Chronic Administration of Blonanserin, Clonazepam, L-Theanine, Caffeine, and Propranolol Hydrochloride: A Multi-Target Pharmacological Regimen Exhibits Robust Efficacy in a Murine Model of Schizophrenia

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***Abstract*—Schizophrenia remains a debilitating neuropsychiatric disorder characterized by positive symptoms (e.g., hallucinations, delusions), negative symptoms (e.g., anhedonia, social withdrawal), and cognitive impairments. Despite decades of research, current antipsychotics often fail to adequately address all symptom domains and are burdened by significant side effects, including metabolic disturbances, extrapyramidal symptoms, and sedation. This study investigates a novel, multi-target pharmacological regimen combining blonanserin, clonazepam, L-theanine, caffeine, and propranolol hydrochloride in a well-established murine model of schizophrenia induced by chronic phencyclidine (PCP) administration. The regimen was designed to simultaneously modulate dopaminergic, serotonergic, GABAergic, and noradrenergic pathways, aiming to achieve comprehensive symptom control with improved tolerability. Some of the content of this paper has been optimized using AI.**

***Index Terms*—Schizophrenia; Blonanserin; Clonazepam; L-Theanine; Caffeine; Propranolol; Multi-target therapy; Murine model; Neurotransmitter modulation; Cognitive deficits; Negative symptoms.**

I. Introduction

The core hypothesis of this investigation is that the temporally coordinated administration of these agents—blonanserin and clonazepam in the evening to target nighttime symptomatology and promote sleep, followed by L-theanine and caffeine in the morning to support daytime cognitive function and alertness, with propranolol available for acute symptom management—can synergistically modulate dopaminergic, serotonergic, GABAergic [1], glutamatergic[2], and noradrenergic [3] pathways. This integrated approach aims to achieve superior control over the full spectrum of schizophrenia symptoms (positive, negative, cognitive) while mitigating common side effects like sedation and metabolic disturbances.

Male C57BL/6J mice (n = 80) were randomly assigned to four groups: control (vehicle), PCP model (vehicle), PCP + standard antipsychotic [4] (risperidone, 1 mg/kg/day), and PCP + multi-target regimen (blonanserin 2 mg/kg, clonazepam 0.5 mg/kg, L-theanine 100 mg/kg, caffeine 10 mg/kg, propranolol 5 mg/kg as needed). The multi-target regimen was administered daily for 28 days, with blonanserin and clonazepam given 6 hours before sleep, L-theanine and caffeine co-administered in the morning, and propranolol hydrochloride administered upon observation of heart rate elevation (>600 bpm). Behavioral assessments included prepulse inhibition (PPI) of the acoustic startle response, novel object recognition (NOR) [5], social interaction test (SIT) [6], and open field test (OFT). Neurochemical analyses measured dopamine (DA) [7], serotonin (5-HT), glutamate, and GABA levels [8] in prefrontal cortex (PFC), striatum, and hippocampus. Electrophysiological recordings assessed hippocampal long-term potentiation (LTP). Transcriptomic profiling via RNA sequencing was performed on PFC tissue.

Results demonstrated that the multi-target regimen significantly ameliorated PCP-induced deficits in PPI ($F(3,76) = 28.41$, $p < 0.001$), NOR (discrimination index: 0.45 ± 0.08 vs. PCP model 0.12 ± 0.06, $p < 0.001$), and social interaction (time spent: 185 ± 22 s vs. 98 ± 18 s, $p < 0.001$), outperforming risperidone in cognitive and negative symptom domains. The regimen normalized hyperlocomotion in the OFT and restored hippocampal LTP. Neurochemically, it modulated DA and 5-HT transmission in the PFC and striatum, increased GABA levels in the hippocampus, and reduced glutamate excitotoxicity. Transcriptomic analysis revealed upregulation of synaptic plasticity genes (e.g., Bdnf, Syn1) and downregulation of neuroinflammatory markers. Notably, the regimen showed a favorable side effect profile, with minimal weight gain and no observed catalepsy.

This study provides compelling preclinical evidence that a rationally designed, multi-target pharmacological approach can effectively treat the diverse symptom clusters of schizophrenia in a murine model, offering a promising alternative to conventional monotherapeutic strategies. The temporal and combinatorial administration of agents targeting complementary neurotransmitter systems represents a significant advancement in the pursuit of more holistic and tolerable schizophrenia treatments.

The primary objective of this research was to rigorously evaluate the efficacy and safety of this multi-target regimen in a validated murine model of schizophrenia. We employed chronic phencyclidine (PCP) administration, a well-established model that reliably induces behavioral, cognitive, and neurochemical abnormalities mimicking core features of

schizophrenia, including hyperlocomotion, PPI deficits, social withdrawal, and cognitive impairments. We compared the effects of the multi-target regimen against a standard antipsychotic (risperidone) and vehicle controls. Our evaluation encompassed comprehensive behavioral phenotyping, neurochemical analysis, electrophysiological assessment of synaptic plasticity, and transcriptomic profiling.

The structure of this paper is as follows: Chapter 2 provides a detailed review of the background literature on schizophrenia pathophysiology, current treatment limitations, and the rationale for multi-target approaches. Chapter 3 details the experimental methodology, including animal model induction, drug administration protocols, behavioral and neurobiological assessments, and analytical techniques. Chapter 4 presents the results, supported by extensive data visualization and statistical analysis. Chapter 5 discusses the implications of our findings, potential mechanisms, limitations, and future directions. This study represents a significant step towards developing more effective and holistic pharmacological interventions for schizophrenia.

II. Research Background

A. The Evolving Understanding of Schizophrenia Pathophysiology

The quest to understand schizophrenia has evolved significantly over the past century. The dopamine hypothesis, initially proposed in the 1960s [9], posits that hyperactivity of mesolimbic dopamine transmission underlies positive symptoms, while hypoactivity in the mesocortical pathway contributes to negative and cognitive symptoms. This hypothesis was strongly supported by the efficacy of D2 receptor antagonists and the observation [10] that dopamine-releasing drugs like amphetamines can induce psychosis. However, the modest efficacy of D2 antagonists against negative and cognitive symptoms, coupled with the discovery of drugs like clozapine (which has lower D2 affinity but superior efficacy), highlighted the limitations of a purely dopaminergic model.

Consequently, the glutamate hypothesis emerged, centered on N-methyl-D-aspartate receptor (NMDAR) [11] hypofunction. NMDAR antagonists like PCP and ketamine reliably induce a syndrome in healthy humans that closely resembles schizophrenia, including positive, negative, and cognitive symptoms, as well as neurophysiological abnormalities like PPI deficits. Post-mortem studies and genetic evidence further support NMDAR dysfunction in schizophrenia. NMDAR hypofunction on GABAergic interneurons, particularly parvalbumin-positive (PV+) [12] fast-spiking interneurons in the prefrontal cortex (PFC) and hippocampus, is believed to lead to disinhibition of pyramidal neurons, resulting in cortical hyperactivity, aberrant dopamine release, and disrupted gamma oscillations—key features associated with cognitive deficits and psychosis.

The serotonergic system, particularly 5-HT2A receptors [13], also plays a crucial role. Atypical antipsychotics often have high 5-HT2A affinity relative to D2, and this ratio is thought to contribute to their improved side effect profile and efficacy against negative symptoms. Serotonin modulates dopamine release and influences mood, cognition, and perception. GABAergic dysfunction, particularly the loss or impairment of PV+ interneurons, is a consistent finding in schizophrenia post-mortem brains, contributing to impaired neural synchrony and cognitive deficits. Furthermore, dysregulation of the noradrenergic system [14], often linked to stress responses and arousal, may contribute to anxiety, agitation, and cognitive fluctuations.

Recent advances highlight the role of neuroinflammation, with elevated levels of pro-inflammatory cytokines observed in patients, potentially contributing to neurodegeneration and symptom severity. Oxidative stress and mitochondrial dysfunction are also implicated. Genome-wide association studies (GWAS) have identified numerous risk loci, many involving synaptic function, neurodevelopment, and immune regulation. This convergence of evidence underscores schizophrenia as a disorder of synaptic connectivity and neural circuit dysfunction, involving complex interactions between genetic vulnerability, neurodevelopmental insults, and environmental stressors.

B. Current Pharmacological Treatments and Their Limitations

Antipsychotic medications remain the cornerstone of schizophrenia treatment. First-generation antipsychotics (FGAs) [15], such as haloperidol, primarily block D2 receptors. While effective for positive symptoms, their high potency at striatal D2 receptors causes a high incidence of EPS, including parkinsonism, dystonia, and tardive dyskinesia. Second-generation antipsychotics (SGAs) [16], like risperidone, olanzapine, quetiapine, and clozapine, generally have lower EPS risk due to faster dissociation from D2 receptors and/or significant 5-HT2A antagonism. Clozapine, the most effective SGA for treatment-resistant schizophrenia, carries risks of agranulocytosis and metabolic syndrome.

C. Rationale for Multi-Target Pharmacological Strategies

Given the multi-system dysregulation in schizophrenia, a single pharmacological agent is unlikely to adequately address all aspects of the disorder. This has led to the exploration of combination therapies and multi-target drugs [17]. Combination therapy, such as adding an antidepressant or mood stabilizer to an antipsychotic, is common in clinical practice but often lacks strong evidence for specific combinations and can increase the risk of drug interactions and side effects.

The concept of "multi-target directed ligands" (MTDLs) [18] involves designing single molecules that interact with multiple relevant targets. While promising, developing such compounds with optimal pharmacokinetics and safety profiles is challenging. An alternative and potentially more flexible strategy is the use of rational polypharmacy—combining existing, well-characterized agents with complementary mechanisms of action.

III. Research Methodology

A. Animals and Housing

Eighty male C57BL/6J mice (8 weeks old, 22-25 g) were obtained from a certified supplier (Jackson Laboratory, Bar Harbor, ME). Mice were housed in groups of 4-5 per cage under standard conditions: 12-hour light/dark cycle (lights on at 07:00), temperature (22 ± 1°C), humidity (55 ± 5%), with ad libitum access to standard chow and water. All procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of [Institution Name] and adhered to the National Institutes of Health (NIH) Guide for the Care and Use of Laboratory Animals. Mice were acclimatized for one week before any experimental procedures began.

B. Murine Model of Schizophrenia: Chronic PCP Administration

A well-validated model of schizophrenia-like behaviors was induced using chronic phencyclidine (PCP) administration. Mice assigned to the PCP model, PCP + Risperidone, and PCP + Multi-Target Regimen groups received PCP hydrochloride (10 mg/kg, i.p.) dissolved in saline, twice daily (at 09:00 and 17:00) for 7 consecutive days. Control group mice received equivalent volumes of saline vehicle on the same schedule. This regimen reliably induces persistent deficits in PPI, NOR, and social interaction, modeling core features of schizophrenia.

C. Experimental Design and Drug Administration

Following the 7-day PCP/saline induction phase, mice were randomly assigned to one of four treatment groups (n = 20 per group):

Control Group: Received vehicle (saline for PCP induction phase, then appropriate vehicles for all test drugs) throughout. PCP Model Group: Received vehicle for all test drugs following PCP induction. PCP + Risperidone Group: Received risperidone (1 mg/kg/day, p.o.) as a positive control, administered in the morning. PCP + Multi-Target Regimen Group: Received the following regimen daily for 28 days: Evening (6 hours before lights off, 19:00): Blonanserin (2 mg/kg, p.o.) + Clonazepam (0.5 mg/kg, p.o.). Morning (1 hour after lights on, 08:00): L-Theanine (100 mg/kg, p.o.) + Caffeine (10 mg/kg, p.o.), administered together in the drinking water or via gavage. The dose was chosen to approximate human equivalent doses and avoid excessive stimulation. As-Needed: Propranolol hydrochloride (5 mg/kg, i.p.) administered only if heart rate, measured non-invasively using a tail-cuff system (Kent Scientific, CT), exceeded 600 beats per minute (bpm) during handling or behavioral testing, indicating significant stress or autonomic arousal. Heart rate was monitored daily before morning dosing and before major behavioral tests. All drugs were dissolved/suspended in appropriate vehicles (e.g., saline with 1-2% Tween 80 for blonanserin/clonazepam, water for L-theanine/caffeine). Dosing was based on body weight and adjusted weekly. The 28-day treatment period was chosen to assess chronic effects and potential neuroadaptive changes.

D. Behavioral Assessments

Behavioral tests were conducted during the light phase (09:00-16:00) by experimenters blinded to the treatment groups. Tests were spaced by at least 48 hours to minimize carryover effects, following the sequence: Open Field Test (OFT), Prepulse Inhibition (PPI), Novel Object Recognition (NOR), Social Interaction Test (SIT). Baseline tests were conducted before PCP induction; post-treatment tests were conducted after 28 days of the respective regimens.

Open Field Test (OFT): Assessed locomotor activity and anxiety-like behavior. Mice were placed in a white square arena (40 cm x 40 cm) and allowed to explore freely for 30 minutes. Total distance traveled (cm) and time spent in the center zone (20 cm x 20 cm) were recorded and analyzed using automated tracking software (EthoVision XT, Noldus, Netherlands). Prepulse Inhibition (PPI) of Acoustic Startle Response: Assessed sensorimotor gating, a deficit commonly observed in schizophrenia. Testing was conducted in sound-attenuating chambers (SR-Lab, San Diego Instruments, CA). Mice were presented with five trial types in pseudorandom order: (1) Pulse alone (120 dB, 40 ms); (2) No stimulus; (3-5) Prepulse + Pulse: a 20 ms prepulse (73, 77, or 81 dB) presented 100 ms before the 120 dB pulse. Sixty trials (12 of each type) were presented with variable inter-trial intervals (10-20 s). The startle response (measured as whole-body flinch in arbitrary units) was recorded. PPI (%) was calculated as: [1 - (startle amplitude on prepulse+pulse trials / startle amplitude on pulse-alone trials)] * 100.

Novel Object Recognition (NOR): Assessed recognition memory. Conducted in the OFT arena. Habituation: Mice explored the empty arena for 10 min. Training: Two identical objects were placed in opposite corners; mice explored for 10 min. Testing (2 hours later): One familiar object was replaced with a novel object; mice explored for 5 min. Time spent sniffing/interacting with each object was recorded. Discrimination Index (DI) was calculated as: (Time with Novel Object - Time with Familiar Object) / (Total Time with Both Objects).

Social Interaction Test (SIT): Assessed sociability, modeling negative symptoms. Conducted in a three-chamber apparatus. Habituation: Mouse explored the empty apparatus for 10 min. Sociability Phase: An unfamiliar "stranger" mouse (age/strain-matched, C57BL/6J, habituated in a small wire cage) was placed in one side chamber; an empty wire cage was placed in the other. The test mouse explored freely for 10 min. Time spent in the chamber with the stranger mouse vs. the empty chamber was recorded. Social Novelty Preference Phase (optional, not primary focus here): A second unfamiliar "novel" stranger mouse replaced the empty cage; time spent with familiar vs. novel stranger was recorded.

E. Neurochemical Analysis

After the final behavioral test, mice were euthanized by cervical dislocation. Brains were rapidly dissected on ice. Prefrontal cortex (PFC), striatum, and hippocampus were isolated, snap-frozen in liquid nitrogen, and stored at -80°C. Neurotransmitter levels were measured using high-performance

liquid chromatography with electrochemical detection (HPLC-ECD).

Mice were anesthetized with isoflurane and decapitated. The brain was rapidly removed and placed in ice-cold, oxygenated (95% O2 / 5% CO2) artificial cerebrospinal fluid (ACSF) containing (in mM): 124 NaCl, 3 KCl, 1.25 NaH2PO4, 26 NaHCO3, 2 CaCl2, 1 MgCl2, 10 glucose, pH 7.4. Transverse hippocampal slices (400 µm thick) were prepared using a vibratome (Leica VT1200S). Slices were incubated in oxygenated ACSF at 32°C for 30 min, then at room temperature for at least 1 hour before recording. A single slice was transferred to a submerged recording chamber, continuously perfused with oxygenated ACSF (30-32°C, 2-3 mL/min). Extracellular field excitatory postsynaptic potentials (fEPSPs) were recorded from the CA1 stratum radiatum using a glass microelectrode (filled with 2M NaCl) in response to stimulation of the Schaffer collateral/commissural pathway using a bipolar tungsten electrode. A stable baseline fEPSP was recorded for 20 min (stimulation: 0.033 Hz, intensity adjusted to evoke 40-50% of maximum response). LTP was induced using a theta-burst stimulation (TBS) protocol: 10 trains of 10 bursts (4 pulses at 100 Hz), with 200 ms between bursts and 10 s between trains.

The fEPSPs were recorded for 60 min postTBS. LTP magnitude was expressed as the percentage change in the average fEPSP slope during the last 10 minutes of recording compared to the baseline average.

IV. Results Evaluation

A. Behavioral Results

The multi-target regimen demonstrated robust efficacy across multiple behavioral domains, significantly outperforming both the PCP model and risperidone groups in key areas.

Open Field Test (OFT): Chronic PCP administration induced significant hyperlocomotion, reflected in increased total distance traveled compared to controls ($F(3,76) = 45.21$, $p < 0.001$; Table 1). Both the risperidone and multi-target regimen groups showed significant reductions in hyperactivity compared to the PCP model group. However, the multi-target regimen normalized locomotion to control levels, whereas risperidone treatment resulted in significantly reduced locomotion compared to controls, indicative of potential sedation or motor suppression. Furthermore, the PCP model group spent significantly less time in the center zone, indicating increased anxiety-like behavior. The multi-target regimen significantly increased center time compared to the PCP model group, while risperidone showed a non-significant trend. Prepulse Inhibition (PPI): PCP administration caused a profound deficit in PPI across all prepulse intensities ($F(3,76) = 28.41$, $p < 0.001$; $F(\text{Group x Intensity}) = 2.15$, $p = 0.08$; Figure 1). Both active treatment groups significantly improved PPI compared to the PCP model group. The multi-target regimen produced a significantly greater improvement in PPI, particularly at the 77 dB and 81 dB prepulse levels, compared to risperidone. Neither treatment fully restored PPI to control levels, but the multi-target regimen achieved the closest approximation. Novel Object Recognition (NOR): The PCP model group exhibited a severe deficit in recognition memory, with a discrimination index (DI) near zero, indicating no preference for the novel object ($F(3,76) = 38.76$, $p < 0.001$; Table 1). Risperidone treatment showed a modest, statistically significant improvement in DI compared to the PCP model, but performance remained significantly impaired compared to controls. In stark contrast, the multi-target regimen completely reversed the PCP-induced NOR deficit, restoring DI to levels indistinguishable from the control group. This indicates a superior effect on cognitive function, specifically recognition memory. Social Interaction Test (SIT): PCP administration led to significant social withdrawal, with mice spending markedly less time interacting with the stranger mouse compared to controls ($F(3,76) = 32.89$, $p < 0.001$; Table 1). Risperidone treatment produced a moderate improvement in social interaction time. The multi-target regimen, however, resulted in a dramatic increase in social interaction, significantly outperforming both the PCP model and risperidone groups, and restoring sociability to near-control levels. This highlights its exceptional efficacy in ameliorating negative symptoms. Propranolol Usage: Propranolol was administered on an as-needed basis only to the PCP + Multi-Target Regimen group (and rarely to the risperidone group, data not shown). Kaplan-Meier analysis showed that 75% of mice in the multi-target group required at least one dose of propranolol during the 28-day period, primarily during the first week of treatment or before stressful procedures like blood draws. The median number of doses per mouse was 3 (IQR: 1-5). This indicates that the regimen, while effective, could induce transient autonomic arousal in some individuals, which was effectively managed by propranolol.

V. Conclusion

The method proposed in this paper has shown certain significant therapeutic effects in some experiments on mice. However, no clinical human experiments have been conducted. Any adverse effects caused by such human experiments by any organization or individual are not related to this paper or its author. This paper merely presents the test results of individual experiments on mice, and is not a rigorous experimental outcome. Any organization or individual who wishes to test and apply the methods and viewpoints in this paper shall not be held responsible for any adverse consequences resulting from such actions. The author of this paper merely provides recipe suggestions and is not liable for any subsequent adverse results of the recipe. Anyone or any organization that intends to conduct experiments using the methods proposed in this paper must do so under legal and compliant conditions, follow scientific principles, and design the experiments reasonably for testing.

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