Original Investigation

Add-on Treatment of Benzoate for Schizophrenia
A Randomized, Double-blind, Placebo-Controlled Trial of D-Amino Acid Oxidase Inhibitor

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IMPORTANCE In addition to dopaminergic hyperactivity, hypofunction of the *N*-methyl-D-aspartate receptor (NMDAR) has an important role in the pathophysiology of schizophrenia. Enhancing NMDAR-mediated neurotransmission is considered a novel treatment approach. To date, several trials on adjuvant NMDA-enhancing agents have revealed beneficial, but limited, efficacy for positive and negative symptoms and cognition. Another method to enhance NMDA function is to raise the levels of D-amino acids by blocking their metabolism. Sodium benzoate is a D-amino acid oxidase inhibitor.

OBJECTIVE To examine the clinical and cognitive efficacy and safety of add-on treatment of sodium benzoate for schizophrenia.

DESIGN, SETTING, AND PARTICIPANTS A randomized, double-blind, placebo-controlled trial in 2 major medical centers in Taiwan composed of 52 patients with chronic schizophrenia who had been stabilized with antipsychotic medications for 3 months or longer.

INTERVENTIONS Six weeks of add-on treatment of 1 g/d of sodium benzoate or placebo.

MAIN OUTCOMES AND MEASURES The primary outcome measure was the Positive and Negative Syndrome Scale (PANSS) total score. Clinical efficacy and adverse effects were assessed biweekly. Cognitive functions were measured before and after the add-on treatment.

RESULTS Benzoate produced a 21% improvement in PANSS total score and large effect sizes (range, 1.16-1.69) in the PANSS total and subscales, Scales for the Assessment of Negative Symptoms–20 items, Global Assessment of Function, Quality of Life Scale and Clinical Global Impression and improvement in the neurocognition subtests as recommended by the National Institute of Mental Health's Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative, including the domains of processing speed and visual learning. Benzoate was well tolerated without significant adverse effects.

CONCLUSIONS AND RELEVANCE Benzoate adjunctive therapy significantly improved a variety of symptom domains and neurocognition in patients with chronic schizophrenia. The preliminary results show promise for D-amino acid oxidase inhibition as a novel approach for new drug development for schizophrenia.

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Schizophrenia is a devastating mental disorder of high morbidity and mortality. A substantial portion of patients with schizophrenia experience deteriorating function and lifelong illness.[1] Clinical manifestation of schizophrenia consists of several domains, including positive symptoms, negative symptoms, and cognitive deficits.[2] Negative symptoms and cognitive deficits have been considered as the main outcome predictors for schizophrenia.[3] Unfortunately, the pharmacologic therapy for them remains elusive. A large percentage of patients are resistant or only partially responsive to available antipsychotic medications.[4] Health-threatening adverse effects further limit their clinical use.[5] There is a great need to develop new therapies with better outcome and safer adverse effect profiles.

Effective treatment for schizophrenia should be based on its neurobiological basis. However, the discovery of antipsychotic medications has been serendipitous so far. In addition to the dopaminergic system, hypofunction of the *N*-methyl-D-aspartate subtype inotropic glutamate receptor (NMDAR) may play a role in the pathophysiology of schizophrenia.[6-9] The NMDAR is critically involved in neurocognition and neurotoxicity. Many studies[7] suggest that the glutamatergic system is involved in the aberrant neurotransmission of schizophrenia. The NMDAR antagonists, such as ketamine and phencyclidine, induce a psychotic state that resembles schizophrenia more closely than dopamine agonists[6] because they cause not only positive symptoms but also negative symptoms and cognitive deficits associated with schizophrenia.

Although NMDAR antagonism is well defined for the phenomenology of schizophrenia, a critical challenge is whether it can be a pharmacotherapeutic basis for developing new treatment. Glycine was the first agonist applied to enhance NMDA function in schizophrenia.[10] To date, several trials on adjuvant NMDA-enhancing agents, including the coagonists (such as glycine, D-serine, and D-alanine)[11] and the glycine transporter I inhibitors (such as sarcosine and bitopertin), revealed beneficial, but limited, efficacy on clinical symptoms.[12-16] A meta-analysis[11] of the studies revealed modest effect sizes (ESs) for domains of clinical symptoms. The results of 26 studies with 800 patients revealed that the NMDA-enhancing agents are significantly effective in most schizophrenic symptom domains, including depressive (ES = 0.40), negative (ES = 0.38), positive (ES = 0.26), and general psychopathology (ES = 0.26) symptoms. However, these small studies[11-16] virtually had no or limited[17] data on cognition. In addition, the Cognitive and Negative Symptoms in Schizophrenia Trial[18] contained a substantially larger sample size along with a design relevant for interpreting negative symptoms and cognition effects of glycine and D-cycloserine. The results were unequivocally negative.

D-serine is more potent than glycine as the neurotransmitter for the coagonist site of the NMDAR.[17,19-22] D-amino acid oxidase (DAAO), a flavoenzyme of peroxisomes that exists in the central nervous system, is responsible for degrading D-serine and D-alanine.[23-25] Another alternative to enhance NMDA function is to inhibit DAAO activity and raise levels of D-amino acids. More than 30 studies demonstrated the association of DAAO and DAAO activator (G72) with schizophrenia.[26,27] The expression and activity of DAAO are increased in patients with schizophrenia.[28,29] $DAAO^{+/-}$ mice exhibit elevated D-serine levels and enhanced NMDAR function.[30-32]

The DAAO inhibitors have been considered as new therapeutics for schizophrenia,[33] but they have been unsuccessful so far.[34] A review[34] concluded, "collectively, the limited experience with a small number of structurally diverse inhibitors indicates that extensive inhibition of peripheral and central DAAO has a limited effect on brain or extracellular D-serine concentration" and "behavioral effects of DAAO inhibitors are fairly modest and inconsistent." Therefore, instead of sole use of a DAAO inhibitor or D-serine, coadministration of DAAO inhibitors and D-serine was recommended.[33,35,36]

The litmus test for DAAO inhibition therapy is a clinical trial in patients with schizophrenia.[37] Benzoate is a DAAO inhibitor readily available to test this novel therapeutic approach.[38] Benzoic acid was discovered in the 16th century by the dry distillation of gum benzoin, first described by Nostradamus. Benzoic acid occurs freely in nature, is bound as benzoic acid esters in many plants and animals, and is a natural constituent of many kinds of food, including milk products.[39] Benzoic acid and its salts are generally recognized as safe food preservatives[40] and are widely used in manufacturing fruit jelly, buffer, soybean sauce, and processed meat.

To test the hypothesis that DAAO inhibition is a useful therapeutic approach for the treatment of schizophrenia, we examined the efficacy of sodium benzoate add-on treatment for clincal symptoms and safety in patients with chronically stable schizophrenia. Because of the critical role of the NMDA system in cognition, we also hypothesized that neurocognition can be improved by DAAO inhibition.

Methods

Study Participants

Patients with schizophrenia were recruited from the Department of Psychiatry, China Medical University Hospital (Taichung, Taiwan), and Kaohsiung Municipal Kai-Syuan Psychiatric Hospital (Kaohsiung, Taiwan). The research protocol was approved by the institutional review boards, and all patients provided written informed consent after complete description of the study.

Patients were enrolled in this study if they (1) were physically healthy and had all laboratory assessments (including routine urine and blood tests, biochemical tests, and electrocardiography) within normal limits, (2) were aged 18 to 65 years, (3) satisfied *DSM-IV* criteria for schizophrenia confirmed by the Structured Clinical Interview for *DSM-IV*,[41,42] (4) remained symptomatic but without clinically significant fluctuation and if the antipsychotic doses were unchanged for at least 3 months and would be maintained during the period of the 6-week trial, (5) had a minimum baseline total score of 60 on the Positive and Negative Syndrome Scale (PANSS),[43] and (6) agreed to participate in the study and provide informed consent. Exclusion criteria included *DSM-IV* diagnosis of mental retardation or substance (including alcohol) abuse or dependence; history of

epilepsy, head trauma, or central nervous system diseases; pregnancy or lactation; or inability to follow protocol. The clinical characteristics were similar to the other study.[16]

Procedures

Sodium benzoate is a food preservative approved by the World Health Organization and is also approved for treatment of urea cycle enzymopathies. An earlier open-label, pilot, dose-finding trial was performed by dosing sodium benzoate between 250 and 1000 mg/d. Three of 5 patients received 1000 mg/d of benzoate, and their PANSS total scores decreased from 78 to 58, 80 to 59, and 84 to 60, respectively. The other 2 patients received lower dosages and did not improve. None of the 5 patients had evident adverse effects. We decided to apply the 1000-mg/d dose in the double-blind trial.

In this 6-week double-blind study, patients were randomized in a cluster of 6 through a computer-generated randomization table to receive active treatment or placebo in a 1:1 ratio. Study medications were given twice daily. Medication was provided in coded containers with identical-appearing capsules of placebo or sodium benzoate. Patient adherence and safety were closely monitored by the research staff.

Clinical Assessments

Clinical assessments were conducted biweekly, and cognitive function was measured at baseline and end point. The primary outcome measure was PANSS total score.[43] Secondary outcome measures included scores on the PANSS subscales, Scale for the Assessment of Negative Symptoms-20 items (SANS),[44] Global Assessment of Function (GAF),[42] Quality of Life Scale (QOLS),[15,45] Clinical Global Impression (CGI),[46] Hamilton Depression Rating Scale-17 items (HDRS),[47] and cognitive function tests.

Measurements of Cognitive Function

Cognitive function was assessed using a battery of tests that were the same as or were the analogs of (due to lack of Chinese versions) the tests included in the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB).[48] This study was started before a commercial version of the MCCB was available in Chinese and can be considered similar to the Chinese MCCB. The battery assesses 7 domains: (1) speed of processing, consisting of Category Fluency, Trail Marking A, and Wechsler Adult Intelligence Scale III Digit Symbol-Coding; (2) sustained attention by Continuous Performance Test[49]; (3) working memory, verbal (backward digit span)[50] and nonverbal (Wechsler Memory Scale III, spatial span)[51]; (4) verbal learning and memory (Wechsler Memory Scale III, word listing); (5) visual learning and memory (Wechsler Memory Scale III, visual reproduction); (6) reasoning and problem solving (Wechsler Intelligence Scale for Children III, maze)[52]; and (7) social cognition, (the Managing Emotions Branch of the Mayer-Salovey-Caruso Emotional Intelligence Test [MSCEIT]), version 2.[53] The Chinese version of the MSCEIT tasks was translated and back-translated from English to Mandarin Chinese with satisfactory reliability, validity,[54] and applicability.[55,56]

One of the developers of the MCCB (M.F.G.) reviewed the tests used in this study. Each domain and composite score was standardized to a T score (mean of 50 and SD of 10) using the data from all of the study participants at baseline.

The MCCB allows for the calculation of a general composite score (that includes all 7 domains) and a neurocognitive composite score (that includes the 6 neurocognitive domains without social cognition). This latter score is considered to be preferable if a drug is thought to have effects that are limited to nonsocial domains. Because we did not have a clear expectation, we considered both in the analyses.

Measurements of Adverse Effects

Adverse effect assessments included the Simpson-Angus Rating Scale for extrapyramidal symptoms (EPSs),[57] Abnormal Involuntary Movement Scale (AIMS) for dyskinesia, and Barnes Akathisia Scale. System adverse effects were examined biweekly by routine physical and neurologic examinations and the Udvalg for Kliniske Undersogelser Side-effects Rating Scale.[58] Routing laboratory tests, including complete blood cell count, biochemical analysis, urinanalysis, and electrocardiography, were performed at screening, baseline, and end point.

Statistical Analysis

All data were analyzed with SPSS statistical software, version 17.0 (SPSS Inc), or SAS statistical software, version 9.3 (SAS Institute Inc). The Fisher exact test was used to compare differences of nominal variables. An independent sample *t* test or the Mann-Whitney test was used to compare clinical characteristics. Because there were repeated assessments, mean changes in clinical assessment were assessed using mixed-model repeated-measure (MMRM) methods with treatment, week, and treatment-week interaction as fixed effects and intercept as the only random effect; baseline value was the covariant. An autoregressive covariance matrix was fit to the within-patient repeated measures. The MMRM analyses were performed using the SAS PROC Mixed procedure. Therapeutic ES (Cohen *d*) was used to determine the magnitude of improvement that resulted from benzoate add-on treatment compared with placebo. The ES was calculated using the MMRM analysis model as the least squares mean difference between benzoate and placebo divided by estimated pooled SD obtained from the SE times the square root of the number of group participants. To compare effects of add-on benzoate treatment on 2 major types of drugs, haloperidol and risperidone (**Table 1**), post hoc MMRM analyses were used with the drug-treatment week interaction term.

For assessing the general cognitive ability of the patients, a general composite score and a neurocognitive composite score were calculated by standardizing the sum of the T scores.[59] The MMRM, adjusted for age, sex, educational level, treatment, and visit, was used to analyze the difference.

For checking effects of improvements of positive and negative domains on improvement of negative symptoms and on cognitive function, multiple regression analyses were applied. All *P* values were based on 2-tailed tests with a significance level of .05.

Table 1. Demographic, Clinical, and Antipsychotic Characteristics of Patients Assigned to Placebo or Sodium Benzoate Treatment

Characteristic	Treatment Groups		*P* Value
	Placebo (n = 27)	Benzoate (n = 25)	
Female, No. (%)	12 (44.4)	14 (56.0)	.58[a]
Age, mean (SD), y	36.3 (7.9)	38.4 (9.7)	.39[b]
Age at illness onset, mean (SD), y	23.4 (6.2)	22.2 (6.0)	.40[c]
No. of hospitalizations, mean (SD)	3.1 (2.8)	3.3 (3.2)	.91[c]
Educational level, mean (SD), y	10.5 (2.0)	11.1 (2.3)	.32[b]
Body weight, mean (SD), kg	64.4 (12.4)	68.6 (11.7)	.21[b]
No. of patients using typical/atypical antipsychotics	13/14	14/11	.59[a]
Amisulpride	1	2	
Chlorpromazine	1	4	
Flupenthixol	2	0	
Haloperidol	9	9	
Quetiapine fumarate	2	1	.58[a]
Risperidone	7	6	
Sulpiride	1	1	
Ziprasidone	0	1	
Zotepine	4	1	
Chlorpromazine equivalent dose, mean (SD), mg/d[d]	561.3 (308.0)	587.5 (449.3)	.50[c]

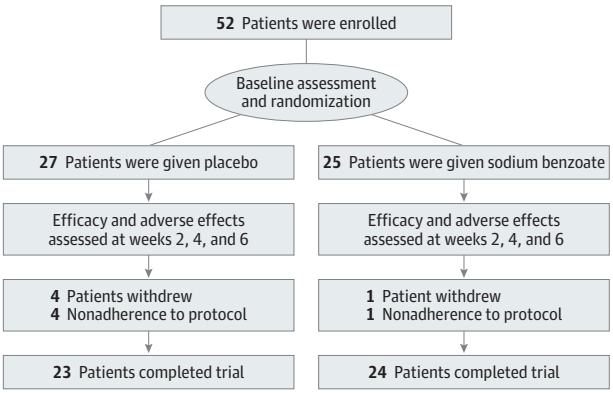
[a] Fisher exact test.

[b] Independent *t* test.

[c] Mann-Whitney test.

[d] Of the 52 patients, 27 received concurrent typical antipsychotics and the other 25 received concurrent atypical antipsychotics. Of the 27 using typical agents, 13 were randomized to the placebo group, and their mean (SD) chlorpromazine equivalent dose was 660.0 (409.9) mg/d; the other 14 were allocated to the benzoate group, and their mean (SD) chlorpromazine equivalent dose was 730.7 (552.8) mg/d. There was no between-group difference in chlorpromazine dose equivalency (Mann-Whitney test, $P = .90$). Of the other 25 who received concurrent atypical antipsychotics, 14 were randomized to the placebo group, and their mean (SD) olanzapine equivalent dose was 15.7 (4.2) mg/d; the other 11 received benzoate treatment, and their mean (SD) olanzapine equivalent dose was 13.5 (4.9) mg/d (Mann-Whitney test, $P = .20$).

Figure. Patient Progress Through Phases of the Study



Progress through phases of a randomized, double-blind, placebo-controlled trial of the add-on treatment of sodium benzoate for schizophrenia.

Results

Patient Disposition and Characteristics

Fifty-two patients were eligible and randomized (27 to placebo and 25 to benzoate) (**Figure**). Baseline demographics are summarized in Table 1. Results are presented as mean (SD). The mean age of the 52 patients was 37.3 (8.8) years, the mean age at illness onset was 22.9 (6.1) years, the mean number of hospitalizations was 3.2 (3.0), the mean educational level was 10.8 (2.2) years, and the mean body weight was 66.4 (12.1) kg. No significant difference was found between the 2 treatment groups in terms of sex, age, age at illness onset, number of hospitalizations, educational level, body weight, and the antipsychotic equivalent dose[60] used to stabilize the patients (Table 1).

PANSS Scores

The mean scores of the 2 groups are given in **Table 2**. At week 0 (baseline), no significant differences were found between the 2 groups in the scores of PANSS total ($t = 0.82$, $P = .42$), positive subscale ($t = 0.17$, $P = .87$), negative subscale ($t = 0.84$, $P = .40$), and general psychopathology subscale ($t = 0.80$, $P = .43$).

After treatment, benzoate produced greater improvement in PANSS total, PANSS positive, PANSS negative, and PANSS general psychopathology scores than placebo therapy ($P<.001$ for all; ES = 1.16-1.69) (Table 2). In addition, MMRM analyses for measurements at the end point and for patients who completed the 6 weeks of treatment both revealed that benzoate surpassed placebo in all outcome measures (data not shown).

Post hoc MMRM analyses revealed that add-on benzoate treatment was effective on 2 major types of drugs, risperidone and haloperidol. Among risperidone-treated patients, benzoate treatment was significantly better than placebo in scores of PANSS total (score reduction from 81.5 to 71.0 for the benzoate group and 83.9 to 79.4 for the placebo group, $P < .001$), PANSS positive, and PANSS negative but not PANSS general (data not shown). Among haloperidol-treated patients, benzoate treatment was also significantly better than placebo in scores of PANSS total (score reduction from 89.6 to 69.3 for the benzoate group and 88.8 to 78.7 for the placebo group, $P = .001$), PANSS positive, PANSS negative, and PANSS general (data not shown).

SANS, GAF, QOLS, CGI, and HDRS

The mean scores of the assessments other than PANSS are given in **Table 3**. At baseline, no significant difference were found between the 2 groups in SANS total score ($t = 1.13$, $P = .26$), GAF score ($t = 0.36$, $P = .72$), QOLS score ($t = 0.42$, $P = .68$), CGI score ($t = 0.42$, $P = .68$), and HDRS score ($t = 0.57$, $P = .57$).

After treatment, benzoate produced greater improvement in SANS, GAF, QOLS, CGI, and HDRS scores than placebo therapy ($P <.001$ for all; ES = 0.74-1.56) (Table 3). In addition, MMRM analyses for measurements at the end

Table 2. Clinical Measures of the Positive and Negative Syndrome Scale (PANSS) During the 6-Week Treatment[a]

Scale and Treatment Group	Mean (SD)				Difference in Score Changing Rate vs Placebo, Mean (SE)	t_{146} Value	*P* Value	Effect Size (Cohen *d*)
	Baseline	Week 2	Week 4	Week 6				
Total					−2.1 (0.3)	−7.6	<.001	1.53
Placebo	87.3 (8.6) (n = 27)	84.3 (10.3) (n = 27)	83.1 (9.6) (n = 24)	81.4 (10.0) (n = 23)				
Benzoate	90.3 (16.3) (n = 25)	82.4 (13.9) (n = 25)	76.5 (12.8) (n = 25)	71.7 (14.3) (n = 24)				
Positive subscale					−0.6 (0.1)	−7.4	<.001	1.69
Placebo	20.4 (4.4)	20.0 (4.7)	19.5 (4.2)	18.8 (4.1)				
Benzoate	20.6 (3.6)	18.4 (3.4)	17.0 (3.3)	15.3 (3.4)				
Negative subscale					−0.6 (0.1)	−6.2	<.001	1.19
Placebo	24.8 (3.6)	23.9 (3.9)	23.4 (3.4)	23.1 (3.6)				
Benzoate	26.1 (6.9)	24.0 (6.1)	22.1 (5.6)	20.8 (6.0)				
General psychopathology subscale					−0.9 (0.2)	−5.7	<.001	1.16
Placebo	42.2 (4.7)	40.4 (5.3)	40.3 (5.2)	39.6 (5.7)				
Benzoate	43.6 (8.2)	40.0 (7.0)	37.4 (6.5)	35.7 (7.2)				

[a] Mixed-model repeated-measure methods with treatment, week, and treatment-week interaction as the fixed effects and intercept as the random effect; baseline value was the covariant. An autoregressive covariance matrix was fit to the within-patient repeated measures. *P* values were based on 2-tailed tests.

Table 3. Clinical Measures of SANS, CGI, GAF, QOLS, and HDRS During the 6-Week Treatment[a]

Scale and Treatment Group	Mean (SD)				Difference in Score Changing Rate vs Placebo, Mean (SE)	t_{146} Value	*P* Value	Effect Size (Cohen *d*)
	Baseline	Week 2	Week 4	Week 6				
SANS					−2.0 (0.2)	−8.01	<.001	1.56
Placebo	55.0 (13.1) (n = 27)	52.6 (12.8) (n = 27)	52.0 (12.4) (n = 24)	51.3 (12.4) (n = 23)				
Benzoate	59.2 (14.2) (n = 25)	52.5 (13.9) (n = 25)	46.7 (13.4) (n = 25)	42.5 (14.6) (n = 24)				
GAF					1.1 (0.2)	6.07	<.001	1.2
Placebo	41.4 (7.8)	42.5 (7.9)	43.5 (7.9)	45.2 (8.3)				
Benzoate	40.6 (8.6)	44.4 (8.4)	48.0 (8.4)	51.5 (8.7)				
QOLS					1.1 (0.2)	6.88	<.001	1.5
Placebo	16.4 (7.4)	18.2 (7.5)	19.5 (7.2)	20.8 (6.8)				
Benzoate	15.4 (10.0)	19.6 (9.8)	23.3 (9.2)	26.8 (10.9)				
CGI					−0.1 (0.02)	−4.9	<.001	1.21
Placebo	4.5 (0.8)	4.4 (0.8)	4.4 (0.8)	4.3 (0.8)				
Benzoate	4.6 (0.6)	4.1 (0.8)	3.6 (0.7)	3.5 (0.7)				
HDRS					−0.3 (0.1)	−3.55	<.001	0.74
Placebo	6.3 (4.0)	5.7 (3.8)	5.6 (4.2)	5.2 (3.5)				
Benzoate	7.1 (5.4)	5.3 (4.7)	4.4 (3.8)	3.8 (3.1)				

Abbreviations: CGI, Clinical Global Impression; GAF, Global Assessment of Function; HDRS, Hamilton Depression Rating Scale–17 items; QOLS, Quality of Life Scale; SANS, Scales for the Assessment of Negative Symptoms–20 items.

[a] Mixed-model repeated-measure methods with treatment, week, and treatment-week interaction as the fixed effects and intercept as the random effect; baseline value was the covariance. An autoregressive covariant matrix was fit to the within-patient repeated measures. *P* values were based on 2-tailed tests.

point and for the completers revealed that benzoate surpassed placebo in all outcome measures listed in Table 3 (data not shown).

Post hoc MMRM analyses revealed that add-on benzoate treatment was effective on 2 major types of drugs, risperidone and haloperidol. Among risperidone-treated patients, benzoate treatment was significantly better than placebo in scores of SANS, GAF, QOLS, and CGI but not HDRS (data not shown). Among haloperidol-treated patients, benzoate treatment was also significantly better than placebo in scores of SANS, GAF, QOLS, and HDRS but not CGI (data not shown).

For checking the effect of improvement in positive symptoms on improvement in negative symptoms, regression analy-

Table 4. Cognitive Measures in 7 Domains Recommended by the Measurement and Treatment Research to Improve Cognition in Schizophrenia Committee During the 6-Week Treatment[a]

Cognitive Domain and Treatment Group	Mean (SD)		Least Squares, Mean (SE) Change in Benzoate-Placebo	*t* Value	*P* Value[a,b]	Effect Size (Cohen *d*)
	Baseline	End Point				
Speed of processing			3.2 (1.4)	2.3	0.03	0.65
Placebo (n = 25)	49.3 (9.2)	50.0 (8.1)				
Benzoate (n = 22)	50.8 (11.0)	54.7 (13.9)				
Attention/vigilance			2.3 (2.5)	0.93	0.36	0.27
Placebo (n = 26)	50.2 (10.5)	50.2 (10.2)				
Benzoate (n = 23)	49.8 (9.6)	52.1 (7.9)				
Working memory			0.2 (1.9)	0.12	0.91	0.04
Placebo (n = 23)	47.2 (7.1)	47.6 (7.9)				
Benzoate (n = 22)	53.0 (11.8)	53.7 (12.5)				
Verbal learning and memory			3.4 (2.5)	1.37	0.18	0.39
Placebo (n = 26)	49.2 (9.1)	54.1 (9.4)				
Benzoate (n = 23)	51.0 (11.1)	59.4 (12.4)				
Visual learning and memory			6.3 (2.6)	2.44	0.02	0.7
Placebo (n = 25)	49.0 (8.0)	52.9 (10.3)				
Benzoate (n = 23)	51.1 (11.9)	61.2 (14.2)				
Reasoning and problem solving			1.0 (2.3)	0.43	0.67	0.12
Placebo (n = 26)	50.2 (9.9)	55.4 (8.5)				
Benzoate (n = 23)	49.8 (10.4)	56.1 (8.0)				
Social cognition			−0.1 (3.8)	−0.02	0.98	<0.01
Placebo (n = 20)	46.9 (6.5)	50.0 (9.6)				
Benzoate (n = 19)	53.3 (12.0)	56.2 (11.3)				
Global composite score[b]			2.9 (1.9)	1.49	0.15	0.51
Placebo (n = 17)	47.4 (8.6)	50.9 (8.6)				
Benzoate (n = 17)	52.6 (10.9)	59.0 (12.3)				
Neurocognitive composite[c]			3.7 (1.7)	2.19	0.04	0.67
Placebo (n = 22)	48.9 (9.6)	52.8 (9.6)				
Benzoate (n = 20)	51.3 (10.5)	58.9 (12.8)				

[a] Mixed-model repeated-measure methods, adjusted for age, sex, educational level, treatment, and visit times.

[b] For assessing the global composite, an overall composite T score that included all 7 domains was calculated by standardizing the sum of T scores.

[c] For assessing neurocognitive ability, an overall composite T score that included all 6 neurocognitive domains, excluding social cognition, was calculated by standardizing the sum of T scores.

sis revealed that score changes on the PANSS positive subscale had a marginal effect on score change in SANS after benzoate treatment (B = 0.40, SE = 0.71, t = 1.99, P = .06).

Cognitive Battery

After 6 weeks of treatment, the between-group difference in the overall neurocognitive composite score was significant after treatment (P = .04, ES = 0.67), but the overall composite score was not significant (**Table 4**). The benzoate group was better in speed of processing (P = .03, ES = 0.65) and visual learning and memory (P = .02, ES = 0.70).

To explore the effect of improvement in positive and negative symptoms on improvement in neurocognition after benzoate treatment, multiple regression analysis revealed that score changes on the PANSS positive subscale (B = 0.20, SE = 0.67, t = 0.30, P = .77) and SANS (B = 0.27, SE = 0.20, t = 1.40, P = .18) had no significant effect on change of neurocognitive composite scores.

Adverse Effects

Both treatment groups had minimal EPSs at the beginning of the study. The mean baseline score on the Simpson-Angus Rating Scale was 1.0 (2.0) in the placebo group and 1.3 (2.3) in the benzoate group, the mean AIMS score was 0.9 (2.0) in the placebo group and 1.0 (2.2) in the benzoate group, and the mean Barnes Akathisia Scale score was 0.0 (0.3) in the placebo group and 0.1 (0.3) in the benzoate group. No significant differences were found between the 2 groups in Simpson-Angus Rating Scale (P = .59), AIMS (P = .85), and Barnes Akathisia Scale (P = .58) scores.

At the end point, the severity of the EPSs remained minimal, and no significant differences were found between the groups. The mean Simpson-Angus Rating Scale score at the end point was 0.9 (1.8) in the placebo group and 1.3 (2.2) in the benzoate group (P = .64), the mean AIMS score was 0.5 (1.5) in the placebo group and 0.5 (1.6) in the benzoate group (P = .98), and the mean Barnes Akathisia Scale score

was 0.0 (0.2) in the placebo group and 0.0 (0.2) in the benzoate group (P = .54).

Treatment-emergent adverse events other than EPSs in the placebo group included weight gain (n = 2), insomnia (n = 1), tremor (n = 1), constipation (n = 1), fatigue (n = 1), and salivation (n = 1); in the benzoate group, treatment-emergent adverse events included weight gain (n = 1), insomnia (n = 2), and tachycardia (n = 1). These systemic adverse effects were all mild and brief and did not warrant medical treatment. They were likely coincidental observations.

The routine blood cell count, chemical analysis results, and electrocardiogram after treatment remained unchanged and were all within the normal ranges (data not shown). No dropout was due to adverse effects.

Discussion

This study demonstrated that sodium benzoate, a DAAO inhibitor, can improve a wide variety of symptom domains of schizophrenia. After 6 weeks of benzoate treatment, PANSS total scores decreased by a mean of 21%. This decrement would be less than clinically significant for patients with acute exacerbation.[61] However, it is beneficial for patients with a high level of symptoms who had been stabilized with antipsychotics for 3 months or longer in this study, as reflected by the improvement of CGI severity scores from 4.6 to 3.5. The ESs observed (Table 2 and Table 3) are larger than those in other trials of NMDA-enhancing agents, with most less than 0.4.[11] The large ESs could be due to the good central nervous system bioavailability of benzoate (vs the other small polar amino acids and DAAO inhibitors tested before) to raise the D-amino acid pool by the inhibition of DAAO. It is encouraging that benzoate treatment improves schizophrenia in those who are still highly symptomatic despite treatment with antipsychotics. It remains to be determined whether the treatment is beneficial for the entire spectrum of symptom severity.

In addition to clinical symptoms, neurocognition was improved. The NMDAR regulates synaptic plasticity, memory, and cognition. Attenuation of NMDAR-mediated neurotransmission can result in loss of neuronal plasticity and cognitive deficits. Hypo-NMDA function induced by NMDAR antagonists is neurotoxic, likely accounting for deterioration and brain atrophy.[62] The NMDA-enhancing agents are supposed to work as not only as antipsychotics but also as cognitive enhancers in patients with schizophrenia.[8] Consistently, NMDA-enhancing agents can benefit cognitive function in animal models of schizophrenia.[63] In the current study, benzoate treatment improved neurocognition in general and specifically in processing speed and visual memory (Table 4). The improvement was neither large in terms of ES nor comprehensive across domains, particularly if adjustment for multiple comparisons was conducted. Longer duration and/or higher dose of treatment may facilitate and solidify the gain of function more substantially.

Deficits in cognitive functions have been considered as core symptoms and outcome predictors of schizophrenia more so than hallucinations or delusions.[3,45] Nevertheless, preserving and even enhancing cognitive functioning have recently been recognized as a critical therapeutic goal because the cognitive effects of typical and atypical antipsychotics are negligible at best.[48] Current study is the first double-blind study to find potential efficacy of an NMDA-enhancing agent in a MATRICS-like battery, also lending support to a recent open-label trial[64] determining that 4 weeks of adjunctive treatment with high-dose D-serine improved MATRICS scores. Currently, no cognition enhancer has been approved for the treatment of schizophrenia. Our findings in neurocognition point to a novel approach to reach the goal of improving cognition.

Benzoate improved symptom domains and neurocognition globally in the present study. Considering the issue of pseudospecificity[65,66] and to explore whether the improvement in neurocognitive function was secondary to improvement in other domains,[67] multiple regression analysis revealed that improvement in the positive and negative symptoms contributed little to the improvement of neurocognition. We did not study the influence of EPSs because there was no change in EPSs with benzoate treatment. Depressive symptoms were also not assessed because of the low Hamilton Depression scores (Table 3). Nevertheless, any add-on therapy that outperforms placebo may be attributed to counteracting the adverse effects of antipsychotic drugs. Future studies with a prospective design and a larger sample size are needed to clarify this issue.[67]

Given the fact that D_2-receptor antagonism is the prominent pharmacologic property shared by typical and most atypical antipsychotic medications, determining whether there is an interaction between D_2-dopamine receptor antagonism and facilitation of endogenous NMDAR-mediated neurotransmission[68] that contributes to the therapeutic effect in schizophrenia deserves further neurophysiologic and pharmacodynamic studies.[68] In addition, sodium benzoate also induces anti-inflammatory activity and upregulates a neuroprotective protein, DJ-1 (PARK7), in astrocytes and neurons.[69] Nevertheless, it is unclear how these mechanisms might contribute to therapeutic effects in a short-term trial.

The toxicology of benzoate administration has been studied extensively and exhibits good safety margins.[39] Benzoic acid and its salts are known and used as food preservatives represented by the E-numbers E210 to E213. Concentration as a preservative is limited by the US Food and Drug Administration to 0.1% by weight. The World Health Organization suggests a provisional tolerable intake of 5 mg/kg daily.[39] Sodium benzoate is also an active ingredient of Ammonul, which is a therapy for the treatment of acute hyperammonemia and associated encephalopathy in patients with enzyme deficiencies of the urea cycle. The recommended maintenance dose of intravenous sodium benzoate is 5.5 g/m^2 every 24 hours for patients with a body weight greater than 20 kg (www.accessdata.fda.gov/drugsatfda_docs/label/2011/020645s008lbl.pdf). The body surface area of a person with a weight of 65 kg and a height of 170 cm, the body surface area is 1.75 m^2, and the daily dose of 9.625 g is much higher than the dose used in the current study (1 g/d).

Several concerns have been raised regarding the safety of benzoate. Benzoic acid and its salts may react with ascor-

bic acid to form benzene, a known carcinogen. However, the US Food and Drug Administration did not confirm the presence of benzene in their survey of beverage, which contained both benzoate and ascorbic acid existed (www.fda.gov/Food/FoodborneIllnessContaminants/ChemicalContaminants/ucm055131.htm). Nevertheless, we advise that benzoate and high-content ascorbic acid should not be ingested concurrently. In addition, it was suggested that when certain artificial colors are paired with benzoate, hyperactive behaviors may result.[70] However, combination formulations were tested; it is unclear whether benzoate or the artificial color is the culprit.[71] In our adult population, we did not observe hyperactivity or other adverse effects that would raise safety concerns.

Overall, benzoate treatment gives rise to a favorable profile of improvement in principal clinical symptoms and neurocognition. Inhibition of DAAO (eg, by benzoate treatment) represents a novel therapeutic target for the development of new pharmacotherapy for the clinical efficacy and improvement of life functioning in patients with schizophrenia given that preliminary findings address both the symptom domains and neurocognition. Additional larger, proof-of-principle studies are necessary to substantiate the validity of this novel therapeutic approach.

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