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Case Series

Psychiatry/Mental Health Section

Effect of Sodium Benzoate as an Add-on Therapy on the Clinical and Cognitive Symptoms of Schizophrenia: A Case Series

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ABSTRACT

Schizophrenia is understood as a construct of positive, negative, and cognitive symptoms. There has been considerable proof at a genetic, biochemical, and pharmacological level to support that N-methyl-D-aspartate Receptor (NMDAR) hypofunction is a key factor in the development of clinical and cognitive symptoms of schizophrenia. While most antipsychotics improve positive symptoms of schizophrenia, the negative and cognitive symptoms have usually been much more difficult to treat and have been associated with poor prognosis, poor functional outcome, and long-term morbidity. Sodium benzoate is a molecule that targets D-amino Acid Oxidase (DAAO) and competitively inhibits it, thus acting as an NMDAR agonist. With this background, we started using sodium benzoate as an adjuvant along with the ongoing antipsychotics in certain patients with schizophrenia to observe the change in clinical and cognitive symptoms. The authors have compiled a case series of 12 such patients. They found an improvement ranging from 17% to 21.5% in the Positive and Negative Syndrome Scale (PANSS) score and 19% to 32.5% in the Mini-mental State Examination (MMSE) Score after six weeks of administration of sodium benzoate as an add-on agent. None of the patients reported any adverse effects after six weeks. Thus, sodium benzoate as an add-on treatment can act as a neurocognitive enhancer as well as a novel antipsychotic that can bridge the gap in the treatment of schizophrenia.

Keywords: Antipsychotics, Cognition, D amino acid oxidase

INTRODUCTION

Schizophrenia affects 1% of the general population and often has a chronic and disabling course. It can be understood as a construct of positive, negative, and cognitive symptoms [1]. The negative symptoms have usually been much more difficult to treat and have been associated with poor prognosis, poor functional outcome, and long-term morbidity [2]. Similarly, impairment in the cognitive domain has been considered another core feature of schizophrenia that affects long-term prognosis, functional outcome, and rehabilitation [3]. Regarding management, while current antipsychotics help address the positive symptoms, they play a limited role in managing both negative and cognitive symptoms. Conventional antipsychotics cause extrapyramidal side-effects, further worsening negative symptoms, and the addition of an anticholinergic agent impairs cognition, especially memory. Bilder RM et al., highlighted that, in comparison, most second-generation antipsychotics do not notably improve cognition, apart from clozapine, which only improves motor function and no other cognitive realm [4]. Hence, the search for a new molecule that addresses negative as well as cognitive symptoms of schizophrenia is an encouraging area for future exploration.

The role of alteration in the functioning of NMDAR as an important process in the aetiology of schizophrenia has been extensively investigated and is now well known [5]. Randomised clinical trials conducted in the past have shown the beneficial effect of the addition of sodium benzoate on the clinical and cognitive symptoms of schizophrenia [6,7]. With this background, the authors started using sodium benzoate as an adjuvant along with the ongoing antipsychotics in certain patients with schizophrenia to observe the change in clinical and cognitive symptoms. They have compiled a case series of 12 such patients.

CASE SERIES

The authors enrolled 12 patients from the psychiatry Out Patient Department (OPD) of the Himalayan Institute of Medical Sciences, a tertiary care hospital, who were diagnosed with schizophrenia as per Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) criteria [8]. They explained the purpose of the study to them and their caregivers and obtained written informed consent. These cases were aged between 18 and 29 years, physically healthy, and had been on regular and adequate doses of second-generation antipsychotic medications (such as olanzapine, risperidone, amisulpride, etc.) for the past six months, with no significant change in the medication dose for the past three months.

The authors selected patients in this age group to exclude the effects of ageing on cognitive impairment. These patients underwent basic biochemical and radiological investigations (complete blood count, liver and renal function tests, thyroid profile, random blood sugar, and Computed Tomography (CT) scan of the head). They only included patients with normal test reports to avoid any confounding effects. Patients were evaluated to rule out extrapyramidal symptoms or any other causes of negative/cognitive symptoms (e.g., Central Nervous System (CNS) abnormalities, infections, epilepsy, vitamin deficiencies).

The authors did not include pregnant/lactating females or patients suffering from any other psychiatric illness. The group comprised eight male patients and four female patients. They used the PANSS for schizophrenia [9] to assess positive, negative, and global psychopathology and the MMSE [10] to evaluate cognition (orientation, registration, attention, calculation, and language) of these patients, recording the baseline scores. A cut-off total score of 60 on PANSS was used as the inclusion criteria [6].

These patients were then prescribed sodium benzoate at a dose of 500 mg twice daily along with their ongoing antipsychotic medication for the next six weeks. Following this period, PANSS

and MMSE assessments were conducted again, and the obtained scores were compared with the baseline scores. The percentage difference was calculated to determine the improvement percentage in PANSS and MMSE, and the change in mean scores was analysed using the Statistical Package for the Social Sciences (SPSS) version 27.0 [11].

The basic socio-demographic variables (age and gender) and the comparative scores of the patients are presented in [Table/Fig-1]. The authors observed an improvement ranging from 17% to 21.5% in the PANSS score and 19% to 32.5% in the MMSE score after six weeks of administering sodium benzoate as an add-on agent. None of the patients reported any adverse effects after the six-week period.

The mean PANSS score before sodium benzoate treatment was 69.58±3.09, which decreased to 56.67±2.74 after six weeks of administration as shown in [Table/Fig-2]. Upon applying the t-test, a statistically significant difference was observed ($p<0.001^*$). Similarly, the mean MMSE score before sodium benzoate treatment was 20.08±1.88, which changed to 25.75±1.91 after six weeks of administration, also demonstrating statistical significance ($p<0.001^*$) (Paired t-test).

Age (years)	Gender	Baseline PANSS total score	PANSS total score after 6 weeks of sodium benzoate administration	Percentage of improvement in PANSS (% of difference)	Baseline MMSE score	MMSE score after 6 weeks of sodium benzoate administration	Percentage of improvement in MMSE (% of difference)
20	M	72	58	21.5%	18	24	28.5%
24	F	69	57	19.04%	21	26	21.2%
26	M	68	55	21.1%	22	27	20.4
27	F	64	52	20.7%	23	28	19.6%
24	M	71	57	21.9%	19	25	27.3%
28	M	74	60	20.9%	17	22	25.6%
20	F	75	62	18.9%	18	25	32.5%
19	M	67	56	17.9%	22	28	24%
22	F	66	54	20%	21	27	25%
21	M	70	58	18.7%	19	24	23.3%
24	M	68	54	20.5%	21	28	28.6%
25	M	71	57	19.7%	20	25	22.2%

[Table/Fig-1]: Sociodemographic and clinical variables of study patients.

Clinical variables	Baseline mean score (with standard deviation)	Mean score (with standard deviation) after 6 weeks of sodium benzoate administration	p-value (after applying paired t-test)
PANSS	69.58±3.09	56.67±2.74	<0.001**
MMSE	20.08±1.88	25.75±1.91	<0.001**

[Table/Fig-2]: Comparison of change in clinical parameters.
Paired t-test

DISCUSSION

The DAAO is an enzyme that deaminates neutral D-amino acids like D-serine, a major co-agonist at the NMDA receptor. Reduction in the level of D-serine, as well as a reduced ratio of D-serine to total serine, has been found in blood and Cerebrospinal Fluid (CSF) samples of patients with schizophrenia [12]. Sodium benzoate is a molecule that targets DAAO and competitively inhibits it. It is a sodium salt of benzoic acid that has been used in the past as a common food preservative [13].

Jadi MP et al., mentioned the role of NMDAR hypofunctioning in the emergence of cognitive symptoms based on the changes in cortical γ-Amino-butyric Acid (GABA) interneurons, leading to alterations in cortical network oscillations. [14]. The hypofunction of NMDAR on cortical neurons leads to an increase in glutamatergic projection tone, which shunts the mesocortical dopamine pathway, preventing appropriate dopamine release in the prefrontal cortex, associated with the development of negative and cognitive symptoms [15]. The cortical interneuronal disinhibition responsible for the increased firing of cortical glutamatergic projections also leads to sensitisation of the mesolimbic pathway, resulting in positive symptoms [15].

The present case series highlights the change in clinical and cognitive symptoms of schizophrenia based on PANSS and MMSE scores after adding sodium benzoate for six weeks to ongoing antipsychotic medication in patients diagnosed with schizophrenia who were chronically stable.

The present study results are similar to a study published by Lane HY et al., who found a 21% improvement in the PANSS total score after six weeks of benzoate treatment [6]. They also reported an improvement in cognition after using sodium benzoate, especially in processing speed, visual memory, and learning memory. Similar results were found by Lin CH et al., who observed improvement in clinical symptoms of patients with clozapine-resistant schizophrenia after six weeks of treatment [7]. They also reported that sodium benzoate did not have any side-effects when used up to 2 gm/day for six weeks. A meta-analysis by Seetharam JC et al., reported improvement in positive symptoms after using sodium benzoate but failed to find an improvement in negative symptoms, PANSS total score, and cognition, unlike the present study results [12].

There is considerable evidence at genetic, biochemical, and pharmacological levels supporting that NMDAR hypofunction is a key factor in the development of clinical and cognitive symptoms of schizophrenia [5]. NMDAR hypofunction has been associated with excitotoxicity, causing neurotoxic changes in the brain leading to impairment in cognition and brain atrophy. It also contributes to the worsening of positive and negative symptoms in patients with schizophrenia [16]. Therefore, NMDA agonist drugs have been suggested to work both as antipsychotic agents and cognitive enhancers.

Regarding antipsychotics, second-generation antipsychotics offer only a limited range of improvement in the clinical symptoms of schizophrenia, especially the negative symptoms. Hill SK et al., highlighted that clinical trials conducted on patients with schizophrenia using second-generation antipsychotics showed only modest improvement in cognition compared to first-generation ones [17]. Therefore, sodium benzoate as an add-on treatment can act as a neurocognitive enhancer and a novel antipsychotic, potentially bridging this gap in the treatment of schizophrenia.

The authors did not segregate the various segments of PANSS to observe the effects of sodium benzoate on positive, negative, and global symptoms individually. Additionally, they did not follow-up with the patients for a long enough period to assess the long-term effects of sodium benzoate on clinical and cognitive symptoms.

CONCLUSION(S)

The present case series of 12 patients with schizophrenia who were given adjuvant sodium benzoate along with their ongoing antipsychotic treatment demonstrates consistently improved outcomes in their overall clinical and cognitive symptoms. This highlights the role of sodium benzoate in the management of schizophrenia and suggests that it should be considered as a novel treatment option for such patients.

REFERENCES

[1] Galderisi S, Mucci A, Buchanan RW, Arango C. Negative symptoms of schizophrenia: New developments and unanswered research questions. Lancet Psychiatry. 2018;5(8):664-77. Doi: 10.1016/S2215-0366(18)30050-612.

[2] Carbon M, Correll CU. Thinking and acting beyond the positive: The role of the cognitive and negative symptoms in schizophrenia. CNS Spectr. 2014;19(Suppl 1):38-52; quiz 35-37, 53. Doi: 10.1017/S1092852914000601.

[3] Cornblatt BA, Erlenmeyer-Kimling L. Global attentional deviance as a marker of risk for schizophrenia: Specificity and predictive validity. J Abnorm Psychol. 1985;94(4):470-86.

[4] Bilder RM, Goldman RS, Volavka J, Czobor P, Hoptman M, Sheitman B, et al. Neurocognitive effects of clozapine, olanzapine, risperidone, and haloperidol in patients with chronic schizophrenia or schizoaffective disorder. Am J Psychiatry. 2002;159(6):1018-28.

[5] Balu DT. The NMDA receptor and schizophrenia: From pathophysiology to treatment. Adv Pharmacol. 2016;76:351-82. Doi: 10.1016/bs.apha.2016.01.006. Epub 2016 Mar 4. PMID: 27288082; PMCID: PMC5518924.

[6] Lane HY, Lin CH, Green MF, Hellemann G, Huang CC, Chen PW, et al. Add-on treatment of benzoate for schizophrenia: A randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. JAMA Psychiatry. 2013;70(12):1267-75.

[7] Lin CH, Chen YM, Lane HY. Novel treatment for the most resistant schizophrenia: Dual activation of NMDA receptor and antioxidant. Curr Drug Targets. 2020;21(6):610-15. Doi: 10.2174/1389450120666191011163539. PMID: 31660823.

[8] DSM-5: American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. (5th edn). APA, 2013.

[9] Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull. 1987;13(2):261-76.

[10] Davey RJ, Jamieson S. The validity of using the mini mental state examination in NICE dementia guidelines. J Neurol Neurosurg Psychiatry. 2004;75(2):343-44.

[11] IBM Corp. IBM SPSS Statistics for Windows [Internet]. Armonk, NY: IBM Corp; 2020. Available from: https://hadoop.apache.org.

[12] Seetharam JC, Maiti R, Mishra A, Mishra BR. Efficacy and safety of add-on sodium benzoate, a D-amino acid oxidase inhibitor, in treatment of schizophrenia: A systematic review and meta-analysis. Asian J Psychiatry. 2022;68:102947.

[13] Ferraris D, Duvall B, Ko YS, Thomas AG, Rojas C, Majer P, et al. Synthesis and biological evaluation of d-amino acid oxidase inhibitors. J Med Chem. 2008;51(12):3357-59.

[14] Jadi MP, Margarita Behrens M, Sejnowski TJ. Abnormal gamma oscillations in N-Methyl-D-Aspartate Receptor hypofunction models of schizophrenia. Biol Psychiatry. 2016;79(9):716-26.

[15] Ellaithy A, Younkin J, Gonzalez-Maeso J, Logothetis DE. Positive allosteric modulators of metabotropic glutamate 2 receptors in schizophrenia treatment. Trends Neurosci. 2015;38(8):506-16.

[16] Lin CH, Lane HY, Tsai GE. Glutamate signaling in the pathophysiology and therapy of schizophrenia. Pharmacol Biochem Behav. 2012;100(4):665-77.

[17] Hill SK, Bishop JR, Palumbo D, Sweeney JA. Effect of second-generation antipsychotics on cognition: Current issues and future challenges. Expert Rev Neurother. 2010;10(1):43-57. Doi: 10.1586/ern.09.143. PMID: 20021320; PMCID: PMC2879261.

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