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The Therapeutic Effects of Baclofen as Adjunctive Therapy on Positive and Negative Symptoms of Schizophrenia: A Double-Blind Randomized Placebo-Controlled Clinical Trial

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Abstract

Background: Schizophrenia is a chronic psychiatric disorder characterized by positive symptoms, such as hallucinations and delusions, and negative symptoms, including affective flattening and social withdrawal.

Objectives: This study investigated the adjunctive effects of baclofen across multiple symptom domains, including positive and negative symptoms, anxiety, depression, disorganization, and agitation, and assessed motor safety.

Methods: In this double-blind, randomized, placebo-controlled trial, 144 hospitalized patients receiving risperidone were assigned to receive baclofen (n = 72) or placebo (n = 72) for 8 weeks. Symptom severity was assessed at baseline and at weeks 2, 4, and 8 using the Positive and Negative Syndrome Scale (PANSS), the Calgary Depression Scale for Schizophrenia (CDSS), and the Abnormal Involuntary Movement Scale (AIMS). Repeated-measures ANOVA was used to evaluate the effects of time, group, and the time × group interaction. Analyses were conducted using a per-protocol approach.

Results: Baseline demographic characteristics, including age and sex, were comparable between the groups. Compared with placebo, baclofen significantly reduced positive, negative, anxiety, depression, disorganization, and agitation symptoms (all $P < 0.001$). Improvement in positive symptoms emerged by week 2, whereas improvement in negative symptoms became more pronounced from week 4 onward. Effect sizes ranged from partial $\eta^2 = 0.100$ to 0.365, indicating small-to-large interaction effects. Baclofen was well tolerated; 8 patients (11.1%) discontinued treatment because of mild adverse effects, including dizziness or nausea, and mild psychomotor slowing was observed in 8.3% of patients, with no rigidity, fasciculations, or clinically significant extrapyramidal symptoms.

Conclusions: Baclofen demonstrated statistically significant adjunctive effects across multiple symptom domains of schizophrenia over 8 weeks, with a favorable short-term motor safety profile. These preliminary findings from a single-center study with fixed dosing require confirmation in larger, multicenter trials.

Keywords: Baclofen, Positive Symptoms, Negative Symptoms, Schizophrenia

1. Background

Schizophrenia is a chronic, severe psychiatric disorder characterized by a complex constellation of positive symptoms, such as hallucinations and delusions, and negative symptoms, including social withdrawal, anhedonia, and blunted affect (1). Despite decades of research, the pathophysiology of schizophrenia remains incompletely understood; however, disruptions in neurotransmitter systems, particularly dopaminergic, glutamatergic, and GABAergic pathways, have been implicated (2).

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The dopamine hypothesis, originally proposed more than 50 years ago, posits that hyperactivity of dopamine transmission in the mesolimbic pathway underlies the positive symptoms of schizophrenia, whereas hypodopaminergia in the mesocortical pathway is linked to negative and cognitive symptoms (2). Although dopamine D2 receptor antagonists have been the cornerstone of antipsychotic treatment, they are often insufficient for managing negative symptoms and cognitive deficits, which substantially impair functional outcomes (3). These limitations underscore the need for novel therapeutic strategies that target additional neural circuits.

Among neurotransmitter systems, gamma-aminobutyric acid (GABA), the brain's primary inhibitory neurotransmitter, has received increasing attention for its role in the pathophysiology of schizophrenia. Postmortem and imaging studies have shown alterations in GABAergic interneurons, particularly parvalbumin-expressing interneurons in the prefrontal cortex, contributing to impaired cortical inhibition and disrupted neural synchrony (4, 5). This dysfunction may underlie both cognitive deficits and negative symptoms, supporting the hypothesis that GABAergic modulation may represent a potential therapeutic target, although clinical evidence remains limited (6).

Baclofen, a selective agonist of $GABA_B$ receptors, is primarily used as a muscle relaxant for spasticity but has demonstrated neuropsychiatric effects in preclinical and clinical studies. $GABA_B$ receptors are metabotropic receptors that modulate neurotransmitter release through inhibitory G-protein-coupled mechanisms (7). Activation of these receptors reduces the release of excitatory neurotransmitters, such as glutamate, and modulates dopaminergic transmission, which may help restore the balance between excitatory and inhibitory signaling disrupted in schizophrenia (8, 9).

In addition, baclofen-mediated modulation of glutamatergic transmission may alleviate negative symptoms by improving prefrontal cortical function (10). Human studies, although limited, suggest that baclofen may reduce irritability and anxiety in psychiatric populations, further supporting its potential benefit in schizophrenia (11).

Currently, most antipsychotic treatments focus on dopamine D2 receptor antagonism, with only modest efficacy in addressing negative symptoms and cognitive impairments (12). Given the critical role of GABAergic dysfunction in the pathophysiology of schizophrenia and the involvement of $GABA_B$ receptors in regulating both dopaminergic and glutamatergic systems, investigating baclofen as an adjunctive or alternative therapeutic agent is a promising avenue for future research. Recent studies further indicate that $GABA_B$ receptor activation modulates both mesolimbic dopamine hyperactivity and prefrontal glutamatergic dysregulation, which may contribute to improvements in both positive and negative symptom domains (13-15).

Despite this potential, clinical trials examining the efficacy of baclofen in schizophrenia remain scarce. Existing data from other neuropsychiatric disorders indicate that $GABA_B$ receptor agonists can exert anxiolytic and neuroprotective effects, potentially translating into symptom reduction in schizophrenia (8, 9). Moreover, baclofen's ability to modulate neuroplasticity through enhanced brain-derived neurotrophic factor (BDNF) expression may contribute to improved neural connectivity and functional outcomes (6).

This study investigated the therapeutic effects of baclofen on positive symptoms, including hallucinations and delusions, and negative symptoms, including emotional blunting and social withdrawal, in patients with schizophrenia over 8 weeks in a randomized controlled trial. It also examined demographic factors, such as age and sex, that may influence treatment response. The aim was to explore baclofen as a potential alternative or adjunctive therapy for patients unresponsive to standard antipsychotics, including its impact on motor symptoms.

2. Methods

2.1. Study Design and Participants

This double-blind randomized clinical trial was conducted at Golestan Hospital, Ahvaz, between 2023 and 2024. Hospitalized patients aged 18 - 65 years with a confirmed diagnosis of schizophrenia according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), established using the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV), who were receiving risperidone and had a disease duration of at least 2 years were eligible.

Risperidone was selected to standardize background antipsychotic treatment and minimize pharmacological heterogeneity, thereby allowing a clearer assessment of the adjunctive effects of baclofen. Exclusion criteria included the use of other antipsychotics, antidepressants, valproate, lithium, or benzodiazepines; comorbid psychiatric disorders; severe personality disorders; and alcohol or substance use disorder, except nicotine, within the previous 12 months. Sampling was performed using a convenience sampling approach because of the limited availability of eligible hospitalized patients during the study period. This approach may limit external validity and generalizability. The sample size was determined based on an expected medium effect size (f = 0.25), power of 0.80, and alpha of 0.05 for repeated-measures ANOVA, resulting in a minimum required sample of 128 participants. To account for potential attrition, 144 participants were enrolled. Patients with significant neurological disorders, uncontrolled metabolic conditions, or other severe medical comorbidities were excluded based on medical history and clinical examination.

2.2. Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki and institutional guidelines. Ethical approval was obtained from the University Ethics Committee (approval code: IR.AJUMS.HGOLESTAN.REC.1403.635). The trial was registered in a clinical trial registry (registration number: 20250312065047N1). Written informed consent was obtained from each participant and, when required, from their legal guardian. Patients with sufficient decisional capacity provided written consent themselves.

2.3. Assessment Instruments

Diagnostic evaluation was performed using the SCID-5-CV, a standardized interview for establishing DSM-5 diagnoses (16). Symptom severity was assessed with the PANSS, which evaluates positive, negative, and general psychopathology domains (17). Depressive symptoms specific to schizophrenia were measured using the CDSS (18). Extrapyramidal and involuntary movements were assessed with the AIMS (19).

2.4. Randomization and Blinding

Sampling was performed using convenience sampling. Participants were assigned using block randomization with a block size of 4, generated on the Sealed Envelope platform. Allocation codes were placed in sequentially numbered opaque envelopes and opened at enrollment. Patients, clinical evaluators, and medication administrators were blinded to treatment allocation. Inter-rater reliability for PANSS and CDSS scoring was assessed before study initiation, with an intraclass correlation coefficient greater than 0.80. Blinding integrity was not formally tested at study completion, which represents a methodological limitation.

2.5. Intervention

The baclofen group started with 5 mg/day, which was titrated to 20 mg/day during the first week. This dose was selected based on prior clinical studies indicating tolerability and minimal motor adverse effects at low-to-moderate doses (11, 20). An 8-week duration was chosen to allow observation of both early changes in positive symptoms and later improvements in negative symptoms, consistent with typical acute-phase antipsychotic trials. The placebo group received identical inert tablets. Clinical assessments were performed at baseline, week 2, week 4, and week 8 by a trained psychiatric resident. Medication was administered by a blinded nurse.

3. Results

3.1. Demographic Characteristics

A total of 144 patients with schizophrenia participated in the study. In the baclofen group, 28 females (38.9%) and 44 males (61.1%) were enrolled, whereas the placebo group included 32 females (44.4%) and 40 males (55.6%). The mean ± SD age was 37.3 ± 10.5 years in the baclofen group and 36.9 ± 10.1 years in the placebo group. Independent-samples t-test confirmed no significant difference in mean age between groups (P = 0.78), and chi-square analysis showed no significant difference in sex distribution (P = 0.49). Age and sex distributions were comparable, indicating balanced baseline demographic characteristics (Table 1). During the study, 8 patients (11.1%) in the baclofen group discontinued treatment because of adverse effects, including 6 due to dizziness and 2 due to nausea. No discontinuations were attributed to motor adverse

Table 1. Demographic Characteristics of Participants by Age and Sex (N = 72) [a]

Variables	Baclofen Group	Placebo Group
Age (y)		
18 - 30	19 (26.4)	21 (29.2)
30 - 40	26 (36.1)	18 (25.0)
40 - 50	20 (27.8)	24 (33.3)
50 - 65	7 (9.7)	9 (12.5)
Mean ± SD	37.3 ± 10.5	36.9 ± 10.1
Sex		
Female	28 (38.9)	32 (44.4)
Male	44 (61.1)	40 (55.6)

[a] Values are expressed as No. (%) or mean ± SD.

Table 2. Positive Symptom Scores Over Time [a]

Time	Baclofen	Placebo	P-Value
Baseline	23.72 ± 5.31	23.53 ± 6.11	-
Week			
2	19.67 ± 4.53	23.44 ± 6.03	< 0.001
4	16.53 ± 3.72	23.78 ± 6.36	< 0.001
8	16.25 ± 4.47	24.42 ± 6.40	< 0.001

[a] Values are expressed as mean ± SD.

effects. Analyses were performed using a per-protocol approach. No imputation was performed for missing data.

3.2. Positive Symptoms

At baseline, mean positive symptom scores were similar between the baclofen (mean = 23.72) and placebo (mean = 23.53) groups. Over the 8-week period, the baclofen group showed decreasing mean scores (week 8: mean = 16.25), whereas the placebo group showed scores that remained stable or slightly increased (week 8: mean = 24.42). Repeated-measures ANOVA indicated significant effects of time ($F(3, 426) = 47.058$, $P < 0.001$, partial $\eta^2 = 0.249$), group ($F(1, 142) = 34.044$, $P < 0.001$, partial $\eta^2 = 0.193$), and the time × group interaction ($F(3, 426) = 66.465$, $P < 0.001$, partial $\eta^2 = 0.319$). Related data are presented in Table 2.

3.3. Negative Symptoms

Baseline negative symptom scores were comparable between the baclofen (mean = 28.17) and placebo (mean = 28.36) groups. Mean scores in the baclofen group decreased over time (week 8: mean = 20.86), whereas the placebo group showed relatively stable values (week 8: mean = 27.83). Repeated-measures ANOVA showed significant effects of time ($F(3, 426) = 46.135$, $P < 0.001$, partial $\eta^2 = 0.245$), group ($F(1, 142) = 15.761$, $P < 0.001$, partial $\eta^2 = 0.100$), and the time × group interaction ($F(3, 426) = 37.965$, $P < 0.001$, partial $\eta^2 = 0.211$). Results are presented in Table 3.

3.4. Anxiety and Depression Symptoms

Pretest scores for anxiety and depression were similar between the baclofen (mean = 15.03) and placebo (mean = 15.36) groups. Mean scores in the baclofen group decreased from week 2 onward, whereas the placebo group showed values that remained stable or increased (week 4: mean = 17.81). Repeated-measures ANOVA revealed significant effects of time ($F(3, 426) = 24.689$, $P < 0.001$, partial $\eta^2 = 0.148$), group ($F(1, 142) = 52.424$, $P < 0.001$, partial $\eta^2 = 0.270$), and the time × group interaction ($F(3, 426) = 63.363$, $P < 0.001$, partial $\eta^2 = 0.309$). The corresponding values are shown in Table 4.

Table 3. Negative Symptom Scores Over Time [a]

Time	Baclofen	Placebo	P-Value
Baseline	28.17 ± 5.08	28.36 ± 6.84	-
Week			
2	23.72 ± 8.04	27.50 ± 6.59	0.01
4	22.44 ± 7.17	28.47 ± 7.04	< 0.001
8	20.86 ± 7.11	27.83 ± 6.96	< 0.001

[a] Values are expressed as mean ± SD.

Table 4. Anxiety and Depression Scores Over Time [a]

Time	Baclofen	Placebo	P-Value
Baseline	15.03 ± 4.36	15.36 ± 3.83	-
Week			
2	12.06 ± 3.00	14.78 ± 4.31	0.002
4	10.31 ± 2.48	17.81 ± 3.35	< 0.001
8	10.89 ± 2.48	15.22 ± 4.71	< 0.001

[a] Values are expressed as mean ± SD.

3.5. Disorganization Symptoms

Mean disorganization scores decreased in the baclofen group from baseline (mean = 24.11) to week 8 (mean = 16.08), whereas the placebo group showed stable or increased values (week 8: mean = 23.72). Repeated-measures ANOVA indicated significant effects of time ($F(3) = 52.49$, $P < 0.001$, partial $\eta^2 = 0.270$), group ($F(1) = 81.45$, $P < 0.001$, partial $\eta^2 = 0.365$), and the time × group interaction ($F(3) = 64.68$, $P < 0.001$, partial $\eta^2 = 0.313$). Data are summarized in Table 5.

3.6. Excitement Symptoms

Mean excitement scores in the baclofen group decreased from baseline (mean = 15.31) to week 8 (mean = 9.94). The placebo group showed mean scores between 15 and 16 throughout the study. Repeated-measures ANOVA showed significant effects of time ($F(3) = 44.40$, $P < 0.001$, partial $\eta^2 = 0.238$), group ($F(1) = 70.97$, $P < 0.001$, partial $\eta^2 = 0.333$), and the time × group interaction ($F(3) = 42.62$, $P < 0.001$, partial $\eta^2 = 0.231$). Corresponding data are presented in Table 6.

3.7. Involuntary and Motor Movements

Motor assessments included movement disorders, psychomotor slowing, rigidity, tongue and oral fasciculations, and extrapyramidal symptoms (EPS). Most patients in both groups did not show motor disturbances. Mild psychomotor slowing was observed in a small number of patients, whereas rigidity and tongue and oral fasciculations were absent in all cases. No notable motor changes were observed in patients with blunted or restricted affect. Overall motor findings are presented in Table 7.

4. Discussion

The results indicated that baclofen administration in patients with schizophrenia led to significant reductions in positive and negative symptoms, with disorganization and agitation also showing marked improvement. In addition, anxiety and depression scores decreased significantly. Symptom reduction in the baclofen group began in the second week and continued consistently throughout the 8-week period, whereas the placebo group showed no meaningful change. Statistical analyses indicated that the main effects of time, group, and the time × group interaction were significant for all variables. These findings suggest a statistically significant therapeutic signal; however, clinical significance should be interpreted cautiously given the single-center design. Overall, the results

Table 5. Disorganization Symptom Scores Over Time [a]

Time	Baclofen	Placebo	P-Value
Baseline	24.11 ± 4.80	24.44 ± 4.74	-
Week			
2	19.97 ± 5.05	24.28 ± 5.03	< 0.001
4	13.89 ± 4.68	25.47 ± 4.23	< 0.001
8	16.08 ± 5.89	23.72 ± 5.62	< 0.001

[a] Values are expressed as mean ± SD.

Table 6. Excitement Symptom Scores Over Time [a]

Time	Baclofen	Placebo	P-Value
Baseline	15.31 ± 2.93	15.32 ± 2.76	-
Week			
2	11.63 ± 3.90	15.14 ± 2.98	< 0.001
4	9.92 ± 3.10	15.61 ± 2.95	< 0.001
8	9.94 ± 3.71	14.92 ± 3.31	< 0.001

[a] Values are expressed as mean ± SD.

Table 7. Patients' Motor Status During the Study

Motor Feature	Number of Patients (%)	Description
No motor disorder	132 (91.7)	Most patients had no motor disturbances
Mild psychomotor slowing	12 (8.3)	Movements were slowed, but no rigidity or fasciculations were observed
Rigidity	0 (0)	No patients exhibited rigidity
Tongue fasciculations	0 (0)	Not observed
Oral fasciculations	0 (0)	Not observed
EPS (drug-induced motor side effects)	0 (0)	No side effects were reported
Blunted/restricted affect with normal motor status	100% of patients with blunted/restricted affect	No additional motor disturbances were observed

indicate that baclofen influenced a wide range of schizophrenia symptoms, but the magnitude and speed of improvement should be considered preliminary until replicated in larger trials.

Positive symptoms of schizophrenia, such as delusions and hallucinations, are largely attributed to dopamine hyperactivity in the mesolimbic pathway (21). In this study, a significant reduction in these symptoms was observed in the baclofen group. The mechanism of action of baclofen involves activation of presynaptic GABA-B receptors and inhibition of glutamate and dopamine release, thereby reducing pathological excitability in the mesolimbic pathway (7). In addition, modulation of the prefrontal cortical excitatory/inhibitory balance may improve negative symptoms, including reduced motivation and social withdrawal (22, 23). This dual action may underlie the observed effects on both positive and negative symptom domains. Animal and human evidence indicates that GABA-B agonists reduce hyperactive behaviors induced by dopaminergic stimulation and modulate neuronal circuits linked to anxiety and impulsive behaviors (20, 24). Although these mechanisms may help contextualize the findings, the present clinical trial cannot establish causal neurobiological relationships.

Regarding negative symptoms, including affective flattening, reduced motivation, and impaired social interaction, the findings indicated that baclofen

reduced these symptoms as well. This effect is attributed to rebalancing of the GABA-glutamate system in the prefrontal cortex, where decreased glutamatergic activity and modulation of GABAergic neurons may improve motivation and executive functioning (22). Moreover, chronic stimulation of GABA-B receptors may increase BDNF expression, which plays a key role in neuroplasticity and cognitive improvement (25, 26). The timing of therapeutic effects indicated that benefits began around week 4 and continued through week 8, which aligns with previous findings concerning the gradual accumulation of the pharmacological impact of baclofen and other GABA-B agonists (27). The pattern of improvement observed in this trial, emerging gradually and continuing through week 8, is consistent with these proposed mechanisms, although neurobiological confirmation requires further study.

In the domain of anxiety and depression, the study findings showed that the baclofen group experienced a steady and significant reduction in anxiety and depression scores, whereas the placebo group showed no clear improvement. This effect may arise through modulation of neurotrophic pathways, reduction of hyperactivity in the hypothalamic-pituitary-adrenal axis, and decreased glutamatergic activity—mechanisms consistent with prior research in anxiety and depressive disorders (13). The significant time × group interaction further demonstrated that reductions in anxiety and depression occurred more rapidly and strongly in the baclofen group than in the placebo group. Given the high prevalence of comorbid affective symptoms in schizophrenia, these preliminary results may hold clinical relevance.

Disorganization and agitation symptoms were also significantly reduced in patients treated with baclofen, whereas the placebo group showed no meaningful change. These findings suggest that baclofen may help regulate impulsive behaviors and emotional dysregulation, likely by reducing excessive glutamate release and enhancing GABAergic activity in frontal and mesolimbic regions (28). These observations are consistent with the known effects of baclofen on excitatory/inhibitory balance, although additional controlled studies are needed.

Importantly, baclofen treatment was not associated with significant motor side effects, and most patients exhibited normal motor functioning throughout the study. Mild psychomotor slowing was observed in 8.3% of patients; however, no accompanying rigidity, tremor, or abnormal involuntary movements were detected on the AIMS assessment. Differentiation from negative symptoms was based on the temporal association with medication initiation and the absence of changes in affective flattening. Patients with blunted or restricted affect did not show notable motor changes, and most patients did not exhibit negative motor symptoms. This safety profile suggests that low-dose baclofen was not associated with major extrapyramidal or motor disturbances during the 8-week study period. These findings differ from earlier reports, such as the study by Bigelow et al. (11), which documented adverse behavioral effects at higher doses or under different treatment conditions; such discrepancies may relate to differences in dose, study population, and concurrent antipsychotic use.

Previous studies have shown that GABA-B receptor agonists, such as baclofen, can play a meaningful therapeutic role in psychiatric disorders. Their primary mechanism involves enhancing GABA-B receptor activity and modulating dopaminergic pathways in the mesolimbic system, thereby reducing positive symptoms as well as anxiety and agitation (14, 15). For negative symptoms, GABA-B receptor activation is associated with reduced glutamatergic activity and improved cognitive functioning (4, 23). Comparisons with other GABAergic medications, such as gabapentin, suggest that enhancing GABAergic function can be beneficial as adjunctive therapy in schizophrenia; however, baclofen, with its more selective affinity for GABA-B receptors, may exert more targeted effects (29, 30). Despite these findings, the overall evidence base for baclofen in schizophrenia remains limited, underscoring the need for replication in larger samples.

Strengths of this study include its randomized, double-blind, placebo-controlled design; use of consistent antipsychotic therapy; repeated assessments across multiple symptom domains; and inclusion of both affective and non-affective measures, which together provide a comprehensive view of treatment response.

Nevertheless, several limitations must be acknowledged. This was a single-center study with a fixed baclofen dose of 20 mg/day, precluding evaluation of dose-response effects. Only risperidone-treated patients were included, limiting generalizability across antipsychotic regimens. Serum drug levels were not

measured, motor assessments were clinical rather than instrumental, and the 8-week duration does not allow conclusions regarding long-term safety or durability of effects.

4.1. Conclusions

Baclofen may represent a potential adjunctive treatment option for schizophrenia; however, conclusions regarding its robust therapeutic efficacy should await confirmation in larger multicenter dose-ranging trials with longer follow-up.

Footnotes

AI Use Disclosure: The authors declare that no generative AI tools were used in the creation of this article.

Authors' Contribution: S. S., F. B., and M. P. conceived and designed the study. S. B. and F. R. collected the data. M. P. supervised the project and provided critical revisions. All authors contributed to data analysis, interpretation of results, and approved the final manuscript.

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Conflict of Interests Statement: The authors declare no conflict of interest.

Data Availability: The dataset used and/or analyzed during the current study is available from the corresponding author on reasonable request. The data are not publicly available due to patient confidentiality and institutional data protection policies.

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