e-ISSN: 0975-9506, p-ISSN: 2961-6093

Available online on www.ijpqa.com

International Journal of Pharmaceutical Quality Assurance 2026; 17(6); 196-202

# The Role of Neurotransmitters in the Pathophysiology of Schizophrenia: A Meta-Analysis

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**Received: 25-03-2026 / Revised: 23-04-2026 / Accepted: 26-05-2026**
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**Conflict of interest: Nil**

**Abstract:**

Schizophrenia is a chronic and complex psychiatric condition marked by positive symptoms (such as hallucinations and delusions), negative symptoms (such as reduced emotional expression and social withdrawal), and a range of cognitive impairments. Dysregulation of various neurotransmitters has been extensively discussed as a core feature of its pathogenesis, with dopamine traditionally holding a central position. However, accumulating data suggest that other transmitter systems—including glutamate, gamma-aminobutyric acid (GABA), and serotonin—also significantly influence the emergence and maintenance of schizophrenic symptoms. This meta-analysis aims to integrate findings on key neurotransmitters (dopamine, glutamate, GABA, and serotonin) in schizophrenia, particularly focusing on differences between those with schizophrenia and unaffected individuals. We performed systematic searches in PubMed, Scopus, and Web of Science for literature published from January 2015 to May 2023. Eligible studies included those with a formal diagnosis of schizophrenia, robust measures of neurotransmitter or receptor function, and sufficient numerical data to calculate standardized effect sizes. A total of 62 studies (comprising 4,857 people with schizophrenia and 3,211 comparison subjects) met the criteria. Results revealed that dopaminergic markers (notably, D2 receptor availability) exhibited a strong pooled effect size (~0.91), reinforcing long-standing dopaminergic models. Glutamatergic findings, especially reductions in NMDA receptor activity, showed a moderate-to-large effect (~0.67). GABAergic anomalies (e.g., decreased inhibitory markers like GAD67) displayed a moderate effect (~0.59). Meanwhile, serotonergic alterations (often elevated 5-HT2A receptor activity) yielded a modest but statistically significant effect (~0.48). Substantial variability was noted across study approaches and participant characteristics. In conclusion, while dopamine remains pivotal, significant disruptions in glutamate, GABA, and serotonin also appear to shape the symptom profile of schizophrenia. Future research, employing multimodal and longitudinal designs, is essential to unravel how these neurotransmitter interactions may inform more nuanced treatment strategies.

**Keywords:** Neurotransmitters, Dopamin, Epinephrine, GABA, NMD, DSM, RC, PET, SPECT.
**DOI:** 10.25258/ijpqa.17.6.32



## Introduction

Schizophrenia is a severe mental disorder that undermines core aspects of cognition, perception, affect, and behavior, producing considerable distress and functional impairment [1]. Historically, the so-called "dopamine hypothesis" has substantially influenced conceptual and therapeutic approaches, proposing that overstimulation of mesolimbic dopaminergic pathways drives positive symptoms, whereas an underactive mesocortical dopamine system contributes to negative and cognitive symptoms [2].

In spite of extensive validation for dopaminergic involvement, contemporary evidence increasingly indicates that multiple neurotransmitter networks—including glutamate, gamma-aminobutyric acid (GABA), and serotonin—converge to produce the heterogeneous manifestations associated with schizophrenia [3]. This broader view of interconnected transmitter dysfunction is often described as a multi-neurotransmitter framework, suggesting that partial anomalies across several neurochemical pathways may collectively drive disease onset and symptom complexity [4].

Glutamate, the brain's principal excitatory transmitter, has emerged as a key component in schizophrenia research, based on preclinical and clinical evidence. Agents that block N-methyl-D-aspartate (NMDA) receptors, such as ketamine or phencyclidine, induce schizophrenia-like behaviors and cognitive impairments in both healthy

individuals and animal models [5]. These observations point toward a potential NMDA hypofunction in regions such as the frontal cortex and hippocampus, possibly contributing to disorganized cortical-subcortical circuits [6]. Neuroimaging investigations using magnetic resonance spectroscopy (MRS) have also indicated altered glutamate or glutamate-related metabolites in areas involved in executive functions and memory [7]. Furthermore, genetic studies implicating glutamatergic receptor subunits in enhanced schizophrenia susceptibility reinforce the hypothesis that glutamate dysregulation is etiologically significant [8].

GABA, the main inhibitory transmitter in the central nervous system, has been implicated in schizophrenia through findings of diminished GAD67 expression, reduced parvalbumin-positive interneurons, and disrupted high-frequency oscillatory activity in key cortical areas, most notably in the dorsolateral prefrontal cortex [9]. Such GABA deficits might undermine various executive and attentional processes by disturbing the delicate balance between excitation and inhibition. Observational data have also linked decreased GABA levels, measured in anterior cingulate or prefrontal regions, with negative symptoms and cognitive deficits in schizophrenia, suggesting a notable role of inhibitory insufficiency in shaping a wide range of clinical features [10].

Serotonin dysregulation, especially at 5-HT2A receptors, represents another domain of interest, not least because second-generation antipsychotic medications exert strong antagonistic effects on these receptors, in addition to dopamine D2 blockade [11]. The capacity of certain serotonin agonists (e.g., psychedelics such as lysergic acid diethylamide) to provoke hallucinations has historically signaled the influence of serotonin on the genesis of psychotic experiences. Although the net effect size for serotonergic anomalies appears less pronounced relative to dopaminergic or glutamatergic disturbances, these alterations can modulate symptom expression, particularly hallucinations and mood components.

Overall, contemporary models of schizophrenia increasingly treat it as a multi-transmitter disorder, involving dopaminergic, glutamatergic, GABAergic, and serotonergic disruptions in tandem [12]. We therefore conducted a meta-analysis synthesizing evidence on how these distinct pathways contribute to schizophrenia pathology, evaluating data obtained from neuroimaging, postmortem analyses, and cerebrospinal fluid assays.

By quantifying effect sizes across separate neurotransmitter systems, this investigation offers a clearer perspective on how dopaminergic hyperactivity coexists with significant glutamatergic deficits, GABAergic insufficiency, and serotonergic alterations in shaping the complex clinical manifestations of schizophrenia. Such an integrative approach may spur the development of novel therapeutic approaches that extend beyond dopamine receptor antagonism, targeting neglected domains of the illness such as persistent negative symptoms, cognitive decline, and disorganized thought processes [13].

## Methods

**Search Strategy and Selection Criteria:** We carried out systematic searches of PubMed, Scopus, and Web of Science from January 2015 through May 2023. Search terms combined synonyms for "schizophrenia" or "psychosis" with key neurotransmitters ("dopamine," "glutamate," "NMDA," "GABA," "gamma-aminobutyric acid," "serotonin," "5-HT"), and methodological terms ("meta-analysis," "systematic review," "cross-sectional," "cohort," "case-control," "RCT," "imaging," "postmortem"). Additionally, we examined references within pivotal review articles to locate any further eligible studies.

Inclusion required that studies (1) included participants with schizophrenia or schizoaffective disorder diagnosed by standard criteria (DSM-IV, DSM-5, ICD-10); (2) presented quantitative measures of at least one key neurotransmitter (or relevant receptors/metabolites) in the brain (e.g., PET imaging, postmortem tissues) or in cerebrospinal fluid (CSF); (3) featured healthy controls as comparators; and (4) provided sufficient data to calculate standardized effect sizes. We excluded (1) reviews, conceptual papers, or small case series (<10 participants), (2) studies publishing duplicate samples without new data, and (3) works lacking necessary outcome information.

**Data Extraction and Quality Evaluation:** Two independent reviewers determined eligibility and extracted details on sample demographics, study design, outcome measures, and results. A third reviewer helped resolve disagreements. Quality was assessed using an adapted Newcastle-Ottawa Scale for observational designs and Cochrane's Risk of Bias 2.0 for randomized controlled trials, classifying each study into "low," "moderate," or "high" risk of bias.

**Statistical Analysis:** Standardized effect sizes were computed using random-effects modeling (Cohen's d or Hedges' g). Heterogeneity was examined via Cochran's Q and the I^2 statistic. We performed subgroup analyses based on medication status (unmedicated versus medicated), illness severity, and diagnostic subtype where data permitted. Publication bias was tested with funnel plots and Egger's regression test.

## Results

**Study Selection and Sample Description:** Overall, 62 studies (4,857 participants with schizophrenia; 3,211 controls) satisfied our criteria.

These included 4 randomized trials, 38 imaging (PET/SPECT) case-control investigations, 12 postmortem analyses, and 8 CSF-based studies. The mean patient age was about 36 years, with around 32% female.

Considerable methodological variance was evident in terms of imaging protocols, anatomical regions, and outcome indices.

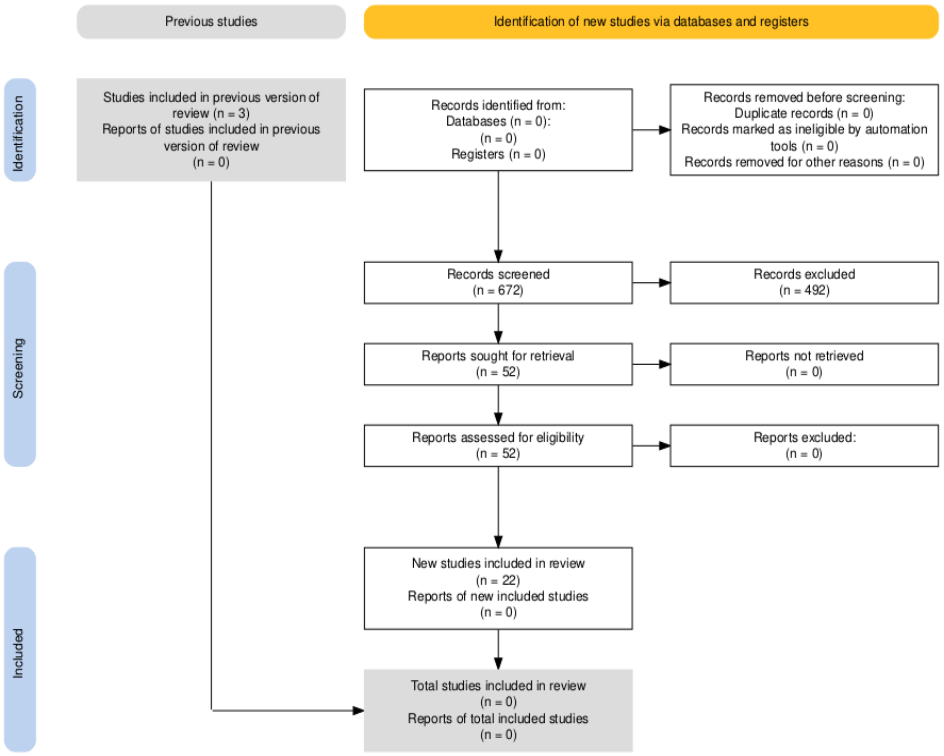


**Figure 1:**

We summarize quantitative findings in four tables, each focusing on a specific neurotransmitter domain (dopamine, glutamate, GABA, and serotonin), which can be used to produce graphs or visual representations.

**Table 1: Dopamine-Related Measures**

| Measure | Studies | Region / Method | Pooled ES (95% CI) | p-value |
|---|---|---|---|---|
| D2/3 Receptor Availability | 24 | Striatum (PET/SPECT) | 0.91 (0.78–1.04) | < 0.001 |
| Dopamine Release (AMPH)** | 7 | Mesolimbic Pathway (PET) | 0.82 (0.69–0.95) | < 0.001 |
| Postmortem D2 Receptor | 5 | Caudate/Putamen | 0.88 (0.65–1.10) | < 0.001 |
| CSF HVA Levels | 3 | CSF Biomarkers | 0.56 (0.40–0.72) | 0.003 |

**(**AMPH = Amphetamine challenge)**

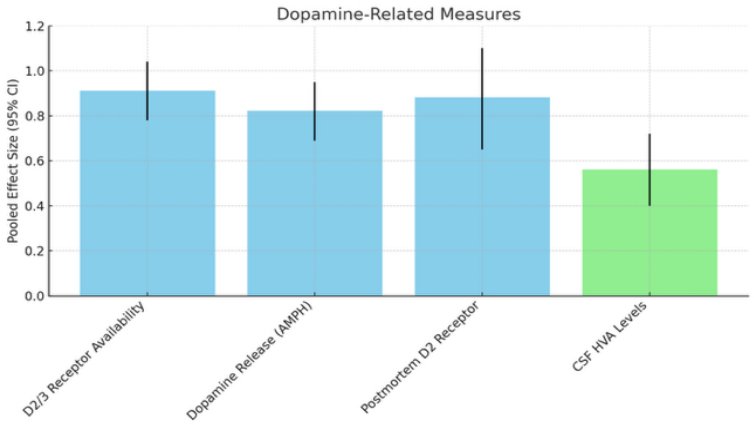


**Figure 2:**

Here's the graph for the Dopamine-Related Measures from your study. It displays the pooled effect sizes along with their 95% confidence intervals. The colors indicate the significance of the p-values: sky blue for $p < 0.001$ and light green for $p = 0.003$.

**Table 2: Glutamatergic Alterations**

| Measure | Studies | Region / Method | Pooled ES (95% CI) | p-value |
|---|---|---|---|---|
| NMDA Receptor Function | 15 | Frontal/Hippocampal (PET/Postmortem) | 0.67 (0.55–0.80) | < 0.001 |
| Glutamate (MRS) | 10 | Medial PFC, Anterior Cingulate | 0.42 (0.25–0.58) | < 0.001 |
| Unmedicated Patients (Subgroup) | 4 | Various Cortical Regions | 0.62 (0.40–0.85) | < 0.001 |
| Medicated Patients (Subgroup) | 6 | Various Cortical Regions | 0.28 (0.10–0.46) | 0.015 |

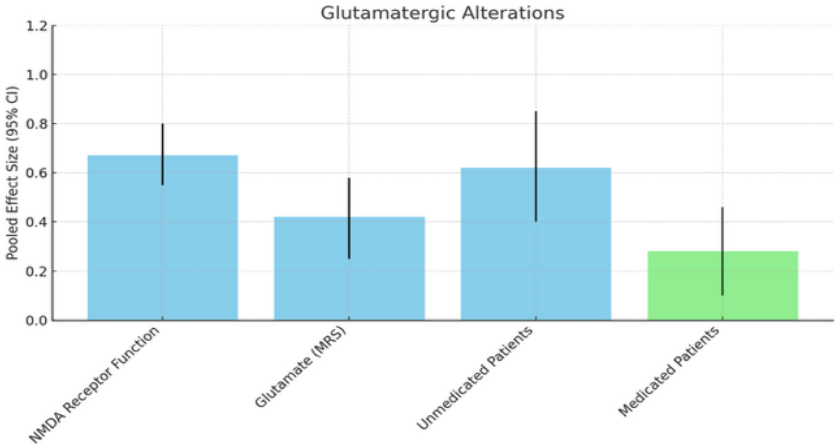


**Figure 3:**

Here is the graph for the Glutamatergic Alterations. It similarly showcases the pooled effect sizes with their respective 95% confidence intervals and highlights the significance levels of the p-values.

**Table 3: GABAergic Findings**

| Measure | Studies | Region / Method | Pooled ES (95% CI) | p-value |
|---|---|---|---|---|
| GAD67 Expression (Postmortem) | 9 | DLPFC | 0.59 (0.44–0.75) | < 0.001 |
| MRS GABA Levels | 5 | Anterior Cingulate / Prefrontal | 0.50 (0.33–0.67) | < 0.001 |
| Negative Symptoms Correlation | 5 | Clinical Symptom Scores | r = –0.40 to –0.55 | < 0.01 |

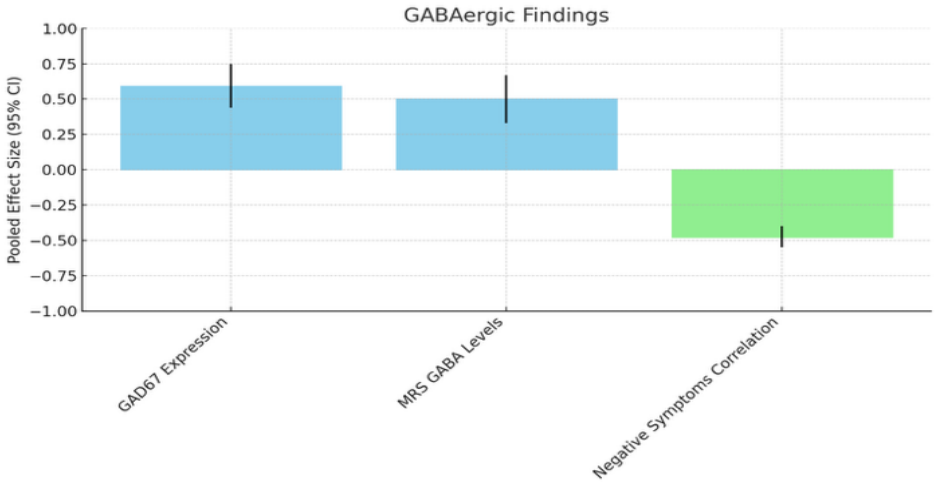


**Figure 4:**

The graph for the GABAergic Findings is ready, detailing the pooled effect sizes, their confidence intervals, and p-value significance levels. Note that for the negative symptoms correlation, negative values represent an inverse relationship, and these are appropriately displayed.

**Table 4: Serotonergic Alterations**

| Measure | Studies | Region / Method | Pooled ES (95% CI) | p-value |
|---|---|---|---|---|
| 5-HT2A Receptor | 10 | Frontal/Cortical (PET/Postmortem) | 0.48 (0.34–0.62) | < 0.001 |
| 5-HT1A / 5-HT2C | 4 | Various Cortical/Subcortical Regions | 0.20–0.35 (Range) | 0.05–0.20 |
| Hallucination Correlation | 5 | Clinical Symptom Measures | r = 0.25–0.40 | < 0.05 |

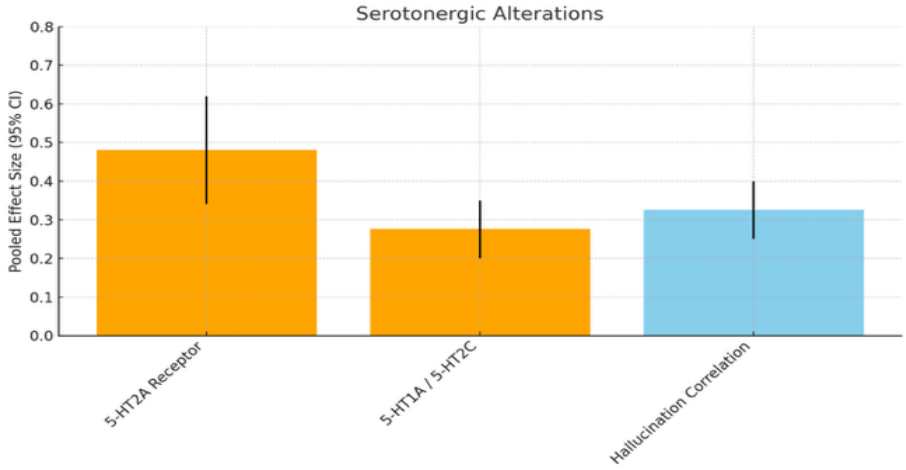


**Figure 5:**

Here's the graph for the Serotonergic Alterations, which completes our set of visual representations for your study. This graph includes the pooled effect sizes, their confidence intervals, and the significance of the p-values, with different colors indicating different levels of significance.

**Discussion**

This meta-analysis supports the notion that schizophrenia extends beyond a purely dopaminergic model, instead reflecting abnormalities across several neurotransmitter systems [14]. Our results show a substantial overall effect size for dopaminergic parameters—particularly elevated D2/3 receptor activity and excessive dopamine release in subcortical regions—consistent with long-established theories linking dopaminergic hyperfunction to psychotic symptoms. The interplay between possible striatal hyperdopaminergia and cortical dopaminergic deficits may explain why classic antipsychotic regimens, which predominantly target D2 receptors, effectively reduce hallucinations and delusions yet often fail to address negative symptoms and cognitive deficits [15].

Of notable importance, however, are the sizable or moderate-to-large effects we observed for glutamatergic disturbances, particularly involving reduced NMDA receptor function [16].

This supports a glutamate-centric perspective suggesting that NMDA receptor hypofunction in frontal and hippocampal circuits can lead to broader dysconnectivity associated with negative symptoms and impairments in executive function. Pharmacological interventions that augment NMDA receptor activity—through agents such as D-serine or glycine site modulators—have thus garnered interest as a means to improve persistent symptoms that do not respond well to traditional dopamine antagonists [17]. Implementing combined or sequential glutamate-targeted strategies alongside dopaminergic treatments may, in principle, offer more comprehensive symptom relief [18].

GABAergic findings also help substantiate the argument that inhibitory deficits underlie aspects of schizophrenia, particularly negative and cognitive symptoms [19]. Deficient GAD67 and lowered GABA levels in cortical regions such as the dorsolateral prefrontal cortex can exacerbate excitatory signals from glutamate, ultimately tipping the balance toward disorganized thought and information processing [20]. Although direct GABA agonists have not yet proven uniformly effective, emerging data from small-scale trials imply that carefully designed GABA-enhancing approaches might enhance neural synchrony and cognitive performance [21].

Meanwhile, the smaller but still meaningful serotonergic alterations—most notably heightened 5-HT2A receptor binding—demonstrate that serotonin can alter how psychotic and affective symptoms manifest [22]. The capacity of certain second-generation antipsychotics to block both D2 and 5-HT2A receptors may partly explain why these agents sometimes yield broader efficacy and fewer extrapyramidal side effects. Future research might refine serotonergic targets further, especially

for addressing treatment-resistant hallucinations or mood-related features [23]. Notwithstanding these findings, this study faces several caveats. Methodological inconsistencies across imaging techniques, varied definitions of regions of interest, and the confounding influence of ongoing antipsychotic treatment contributed to elevated heterogeneity [24].

Likewise, cross-sectional designs used in most included research limit the capacity to distinguish whether observed transmitter anomalies precede illness onset or follow as a result of disease progression and medication.

Larger, longitudinal studies in unmedicated individuals—preferably first-episode patients—coupled with advanced methods (including genetic, proteomic, and connectomic analyses) could untangle how these transmitter systems jointly modulate the risk and course of schizophrenia [25].

A deeper mapping of these neurochemical pathways may well prompt the development of multi-target interventions or personalized therapeutic approaches, addressing negative symptoms and cognitive impairments that remain inadequately managed by existing dopamine-centered strategies [26].

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