Section: Miscellaneous

Original Article

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Sodium Benzoate: A D-Amino Acid Oxidase Inhibitor (Zubilance®) Added to Anti-psychotics for the treatment of schizophrenia Management: An Open-Label Study

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Abstract

Background: Schizophrenia is treated mainly by antipsychotic medication, although one still has to deal with cognitive deficits and suboptimal quality of life often persists. This study evaluates the efficacy of Zubilance®, a sodium benzoate formulation and D-amino acid oxidase inhibitor-as an add-on treatment with antipsychotics-to improve symptom severity, cognitive function, and quality of life in schizophrenia patients. **Subjects and Methods:** This was a randomized controlled trial with a study duration of 6 weeks. The study group received Zubilance® (500 mg sodium benzoate) in combination with antipsychotics, while the control group received antipsychotics only. Outcomes included symptom severity evaluated by PANSS and CGI scale, cognitive functioning assessed by the MoCA, and quality of life evaluated using the WHOQOL scale. **Results**: The study group demonstrated a significant improvement in symptom severity, indicated by lower PANSS and CGI scores compared to the control group ($p < 0.05$). Cognitive function, assessed via MoCA, improved notably in the Zubilance® group, suggesting cognitive enhancement with the add-on treatment. WHOQOL results showed improved quality of life in the study group, correlating with reduced symptoms and cognitive benefits. **Conclusion**: Our study shows that addition of Zubilance® (Sodium benzoate) to standard antipsychotic drugs treatment improves the patient outcome with enhanced symptom control, cognitive function and quality of life.

Keywords: Sodium Benzoate, Schizophrenia, Cognition, Mental Disorder, DAAO inhibitor, NMDA Hypofunction

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Introduction

Schizophrenia is a psychiatric condition that has severe effects on your physical and mental well-being.[1] It affects how a person thinks, feels, and behaves. People with schizophrenia may seem like they have lost touch with reality, which can be distressing for them and for their family and friends.[2] Schizophrenia is a somewhat common condition. Worldwide, it affects 221 in every 100,000 people.[1]

Schizophrenia treatment includes various approaches to help manage symptoms effectively. The predominant treatment is antipsychotic medication, the traditional or first kind (for example, haloperidol), and atypical (for example, risperidone and olanzapine),[3] with the latter generally preferred for their fewer side effects. Psychotherapy is also of tremendous value, with Cognitive Behavioural Therapy (CBT), family therapy, and group therapy so much more the reason, as collaborate the two in offering coping mechanisms and support systems.[4]

Long-Acting Injectable Antipsychotics (for example, LAIs) provide a reliable alternative for those who have are struggling with medical adherence.[5] In severe cases where other treatments fail, Electroconvulsive Therapy (ECT) may be considered as a another treatment option.[6] Some may also explore complementary therapies, such as dietary supplements or mindfulness techniques.

In this regard, the severity of symptoms can be assessed using the Positive and Negative Syndrome Scale,[7,8] while the Clinical Global Impressions (CGI) scale assesses overall improvement. Montreal Cognitive Assessment (MoCA) and World Health Organization Quality of Life (WHOQOL-100) are established tools for the assessment of cognitive function.[9,10] These scales provide a comprehensive framework for evaluating the multifaceted impact of treatment interventions.

A significant proportion of patients who have schizophrenia still have unmet needs despite the treatment available: a sizeable subset of the patients does not respond to available treatment; therefore, the patients develop residual symptoms and reduced quality of life. We will compare the effects and tolerability of add-on treatment and standard care with respect to clinical, cognitive, and quality-of-life outcomes. The major aim of this study was to evaluate the change in

PANSS, CGI, MoCA, and WHOQOL scores over 6 weeks. This study adds to the accumulating literature that suggests that combination therapies may be superior to monotherapy with respect to treatment outcome.

Subjects and Methods

This study was conducted over a 6-week period with participants randomized into two groups: the add-on treatment group (N=26) received Zubilance® (sodium benzoate) along with standard antipsychotic treatment drugs and the control group received antipsychotic drugs (N=45). Participants were assessed using the Positive and Negative Syndrome Scale (PANSS), the Clinician's Global Impressions (CGI) score, the Montreal Cognitive Assessment (MoCA), and the WHOQOL scale. Baseline and week 6 assessments were compared to evaluate the effectiveness of the treatment.

Results

Demographics: The add-on treatment group comprised 34.61% females and 65.38% males, while the control group had 40% females and 60% males. The mean age of participants was 37.07 years in the treatment group and 35.13 years in the control group.

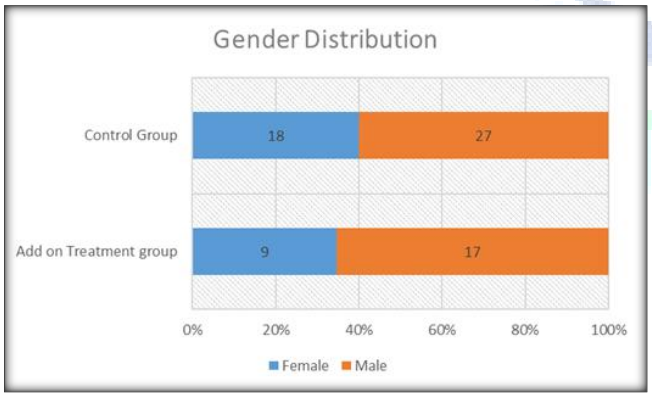

Figure 1: Gender wise distribution of participants in both groups

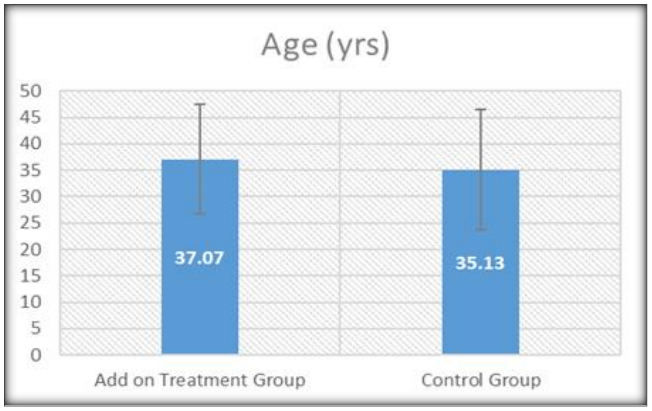

Figure 2: Age wise distribution of participants in both groups

2. Positive and Negative Syndrome Scale (PANSS)

- **Total Positive Scale:** The mean reduction in the total positive scale was 10.73 in the add-on treatment group and 7.84 in the control group, indicating a greater reduction in symptom severity for the treatment group.
- **Total Negative Scale:** The mean reduction in the total negative scale was 11.69 in the treatment group and 9.64 in the control group, showing a higher improvement in the treatment group. [Table 1]
- **General Scale:** The treatment group showed a reduction of 20.03, while the control group exhibited a reduction of 17.44, with both groups showing similar improvements. [Table 2]
- **Overall PANSS Score:** The total PANSS score decreased by 42.46 in the treatment group and by 34.93 in the control group. Baseline PANSS scores indicated a markedly ill condition (93) in the treatment group and a severely ill condition (107.62) in the control group. By week 6, the treatment group improved to a mildly ill condition (50.53), while the control group improved to a moderately ill condition (72.68). [Table 3]

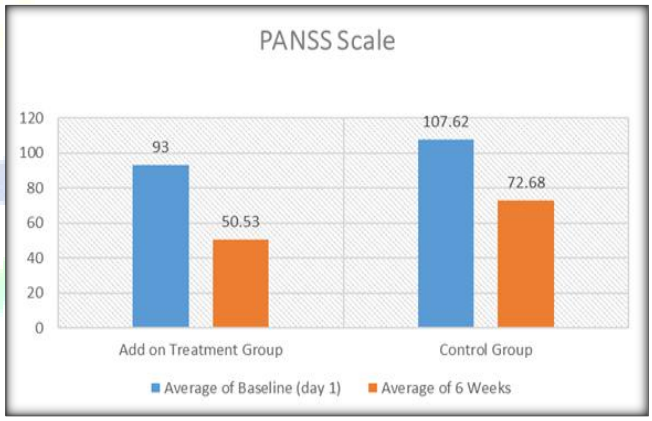

Figure 3: PANSS Total Score

3. Clinician's Global Impressions (CGI)

- **Global Improvement:** By week 6, 23.07% of participants in the treatment group were "very much improved," compared to 8.88% in the control group. Additionally, 38.46% of the treatment group was classified as "much improved," compared to 37.77% in the control group. A smaller proportion of participants in the treatment group were classified as "minimally improved" or showed "no change" compared to the control group.
- **Severity of Illness:** At baseline, 34.61% of the treatment group was classified as severely ill, with 7.69% as extremely ill. By week 6, none of the participants in the treatment group fell into these categories, with 15.38% rated as "not at all ill" and 26.92% as "borderline mentally ill." [Table 4]

4. Montreal Cognitive Assessment (MoCA): The MoCA score for the treatment group improved by 6.57 points from

baseline to week 6, transitioning participants from a moderate to mild cognitive impairment state, suggesting a significant cognitive function improvement. [Table 5]

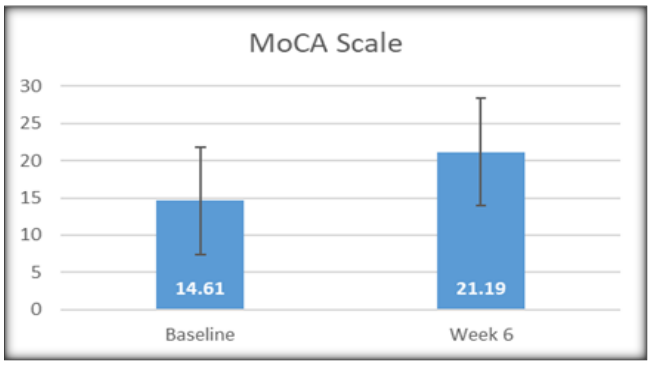

Figure 4: MoCA scale

5. WHOQOL Scale

- **Physical Domain:** The mean physical health score in the control group improved from 39.52 at baseline to 54.28 at week 6, with a statistically significant improvement ($p < 0.001$).
- **Psychological Domain:** The mean psychological health score increased from 39.81 to 57.03, indicating an improved psychological state ($p < 0.001$).
- **Social Domain:** The mean social relationships score improved from 45.37 to 57.22, reflecting enhanced social functioning ($p < 0.001$).

Table 1: PANSS Positive Symptom Scale

	Baseline	Week 06	Change from Baseline
Add on Treatment Group (Zubilance®)			
Mean	23.11	12.38	-10.73
Std Dev	4.41	5.09	0.68
P-Value	-	-	<0.001
Control Group			
Mean	26.71	18.86	-7.84
Std Dev	8.63	5.95	-2.67
P-Value	-	-	<0.001

Table 2: PANSS Negative symptom scale

	Baseline	Week 06	Change from Baseline
Add on Treatment Group(Zubilance®)			
Mean	24.57	12.88	-11.69
Std Dev	4.85	5.65	0.80
P-Value	-	-	<0.001
Control Group			
Mean	27.82	18.17	-9.64
Std Dev	8.56	3.87	-4.96
P-Value	-	-	<0.001

Table 3: PANSS General Psychopathology Scale

	Baseline	Week 06	Change from Baseline
Add on Treatment Group(Zubilance®)			
Mean	45.30	25.26	-20.03
Std Dev	12.53	8.15	-4.38
P-Value	-	-	<0.001
Control Group			
Mean	53.08	35.64	-17.44
Std Dev	16.27	7.01	-9.26
P-Value	-	-	<0.001

Table 4: Clinical Global Impressions (CGI) Score for Global Improvement

	Add on treatment group(Zubilance®) **(N=26) n(%)**	**Control Group (N=45) n(%)**
0 = Not assessed	0 (00)	0 (00)
1 = Very much improved	6 (23.07)	4 (8.88)
2 = Much improved	10 (38.46)	17 (37.77)
3 = Minimally improved	9 (34.61)	22 (48.88)
4 = No change	1 (3.84)	2 (4.44)
5 = Minimally worse	0 (00)	0 (00)
6 = Much worse	0 (00)	0 (00)
7 = Very much worse	0 (00)	0 (00)

Table 5: Clinical Global Impressions (CGI) Score for Severity Illness

	Add on Treatment Group(Zubilance®) N=26 n(%)		Control Group N=45 n(%)	
	Baseline	Weeks 06	Baseline	Weeks 06
0= Not assessed	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
1= Normal, not at all ill	0 (0.00)	4 (15.38)	0 (0.00)	0 (0.00)
2= Borderline mentally ill	0 (0.00)	7 (26.92)	0 (0.00)	22 (48.88)
3= Mildly ill	0 (0.00)	9 (34.61)	4 (8.88)	22 (48.88)
4= Moderately ill	10 (38.46)	6 (23.07)	20 (44.44)	1 (2.22)
5= Markedly ill	5 (19.23)	0 (0.00)	9 (20.00)	0 (0.00)
6= Severely ill	9 (34.61)	0 (0.00)	12 (26.66)	0 (0.00)
7= Among the most extremely ill	2 (7.69)	0 (0.00)	0 (0.00)	0 (0.00)

Table 6: Montreal Cognitive Assessment (MoCA) Scores

	Add on Treatment Group(Zubilance®)		
	Baseline	Week 6	Change from Baseline
Mean	14.61	21.19	6.57
STD	7.19	7.24	0.05
P-value	-	-	<0.001

Table 7: WHOQOL Scale Results for Control Group

Control Group			
	Baseline	6 Week	Change from baseline
Physical Domain			
Mean	39.52	54.28	14.76
Std	16.21	6.79	-9.41
P value	-	-	<0.001
Psychological Domain			
Mean	39.81	57.03	17.22
Std	11.43	7.93	-3.49
P value	-	-	<0.001
Social Domain			
Mean	45.37	57.22	11.85
Std	12.88	10.6	-2.27
P value	-	-	<0.001

Discussion

The objectives of the present study were to assess if sodium benzoate, a D-amino acid oxidase inhibitor, exerts any anti-psychotic effects when used as a supplementary treatment for schizophrenia. The results obtained suggest a decrease in positive symptoms, which is consistent with earlier investigations that emphasized sodium benzoate's efficacy in treatment-resistant schizophrenia. Lin et al,[11] reported in a randomized controlled trial that utilized clozapine as a standard treatment which, when combined with sodium benzoate, improved PANSS total score and negative symptoms, supporting our results regarding its effectiveness in treatment-resistant schizophrenia.

On the other hand, Seetharam et al,[12] included a systemic review with a meta-analysis that demonstrated that there was a statistically significant reduction of positive symptoms but no significant changes in negative symptoms nor changes in the overall PANSS scores. It therefore follows that while sodium benzoate can successfully resolve certain symptoms of schizophrenia, it may be less effective on the rest of the symptoms. Our study is in support of these observations and provides a specific cut out point for positive symptoms, where some changes were apparent while no changes were seen in the negative symptoms and cognitive functionality.

In addition, results from the CADENCE-BZ trial which explored the effects of sodium benzoate on early psychosis patients did not report any enhancement in PANSS scores.[13] These conflicting results suggest that the depend on the timing of the intervention and the phase of schizophrenia. It is necessary to conduct additional studies to determine when it is appropriate to incorporate sodium benzoate into various treatment strategies.

Our study also aligns with the findings of Lane et al,[14] who reported that sodium benzoate significantly improved PANSS scores and cognitive functions when used as an adjunct treatment in chronic schizophrenia patients stabilized on antipsychotics. Additionally, a recent trial by Ryan et al,[13] aims to explore sodium benzoate's role in early psychosis, emphasizing the need for innovative pharmacological interventions in this population.

Despite the promising results, it is crucial to consider the limitations of sodium benzoate treatment. For example, while Seetharam et al,[12] noted a higher incidence of extrapyramidal symptoms in patients receiving sodium benzoate, our study found no significant differences in adverse events compared to the control group. This discrepancy highlights the importance of monitoring and assessing side effects to ensure patient safety.

Sodium benzoate's efficacy as a potentiating add on, for use as a treatment modality for the management of positive symptoms of schizophrenia has been endorsed by conclusions of this study. Although the potential of sodium benzoate on the negative symptoms of schizophrenia is not established, treatment resistant cases present a very strong case for its further development. Further studies are needed to establish, the long-term benefits of the drug, effective ways to dose the drug as well its mechanisms of action, to improve outcomes in patients suffering from schizophrenia.

Conclusion

In summary, this study demonstrates that Zubilance® (Sodium benzoate), as a D-amino acid oxidase inhibitor, shows promise as an adjunctive treatment for schizophrenia, particularly in reducing positive symptoms. Our findings are consistent with existing literature that supports the role of sodium benzoate in enhancing NMDA receptor function and improving treatment outcomes for individuals with schizophrenia. However, the lack of significant effects on negative symptoms highlights the need for continued research to better understand the full therapeutic potential of sodium benzoate, its optimal application in various stages of schizophrenia, and its safety profile.

The integration of sodium benzoate into clinical practice could provide a valuable addition to existing treatment regimens, offering hope for improved management of schizophrenia and better quality of life for patients.

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