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TARGETING THE SIGMA-1/NMDA RECEPTOR COMPLEX TO AMELIORATE COGNITIVE DEFICITS AND NEGATIVE SYMPTOMS IN SCHIZOPHRENIA

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ABSTRACT

Background: The main limitation of contemporary schizophrenia treatment is the insufficient clinical response of negative symptoms and cognitive deficits to current antipsychotics. In light of the NMDA receptor hypofunction hypothesis, research increasingly targets novel glutamatergic modulators.
Aim: This study analyzes the molecular mechanisms linking Sigma-1 receptor (σ1R) dysfunction with glutamate N-methyl-D-aspartate receptor (NMDAR) hypofunction in schizophrenia and assesses the therapeutic potential of σ1R agonists (e.g., fluvoxamine, pridopidine, AF710B) in reducing drug-resistant symptoms. It also examines their broader socioeconomic implications.
Methods: A narrative review of the literature was conducted using the PubMed database, primarily focused on publications from 2006 to 2026; however, earlier studies were incorporated if they provided crucial mechanistic insights. European Brain Council reports were also included.
Results: Accumulated evidence indicates that σ1R stabilizes NMDAR transport to the cell membrane and modulates its activity. Pharmacological stimulation by σ1R agonists promotes the restoration of synaptic plasticity and cellular homeostasis, effectively eliminating endoplasmic reticulum stress and inflammation. This results in the restoration of dendritic spine structure and a significant improvement in memory, cognitive flexibility, and social interactions.
Conclusion: Targeted modulation of the σ1R/NMDAR complex is a highly promising neuropharmacological strategy in schizophrenia management. Augmenting standard treatment with targeted σ1R agonists may effectively address the drug-resistant aspects of schizophrenia pathophysiology, paving the way for a significant improvement in patient functional prognosis.

KEYWORDS

Schizophrenia, Sigma-1 Receptor, NMDA Receptor, Cognitive Deficits, Negative Symptoms

CITATION

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Introduction

Schizophrenia is a chronic and debilitating neurodevelopmental disorder diagnosed in 0.5–1% of the world's population, with an onset generally occurring during late adolescence or early adulthood. The origins of the disease are strongly tied to neurodevelopmental disruptions, where environmental stressors interact with an individual's genetic predisposition to alter the normal structural and functional maturation of the brain. The profound genetic basis of this illness is highlighted by its pronounced heritability, demonstrated by the fact that identical twins of individuals with schizophrenia face a risk that is 40- to 50-fold higher than that of the average person (Balu, 2016). The clinical picture of the disease is highly complex and heterogeneous, encompassing three primary domains: positive symptoms (delusions, hallucinations, disorganized behavior), negative symptoms (asociality, anhedonia, avolition, flat affect), and cognitive deficits (impairments in working memory, attention, executive functions, and information processing speed) (Rafcikova, Novakova, & Stracina, 2023). Although the introduction of first- and second-generation antipsychotics, acting primarily through blockade of dopaminergic D2 and serotonergic 5-HT2A receptors, has revolutionized the treatment of positive symptoms, their efficacy regarding negative symptoms and cognitive impairments remains highly unsatisfactory. Extensive meta-analyses of randomized, double-blind clinical trials utilizing comprehensive neuropsychological tests have consistently demonstrated that these medications offer negligible or highly inconsistent benefits across cognitive domains. Furthermore, recent molecular evidence suggests that chronic administration of certain atypical antipsychotics may paradoxically exert deleterious effects on cortical processing by triggering detrimental compensatory mechanisms (Martínez, Brea, Rico, de los Frailes, & Loza,

2021). These treatment-resistant symptoms are the main prognostic factors for significant direct costs incurred by healthcare systems (Calzavara Pinton et al., 2024).

The N-methyl-D-aspartate receptor (NMDAR) hypofunction hypothesis has gained empirical support, notably through the observation that NMDAR antagonists, such as ketamine, can induce the full spectrum of schizophrenia symptoms in healthy volunteers, including cognitive deficits and negative symptoms (Krystal et al., 1994). As outlined by Coyle (2006), five diverse lines of evidence—encompassing recent genetic discoveries, neuroimaging, postmortem analyses, pharmacological studies, and NMDAR antagonist trials—currently make the NMDA receptor hypofunction hypothesis a much more strongly founded explanation for the schizophrenia endophenotype than the classic dopaminergic paradigm. While dopamine-centric models primarily account for psychotic exacerbations, they fail to explain the pervasive cognitive decline and negative symptoms that most profoundly disable patients. In contrast, the glutamatergic hypothesis bridges this clinical gap. Human challenge studies reveal that low doses of NMDAR antagonists accurately replicate these medication-resistant core deficits in healthy volunteers. Furthermore, advanced neuroimaging and neuropathological analyses demonstrate that structural brain alterations and local γ-aminobutyric acid (GABA) interneuron dysfunctions are direct downstream consequences of impaired NMDAR signaling. This model is definitively reinforced by recent discoveries showing that major schizophrenia susceptibility genes primarily regulate glutamate transmission, and by clinical trials demonstrating that pharmacological enhancement of the NMDAR complex effectively ameliorates the exact neurocognitive and negative symptoms that conventional antipsychotics leave untreated (Coyle, 2006). NMDAR dysfunction leads to an excitation/inhibition (E/I) imbalance within cortical neural networks, resulting in disorganization of gamma oscillations and impairment of information processing mechanisms (Jadi, Behrens, & Sejnowski, 2016).

In this context, the Sigma-1 receptor (σ1R) emerges as a key, multifunctional regulator of neuronal homeostasis. σ1R is not a classic membrane receptor, but a ligand-dependent chaperone protein, physiologically residing in specific microdomains of the endoplasmic reticulum (ER) called mitochondria-associated membranes (MAMs). Structurally, crystallographic analyses reveal a single transmembrane domain structure, with a short N-terminus and a prolonged C-terminal tail (Ryskamp et al., 2019). According to Pabba and Sibille (2015), functioning as a vital intracellular regulator of calcium balance, the σ1R exhibits a distinct dual mechanism of action. On one side, it drives synaptic plasticity and long-term potentiation by boosting NMDAR-mediated neurotransmission and associated membrane trafficking. Conversely, it acts as a robust neuroprotectant against excitotoxicity triggered by calcium overload. The receptor accomplishes this defense by disrupting harmful macromolecular complexes—specifically, by breaking the destructive linkages among the NMDAR GluN2B subunit, the postsynaptic density protein 95 (PSD-95), and neuronal nitric oxide synthase (nNOS). By interrupting this targeted interaction, σ1R suppresses the synthesis of damaging nitric oxide compounds, thereby actively shielding neurons from degenerative processes (Pabba & Sibille, 2015). Yasui and Su (2016) further elaborate that under conditions of cellular stress or under the influence of agonists, σ1R translocates to other cellular compartments, such as the postsynaptic membrane, where it modulates the activity of ion channels, kinases, and receptors, including the NMDAR, which is essential for synaptic plasticity. The initiation of this activation process involves the dissociation of σ1R from its ER-resident partner, the BiP/GRP78 chaperone, which subsequently unleashes its full functional capabilities. Once mobilized, σ1R profoundly diversifies its regulatory reach across the cell. At the plasma membrane, it directly binds to Kv1.2 subunits, altering delayed-rectifier potassium currents and thereby shaping overall neuronal excitability. Furthermore, σ1R can relocate to the nuclear envelope, where it actively participates in epigenetic gene regulation. By recruiting chromatin-remodeling factors—such as emerin, histone deacetylases (HDAC), and the barrier-to-autointegration factor (BAF)—it efficiently represses the transcription of specific genes, such as monoamine oxidase B (MAOB). Additionally, it acts as a chaperone for inositol 1,4,5-trisphosphate receptors (IP3Rs) at the ER, facilitating optimal calcium transfer into mitochondria to boost ATP production, while simultaneously modulating reactive oxygen species (ROS) signaling pathways and autophagic processes (Yasui & Su, 2016).

Aim of the publication

This paper aims to assess the role of the Sigma-1 receptor dysfunction in inducing glutamatergic pathway hypofunction in schizophrenia. It outlines the role of the σ1R complex in regulating endoplasmic reticulum (ER) stress and mitochondrial function within GABAergic neurons, which are crucial for generating gamma oscillations. A critical assessment of research results on targeted therapies using σ1R ligands (e.g., fluvoxamine, pridopidine, AF710B) for the treatment of cognitive deficits and negative symptoms is also included. The potential for implementing these therapies in the context of the socioeconomic burden of schizophrenia is analyzed.

Methodology

The literature review was carried out using the PubMed database, encompassing publications from 2006 to 2026. Additionally, older literature was reviewed when it offered fundamental context regarding the underlying biological pathways. Relevant public health and macroeconomic reports from official institutional databases, such as the European Brain Council, were included to assess the societal costs of the disease. The search strategy included combinations of keywords in English, such as: "Sigma-1 receptor schizophrenia", "NMDA receptor hypofunction", "cognitive deficits schizophrenia treatment", "negative symptoms schizophrenia", "fluvoxamine schizophrenia", "pridopidine clinical trials", "AF710B", "mitochondria-associated membranes", and "parvalbumin interneurons gamma oscillations." The inclusion criteria covered full-text articles in English or Polish, meta-analyses, systematic reviews, review articles, preclinical studies on animal models (in vivo), retrospective longitudinal studies, clinical studies, socioeconomic, and epidemiological reports.

Results

Analysis of the collected research material allows us to identify several key areas in which σ1R/NMDAR dysfunction contributes to the clinical picture of schizophrenia and to indicate promising therapeutic directions.

Pathophysiological mechanisms of σ1R and NMDAR dysfunction

Understanding the molecular basis of interactions between the σ1R and the NMDAR is fundamental to the development of effective targeted therapies. Research over the past decade has shed new light on the role of σ1R as a "molecular switch" regulating glutamatergic activity at multiple cellular levels.

The Role of σ1R in the Intracellular Trafficking and Stabilization of NMDAR

NMDA receptors are heterotetramers consisting of obligatory GluN1 subunits and GluN2 subunits (four subtypes, A-D) or GluN3 subunits. Their proper expression on the postsynaptic membrane surface is crucial for excitatory signaling and synaptic plasticity (Washburn, Xia, Zhou, Mao & Dalva, 2020). Contemporary neurobiological research, as comprehensively demonstrated by Pabba et al. (2014), provides compelling evidence that the pharmacological stimulation of the σ1 R chaperone—utilizing highly selective agonists such as (+)-SKF-10,047, PRE-084, and (+)-pentazocine—triggers a complex intracellular cascade that fundamentally remodels synaptic architecture. The initial and critical driving force behind this transformation is the rapid induction of de novo protein translation. The necessity of this translational step was firmly demonstrated through the application of anisomycin, a potent protein synthesis inhibitor, which completely abolished the agonist-induced effects when administered prophylactically. This translational surge drives a robust upregulation in the intracellular reservoirs of NMDAR subunits GluN2A and GluN2B, alongside the essential postsynaptic scaffolding protein, PSD-95. Interestingly, the basal expression levels of the obligatory GluN1 subunit and α-amino-3-hydroxy-5-methylisoxazole-4-propionate (AMPA) receptors remain entirely unchanged during this initial phase. This discrepancy strongly suggests that the availability of newly synthesized GluN2 subunits is the primary factor limiting the rate of successful formation of functional NMDAR heterotetrameric complexes. The specificity of this entire molecular cascade was further validated by the introduction of classical σ1R antagonists (such as BD1047 and BD1063), which effectively counteracted protein overproduction, confirming full dependence on sigma signaling pathways.

The researchers note that it is at this molecular junction that the σ1R exhibits its multidimensional nature. Located primarily in microdomains of the endoplasmic reticulum (ER) and mitochondria-associated membranes (MAM), it acts as a highly dynamic intracellular scaffold. Co-immunoprecipitation assays reveal that activation is followed by a marked increase in physical interaction between σ1R molecules and new GluN2 subunits within the ER. Acting as a molecular chaperone, the σ1R actively coordinates their subsequent export to the cellular secretory pathway. Subcellular fractionation studies using discontinuous sucrose gradients provide definitive evidence of this mobilization: upon σ1R activation, NMDAR subunits and PSD-95 are

exported from the ER compartment and accumulate densely in exocytotic transport vesicles destined for the cell membrane.

A particularly innovative mechanistic discovery highlighted by the authors concerns the way in which the σ1R manages this macromolecular cargo during its transport. Experimental data show that activated σ1R has the capacity to selectively and temporarily disrupt the physical connection between the moving GluN2B subunit and the PSD-95 scaffold. Since specific NMDAR subunits exhibit different affinities for different anchor proteins, it is hypothesized that this temporary disconnection provides a highly precise sorting and segregation mechanism. This dynamic allows the neuron to appropriately route migrating receptor complexes, directing specific NMDAR subpopulations to tightly defined areas on the neuronal surface—for example, segregating receptors destined for the synaptic cleft from those destined for extrasynaptic microdomains.

Ultimately, their findings demonstrate that the functional culmination of this complex intracellular journey is the robust exocytotic fusion of these transport vesicles with the postsynaptic membrane. Advanced surface biotinylation techniques have clearly revealed a significant increase in the surface density of fully assembled, functionally active NMDA receptors. Notably, an accompanying increase in GluN1 subunits on the surface was also detected during this final stage, indicating their successful integration into complete heterotetramers with their newly delivered GluN2 counterparts. This complex, σ1R-coordinated receptor transport pathway fundamentally enhances neuronal excitability and provides the molecular basis necessary for long-term potentiation (LTP), synaptic plasticity, and the enhancement of broader cognitive functions, such as learning and memory (Pabba et al., 2014).

MAMs Dysfunctions and Endoplasmic Reticulum Stress

Mitochondria-associated membranes (MAMs), as described by Bui, Santerre, Shcherbik, and Sawaya (2026), function as a highly advanced interorganelle communication network that coordinates metabolic homeostasis and cell survival mechanisms. These structures contain the IP3R–GRP75–VDAC1 complex, which is a fundamental three-component protein system that acts as the physical and functional core of MAM domains, i.e., contact spaces between the endoplasmic reticulum and mitochondria. Structurally, the architecture of this connection is based on the inositol 1,4,5-trisphosphate receptor (IP3R) anchored in the reticulum membrane and the voltage-dependent anion channel 1 (VDAC1) located on the outer membrane of the mitochondrion, which are physically bridged via glucose- regulated protein 75 (GRP75). This protein bridge enforces a highly restricted distance of 10–50 nanometers between the two organelles, allowing them to communicate directly without the risk of complete membrane fusion. The authors emphasize that from a physiological perspective, this system functions as the main transport corridor regulating the targeted flow of calcium ions from the stores in the endoplasmic reticulum directly to the mitochondrial matrix. This precisely controlled flux is critical for bioenergetics, as calcium ions serve as key cofactors driving the enzymes of the tricarboxylic acid cycle and the machinery of oxidative phosphorylation, enabling the cell to rapidly adjust ATP production to current metabolic needs. Furthermore, efficient communication through this transmission axis is essential for triggering intracellular quality control mechanisms, including autophagosome biogenesis and maturation during cellular responses to stress or nutrient deprivation. However, it is important to emphasize the dual nature of this system, as under pathological stress conditions, excessive calcium overload of mitochondria via the IP3R–GRP75–VDAC1 complex results in the opening of the mitochondrial permeability transition pore (mPTP), which is a direct signal irreversibly initiating programmed cell death (apoptosis) (Bui et al., 2026).

According to Ryskamp, Korban, Zhemkov, Kraskovskaya, and Bezprozvanny (2019a), the σ1R is a regulator of MAMs stability and functionality. Under physiological conditions, it forms an inactive complex with the binding immunoglobulin protein (BiP) within the endoplasmic reticulum (ER), acting as an intracellular stress sensor. Their research indicates that under the influence of harmful stimuli or in response to pharmacological stimulation with ligands, the σ1R detaches from BiP and actively protects inositol 1,4,5-trisphosphate type 3 receptors (IP3R3). Due to this chaperoning interaction, this protein prevents premature degradation of IP3R3, which in turn ensures optimal and strictly controlled ion flow and ATP production. In the course of neurodegenerative diseases, profound disturbances in this calcium homeostasis, severe energy deficits, and increased oxidative stress are observed. The loss of normal σ1R function in the course of these pathologies results in IP3R3 instability and a breakdown in calcium flux, which in turn provokes pathological, highly neuron-toxic overproduction of reactive oxygen species (ROS). Furthermore, in specific pathologies such as Huntington's disease, this calcium dysregulation is exacerbated by the hyperactivity of IP3R type 1 (IP3R1) receptors, a distinct mechanism that functional σ1R signaling can also attenuate (Ryskamp et al., 2019a).

Moreover, the authors note that the action of the σ1R in these structures extends far beyond calcium signaling itself. They are critical signaling platforms in which σ1R acts as the central regulator of intracellular lipid homeostasis. Because this receptor has an affinity for cholesterol, it localizes in lipid rafts (microdomains rich in galactosylceramides), from which it precisely regulates the transport of essential lipids that are important, for example, in the processes of proper axon myelination. Additionally, σ1R actively manages the cell's response to ER stress in MAM domains by facilitating the dimerization and activation of a key stress sensor, IRE1 kinase. This phenomenon triggers repair mechanisms dependent on the transcription factor XBP1, leading to the production of new chaperone proteins and simultaneously inhibiting neurotoxic inflammatory pathways. The researchers also highlight that adequate σ1R activity is a prerequisite for maintaining the overall structural integrity of the MAM space. Studies show that the loss of this function (resulting, for example, from rare genetic mutations) leads to a profound disruption of communication between the two organelles, which is one of the main pathomechanisms leading to the death of motor neurons in amyotrophic lateral sclerosis (ALS). It is worth noting, however, that under conditions of full activation and release from BiP, the σ1R gains the ability to leave the MAMs and move throughout the entire endoplasmic reticulum network, allowing it to modulate a wide spectrum of target proteins located in other compartments of the cell (Ryskamp et al., 2019a).

As Steullet et al. (2017) point out, GABAergic interneurons expressing parvalbumin (PV+) are particularly sensitive to these oxidative and metabolic abnormalities due to their high energy demands as fast-spiking cells. The authors explain that the primary role of these interneurons is to orchestrate the activity of large groups of neurons, bringing them into a state of high-frequency synchronization. In electroencephalographic (EEG) recordings, this activity manifests as gamma oscillations (30-80 Hz), which are crucial for attentional processes and working memory (Jadi et al., 2016). Networks mediated by these cells underpin the proper processing of sensory stimuli, effective learning, and the regulation of appropriate social behaviors (Steullet et al., 2017).

According to Ahmed, Abdou, Ibrahim, Mohamed, and El-Boghdady (2025), chronic endoplasmic reticulum (ER) stress is one of the fundamental mechanisms driving the pathogenesis of schizophrenia and other psychiatric disorders. When neurons can no longer cope with an excess of misfolded proteins, pathological overactivity of the unfolded protein response (UPR) pathways occurs, controlled by sensory proteins such as IRE-1, PERK, and ATF-6. If this intracellular crisis persists for too long, adaptive mechanisms break down and transform into destructive proapoptotic and proinflammatory cascades. They observe that at the cellular level, this results in a sharp decline in the levels of key synaptic structural proteins, including the postsynaptic scaffold protein PSD-95 and NMDARs. The ultimate result of these mechanisms is neural circuit dysfunction, a profound loss of synaptic density, and a breakdown in the inhibitory transmission mediated by parvalbumin interneurons (Ahmed et al., 2025).

Building on this, the authors demonstrate that under these conditions, the σ1R takes on a primary protective role. Studies using fluvoxamine, a potent agonist of this receptor, show that pharmacological stimulation of σ1R leads to its dissociation from the BiP/GRP78 protein and the activation of its chaperone properties. The released σ1R actively supports the proper folding of proteins, which results in the mitigation of pathological ER stress – visible as a marked decrease in IRE-1, PERK, and ATF-6 markers. By stopping intracellular apoptosis and reducing inflammation, σ1R preserves neuronal architecture. The result of this action is an extensive restoration of synaptic density (increased expression of NMDAR and PSD-95) and recovery of proper neuronal function (Ahmed et al., 2025). In terms of the behavioral outcomes, intracellular suppression of endoplasmic reticulum stress by σ1R brings substantial therapeutic effects. In schizophrenia models, this intervention effectively reverses the most extensive behavioral deficits, such as severe working memory impairment, cognitive inflexibility, and pronounced social withdrawal. This clearly indicates that targeted pharmacological protection of the endoplasmic reticulum against stress using sigma ligands may be an innovative and highly effective strategy for treating refractory negative and cognitive symptoms of schizophrenia (Ahmed et al., 2025).

Modulation of Neuroplasticity Pathways: BDNF and D-Serine

σ1R – BDNF – TrkB Axis

Brain-derived neurotrophic factor (BDNF) serves as a principal mediator of synaptic plasticity, neuronal survival, and neurogenesis. According to Chen, Li, Zhang, Yang, and Lu (2022b), in the neuropathology of schizophrenia, marked decreases in the concentration of this protein are consistently observed, both in blood serum and in brain regions crucial for cognitive processes, with particular emphasis on the prefrontal cortex (PFC) and hippocampus. This specific protein deficiency constitutes a direct molecular basis for the development of profound cognitive impairments observed in this patient population. The authors note that these pathological changes in the central nervous system have been identified primarily through advanced studies of postmortem brain tissue from patients with schizophrenia, which clearly demonstrated a decrease in BDNF gene transcription and related intracellular signaling cascades. Furthermore, peripheral deficits have been corroborated by systematic laboratory analyses of plasma samples from psychiatric patients, which revealed a highly abnormal, reduced expression of not only the BDNF, but also its target receptor, tropomyosin receptor kinase B (TrkB) (Chen et al., 2022b). Studies clearly demonstrate that σ1R agonists stimulate the expression, secretion, and signaling of BDNF. This occurs on several levels:

- **Transcription regulation:** As demonstrated by Ren et al. (2022), σ1R activation and the subsequent increase in intracellular calcium concentration lead to the activation of Ca2+/calmodulin-dependent protein kinases (CaMKII and CaMKIV). These enzymes phosphorylate the CREB (cAMP response element-binding protein) transcription factor, which upregulates BDNF expression. Experiments using kinase-deficient animal models have proven that this calcium-based pathway is essential, since without it, clinical sigma-1 agonists (such as fluvoxamine or SA4503) completely lose their ability to alleviate depressive symptoms and initiate neurogenesis processes (Ren et al., 2022).
- **Post-translational processing:** σ1R facilitates the conversion of the pro-BDNF precursor to the mature, biologically active form of BDNF and its transport to sites of secretion (Fujimoto, Hayashi, Urfer, Mita & Su, 2012). Acting as a molecular chaperone, this receptor prevents the pathological aggregation of newly produced neurotrophins under stressful conditions in the endoplasmic reticulum, ensuring the robust and efficient release of properly formed BDNF into the synaptic space (Fujimoto et al., 2012).
- **TrkB transactivation:** σ1R can directly or indirectly amplify signaling through TrkB (tropomyosin receptor kinase B), the main receptor for BDNF, ultimately promoting the structural remodeling of dendritic spines and a significant increase in the density of postsynaptic excitatory synapses (Ka, Kook, Liao, Buch & Kim, 2016).

Research by Chen et al. (2022a) on a new allosteric σ1R modulator, the compound SOMCL-668, has demonstrated its ability to reverse BDNF deficits and restore AKT-CREB-BDNF signaling pathway activity in the frontal cortex of PCP-treated mice. This effect was closely correlated with improvements in social interaction and memory, confirming the therapeutic potential of this pathway. Furthermore, the therapeutic efficacy of SOMCL-668 was completely blocked by co-administration of a specific inhibitor of the PI3K/AKT pathway (LY294002). Additionally, experiments conducted on σ1R knockout mice showed a complete lack of biochemical and behavioral recovery, which firmly establishes that the action of the tested compound is entirely dependent on the presence of this specific receptor (Chen et al., 2022a). Similarly, Yang et al. (2025) reported that the agonist YL-0919 also demonstrated the ability to increase BDNF levels and dendritic spine density in the medial prefrontal cortex, resulting in improved attention in stress models. This mechanism was validated under conditions of chronic exogenous corticosterone exposure, which physiologically mimics states of severe depression and anxiety, leading to dendritic atrophy. Pharmacological stimulation with YL-0919 not only reconstructed the lost neuronal architecture, but also increased the expression of other key structural proteins, such as PSD-95 and synapsin-1, which ultimately optimized neural network plasticity and restored normal attentional performance (Yang et al., 2025).

Regulation of D-serine levels and interaction with DISC1

D-serine is an endogenous amino acid that functions as a co-agonist of the NMDAR at the glycine binding site and is essential for the full activation of the receptor and the induction of synaptic plasticity (Jacobi, Halawani, Lynch & Lin, 2019). In schizophrenia, reduced concentrations of D-serine are observed in cerebrospinal fluid, which is associated with NMDAR hypofunction (Jacobi et al., 2019). The enzyme responsible for synthesizing D-serine from L-serine is serine racemase (SR). Research conducted by Ma et al. (2013) indicates a significant interaction between SR and the DISC1 (Disrupted-in-Schizophrenia 1) protein, mutations of which constitute a strong risk factor for schizophrenia. Their findings reveal that DISC1 binds to SR, stabilizing the enzyme and preventing its degradation. Mutant DISC1 loses this ability, leading to a

decrease in D-serine levels (Ma et al., 2013). Although the direct interaction of σ1R with SR still requires further analysis, preclinical studies have clearly established that σ1R activation in astrocytes directly stimulates the production and release of D-serine, which is a fundamental mechanism facilitating NMDAR activity (Moon et al., 2015).

New and Repositioned σ1R Ligands in Current Research

Advances in understanding σ1R biology have led to a re-evaluation of the potential of established drugs and the development of new, highly selective molecules. A detailed analysis of the most prominent candidates is presented below.

Fluvoxamine: From Antidepressant to Pro-Cognitive Modulator

Fluvoxamine, commonly used as a selective serotonin reuptake inhibitor (SSRI) in the treatment of depression and obsessive-compulsive disorder, exhibits a unique pharmacological profile. It is the most potent σ1R agonist among all SSRIs, with a binding affinity of Ki = 17.0 nM (Albayrak & Hashimoto, 2017).

Research on an animal model of ketamine-induced schizophrenia conducted by Ahmed et al. (2025) has shown that fluvoxamine improved cognitive flexibility, learning abilities and sociability functions among treated rats, which was confirmed by behavioral tests. In the three-chamber social interaction test, rats treated exclusively with ketamine showed a notable decrease in sociability index (SI) by 77% and social novelty preference index (SNI) by 76%. After fluvoxamine treatment, social behavior improved significantly—the SI and SNI increased 3-fold and 3.4-fold, respectively, compared to the untreated ketamine group. The Morris Water Maze revealed that ketamine exposure notably impaired performance, evidenced by a 41% reduction in time spent in the target quadrant (SW), decreased entry frequency, and a 4.8-fold delay in target quadrant entrance relative to controls. Fluvoxamine administration reversed these memory deficits. In comparison with the untreated group, rats receiving fluvoxamine spent 54% more time in the target quadrant, achieved 1.4-fold more entries, and reached the target area 71% faster.

The authors demonstrated that at the cellular level, the treatment alleviated endoplasmic reticulum stress (evidenced by the suppression of inositol-requiring enzyme type 1 [IRE-1], protein kinase R-like ER kinase [PERK], activating transcription factor 6 [ATF-6]), reduced neuroinflammation (indicated by a decrease in tumor necrosis factor-α [TNF-α], and ionized calcium-binding adaptor molecule 1 [Iba-1]) and apoptosis (reflected by downregulated B-cell lymphoma 2 protein associated X-protein [Bax] and caspase-12 levels) in the prefrontal cortex. These effects were reversed by the σ1R antagonist (NE-100), confirming that the pro-cognitive and pro-social effects of the drug result from σ1R agonism rather than serotonin transporter blockade. Fluvoxamine also restored parvalbumin (PV) and glutamate decarboxylase 67 (GAD67) levels (diminished expression of these proteins occurs in schizophrenia), which are critical for the proper functioning of GABAergic interneurons. The study indicates that the reduction in GAD67 possibly leads to decreased GABA synthesis and weakened inhibitory control, generating a pathological excitatory-inhibitory imbalance (Ahmed et al., 2025). In conclusion, fluvoxamine demonstrates significant therapeutic potential for schizophrenia through its ability to re-establish cellular balance and mitigate pathological pathways. Despite these promising results, broader investigations utilizing varied etiological models are necessary to firmly establish the drug's translational viability.

Pridopidine: A selective σ1R agonist against neurodegeneration

Pridopidine, originally developed as a “dopamine stabilizer” due to its low affinity for the D2 receptor, has been found in studies to be a highly selective σ1R agonist. Its affinity for σ1R is approximately 100 times higher than for the D2 receptor (Sahlholm, Århem, Fuxe, & Marcellino, 2013). PET studies using the radiotracer [18F] fluspidine in humans have shown that at clinical doses (45 mg b.i.d.), pridopidine occupies approximately 87-91% of σ1 receptors in the brain, with negligible (<3%) occupancy of dopaminergic receptors (Grachev et al., 2021).

Although the main clinical trials of pridopidine focused on Huntington's disease, it is currently also being studied in the context of other neurodegenerative diseases. Exploring its potential beyond these initial indications, Sahlholm, Valle-León, Fernández-Dueñas, and Ciruela (2018) investigated a mouse model in which memory impairment was induced using phencyclidine (PCP). Their findings established that pridopidine effectively reversed these deficits. Research demonstrates that this drug acts strictly through the activation of the σ1R, as its protective and pro-cognitive effects were completely abolished after simultaneous administration of NE-100, a selective σ1R antagonist. The efficacy of the therapy was measured using the classic behavioral Novel Object Recognition (NOR) test, which is considered to be the equivalent of declarative memory testing in humans. Mice treated exclusively with phencyclidine exhibited pronounced recognition memory deficits and failed to show the expected preference for the new object, as confirmed by

the preference index for the new object, which dropped to a level indicating no clear preference for either object. In contrast, animals that were treated with pridopidine after PCP administration achieved a significantly higher preference index for the new object, demonstrating effective recovery of cognitive abilities (Sahlholm et al., 2018).

Focusing on the microscopic architecture, Ryskamp et al. (2019b) reported that pridopidine protects mushroom spines—synaptic structures crucial for memory processes—against the toxicity of amyloid Aβ42 oligomers, reduces pathological calcium levels in the endoplasmic reticulum, and regulates intracellular calcium influx, which was crucial for maintaining synaptic structure. This structural preservation ultimately restores normal long-term potentiation (LTP) in hippocampal circuits. The experiment confirmed that this entire rescue effect was strictly dependent on the σ1R. In neurons where the σ1R receptor was pharmacologically blocked or genetically deleted, pridopidine completely lost its synapse-protecting properties (Ryskamp et al., 2019b). Furthermore, neuroplasticity studies indicate that this drug stimulates synaptogenesis by inducing intracellular survival signaling cascades (such as PI3K/Akt and MAPK/ERK), and protects against oxidative stress and excitotoxicity, which correlated with a significant improvement in the spatial memory in the Morris Water Maze test (Estévez-Silva et al., 2022). Given its ability to promote synaptogenesis and ameliorate PCP-induced deficits independently of D2 receptor engagement, pridopidine presents a unique, σ1R-driven pharmacological profile that is particularly attractive for mitigating the difficult-to-treat cognitive symptoms of schizophrenia.

AF710B: A drug with strong pro-cognitive potential

The detailed analysis published by Fisher et al. (2016) outlines that AF710B (now known as ANAVEX 3-71) possesses a unique, synergistic molecular mechanism of action. The compound functions as a positive allosteric modulator (PAM) of the muscarinic M1 receptor and a highly selective, direct agonist of the σ1R. As a PAM, AF710B binds to a secondary allosteric site on the M1 receptor, significantly enhancing its affinity and efficacy for endogenous acetylcholine. This interaction strikingly amplifies intracellular signaling cascades, specifically the phosphorylation of ERK1/2 kinases and CREB transcription factor activation, both critical for memory consolidation. Furthermore, the team specifies that AF710B targets a hypothesized M1-σ1R heteromeric complex located within dendritic spines. Knockdown of σ1R via lentiviral vectors or M1 blockade using pirenzepine completely abolishes the drug's synaptoprotective properties, confirming that simultaneous activation of both pathways is essential for synaptic preservation. The efficacy and safety profile of this innovative compound have been rigorously validated across diverse preclinical models. In vitro evaluations utilized primary hippocampal neurons derived from mice with specific genetic mutations (PS1-KI and APP-KI), enabling real-time microscopic observation of the drug's restorative effects on degenerating neurite architecture. In vivo functional assessments included acute amnesia models, where rats treated with the memory-blocking agent trihexyphenidyl were evaluated using the Passive Avoidance (PA) test. For chronic pathology, the drug was administered to triple-transgenic (3xTg-AD) mice exhibiting advanced amyloid pathology, with their navigational and spatial memory assessed via the Morris Water Maze (MWM) task.

Findings from these comprehensive evaluations confirmed that AF710B contributes to the reduction of key pathological features associated with Alzheimer's disease such as Beta-Secretase 1 (BACE1), Glycogen Synthase Kinase 3β (GSK3β), and Cyclin-Dependent Kinase 5 (CDK5) activator peptide (p25). Furthermore, it decreases neuroinflammation, lowers the levels of soluble and insoluble Aβ40 and Aβ42, and mitigates the deposition of neurofibrillary tangles and amyloid plaques.

From a psychopharmacological perspective, the most profound effect of this compound, as characterised in the study, is the rescue of neuroplasticity. Advanced three-dimensional structural analyses demonstrate that it almost completely prevents the pathological loss of mushroom spines—large, fully functional synaptic protrusions that serve as the physical substrate for consolidated memory traces. The preservation of this synaptic architecture translates into pivotal cognitive outcomes; animal subjects rapidly recovered spatial reference memory and associative learning capabilities. Notably, these fundamental structural and cognitive benefits were achieved using ultra-low microgram doses. Moreover, the improvements in brain function exhibited a remarkably long duration of action, with sustained anti-amnesic effects observed up to 72 hours following a single administration. Taken together with the morphological data, these results provide definitive evidence of genuine, long-term neural circuit reconstruction (Fisher et al., 2016).

Ultimately, the demonstrated capacity of AF710B to rebuild synapses and restore plasticity indicates its significant potential not only for Alzheimer's disease but also as a promising therapeutic strategy for schizophrenia, a condition characterized by overlapping neuronal deficits, including decreased dendritic spine density in the prefrontal cortex and hippocampus.

Socioeconomic Implications

Schizophrenia imposes a significant financial burden on healthcare systems and national economies. According to a 2026 economic evaluation of 2024 data by Krasa et al. (2026), the total annual societal cost of schizophrenia in the United States was estimated at $366.8 billion for a population of just over 3 million adult Americans (translating to a prevalence rate of 1.17%). On a per capita basis, this represents a markedly elevated average expenditure of $119,436 per patient. Notably, the researchers observed significant state-level fluctuations, ranging from just under $111,000 in Utah to a striking $126,000 in the resource-rich state of Alaska. From a health policy perspective, the authors note that direct costs—which amount to $75 billion (constituting just over 20% of the total burden)—do not primarily stem from medical treatment itself. Expenditures allocated to professional healthcare consume less than half of this sum ($36.7 billion), while a nearly identical amount—$35.2 billion—is dedicated to maintaining the complex infrastructure of supported housing and interventions for individuals experiencing homelessness. Furthermore, a profoundly concerning cost driver remains the interaction of affected individuals with the justice system and the associated incarceration costs, which burden the budget by $11.9 billion annually. However, the predominant economic burden of this disorder lies in indirect costs, which account for approximately 80% of the total balance ($291.8 billion).

A fundamental, yet often overlooked driver of these losses in political discourse is the care provided by the patients' relatives. The economic losses resulting solely from the unpaid daily labor performed by family members have been valued at an estimated $104.6 billion. When combined with private out-of-pocket expenses, the marked decline in the occupational productivity of caregivers, and healthcare expenditures related to caregiver stress and deteriorating health, the total burden on the caregiving sphere reaches $165 billion annually. The remaining hundreds of billions are a direct derivative of the impact that psychosis inflicts on the patients themselves: their radical exclusion from the labor market generates productivity gaps amounting to $55.4 billion, premature mortality rates result in losses of $47.5 billion, and the cost of lost quality of life has been estimated by researchers at $41.4 billion. Considering long-term projections—in which a diagnosis made at 18 years of age will result in a lifetime economic burden of approximately $2.5 million—investing in early detection, targeted pharmacological treatment, and coordinated community care appears to be the most rational strategy for securing the public budget (Krasa et al., 2026).

Schizophrenia also imposes a substantial burden in Poland. According to the European Brain Council (2025), between 200,000 and 400,000 individuals in Poland are currently living with schizophrenia, with an incidence rate of approximately 16,000 newly diagnosed cases each year. It causes the loss of 67,000 disability-adjusted life years (DALYs) annually. The report highlights that in 2022, the National Health Fund (NFZ) spent PLN 2.5 billion on the treatment of this disorder, while the Social Insurance Institution (ZUS) disbursed PLN 5.5 billion on disability benefits. This high prevalence translates into a profound, multidimensional burden on the national healthcare and social security infrastructures. Beyond direct institutional costs, a schizophrenia diagnosis typically results in severe labor market exclusion. Notably, 70% of patients become permanently dependent on state disability pensions, while only 15% successfully reintegrate into the workforce. Consequently, a substantial, informal caregiving burden falls directly upon the patients' families. Statistical data reveal that 81% of caregivers share a household with the affected individual, and 72% are compelled to out-of-pocket finance their medical and daily living expenses. Furthermore, the necessity of providing continuous, day-to-day supervision forces 13% of relatives to reduce their own working hours. This cascade of occupational and financial disruption leads to progressive impoverishment, chronic psychological stress, and a markedly elevated risk of developing clinical depression among the caregiver population (European Brain Council, 2025).

Evidence from health-economic analyses indicates that negative symptoms and moderate-to-severe cognitive impairment are associated with significantly higher rates of healthcare utilization and costs. Notably, patients with moderate-to-severe cognitive impairment have nearly double the risk of relapse-related hospitalization (aIRR ≈ 1.85) (Correll, Xiang, Sarikonda, Bhagvandas, & Gitlin, 2024).

Discussion

Based on the evidence synthesized in this review, it has been shown that σ1R dysfunction plays a fundamental role in the pathophysiology of negative symptoms and cognitive deficits in schizophrenia. Numerous studies indicate that these disruptions are intertwined at the molecular, cellular, and systemic levels, constituting a common denominator for critical neuropathological processes. According to the analyzed literature, the loss of the physiological σ1R chaperone function leads to severe impairments in the trafficking and stabilization of NMDARs within the postsynaptic membrane (Pabba & Sibille, 2015; Pabba et al., 2014). The consequence of this phenomenon is chronic hypofunction of the glutamatergic system and progressive synaptic atrophy (Balu, 2016; Coyle, 2006). Furthermore, potential pathophysiological mechanisms encompass dysfunctions at the level of mitochondria-associated membranes (MAMs) (Bui et al., 2026). The lack of proper σ1R activity within these structures results in exacerbated endoplasmic reticulum (ER) stress, a breakdown of calcium homeostasis, and oxidative stress (Ryskamp et al., 2019a). These phenomena are particularly detrimental to parvalbumin-expressing (PV+) GABAergic interneurons, which, due to their specific physiology, exhibit exceptionally high energy demands (Steullet et al., 2017). Their impairment and the subsequent decline in GABA synthesis lead to a pathological excitatory-inhibitory imbalance and the ultimate disorganization of gamma oscillations (30-80 Hz)—the neurophysiological foundation of attention and working memory processes (Ahmed et al., 2025; Jadi et al., 2016; Steullet et al., 2017). Moreover, this pathophysiological landscape is complicated by a progressive decline in D-serine concentration, an essential NMDAR co-agonist, which is associated with, among other factors, the dysfunction of the mutant DISC1 protein (Jacobi et al., 2019; Ma et al., 2013).

In light of the described pathomechanisms, the application of pharmacologically targeted σ1R agonists, such as repurposed fluvoxamine, pridopidine, and the novel compound ANAVEX 3-71 (AF710B), emerges as a highly promising and novel therapeutic strategy (Ahmed et al., 2025; Fisher et al., 2016; Ryskamp et al., 2019b). Studies demonstrate that these substances effectively restore ER and mitochondrial homeostasis, suppress inflammatory pathways, and protect neurons against apoptosis (Ahmed et al., 2025; Fisher et al., 2016). They also stimulate neuroplasticity cascades in multiple ways (e.g., through robust activation of the BDNF-TrkB pathway), resulting in the structural restoration of dendritic spine density, including the mushroom spines that are crucial for memory consolidation (Fisher et al., 2016; Ka et al., 2016; Ryskamp et al., 2019a, 2019b). At the behavioral level, this results in the improvement of cognitive functions, recovery of learning capacity, and restoration of social flexibility, as evidenced in standardized behavioral tests (Ahmed et al., 2025; Fisher et al., 2016; Sahlholm et al., 2018). The introduction of such effective therapies is also critical from a macroeconomic perspective. Schizophrenia generates considerable indirect costs resulting from the radical exclusion of patients from the labor market—statistics for Poland indicate that a mere 15% of patients successfully return to employment, while 70% remain permanently dependent on state disability pensions (European Brain Council, 2025). These costs consume the budgets of institutions such as the Social Insurance Institution (ZUS), amounting to billions of PLN annually, while simultaneously transferring a drastic, informal financial and psychological burden directly onto the patients' families (European Brain Council, 2025). A marked improvement in cognitive status could reduce the rates of relapse and associated costly hospitalizations, thereby relieving the social security system and facilitating the reintegration of patients (Correll et al., 2024; Krasa et al., 2026).

However, it is necessary to maintain objectivity and critically address certain limitations of the studies discussed in this paper, applying standards analogous to those used in reviews of other innovative drugs and chronic diseases. Primarily, the vast majority of compelling evidence confirming the molecular mechanisms of action of the new ligands is based on preclinical studies involving diverse animal models (e.g., transgenic mutant mice and pharmacological models subjected to ketamine and phencyclidine). The direct translation of results from animal models to the highly complex human nervous system always requires caution and verification. Secondly, the analyzed preclinical interventions are characterized by high heterogeneity, utilizing various etiological models of schizophrenia, which complicates the standardization of conclusions. Furthermore, there is a lack of large-scale, longitudinal clinical trials on rigorously selected patient cohorts that would definitively confirm the long-term durability of the achieved pro-cognitive effects and the direct impact of biomarker normalization on the tangible improvement of patients' daily functioning in society.

In conclusion, the modulation of the σ1R/NMDAR pathway is an innovative and strongly evidence-based approach that holds real potential to address the unmet clinical needs associated with the drug-resistant aspects of schizophrenia. However, for the full implementation of this method into clinical practice, future scientific efforts must focus on multicenter human trials. Equally important will be the rigorous stratification

of patients based on genetic testing (e.g., SIGMAR1 gene polymorphisms) and sensitive electrophysiological biomarkers (e.g., EEG recordings), which will allow for a highly personalized selection of the patient population that will derive the optimal and most enduring benefits from the new therapy.

Conclusions

The gathered evidence strongly advocates for a fundamental paradigm shift in the pharmacological approach to schizophrenia. The σ1R emerges not merely as an auxiliary neuromodulator, but as a critical nexus linking endoplasmic reticulum homeostasis, synaptic plasticity, and glutamatergic transmission. The chronic hypofunction of the NMDARs and the progressive deterioration of parvalbumin interneurons—which constitute the core drivers of cognitive deficits and negative symptoms—are deeply rooted in σ1R dysregulation. Consequently, targeted activation of this chaperone protein via novel or repositioned ligands represents a transition from conventional, purely symptomatic management of psychosis to a potentially disease-modifying strategy aimed at the structural restoration of neural networks.

Furthermore, effectively addressing these treatment-resistant domains is an absolute priority from a macroeconomic perspective. Restoring cognitive flexibility and psychosocial functioning through σ1R modulation holds the potential to substantially reduce the immense indirect societal costs associated with permanent disability, caregiving burdens, and premature mortality, thereby facilitating patients' reintegration into the competitive labor market. Ultimately, unlocking the full potential of these novel interventions will require a transition toward personalized treatment models, where multidimensional biomarker screening strictly guides optimal patient selection.

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