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Sodium benzoate for the treatment of behavioral and psychological symptoms of dementia (BPSD): A randomized, double-blind, placebo-controlled, 6-week trial

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Abstract

Objective: Sodium benzoate, a D-amino acid oxidase (DAAO) inhibitor, improved cognitive function of early-phase Alzheimer's disease (AD) after 24-week treatment. This study examined benzoate treatment for behavioral and psychological symptoms of dementia (BPSD).

Methods: In a double-blind, 6-week trial, 97 patients with BPSD were randomized to receive placebo or benzoate (mean dose: 622.0 mg/day). The primary outcomes were ADAS-cog and BEHAVE-AD.

Results: Two treatments showed similar safety and primary and secondary outcomes.

Conclusions: Compared to antecedent 24-week, higher-dose treatment for early-phase AD, benzoate appeared ineffective in this 6-week trial. Longer-duration, higher-dose trials are warranted to clarify its efficacy for BPSD.

Keywords

Behavioral and psychological symptoms of dementia (BPSD), *N*-methyl-D-aspartate, D-amino acid oxidase (DAAO) inhibitor, sodium benzoate

Introduction

Behavioral and psychological symptoms of dementia (BPSD) develop in various types of dementia (Steinberg et al., 2008). No medication has been approved by the US FDA.

N-Methyl-D-aspartate receptor (NMDAR) over-activation leads to neurotoxicity; NMDAR hypofunction leads to neurodegeneration (Lin et al., 2014b). One avenue to activate NMDAR is by inhibiting D-amino acid oxidase (DAAO) (Huang et al., 2012). In a recent trial (Lin et al., 2014a), sodium benzoate, a pivotal DAAO inhibitor, improved cognitive function of patients with early-phase Alzheimer's disease (AD), without BPSD. This study testified to the efficacy and safety of benzoate for treatment of BPSD.

Methods

The trial was conducted in three medical centers in Taiwan in accordance with the Declaration of Helsinki, approved by institutional review boards (IRBs), and was registered (https://clinicaltrials.gov/ct2/show/NCT02103673).

Patients were evaluated by experienced research psychiatrists and neurologists. Written informed consent was obtained from all participants and guardians.

Study design

Inclusion criteria included NINCDS-ADRDA criteria for probable AD or NINDS-AIREN criteria for probable vascular dementia (VaD): ⩾50 years of age; post-stroke period ⩾3 months for VaD patients; MMSE scores of 5–26; CDR ⩾1; Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD) (Reisberg et al., 1987) ⩾2; literate with ⩾6 years of education or work experience; and being able to understand the purpose, procedures, risks and rights of the study.

For patients receiving anti-dementia medications, these needed to be maintained at optimal and stable doses for ⩾3 months prior to randomization and remained unchanged during the trial. For patients without anti-dementia medication, anti-dementia medication was forbidden during the trial. For patients receiving antipsychotics, these needed to be maintained at an optimal and stable dose for ⩾3 weeks prior to the study and remained unchanged during the trial.

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Table 1. Baseline demographic and clinical characteristics of sodium benzoate and placebo treatment groups.

	Treatment groups		*P* value
	Sodium benzoate ($n = 49$)	Placebo ($n = 48$)	
Demographics			
Gender, female, *n* (%)	30 (61.2)	32 (66.7)	0.67[a]
Age in years, mean (SD)	75.7 (7.1)	75.2 (8.4)	0.77[b]
Diagnosis, *n* (%)			0.55[a]
Alzheimer dementia	44 (89.8)	41 (85.4)	
Vascular dementia	5 (10.2)	7 (14.6)	
Age at illness onset in years, mean (SD)	74.1 (7.1)	72.7 (8.9)	0.38[b]
CDR at baseline, *n* (%)			0.70[a]
CDR 1	28 (57.1)	30 (62.5)	
CDR 2	16 (32.7)	12 (25.0)	
CDR 3	5 (10.2)	6 (12.5)	
Education in years, mean (SD)	4.6 (4.0)	4.8 (4.2)	0.81[c]
Body mass index (BMI), mean (SD)	22.7 (3.5)	24.2 (4.5)	0.07[b]
No. of patients using anti-dementia drugs			
Total	15	11	0.49[a]
Donepezil (dose, mean ± SD)	11 (10.0 ± 0.0)	6 (10.0 ± 0.0)	1.00[c]
Rivastigmine (dose, mean ± SD)	2 (7.5 ± 2.1)	4 (8.3 ± 1.5)	0.80[c]
Galantamine (dose, mean)	1 (16.0)	1 (16.0)	1.00[c]
Memantine (dose, mean)	1 (20.0)	0	0 NA
No. of patients using antipsychotics			
Total	25	22	0.69[a]
Quetiapine (dose, mean ± SD)	17 (46.3 ± 38.0)	11 (64.8 ± 59.4)	0.49[c]
Risperidone (dose, mean ± SD)	8 (0.9 ± 0.5)	8 (0.8 ± 0.6)	0.38[c]
Olanzapine (dose, mean ± SD)	2 (7.5 ± 3.5)	2 (7.5 ± 3.5)	1.00[c]
Aripiprazole (dose, mean ± SD)	1 (5.0)	1 (5.0)	1.00[c]
Sulpiride (dose, mean ± SD)	1 (800.0)	1 (100.0)	1.00[c]

[a]Fisher's exact test.
[b]Independent *t* test.
[c]Mann–Whitney *U* test, if the distribution was not normal.
CDR: Clinical Dementia Rating Scale; NA: not associated.

Exclusion criteria included: current substance abuse or history of substance dependence in the past 6 months; other major psychiatric diagnoses; serious medical or neurological illness; and inability to follow protocol.

Eligible patients were double-blindly randomized to 6-week placebo or benzoate treatment (dose range: 250–1500 mg/day). The dose was started at 250–500 mg/day (250 mg q.d. or b.i.d.), and was increased by 250–500 mg/day from week 3, and further increased by another 250–500 mg/day from week 5, if clinically indicated.

Assessments

The primary outcomes were the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) (Rosen et al., 1984) measured at baseline and endpoint, and BEHAVE-AD assessed bi-weekly.

The secondary outcomes included the Neuropsychiatric Inventory, Instrumental Activities of Daily Living and Zarit Caregiver Burden Interview assessed at baseline and endpoint, and Geriatric Depression Scale assessed bi-weekly.

Systemic side-effects were evaluated bi-weekly by physical and neurological examinations, and the UKU Side-effects Rating Scale. Laboratory tests including complete blood count (CBC) and biochemistry were performed at baseline and endpoint.

Data analysis

Under a medium effect (Cohen's $f = 0.33$), the sample size required was $\geqslant 74$ to achieve a group-difference of ADAS-cog score of 4, with SD estimated at 6.

Chi-square or Fisher's exact test was used for group differences of categorical variables, and Student's *t* test or Mann–Whitney U test for continuous variables.

Changes from baseline were assessed using the generalized estimating equation.

Effect sizes (Cohen's *d*) were used to determine between-group improvements for continuous variables. All *p* values were based on two-tailed tests with a significance level of 0.05.

Results

Among 121 screened patients, 97 (49 receiving benzoate, 48 placebo) were randomized. Eighty-four patients (43 benzoate, 41 placebo) completed the trial.

Table 2. Measures of ADAS-cog and BEHAVE-AD over the 6-week treatment using independent t test, Mann–Whitney U test or generalized estimating equations (GEE) method.

Scale	Sodium benzoate mean ± SD (*N*)	Placebo mean ± SD (*N*)				
Primary Outcomes						
ADAS-cog			**Cohen's *d***		**Test value**	***p* Value**
Baseline	30.3 ± 12.6 (48)	28.3 ± 12.6 (47)			0.761[a]	0.448
Endpoint	27.8 ± 13.3 (45)	25.8 ± 12.7 (41)			0.690[a]	0.492
Difference	−1.7 ± 6.9 (45)	−1.4 ± 5.8 (41)	0.04		−0.035‡	0.972
BEHAVE-AD			**Estimate[b]**	**SE**	***Z***	***p* Value**
Baseline	10.7 ± 8.0 (49)	11.1 ± 8.8 (48)				
Week 2	8.8 ± 7.8 (49)	9.5 ± 7.5 (48)	−1.6542	0.6879	−2.40	0.0162
Week 4	8.5 ± 7.0 (43)	6.8 ± 4.5 (42)	−3.6567	0.8302	−4.40	<0.0001
Week 6	7.1 ± 6.0 (41)	7.3 ± 6.0 (41)	−3.2889	1.0833	−3.04	0.0024
Endpoint	8.3 ± 7.7 (49)	8.5 ± 7.6 (48)	−2.6667	0.9688	−2.75	0.0059
Drug			−0.4537	1.7126	−0.26	0.7911
Week 2 × drug			−0.4274	0.9977	−0.43	0.6684
Week 4 × drug			1.8909	1.1765	1.61	0.1080
Week 6 × drug			0.1711	1.4364	0.12	0.9052
Endpoint × drug			0.0748	1.3394	0.06	0.9554

[a]Independent *t* test; ‡Mann–Whitney *U* test, if the distribution was not normal.
[b]Estimate is the coefficient of treatment-visit interaction term in the GEE method with treatment, visit and treatment–visit interaction as covariates; baseline value as the reference. No imputation for the incomplete data was used. An autoregressive AR(1) covariance matrix was fit to the within-patient repeated measures. *P* values were based on two-tailed tests.
In the "Estimate" column for BEHAVE-AD, the upper four rows are for the placebo group only, while the bottom five are for benzoate, placebo interaction terms.

Two treatment groups showed similar demographic and clinical characteristics and medication use at baseline (Table 1).

The mean benzoate doses at weeks 2, 4 and 6 were 341.8 ± 121.8 (SD), 528.4 ± 248.3 and 622.0 ± 340.6 mg/day, respectively. For both primary outcomes, the baseline scores and score changes after treatment were similar between the two treatment groups (Table 2). For all secondary outcomes, the baseline scores and score changes after treatment were also similar between the two groups.

Benzoate and placebo were well tolerated. One benzoate recipient reported mild and brief polyuria; one placebo receiver experienced moderate tension sensation. The laboratory parameters were all within the normal ranges and remained unchanged after treatment.

Discussion

Benzoate and placebo showed similar efficacy and safety in the current trial, while benzoate benefited early-phase AD (Lin et al., 2014a).

Several reasons may have contributed to the negative findings: the subjects in this trial were older than those previously studies (Lin et al., 2014a) (mean age: 75.5 vs. 70.2 years), had more severe dementia (CDR: 1.52 vs. 0.74; ADAS-cog: 29.3 vs. 15.3), and were less educated (4.7 vs. 6.7 years). Their course of benzoate treatment was shorter (6 vs. 24 weeks) and at a lower dose (622.0 vs. 716.7 mg/day). Higher-dose benzoate (2 g/day) can improve clozapine-resistant schizophrenia (Lin et al., 2018); therefore, the efficacy of higher-dose benzoate for BPSD requires further studies. Finally, benzoate does not alter CSF D-alanine levels in dogs (Popiolek et al., 2018), but its activity in human brains requires investigation.

Longer-duration, higher-dose clinical trials are necessary to determine the efficacy and safety of benzoate treatment for BPSD.

Author contributions

CHL and HYL designed the study, recruited the subjects, analyzed the data and wrote the manuscript. PKC recruited the subjects. SHW performed the statistical analysis.

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ClinicalTrials.gov: DAOIB for the treatment of cognitive function and behavioral and psychological symptoms of dementia; https://clinicaltrials.gov/ct2/show/NCT02103673.
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Declaration of conflicting interests

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