.4 $\pm$ 6.0	0.43

Value are mean  $\pm$  SD or n. MMSE: Mini-Mental state Examination; NPI: Neuropsychiatric Inventory

**Table 1:** Subject characteristics.

	Sodium Valproate therapy group (n=20)				Lamotrigine Therapy group				a F- Value	b P-value
	Baseline		Change from baseline to 16weeks		Baseline (n=25)		Change from baseline to 16 weeks (n=22)			
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D		
NPI										
Total	36.6	11.7	-7.2	6.3*	34.4	6.0	-9.4	5.5*	1.47	0.23
Delusions	1.6	2.8	-0.4	0.9	1.8	3.4	-0.3	0.7	0.27	0.60
Hallucinations	2.4	2.9	-0.6	1.1**	0.5	1.7	-----	-----	6.62	0.01
Agitation	8.7	3.5	-3.3	2.5	9.0	3.1	-4.0	2.2*	1.08	0.30
Depression	0.05	0.2	---	---	0.3	1.1	---	---	-----	-----
Anxiety	1.2	2.7	-0.3	1.0	5.1	4.5	-1.5	2.1**	5.20	0.03
Euphoria	1.2	3.2	-0.3	1.0	0.2	0.8	---	---	2.07	0.16
Apathy	7.3	2.0	---	---	5.6	2.6	-----	-----	---	-----
Disinhibition	1.9	4.0	-1.2	3.1	0.0	0.0	-----	-----	3.22	0.08
Irritability	9.2	3.2	-2.0	2.4*	9.0	3.1	-3.2	2.6*	2.31	0.14
Aberrant motor behaviour	4.3	4.1	-0.6	1.3**	1.6	3.8	-----	-----	4.60	0.04
MMSE Score	2.4	6.3	---	---	3.6	5.8	-----	-----	-----	-----

Value is mean ± SD. MMSE, Mini-Mental State Examination : NPI, Neuropsychiatric Inventory  
\*P<0.005 vs. Baseline, \*\*P<0.05 vs. baseline

**Table 2:** Clinical efficacy.

	Sodium Valproate therapy group (n=20)				Lamotrigine Therapy group				P - Value
	Baseline		Change from baseline to 16 weeks		Baseline (n=25)		Change from baseline to 16 weeks (n=22)		
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	
Risperidone equivalent dose ( mg/day)	0.4	0.7	0.03	0.08	0.3	0.3	0.007	0.06	0.39
Diazepam equivalent dose (mg/day)	0.8	0.7	-----	-----	2.1	2.7	-1.8	2.5*	0.002

\*Significant difference was found by Wilcoxon signed – rank test (p<0.05).  
Mean ± standard deviation.

**Table 3:** The change over time in the risperidone equivalent dose and diazepam equivalent dose.

mean decrease from baseline in the two NPI subscales (hallucination and aberrant motor behavior) was significantly greater in the sodium valproate therapy group than that in the lamotrigine therapy group (p < 0.05) (Table 2).

Moreover, no changes in MMSE scores were found either in the lamotrigine therapy group or in the sodium valproate therapy group.

### Concomitantly used psychotropic drugs

The mean decrease in diazepam-equivalent dose from baseline was significantly greater in the lamotrigine therapy group than that in the sodium valproate therapy group (p < 0.01). The mean amount of change in the risperidone-equivalent dose from baseline was not significantly different between both groups (Table 3).

### Adverse Events

In the lamotrigine therapy group (n=25), the adverse events reported were as follows: somnolence, 4% (n=1); rash, 12% (n=3); nausea, 4% (n=1); and malaise, 4% (n=1). Most adverse events were rated as “mild”, and no serious adverse events, such as Stevens-Johnson syndrome, Lyell syndrome, or any hypersensitivity reactions were noted. However, 3 patients were unable to tolerate lamotrigine and dropped out because of rash. On the other hand, in the sodium valproate therapy group (n=20), the adverse events reported were as follows: somnolence, 30% (n=6); body tilt, 30% (n=6); dizziness, 30% (n=6) and malaise, 5% (n=1).

### Discussion

In the UK, when the MMSE score is 10 or less, the NICE Guidelines recommend stopping the administration of cholinesterase inhibitors. Conversely, in Japan, cholinesterase inhibitors are not stopped unless there are serious adverse effects.

In the present study, since most patients had severe AD with a baseline MMSE score of 10 or lower, anti-dementia drugs were not expected to be efficacious, and the financial burden was expected to increase. Furthermore, it is known that psychiatric symptoms such as irritability and agitation occasionally develop in patients receiving a cholinesterase inhibitor called donepezil, which is an AD drug. In the present study, patients receiving a cholinesterase inhibitor were excluded in order to eliminate the influence of the cholinesterase inhibitor on BPSD.

When BPSD accompanies severe AD, it frequently results in a considerable burden on the caregiver, appreciably complicates treatment and care, and leads to more complicated drug therapy with antipsychotic medications and/or mood stabilizers. In previous studies, gabapentine was reported to be a well-tolerated and effective treatment for BPSD, especially for patients showing agitation, sexual behavior increased [16]. Furthermore, carbamazepine was reported to be an effective treatment for BPSD in general, especially for patients exhibiting aggression and hostility [17]. On the other hand, in the present study, we retrospectively examined the efficacy of lamotrigine and sodium valproate in treating AD with BPSD. The results of this study, as well as previous studies and the effect of other mood stabilizers, suggest that both, lamotrigine and sodium valproate have an effect on agitation and irritability. The lamotrigine therapy group showed a significant decrease in the NPI anxiety subscale score, compared to that in the sodium valproate therapy group. On the other hand, the sodium valproate therapy group showed a significant decrease in the NPI hallucinations and aberrant motor behavior subscales scores, compared to that in the lamotrigine therapy group. The difference in baseline score and risperidone-equivalent doses, in addition to the difference in pharmacological property between the two drugs, possibly has an

effect. Therefore, the results of this study that lamotrigine unlike other mood stabilizers may be potentially effective for specific BPSD, anxiety.

Recent studies on similar subjects have suggested that the mortality of elderly patients with BPSD receiving atypical antipsychotics is approximately 5%. They concluded that changing the dosages of the antipsychotics decreased mortality, but did not significantly affect disease progression [18]. Furthermore, since it is known that the administration of a benzodiazepine to elderly patients could impair their cognitive function and cause delirium, its administration requires careful monitoring [19]. The results of this study suggested that both lamotrigine and sodium valproate could improve the safety of the doses of antipsychotics to a certain extent and avoid cognitive impairment associated with benzodiazepines.

There have been concerns that a serious adverse effect of lamotrigine is a severe skin disorder (Stevens-Johnson syndrome and Lyell syndrome) that can result in death. However, the incidence was approximately 0.5% in clinical trials in Japan and 0.03% in German studies, suggesting an extremely low incidence [20]. This study showed similar results to those of previous studies in that rash developed within 8 weeks after the administration and that the rate of its occurrence was approximately 10% [21-23]. Since the dosage and administration were carefully controlled, the severity of the rash was mild. Furthermore, the administration was immediately discontinued in order to avoid the rash becoming severe; it did not develop into a severe skin manifestation.

On the other hand, it is clear that the administration of sodium valproate to patients with AD causes adverse effects, particularly somnolence and gait disturbance, and that the incidence of adverse events tends to increase [24,25]. Since the occurrence rates of somnolence, body tilt, and dizziness were all 30% in this study, special attention might be required in the daily use of sodium valproate for treating AD with BPSD.

## Limitations

In this study, the subjects had quite advanced (severe) dementia. It is very challenging to assess the behavioral features, especially with regard to hallucinations, of patients with average MMSE scores as low as 3 or 4. We evaluated the behavioral features of dementia patients based on the interview of the caregivers who could observe the patient behavior closely and did it with a point zero when still an evaluation was impossible. Consequently, the NPI subscale scores were low; therefore, we chose clinical assessments that could be investigated practically in common clinical settings. Therefore, significant behavioral problems were not commonly associated with advanced stages of AD dementia, and there was very little information about their clinical presentation [26,27]. The greatest limitation of this study was that it was a short-term study (16 weeks) with a relatively small sample size. Another limitation stems from the fact that it was a retrospective open-label, rather than a double-blind study; therefore, the possibility that bias was introduced into the results cannot be ruled out. Consequently, there are limits to the conclusions that can be drawn from this study. A double blind, randomized, controlled study of lamotrigine monotherapy, mood stabilizers, and placebo in AD patients with BPSD may be necessary in the future in order to clarify the efficacy of and the effects on doses of concomitant psychotropic drugs. Further, if possible, patients with mild or even prodromal AD (though with a lot of BPSD and hardly no concomitantly used drugs) need to be included.

## Conclusion

The results of this study suggested that while the administration

of lamotrigine or sodium valproate might be effective in patients with severe AD with BPSD, special attention is required when using sodium valproate on a daily basis.

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