USE OF BENZOIC ACID SALT IN THE MANUFACTURE OFA COMPOSITION FOR PREVENTING OR TREATING DEMENTIA OR MILD COGNITIVE IMPAIRMENT

BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to a novelty treatment for dementia or mild cognitive impairment, and more specifically to a use of benzoic acid salt in the manufacture of a composition for preventing or treating dementia or mild cognitive impairment.

Description of Related Art

The prevalence of dementia in the elderly is increasing rapidly in the aging society, of which the deteriorating clinical course is a heavy burden to both the patients and their family. Early detection and intervention of Alzheimer's disease (referred to as "AD" hereinafter) is pivotal for the outcome (1). Mild cognitive impairment (referred to as "MCI" hereinafter), particularly amnestic MCI (referred to as "aMCI" hereinafter), is a risk factor and may be a prodromal stage of AD. The mainstream treatment for mild and moderate AD is acetylcholine esterase inhibitor (referred to as "AChEI" hereinafter). However, its efficacy and tolerability are unsatisfactory. Besides, AChEI does not show convincing efficacy for MCI (2-4), implying that other mechanism(s) may underlie the pathogenesis of MCI.

Although NMDAR activity is essential for cognitive function, its role in AD is still not fully understood. NMDAR over-activation by glutamate results in cell death. The excitotoxicity is one of the theories of AD, particularly in the late stage (54). Based on the hypothesis of NMDAR overactivation (7), NMDAR antagonists are developed for the treatment of AD. Memantine is an uncompetitive NMDAR partial antagonist of low affinity, which supposedly can block NMDAR overactivation by preventing excessive influx of calcium (8-10) and has been used for the treatment of moderate-severe AD. However, it has

limited efficacy at the early phase, including MCI and mild AD (12). NMDAR antagonists such as MK-801 also induce apoptosis and neurodegeneration in both *in vitro* and *in vivo* studies (13). Ketamine, another NMDAR antagonist, impaired spatial learning and verbal information ability in healthy humans in a double-blind, randomized, placebo-controlled trial (14). These findings raise concern that NMDA antagonist may impair cognition and memory in early AD.

Optimal NMDAR activation is pivotal for synaptic plasticity (15), memory and cognitive function (16). Attenuation of NMDAR-mediated neurotransmission can result in loss of neuronal plasticity and cognitive deficits in the aging brain, which may account for clinical deterioration and brain atrophy (17). Age-related decrease in the density of NMDAR in cerebral cortex and hippocampus was observed in humans (18). Earlier studies also found a decrease of glycine-dependent radioligand binding to the NMDAR in cerebral cortices from post-mortem and neurosurgical tissues in patients with AD (19, 20). D-cycloserine, a partial agonist at the glycine site of NMDAR, was reported in some clinical studies to activate the NMDAR in brains of AD patients (21) and improve their score on the cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-cog) (22).

The current study suggests that NMDAR enhancement be beneficial for early and mild dementia. There is an age-related decrease of glutamate content and synthesis in human cerebral cortex and hippocampus (18, 55), of which the most significant and consistent finding is decreased density of NMDAR in the elderly and in patients with AD (18). Lower levels of D-serine and higher levels of L-serine in the serum were also observed in patients with AD (56). Therefore, in addition to the cholinergic system, dysfunction of NMDA neurotransmission may also play an important role in the pathophysiology of AD.

There are several avenues to enhance NMDA activation. One of them is inhibiting the activity of D-amino acids oxidase (DAAO), a flavoenzyme of peroxisomes responsible for

degrading D-serine and D-alanine (24-26), and thereby raising levels of the D-amino acids which are the neurotransmitters for the coagonist site of the NMDAR. Recent data indicate that aging is related with reduced D-serine levels and thereby impaired NMDAR transmission, and D-serine treatment significantly decreases the extent of neuron death, suggesting that D-serine has neuroprotective effect against apoptosis (27). In addition, neural stem cells from postnatal mouse forebrain can synthesize D-serine and, thereby, stimulate proliferation and neuronal differentiation of the stem cells (28).

Enhancing NMDAR through DAAO inhibition may be a safe way to reduce nephrotoxicity of D-serine (29), particularly in the elderly population. Sodium benzoate is a DAAO inhibitor. Benzoic acid exists in many plants and is a natural constituent of food, including milk products (30). Benzoic acid and its salts including sodium benzoate, which are generally recognized as safe (GRAS), are also food preservatives widely used in manufacturing fruit jelly, buffer, soy-bean sauce, processed meat, etc. (31).

There are several other preclinical studies supporting the CNS effects of DAAO inhibitors, though the memory effect was not examined (32-34). N-methyl-D-aspartate receptor (NMDAR)-mediated neurotransmission is vital for learning and memory. Hypofunction of NMDAR has been reported to play a role in the pathophysiology of Alzheimer's disease (AD), particularly in the early phase. Enhancing NMDAR activation may be a novel treatment approach. One of the methods to enhance NMDAR activity is to raise the levels of NMDA coagonists by blocking their metabolism. Sodium benzoate is effective in NMDAR models such as pain relief (35,36) and partially prevented cell death in glial cells (37). CNS bioavailability of benzoate is good (38). To test whether that DAAO inhibition is beneficial for the early phase of dementia, the inventors conducted this trial to examine the efficacy and safety of sodium benzoate in patients with aMCI or mild AD.

SUMMARY OF THE INVENTION

On account of the supporting evidence, the inventor proposed that NMDA enhancing agents may be beneficial for the early declining process of AD and mild cognitive impairment due to their role in learning and memory as well as neurogenesis and neuroplasticity, and hence finished the present invention.

The present invention provides a use of benzoic acid salt in the manufacture of a composition for preventing or treating dementia or mild cognitive impairment.

In one aspect of the present application, the benzoic acid salt can be sodium benzoate, potassium benzoate or calcium benzoate, and preferably, the benzoic acid salt is sodium benzoate.

In another aspect of the present application, an effective amount of benzoic acid salt can be 200 milligrams (mg)/day to 2000 mg/day, preferably 500 mg/day to 900 mg/day, and more preferably 750 mg/day.

In a further aspect of the present application, an effective amount of sodium benzoate is 200 mg/day to 2000 mg/day, preferably 500 mg/day to 900 mg/day, and more preferably 750 mg/day.

In one aspect of the present application, the dementia includes early-phase dementia. In one embodiment of the present application, the early-phase dementia includes mild Alzheimer’s disease.

In one aspect of the present application, the mild cognitive impairment includes amnestic mild cognitive impairment.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a flow diagram and disposition for two treatment groups.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following illustrative embodiments are provided to illustrate the disclosure of the

present invention. These and other advantages and effects can be apparently understood by those in the art after reading the disclosure of this specification.

Term definition

As used herein, the term “dementia” refers to a group of symptoms affecting intellectual and social abilities severe enough to interfere with daily functioning, including memory loss, language problems, inability to learn or remember new information, etc (78). The term “early-phase dementia” refers to the condition of dementia patients whose CDR (Clinical Dementia Rating) score is not more than 1.

As used herein, the term “Alzheimer’s disease (AD)” refers to a kind of progressive mental deteriorative disease that can occur in middle or old age, due to generalized degeneration of the brain, and meet the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer’s Disease and Related Disorders Association criteria. Excessive glutamatergic neurotransmission, particularly through the N-methyl-D-aspartate receptor (NMDAR), leads to neurotoxicity (5,6), which is implicated in the pathophysiology of AD, especially in the late phase. The term “mild Alzheimer’s disease” refers to the condition of dementia patients whose CDR (Clinical Dementia Rating) score is 0.5 or 1.

As used herein, the term “mild cognitive impairment (MCI)” refers to a kind of mental deterioration with CDR (Clinical Dementia Rating) score less than 1. The term “amnestic mild cognitive impairment (aMCI)” refers to a kind of MCI in which memory is primarily affected.

As used herein, the term “Clinical Dementia Rating (CDR)” refers to a kind of evaluation system to evaluate the staging severity of dementia. The Clinical Dementia Rating is a five-point scale in which CDR-0 connotes no cognitive impairment, and then the remaining four points are for various stages of dementia: CDR within 0.5-1 = very mild to

mild dementia, CDR within 1-2 = mild to moderate, CDR within 2-3 = moderate to severe, CDR > 3 = severe.

Example

The present invention examined the efficacy and safety of sodium benzoate, a D-amino acid oxidase (DAAO) inhibitor, for the treatment of amnestic mild cognitive impairment (aMCI) and mild AD.

The inventors conducted a randomized, double-blind, placebo-controlled trial in four major medical centers in Taiwan. Sixty patients with aMCI or mild AD were treated with 250-750 mg/day of sodium benzoate or placebo for 24 weeks. Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog, the primary outcome) and global function (assessed by Clinician Interview Based Impression of Change plus Caregiver Input (CIBIC-plus)) were measured every eight weeks. Additional cognition composite was measured at baseline and endpoint.

Participants

Patients were recruited from the outpatient clinics at the Department of Psychiatry and Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Department of Psychiatry, China Medical University Hospital, Taichung, Department of Psychiatry, Taichung Veterans General Hospital, Taichung, and Department of Neurology, Lin-Shin Hospital, Taichung, which are four major medical centers in Taiwan. The study was approved by the institutional IRB at four sites and conducted in accordance with the current revision of the Declaration of Helsinki. Patients were evaluated by research psychiatrists and neurologists after a thorough medical and neurological workup.

Patients were enrolled into this study if they: 1) satisfied NINCDS-ADRDA (National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's

Disease and Related Disorders Association) (39) criteria for probable AD and had a Clinical Dementia Rating (CDR) (40) score of 1, or criteria for aMCI (41) of a presumably degenerative nature defined as subjective memory complaint corroborated by an informant and insufficient global cognitive and functional impairment to meet NINCDS-ADRDA criteria and had a CDR score of 0.5, 2) 50–90 years of age, 3) were physically healthy and had all laboratory assessments (including urine/blood routine, biochemical tests, and electrocardiograph) within normal limits, 4) had a Mini-Mental State Examination (MMSE) (42) score of 17-26, 5) had sufficient education to communicate effectively and were capable of completing the assessments of the study, and 6) agreed to participate in the study and provided informed consent. For patients who had already been on AChEI therapy, AChEI had to be continued for at least three months before enrollment. AChEI dose had to be kept unchanged during the study duration. For patients who had not yet been on AChEI therapy, AChEI or other anti-dementia medication was forbidden during the study duration.

Exclusion criteria included history of significant cerebrovascular disease; Hachinski Ischemic Score >4; major neurological, psychiatric or medical conditions other than AD; substance (including alcohol) abuse or dependence; delusion, hallucination or delirium symptoms; severe visual or hearing loss; and inability to follow protocol.

Study Design

All patients were randomly assigned to receive a 24-week treatment of sodium benzoate or placebo in a double-blind manner. Efficacy and safety were evaluated at baseline and at the ends of weeks 8, 16, and 24. Two hundred and fifty mg of sodium benzoate or placebo were packed with identical capsules provided in coded containers. The dose was started at 250-500 mg/day (250mg once or twice daily) in the first eight weeks, then increased by 250-500 mg/day from the 9^{th} week, and further increased by another 250-500 mg/day from the 17^{th}

week of the study if clinically indicated. The inventors decided to apply 250-750 mg/day, considering the older age of the subjects in the present study. Patients were randomized in a cluster of 6 subjects to receive sodium benzoate or placebo in a 1:1 ratio by an independent investigational pharmacist.

Patients, caregivers and investigators, except the investigational pharmacist, were all blind to the assignment. Patient's medical adherence and safety were closely monitored by caregivers and research physicians and pill-counting by the study staff.

Assessments

The primary outcome was the Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog) (43) measured at weeks 0, 8, 16, and 24. ADAS-cog is the most popular cognitive assessment instrument used in AD clinical trials. It consists of 11 tasks, including word recall, naming, commands, constructional praxis, ideational praxis, orientation, word recognition, instructions remembering, spoken language ability, word-finding difficulty and comprehension. Its scores range from 0 (best) to 70 (worst).

The secondary outcome measurements included the Clinician's Interview-Based Impression of Change plus Caregiver Input (CIBIC-plus) (44) measured at weeks 8, 16 and 24, and the additional cognition composite measured at baseline and endpoint (was measured at the end of each patent's additional cognition composite measurement).

CIBIC-plus is a global assessment of change based on a comprehensive, semi-structured interview which includes caregiver-supplied information. It is a 7-point rating scale ranging from 1-7, where 1 represents markedly improved; 4, no change; and 7, markedly worse.

The additional cognition composite was calculated by the average of the T scores of speed of processing (Category Fluency), working memory (WMS-III, Spatial Span) (45) and

verbal learning and memory tests (WMS-III, Word Listing) (45). The raw score of speed of processing, working memory and verbal learning and memory tests was standardized to a T score with a mean of 50 and a standard deviation of 10 for making each test comparative. The additional cognition composite was applied in combination with ADAS-cog to make the cognitive assessment more thorough. Decrease in processing speed has been found to be associated with aging (46, 47). Working memory (48) and verbal learning/memory (49) also decline in patients with AD.

Systemic side effects of treatments were evaluated by means of physical and neurological examinations, laboratory tests including CBC and biochemistry and reviewed by applying the Udvalg for Kliniske Undersogelser (UKU) Side-effects Rating Scale (50) at baseline, week 8, 16 and 24.

Clinical ratings were performed by the research psychiatrists and neurologists who were trained and experienced in the rating scales. Inter-rater reliability was analyzed with the ANOVA test. Only raters reaching the intra-class correlation coefficients of ≥ 0.90 during pre-study training were allowed to rate the study patients. To maintain high inter-rater reliability and to prevent rater drift, raters met at least once a quarter for training and reliability re-testing. To minimize inter-rater variability, each individual patient was assessed by the same research psychiatrist or neurologist throughout the trial.

Data analysis

Chi-square test (or Fisher's exact test) was used to compare differences of categorical variables and Student's two-sample *t*-test (or Mann-Whitney U test if the distribution was not normal) for continuous variables between two treatment groups. Mean changes from baseline in repeated-measure assessments (ADAS-cog) were assessed using the generalized estimating equation (GEE) method with treatment, visit and treatment-visit interaction as fixed effects

and intercept as the only random effect; baseline value as the covariance. The GEE analyses were performed using the SAS/STAT (SAS Institute, Cary, North Carolina) “PROC GENMOD” procedure with AR (autoregressive)(*1*) working correlation structure with the marginal model instead of the mixed effect model. Therapeutic effect sizes (Cohen's *d*) were used to determine the magnitude of improvement for the continuous variables (51) resulting from sodium benzoate treatment compared with placebo.

Finally, all of the 60 randomized patients completed at least one follow-up, and 50 (90 %) of them completed the 24-week trial (as shown in Figure 1). No imputation for the incomplete data was used for the GEE analysis.

There were no baseline scores for the CIBIC-plus because this was scored as a judgment of change from baseline. Differences in CIBIC-plus scores at week 8, 16, 24 and endpoint between groups were assessed by Student’s two-sample *t*-test (or Mann-Whitney U test if the distribution was not normal).

Fisher’s exact test was used to compare differences in the dropout rates between the two groups. Cohen’s *w* was applied for determining the effect size of categorical variables (52). All data were analyzed by IBM SPSS Statistics (version 18.0; SPSS Inc.) or SAS version 9.3. All p values for clinical measures were based on two-tailed tests with a significance level of 0.05.

Results

Sixty patients were eligible and randomized (as shown in Figure 1). Demographic data, education level, age at illness onset, illness duration, CDR, body mass index (BMI) and AChEI use at baseline were similar between the sodium benzoate group (N = 30) and the placebo group (N = 30) ($p > 0.05$) (as shown in Table 1). AChEI doses were within the therapeutic range and similar between two groups (as shown in Table 1). Mean dose of

sodium benzoate at weeks 8, 16, and 24 were 275.0 ± 76.3, 525.0 ± 100.6, and 716.7 ± 182.6 mg/day, respectively.

Table 1. Baseline Demographic Characteristics of the Placebo or Sodium Benzoate Treatment Group

	Treatment Groups		
	Benzoate (n = 30)	Placebo (n = 30)	p
Demographic Data			
Female, n (%)	18 (60.0)	19 (63.3)	1.0[a]
Male, n (%)	12 (40.0)	11 (36.7)	1.0
Age, yrs, mean (SD)	70.7 (7.9)	69.7 (9.0)	0.64[b]
Age at illness onset, yrs, mean (SD)	69.8 (7.1)	68.5 (8.9)	0.54[b]
Illness duration, months, mean (SD)	14.2 (15.6)	13.6 (17.9)	0.47[c]
CDR at baseline, n (%)			1.0[a]
CDR 0.5	15 (50.0)	16 (53.3)	
CDR 1	15 (50.0)	14 (46.7)	
Education, yrs, mean (SD)	5.9 (4.7)	7.5 (5.2)	0.36[c]
BMI, mean (SD)	24.6 (4.1)	23.9 (3.4)	0.51[b]
Patients using AChEIs, n			
Total	9	9	1.0[a]
Donepezil (dose, mean ± SD)	7 (7.9 ± 2.7)	5 (8.0 ± 2.7)	1.0[c]
Rivastigmine (dose, mean ± SD)	0 (0.0 ± 0.0)	3 (7.5 ± 2.6)	NA
Galantamine (dose, mean ± SD)	2 (16.0 ± 0.0)	1 (16.0 ± 0.0)	1.0[c]

AChEI, acetylcholine esterase inhibitor; BMI, body mass index; CDR, Clinical Dementia Rating; NA, not associated.

[a]Fisher's exact test.

[b]Independent t test.

[c]Mann-Whitney U test

The mean ± SD scores for both primary and secondary outcomes, including ADAS-cog, additional cognition composite and CIBIC-plus, of the two groups of patients are shown in Table 2. At week 0 (baseline), there were no significant differences between the two groups in ADAS-cog and additional cognition composite (p = 0.75 and 0.27, respectively).

Table 2. Mean ± SD Scores of Both Primary and Secondary Outcomes

Scale	Benzoate Mean ± SD (n)	Placebo Mean ± SD (n)	Estimate[a]	SEM	Z	p
Primary Outcome						
ADAS-cog						
Baseline	15.6 ± 7.6 (30)	15.0 ± 7.3 (30)				
Week 8	11.6 ± 6.5 (30)	11.7 ± 8.5 (30)	-2.8819	0.9592	-3.00	0.0027
Week 16	9.8 ± 6.2 (29)	12.3 ± 9.1 (26)	-1.7582	1.2270	-1.34	0.1519
Week 24	9.7 ± 6.4 (30)	11.3 ± 9.2 (25)	-2.7456	1.1845	-2.32	0.0205
Endpoint	9.6 ± 6.2 (30)	12.4 ± 9.1 (30)	-1.8067	1.1255	-1.61	0.1084
Drug			-2.1860	2.2676	-0.96	0.3351
Week 8 x drug			-1.0236	1.1491	-0.89	0.3730
Week 16 x drug			-4.1835	1.3608	-3.07	0.0021
Week 24 x drug			-3.3543	1.3294	-2.52	0.0116
Endpoint x drug			-3.9648	1.3424	-2.95	0.0031

Secondary Outcome					
Additional cognition composite (*T* score)			Cohen's *d*	*t*	
Baseline	48.9 ± 6.6 (26)	51.2 ± 8.4 (27)		-1.111	0.272[b]
Endpoint	50.4 ± 6.6 (26)	49.6 ± 8.7 (27)		0.404	0.688[b]
Difference	1.5 ± 3.1 (26)	-1.6 ± 4.8 (27)	0.7826	2.837	0.007[b]
CIBIC-plus			Cohen's *d*	*Z*	*p*
Week 8	3.4 ± 0.5 (30)	3.5 ± 0.6 (30)	0.2441	-0.869	0.385[c]
Week 16	3.3 ± 0.6 (30)	3.7 ± 0.7 (26)	0.6637	-2.445	0.015[c]
Week 24	3.2 ± 0.7 (28)	3.7 ± 0.7 (27)	0.6973	-2.416	0.016[c]
Endpoint	3.2 ± 0.7 (30)	3.7 ± 0.8 (30)	0.7290	-2.520	0.012[c]

Results of measures of Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), additional cognitive tests, and Clinician Interview Based Impression of Change plus Caregiver Input (CIBIC-plus) over the 24-week treatment with generalized estimating equations (GEE) method. Additional cognition composite: the composite test score of speed of processing, working memory, and verbal learning, and memory.

[a]Estimate is the coefficient of treatment–visit interaction term in the GEE method multiple linear regression model. A first-order autoregressive covariance matrix was fit to the within-patient repeated measures. The p values were based on two-tailed tests.

[b]Independent t test.

[c]Mann-Whitney U test was used, because the distribution of CIBIC-plus score was not normal.

For the primary outcome, sodium benzoate produced greater improvement in ADAS-cog score than the placebo therapy throughout the study (mean differences from baseline were 3.8,

5.4, 5.9 and 5.9 in the benzoate group, and 2.4, 1.7, 2.7 and 1.7 in the placebo group, at weeks 8, 16, 24 and endpoint; p = 0.3730, 0.0021, 0.0116 and 0.0031, respectively), with effect size of 0.86 at the end of the study (as shown in Table 2). The results were similar when the baseline ADAS-cog score was controlled in the GEE model (as shown in Table S1).

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Table S1. Results of measures of ADAS-cog over the 24-week Treatment using generalized estimating equations (GEE) method adjusted for the baseline effect

Scale	**Benzoate**	**Placebo**	**Estimate***	**SE**	***Z***	***P* Value**
	Mean ± SD (*n*)	**Mean ± SD (*n*)**				
ADAS-cog						
Baseline	15.6 ± 7.6 (30)	15.0 ± 7.3 (30)				
Week 8	11.6 ± 6.5 (30)	11.7 ± 8.5 (30)	-2.6070	0.8801	-2.96	**0.0031**
Week 16	9.8 ± 6.2 (29)	12.3 ± 9.1 (26)	-1.3145	1.0526	-1.25	0.2118
Week 24	9.7 ± 6.4 (28)	11.3 ± 9.2 (25)	-2.0495	0.9114	-2.25	**0.0245**
Endpoint	9.6 ± 6.2 (30)	12.4 ± 9.1 (30)	-1.9247	0.9507	-2.02	**0.0429**
Drug			0.5135	0.3616	1.42	0.1555
Week 8 x drug			-1.2397	1.1366	-1.09	0.2754
Week 16 x drug			-4.4638	1.2601	-3.54	**0.0004**
Week 24 x drug			-3.7523	1.2379	-3.03	**0.0024**
Endpoint x drug			-3.6255	1.2278	-2.95	**0.0031**

***** Estimate is the coefficient of treatment-visit interaction term in the GEE method's multiple linear regression model. An autoregressive AR(1) covariance matrix was fit to the within-patient repeated measures. *P* values

were based on two-tailed tests.

ADAS-cog: Alzheimer's disease assessment scale-cognitive subscale.

Bolded *p* values indicate significance.

For the secondary outcomes, sodium benzoate was better than placebo in the additional cognition composite at endpoint (p = 0.007, effect size = 0.78). Benzoate treatment also produced greater improvement in CIBIC-plus score than placebo therapy at week 16 (p = 0.015), week 24 (p = 0.016) and endpoint (p = 0.012, effect size = 0.73 at endpoint) (as shown in Table 2).

The dropout rate (3.3%) of sodium benzoate group tended to be lower than that (16.7%) of the placebo group, yet insignificantly (p = 0.195).

For subgroup analysis, we further examined efficacy of sodium benzoate vs. placebo in CDR 0.5 and CDR 1 subgroups. For ADAS-cog, sodium benzoate produced greater improvement than placebo therapy at week 16, 24 and endpoint (p = 0.0151, 0.0387 and 0.0092, respectively) in the CDR 1 subgroup. However, sodium benzoate was not superior to the placebo therapy in the CDR 0.5 subgroup throughout the study ($p > 0.05$) (as shown in Table 3).

Although ADAS-cog is widely used in AD clinical trials, it may be less sensitive for MCI (67). One of the strategies to improve the detection of responsiveness for MCI is to add additional cognitive tests. People with MCI have been found to be impaired in neuropsychological functions (68) such as speed of processing (69), working memory (70) and verbal learning and memory (71). In the aMCI subgroup of the present invention, sodium benzoate showed borderline significance in improving the additional cognition composite, consisting of speed of processing, working memory, and verbal learning/memory, but not in ADAS-cog score. Our result echoes the suggestion that additional neuropsychological tests

which are more sensitive to subtle deficits should also be applied in the trials for MCI.

Table 3. Results of Measures of ADAS-cog Over 24-Week Treatment With GEE Method in Subgroups

Scale	Benzoate Mean ± SD (n)	Placebo Mean ± SD (n)	Estimate[a]	SEM	*Z*	*p*
CDR 0.5						
Baseline	13.8 ± 6.1 (15)	11.9 ± 5.4 (16)	Reference			0.3560
Week 8 x drug	10.4 ± 6.0 (15)	8.3 ± 4.0 (16)	0.3213	0.9690	0.33	0.7402
Week 16 x drug	9.1 ± 6.1 (15)	10.2 ± 5.6 (15)	-3.2694	1.9222	-1.70	0.0890
Week 24 x drug	9.5 ± 6.2 (14)	8.7 ± 5.0 (14)	-1.8480	1.7834	-1.04	0.3001
Endpoint x drug	9.2 ± 6.1 (15)	9.8 ± 5.9 (16)	-2.3444	1.9664	-1.19	0.2332
CDR 1						
Baseline	17.1 ± 8.6 (15)	16.7 ± 8.2 (14)	Reference			0.8910
Week 8 x drug	13.0 ± 7.1 (15)	15.6 ± 10.6 (14)	-2.5727	2.0872	-1.23	0.2177
Week 16 x drug	10.6 ± 6.4 (14)	15.2 ± 12.2 (11)	-55.0788	2.0897	-2.43	0.0151
Week 24 x drug	9.9 ± 6.8 (14)	14.5 ± 12.3 (11)	-4.6262	2.2375	-2.07	0.0387
Endpoint x drug	10.0 ± 6.6 (15)	15.4 ± 11.3 (14)	-5.4755	2.1031	-2.60	0.0092

Abbreviations are the same as those in Tables 1 and 2.

[a]Estimate is the coefficient of treatment–visit interaction term in the GEE method multiple linear regression model. A first-order autoregressive covariance matrix was fit to the within-patient repeated measures. The p values were based on two-tailed tests.

Sodium benzoate showed better efficacy in the CDR 1 subgroup (p = 0.041) and borderline significance in the CDR 0.5 subgroup (p = 0.063) in improving the additional

cognition composite (as shown in Table 4). For CIBIC-plus, sodium benzoate produced greater improvement than placebo therapy at week 24 and endpoint (p = 0.040 and 0.018, respectively) in the CDR 1 subgroup, but not in the CDR 0.5 subgroup (as shown in Table 5).

Sodium benzoate also did not improve CIBIC-plus score in the aMCI subgroup. A possible explanation is a ceiling effect that functional impairment is minimal in the MCI individuals, thereby restricting the space for further improvement.

Table 4. Results of Measures of Additional Cognition Composite Over 24-Week Treatment with Independent t Test in Subgroups

	Benzoate	Placebo			
Scale	Mean ± SD (n)	Mean ± SD (n)	Cohen's d	t	p
CDR 0.5					
Baseline	49.0 ± 6.9 (14)	52.8 ± 7.6 (15)		-1.395	.174
Endpoint	50.5 ± 7.1 (14)	50.8 ± 8.5 (15)		-.108	.915
Difference	1.5 ± 3.5 (14)	-1.9 ± 5.8 (15)	.7098	1.939	.063
CDR 1					
Baseline	48.8 ± 6.6 (12)	49.3 ± 9.3 (12)		-.150	.882
Endpoint	50.3 ± 6.1 (12)	48.0 ± 9.0 (12)		.742	.466
Difference	1.6 ± 2.8 (12)	-1.3 ± 3.5 (12)	.9150	2.176	.041

The *p* values were based on two-tailed tests. Additional cognition composite, the composite test score of speed of processing, working memory, and verbal learning and memory. CDR, Clinical Dementia Rating.

Table 5. Results of Clinical Measures of CIBIC-Plus Over 24-Week Treatment with Mann-Whitney U Test in Subgroups

	Benzoate	Placebo			
Scale	Mean ± SD (*n*)	Mean ± SD (*n*)	Cohen's *d*	*Z*	*p*
CDR 0.5					
Week 8	3.5 ± .5 (15)	3.4 ± .5 (16)	.1771	-.508	.611
Week 16	3.3 ± .5 (15)	3.7 ± .8 (15)	-.6042	-1.720	.085
Week 24	3.3 ± .5 (14)	3.6 ± .6 (16)	-.4867	-1.260	.208
Endpoint	3.3 ± .5 (15)	3.6 ± .6 (16)	-.4086	-1.029	.303
CDR 1					
Week 8	3.3 ± .5 (15)	3.6 ± .6 (14)	-.6697	-1.719	.086
Week 16	3.2 ± .7 (15)	3.6 ± .5 (11)	-.7374	-1.678	.093
Week 24	3.1 ± .8 (14)	3.8 ± .9 (11)	-.8805	-2.052	.040
Endpoint	3.1 ± .8 (15)	3.9 ± .9 (14)	-.9494	-2.370	.018

The *p* values were based on two-tailed tests. Mann-Whitney *U* test was used because the distribution of CIBIC-plus score was not normal.

CDR, Clinical Dementia Rating;

CIBIC-plus, Clinician Interview Based Impression of Change plus Caregiver Input.

It is critical to identify and treat AD as early as possible, potentially to arrest its progression (53). The present invention is the first to apply a DAAO inhibitor, sodium benzoate herein, as a novel treatment for the early stage of cognitive decline. The result showed that sodium benzoate had better efficacy than placebo in improving ADAS-cog score, additional cognition composite (consisting of speed of processing, working memory, verbal learning and memory) and global function in all subjects as a whole. Subgroup comparisons found that sodium benzoate was beneficial for all outcome measures among patients with mild AD. In the aMCI subgroup, sodium benzoate showed borderline significance in improving the cognition composite. Moreover, sodium benzoate also demonstrated favorable safety profiles.

As to the dosing strategy, sodium benzoate provided better efficacy than placebo at week 16 and week 24, with the mean dose of 525 mg/day and 716 mg/day respectively, possibly implying that sodium benzoate at 500-750 mg/day is more effective than 250 mg/day. Another possibility is that longer sodium benzoate treatment duration yields better treatment response.

AChEIs are commonly used for the treatment of AD (57, 58), but are not recommended for the treatment of MCI due to weak beneficial effects and risk of side effects (59, 60). The consensus statement from the British Association for Psychopharmacology concludes that neither AChEIs nor memantine is effective in treating MCI (61). Other compounds commonly used for the treatment of MCI, such as vitamin E (62), folic acid (63), omega-3

fatty acid (64), piracetam (65) and Ginkgo biloba (66), also failed to show convincing evidence for a cognitive enhancing effect. Sodium benzoate is generally safe and its efficacy for aMCI reached a trend of improvement in the current small-sized study.

Very high levels of DAAO are detected in the cerebellum of adult brain whereas the activity of DAAO is low in the forebrain such as prefrontal cortex and hippocampus despite robust expression (75, 76). The cellular localization and function of DAAO are likely different between forebrain and cerebellum: it is glial in the cerebellum, but mainly neuronal in the cerebral cortex. However, the effect of DAAO inhibitors on forebrain D-serine level is inconsistent. Most DAAO inhibitors can, while some inhibitors may not cause a measurable increase in D-serine in the forebrain as observed in the cerebellum (77). Nevertheless, cerebellum is involved in cognition. Sodium benzoate may exert its procognitive effects by not only cerebral but also cerebellar mechanism.

The present invention suggests that sodium benzoate, a DAAO inhibitor, is beneficial for cognitive and overall function in patients with early-phase AD and potentially beneficial for aMCI. The use of sodium benzoate for early AD and aMCI will bring hope for the growing aging population with cognitive decline. The results of the present application suggest that benzoate treatment for early-phase dementia may be due to activation of neurogenesis and anti-apoptosis.

Adverse Effects

Both sodium benzoate and placebo were well tolerated. Only one patient in the placebo group reported dizziness at week 16. The side effect was mild and not warranting medical treatment. There was no reported side effect in the sodium benzoate group assessed by the UKU Side-effects Rating Scale at all visits. No dropout was due to side effect.

The routine blood cell count and chemistry were all within the normal ranges and remained unchanged after treatment (data not shown).

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The foregoing descriptions of the detailed embodiments are only illustrated to disclose the principle and functions of the present invention and do not restrict the scope of the present invention. It should be understood to those in the art that all modifications and variations according to the spirit and principle in the disclosure of the present invention should fall within the scope of the appended claims. It is intended that the specification and examples are considered as exemplary only, with a true scope of the invention being indicated by the following claims.

The references listed below in the application are each incorporated by reference as if they were incorporated individually.

1. Budd D, Burns LC, Guo Z, L'Italien G, Lapuerta P (2011): Impact of early intervention and disease modification in patients with predementia Alzheimer's disease: a Markov model simulation. *ClinicoEconomics and outcomes research : CEOR*. 3:189-195.

2. Loy C, Schneider L (2006): Galantamine for Alzheimer's disease and mild cognitive impairment. *Cochrane Database Syst Rev*.CD001747.

3. Raschetti R, Albanese E, Vanacore N, Maggini M (2007): Cholinesterase inhibitors in mild cognitive impairment: a systematic review of randomised trials. *PLoS medicine*. 4:e338.

4. Birks J, Flicker L (2006): Donepezil for mild cognitive impairment. *Cochrane Database Syst Rev*.CD006104.

5. Lipton SA, Rosenberg PA (1994): Excitatory amino acids as a final common pathway for neurologic disorders. *N Engl J Med*. 330:613-622.

6. Kalia LV, Kalia SK, Salter MW (2008): NMDA receptors in clinical neurology: excitatory times ahead. *Lancet Neurol*. 7:742-755.

7. Choi DW (1992): Excitotoxic cell death. *Journal of neurobiology*. 23:1261-1276.

8. Scarpini E, Scheltens P, Feldman H (2003): Treatment of Alzheimer's disease: current status and new perspectives. *Lancet neurology*. 2:539-547.

9. Gardoni F, Mauceri D, Malinverno M, Polli F, Costa C, Tozzi A, et al. (2009): Decreased NR2B subunit synaptic levels cause impaired long-term potentiation but not long-term depression. *J Neurosci*. 29:669-677.

10. Pallàs M, Camins A (2006): Molecular and Biochemical Features in Alzheimer disease. *Curr Pharm Des*. 12:4389-4408.

11. Reisberg B, Doody R, Stöffler B, Schmitt F, Ferris S, Möbius HJ (2003): Memantine in Moderate-to-Severe Alzheimer Disease. *N Engl J Med*. 348:1333-1341.

12. Schneider LS, Dagerman KS, Higgins JP, McShane R (2011): Lack of evidence for the efficacy of memantine in mild Alzheimer disease. *Arch Neurol*. 68:991-998.

13. Yoon WJ, Won SJ, Ryu BR, Gwag BJ (2003): Blockade of ionotropic glutamate receptors produces neuronal apoptosis through the Bax-cytochrome C-caspase pathway: the causative role of Ca2+ deficiency. *J Neurochem*. 85:525-533.

14. Rowland LM, Astur RS, Jung RE, Bustillo JR, Lauriello J, Yeo RA (2005): Selective cognitive impairments associated with NMDA receptor blockade in humans. *Neuropsychopharmacology*. 30:633-639.

15. Mattson MP (2008): Glutamate and neurotrophic factors in neuronal plasticity and disease. *Ann N Y Acad Sci*. 1144:97-112.

16. Tilleux S, Hermans E (2007): Neuroinflammation and regulation of glial glutamate uptake in neurological disorders. *J Neurosci Res*. 85:2059-2070.

17. Olney JW, Farber NB (1995): Glutamate receptor dysfunction and schizophrenia. *Arch*

Gen Psychiatry. 52:998-1007.

18. Segovia G, Porras A, Del Arco A, Mora F (2001): Glutamatergic neurotransmission in aging: a critical perspective. *Mech Ageing Dev*. 122:1-29.

19. Procter AW, Stirling JM, Stratmann GC, Cross AJ, Bowen DM (1989): Loss of glycine-dependent radioligand binding to the N-methyl-D-aspartate-phencyclidine receptor complex in patients with Alzheimer's disease. *Neurosci Lett*. 101:62-66.

20. Procter AW, Wong EH, Stratmann GC, Lowe SL, Bowen DM (1989): Reduced glycine stimulation of [3H]MK-801 binding in Alzheimer's disease. *J Neurochem*. 53:698-704.

21. Chessell IP, Procter AW, Francis PT, Bowen DM (1991): D-cycloserine, a putative cognitive enhancer, facilitates activation of the N-methyl-D-aspartate receptor-ionophore complex in Alzheimer brain. *Brain Res*. 565:345-348.

22. Tsai GE, Falk WE, Gunther J, Coyle JT (1999): Improved cognition in Alzheimer's disease with short-term D-cycloserine treatment. *Am J Psychiatry*. 156:467-469.

23. Lane HY, Lin CH, Green MF, Hellemann G, Huang CC, Chen PW, et al. (2013): A Randomized, Double-Blind, Placebo-Controlled Add-on Treatment of Benzoate, a D-Amino Acid Oxidase Inhibitor, for Schizophrenia. *JAMA Psychiatry. 70: 1267-1275*.

24. Fukui K, Miyake Y (1992): Molecular cloning and chromosomal localization of a human gene encoding D-amino-acid oxidase. *The Journal of biological chemistry*. 267:18631-18638.

25. Vanoni MA, Cosma A, Mazzeo D, Mattevi A, Todone F, Curti B (1997): Limited proteolysis and X-ray crystallography reveal the origin of substrate specificity and of the rate-limiting product release during oxidation of D-amino acids catalyzed by mammalian D-amino acid oxidase. *Biochemistry*. 36:5624-5632.

26. Sasabe J, Miyoshi Y, Suzuki M, Mita M, Konno R, Matsuoka M, et al. (2012): D-amino acid oxidase controls motoneuron degeneration through D-serine. *Proc Natl Acad Sci U S A*.

109:627-632.

27. Esposito S, Pristera A, Maresca G, Cavallaro S, Felsani A, Florenzano F, et al. (2012): Contribution of serine racemase/d-serine pathway to neuronal apoptosis. *Aging Cell* 11:588-598.

28. Huang X, Kong H, Tang M, Lu M, Ding JH, Hu G (2012): D-Serine regulates proliferation and neuronal differentiation of neural stem cells from postnatal mouse forebrain. *CNS Neurosci Ther*. 18:4-13.

29. Smith SM, Uslaner JM, Hutson PH (2010): The Therapeutic Potential of D-Amino Acid Oxidase (DAAO) Inhibitors. *The open medicinal chemistry journal*. 4:3-9.

30. WHO-Concise International Chemical Assessment Document No.26. WHO G, 2000 *http://www.inchem.org/documents/cicads/cicads/cicad26.htm*.

31. World Health Organization (2000): Concise International Chemical Assessment. Document No. 26. Geneva: World Health Organization. Available at: http://www.who.int/ipcs/publications/cicad/cicad26_rev_1.pdf..

32. Smith SM, Uslaner JM, Yao L, Mullins CM, Surles NO, Huszar SL, et al. (2009): The behavioral and neurochemical effects of a novel D-amino acid oxidase inhibitor compound 8 [4H-thieno [3,2-b]pyrrole-5-carboxylic acid] and D-serine. *The Journal of pharmacology and experimental therapeutics*. 328:921-930.

33. Adage T, Trillat AC, Quattropani A, Perrin D, Cavarec L, Shaw J, et al. (2008): In vitro and in vivo pharmacological profile of AS057278, a selective d-amino acid oxidase inhibitor with potential anti-psychotic properties. *Eur Neuropsychopharmacol*. 18:200-214.

34. Hashimoto K, Fujita Y, Horio M, Kunitachi S, Iyo M, Ferraris D, et al. (2009): Co-administration of a D-amino acid oxidase inhibitor potentiates the efficacy of D-serine in attenuating prepulse inhibition deficits after administration of dizocilpine. *Biol Psychiatry*. 65:1103-1106.

35. Zhao WJ, Gao ZY, Wei H, Nie HZ, Zhao Q, Zhou XJ, et al. (2010): Spinal D-amino acid oxidase contributes to neuropathic pain in rats. *The Journal of pharmacology and experimental therapeutics*. 332:248-254.

36. Gong N, Gao ZY, Wang YC, Li XY, Huang JL, Hashimoto K, et al. (2011): A series of D-amino acid oxidase inhibitors specifically prevents and reverses formalin-induced tonic pain in rats. *The Journal of pharmacology and experimental therapeutics*. 336:282-293.

37. Park HK, Shishido Y, Ichise-Shishido S, Kawazoe T, Ono K, Iwana S, et al. (2006): Potential role for astroglial D-amino acid oxidase in extracellular D-serine metabolism and cytotoxicity. *Journal of biochemistry*. 139:295-304.

38. Batshaw ML, Hyman SL, Coyle JT, Robinson MB, Qureshi IA, Mellits ED, et al. (1988): Effect of sodium benzoate and sodium phenylacetate on brain serotonin turnover in the ornithine transcarbamylase-deficient sparse-fur mouse. *Pediatric research*. 23:368-374.

39. McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM (1984): Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology*. 34:939-944.

40. Morris JC (1993): The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology*. 43:2412-2414.

41. Lu PH, Edland SD, Teng E, Tingus K, Petersen RC, Cummings JL (2009): Donepezil delays progression to AD in MCI subjects with depressive symptoms. *Neurology*. 72:2115-2121.

42. Folstein MF, Folstein SE, McHugh PR (1975): "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *Journal of psychiatric research*. 12:189-198.

43. Rosen WG, Mohs RC, Davis KL (1984): A new rating scale for Alzheimer's disease. *Am*

J Psychiatry. 141:1356-1364.

44. Schneider LS, Olin JT, Doody RS, Clark CM, Morris JC, Reisberg B, et al. (1997): Validity and reliability of the Alzheimer's Disease Cooperative Study-Clinical Global Impression of Change. The Alzheimer's Disease Cooperative Study. *Alzheimer Dis Assoc Disord*. 11 Suppl 2:S22-32.

45. Wechsler D (1997): Wechsler Memory Scale, 3rd ed. *Psychological Association, San Antonio, TX* :Psychological Association.

46. Salthouse TA (1996): The processing-speed theory of adult age differences in cognition. *Psychological review*. 103:403-428.

47. Habekost T, Vogel A, Rostrup E, Bundesen C, Kyllingsbaek S, Garde E, et al. (2013): Visual processing speed in old age. *Scandinavian journal of psychology*. 54:89-94.

48. Carlesimo GA, Mauri M, Graceffa AM, Fadda L, Loasses A, Lorusso S, et al. (1998): Memory performances in young, elderly, and very old healthy individuals versus patients with Alzheimer's disease: evidence for discontinuity between normal and pathological aging. *Journal of clinical and experimental neuropsychology*. 20:14-29.

49. Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M (2001): Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. *Arch Gen Psychiatry*. 58:853-858.

50. Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K (1987): The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. *Acta psychiatrica Scandinavica Supplementum*. 334:1-100.

51. Rosenthal R RR (1991): Essentials of behavioral research: Methods and data analysis. 2nd ed. New York: McGraw Hill.

52. Cunningham JB M-GE (2007): Power, effect and sample size using GPower: practical

issues for researchers and members of research ethics committees. Evidence Based Midwifery 5:132-136.

53. Sperling RA, Aisen PS, Beckett LA, Bennett DA, Craft S, Fagan AM, et al. (2011): Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's & dementia : the journal of the Alzheimer's Association*. 7:280-292.

54. Huang YJ, Lin CH, Lane HY, Tsai GE (2012): NMDA Neurotransmission Dysfunction in Behavioral and Psychological Symptoms of Alzheimer's Disease. *Current neuropharmacology*. 10:272-285.

55. Riederer P, Hoyer S (2006): From benefit to damage. Glutamate and advanced glycation end products in Alzheimer brain. *J Neural Transm*. 113:1671-1677.

56. Hashimoto K, Fukushima T, Shimizu E, Okada S, Komatsu N, Okamura N, et al. (2004): Possible role of D-serine in the pathophysiology of Alzheimer's disease. *Prog Neuropsychopharmacol Biol Psychiatry*. 28:385-388.

57. Birks J (2006): Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database Syst Rev*.CD005593.

58. Burns A, O'Brien J, Auriacombe S, Ballard C, Broich K, Bullock R, et al. (2006): Clinical practice with anti-dementia drugs: a consensus statement from British Association for Psychopharmacology. *J Psychopharmacol*. 20:732-755.

59. Fellgiebel A (2007): [Alzheimer drugs for mild cognitive impairment]. *Neuropsychiatrie : Klinik, Diagnostik, Therapie und Rehabilitation : Organ der Gesellschaft Osterreichischer Nervenarzte und Psychiater*. 21:230-233.

60. Russ TC, Morling JR (2012): Cholinesterase inhibitors for mild cognitive impairment. *Cochrane Database Syst Rev*. 9:CD009132.

61. O'Brien JT, Burns A (2011): Clinical practice with anti-dementia drugs: a revised (second) consensus statement from the British Association for Psychopharmacology. *J Psychopharmacol*. 25:997-1019.

62. Farina N, Isaac MG, Clark AR, Rusted J, Tabet N (2012): Vitamin E for Alzheimer's dementia and mild cognitive impairment. *Cochrane Database Syst Rev*. 11:CD002854.

63. Malouf R, Grimley Evans J (2008): Folic acid with or without vitamin B12 for the prevention and treatment of healthy elderly and demented people. *Cochrane Database Syst Rev*.CD004514.

64. Sydenham E, Dangour AD, Lim WS (2012): Omega 3 fatty acid for the prevention of cognitive decline and dementia. *Cochrane Database Syst Rev*. 6:CD005379.

65. Flicker L, Grimley Evans G (2001): Piracetam for dementia or cognitive impairment. *Cochrane Database Syst Rev*.CD001011.

66. Birks J, Grimley Evans J (2009): Ginkgo biloba for cognitive impairment and dementia. *Cochrane Database Syst Rev*.CD003120.

67. Skinner J, Carvalho JO, Potter GG, Thames A, Zelinski E, Crane PK, et al. (2012): The Alzheimer's Disease Assessment Scale-Cognitive-Plus (ADAS-Cog-Plus): an expansion of the ADAS-Cog to improve responsiveness in MCI. *Brain imaging and behavior*. 6:489-501.

68. Salmon DP (2012): Neuropsychological features of mild cognitive impairment and preclinical Alzheimer's disease. *Current topics in behavioral neurosciences*. 10:187-212.

69. Price SE, Kinsella GJ, Ong B, Storey E, Mullaly E, Phillips M, et al. (2012): Semantic verbal fluency strategies in amnestic mild cognitive impairment. *Neuropsychology*. 26:490-497.

70. Rios C, Pascual LF, Santos S, Lopez E, Fernandez T, Navas I, et al. (2001): [Working memory and complex activities of everyday life in the initial stages of Alzheimer's disease]. *Revista de neurologia*. 33:719-722.

71. Espinosa A, Alegret M, Valero S, Vinyes-Junque G, Hernandez I, Mauleon A, et al. (2013): A longitudinal follow-up of 550 mild cognitive impairment patients: evidence for large conversion to dementia rates and detection of major risk factors involved. *J Alzheimers Dis*. 34:769-780.

72. Albert M, Blacker D, Moss MB, Tanzi R, McArdle JJ (2007): Longitudinal change in cognitive performance among individuals with mild cognitive impairment. *Neuropsychology*. 21:158-169.

73. Perneczky R, Pohl C, Sorg C, Hartmann J, Komossa K, Alexopoulos P, et al. (2006): Complex activities of daily living in mild cognitive impairment: conceptual and diagnostic issues. *Age and ageing*. 35:240-245.

74. Lai CH, Lane HY, Tsai GE (2012): Clinical and cerebral volumetric effects of sodium benzoate, a D-amino acid oxidase inhibitor, in a drug-naive patient with major depression. *Biol Psychiatry*. 71:e9-e10.

75. Kapoor R, Lim KS, Cheng A, Garrick T, Kapoor V (2006): Preliminary evidence for a link between schizophrenia and NMDA-glycine site receptor ligand metabolic enzymes, d-amino acid oxidase (DAAO) and kynurenine aminotransferase-1 (KAT-1). *Brain Res*. 1106:205-210.

76. Verrall L, Walker M, Rawlings N, Benzel I, Kew JN, Harrison PJ, et al. (2007): d-Amino acid oxidase and serine racemase in human brain: normal distribution and altered expression in schizophrenia. *The European journal of neuroscience*. 26:1657-1669.

77. Strick CA, Li C, Scott L, Harvey B, Hajos M, Steyn SJ, et al. (2011): Modulation of NMDA receptor function by inhibition of D-amino acid oxidase in rodent brain. *Neuropharmacology*. 61:1001-1015.

78. http://www.mayoclinic.org/diseases-conditions/alzheimers-disease/expert-blog/dementia-definitions/bgp-20055922

CLAIMS

What is claimed is:

1. A use of benzoic acid salt in the manufacture of a composition for preventing or treating dementia or mild cognitive impairment, wherein an effective amount of the benzoic acid salt is 200 milligrams (mg)/day to 2000 mg/day.
2. The use according to claim 1, wherein the benzoic acid salt is sodium benzoate, potassium benzoate or calcium benzoate.
3. The use according to claim 1, wherein the benzoic acid salt is sodium benzoate.
4. The use according to claim 1, wherein the dementia is early-phase dementia.
5. The use according to claim 4, wherein the early-phase dementia comprises mild Alzheimer's disease.
6. The use according to claim 1, wherein the mild cognitive impairment comprises amnestic mild cognitive impairment.
7. The use according to claim 1, wherein an effective amount of the benzoic acid salt is 500 milligrams (mg)/day to 1000 mg/day.
8. The use according to claim 1, wherein an effective amount of the benzoic acid salt is 500 mg/day to 900 mg/day.
9. The use according to claim 1, wherein an effective amount of the benzoic acid salt is 750 mg/day.
10. The use according to claim 3, wherein an effective amount of the sodium benzoate is 500 mg/day to 1000 mg/day.
11. The use according to claim 3, wherein an effective amount of the sodium benzoate is 500 mg/day to 900 mg/day.
12. The use according to claim 3, wherein an effective amount of the sodium benzoate is 750 mg/day.