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Review article

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Novel drug treatments for schizophrenia

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Abstract

Until very recently, every drug approved for the treatment of schizophrenia over the past 70 years had the primary mechanism of directly or indirectly antagonizing dopamine D_2 receptor activation. The role of dopamine as a critical mediator of psychosis is well established, and psychotic symptoms such as hallucinations and delusions are key features of schizophrenia. However, other important symptoms, including negative symptoms such as social withdrawal and anhedonia, and cognitive impairments, are largely unaffected by current antipsychotic drugs, resulting in the persistent disability of most individuals with schizophrenia. Schizophrenia also results in premature death due to a high prevalence of cardiovascular disease that can be exacerbated by current antipsychotic medications. Advances in our understanding of the genetics and pathophysiology of schizophrenia demonstrate that the disorder is complex with numerous underlying aetiologies, indicating that a single drug is unlikely to affect all aspects of the disorder. The recent approval of the M_1/M_4 muscarinic acetylcholine receptor agonist xanomeline/trospium chloride has begun to expand the therapeutic toolbox for schizophrenia. This Review covers promising drug targets for schizophrenia treatment that impact neurotransmitter systems, immune processes and inflammation. Despite failed clinical trials of some agents with novel mechanisms, several have recently been shown to improve one or more symptom domains of schizophrenia, suggesting that these targets may lead to more effective treatments.

Sections

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Introduction

Schizophrenia is a chronic, debilitating mental disorder that affects nearly 1% of the population worldwide, although prevalence varies across regions[1]. It is the seventh most costly medical disorder, with an estimated economic burden of US $330 billion per year in the USA alone[2]. This includes direct health-care costs, societal costs associated with hospitalization and housing insecurity, as well as the indirect costs of unemployment and lost productivity[3].

Antipsychotic drugs, most of which act primarily by blocking D_2 dopamine receptors (D_2Rs), are currently the mainstay treatments for schizophrenia. Although they effectively reduce psychotic or positive symptoms in most patients, they produce a myriad of undesirable side effects and are relatively ineffective in treating core negative and cognitive symptoms, which include anhedonia, social isolation and lack of motivation, as well as cognitive impairments involving memory, attention and executive functions. These core symptoms, unresponsive to antipsychotic drugs, account for persistent disability for most individuals with schizophrenia[4].

In September 2024, the FDA approved the first treatment for schizophrenia with no direct D_2R-blocking activity: the dual M_1/M_4 muscarinic acetylcholine receptor (mAChR) agonist xanomeline in combination with the peripherally restricted pan mAChR antagonist trospium chloride. The approval of xanomeline/trospium chloride supports the growing interest in identifying treatment options that do not rely on D_2R blockade and would address the negative and cognitive symptoms.

In this Review, we briefly summarize the advances in neuropathology and genetics of schizophrenia that provide potential targets for drug development. We then discuss a number of potential drug treatments for schizophrenia with novel mechanisms that are currently in mid-stage or late-stage clinical development (Table 1).

Schizophrenia neurobiology

Neuropathology

For 70 years, the striatal D_2R has been the target for the development of antipsychotic drugs, based on the misperception that psychosis encompassed the full spectrum of the schizophrenia syndrome (Box 1). The absence of classical neuropathologic changes seen in typical neurologic disorders, such as stroke and dementia, led to the conclusion that schizophrenia is a 'functional' disorder, consistent with the dopamine hypothesis[5,6]. However, the combination of morphometric magnetic resonance imaging (MRI) and post-mortem histologic analysis has now provided compelling evidence of cortical atrophy in schizophrenia, which correlates with negative symptoms and cognitive impairments but not with positive symptoms[4,7].

The cortical atrophy in schizophrenia is due to the loss of neuropil, the space between neurons that contains the synaptic connections, as well as myelinated axons[8]. However, it is not accompanied by a comparable loss of neurons[9]. Studies in several cortical regions have also revealed loss of synaptic spines, which comprise glutamatergic synapses, and reduced dendritic length and complexity[10–12]. Approximately 30% of cortical glutamatergic synapses are lost in schizophrenia, consistent with the severity of cognitive impairment and negative symptoms of schizophrenia (for review, see Coyle et al.[13]). In addition, the parvalbumin-expressing (PV^+) GABAergic interneurons, which provide recurrent inhibition to pyramidal neurons in the intermediate layers of the cerebral cortex, are significantly diminished, whereas postsynaptic $GABA_A$ receptors are upregulated, suggesting a persistent reduction in the inhibition of pyramidal neurons[14]. This pathology accounts for the disruption of the cortical excitation/inhibition (E/I) balance, which results in cognitive impairments, negative symptoms and psychosis[15,16] (Fig. 1).

Post-mortem neurochemical studies also reveal the downregulation of glutamate receptor *N*-methyl-D-aspartate receptor (NMDAR) subunits and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) subunits, as well as of postsynaptic density–associated proteins in schizophrenia, consistent with the loss of synaptic spines[17–19]. Alterations in the levels of specific proteins or their messenger RNA (mRNA) associated with other neurotransmitter systems, including dopaminergic, serotonergic and cholinergic, as well as peptidergic neurons, have been described in schizophrenia[20,21]. However, it is unclear whether these alterations are due to the disorder itself, the effects of chronic antipsychotic drug treatment, comorbid medical conditions such as type 2 diabetes, and/or the complications of the highly prevalent substance abuse[21].

Genetics of schizophrenia

The most recent genome-wide association study (GWAS) of schizophrenia included 240,000 controls and more than 76,000 people with schizophrenia[22]. It revealed over 200 chromosomal loci associated with a risk of developing schizophrenia. Many of these loci contain genes that affect synaptic structure and function, brain development, and myelination[23] (Table 2). However, most of these single-nucleotide polymorphisms associated with schizophrenia are located in non-coding regions of the genome, which likely affects gene expression and mRNA processing[24]. Although GWASs have identified relatively common genes with small but real effects on schizophrenia risk, exome sequencing studies have identified rare, protein-coding mutations with large effect sizes. Three notable mutations affect subunits of the glutamate receptors NMDAR (encoded by *GRIN2A*) and AMPAR (encoded by *GRIA3*), and the voltage-gated calcium channel (encoded by *CACNA1G*)[25]. Approximately 30 GWAS-identified risk genes affect glutamatergic neurotransmission at presynaptic and postsynaptic sites[26] (Table 2 and Fig. 2). In addition, several risk genes are associated with GABAergic and cholinergic neurons, but only one dopamine-related gene, *DRD2*, encoding D_2R, is a risk gene for schizophrenia (Table 2).

Clinically, the symptoms of schizophrenia can range from individuals with prominent positive symptoms and negligible negative symptoms to those with modest positive symptoms but profound negative and cognitive symptoms, especially in the chronic state[4]. Furthermore, the genetic results unequivocally show that the clinical entity termed schizophrenia is aetiologically heterogeneous, with several risk genes (out of over 200) combined with environmental factors causing the syndrome[27]. This aetiologic heterogeneity suggests that a single drug is unlikely to treat all the symptoms of schizophrenia effectively, and combination therapy to target specific symptoms may be necessary.

Reduced NMDAR function, consistent with the high concentration of risk gene products expressed on the glutamatergic synapse, results in impaired dendritic development and maintenance, as manifested by reduced dendritic length and reduced spine density[28,29]. Notably, an allelic variant of the risk gene encoding complement C4, the most statistically significant risk gene for schizophrenia in the genome, causes excessive pruning of cortical dendritic spines, especially during adolescence[30]. Therefore, two completely separate neuropathologic pathways — NMDAR hypofunction and complement C4-driven excessive spine pruning — produce a similar neuropathology associated with negative and cognitive symptoms. This 'convergent pathology' emphasizes how central the loss of cortical glutamatergic synapses is to schizophrenia and that it is a robust predictor of poor outcome[31].

Table 1 | Potential treatments for schizophrenia with novel mechanisms in clinical development

Drug	Company	Target/properties	Indication	Status
Glutamatergic signalling				
Iclepertin	Boehringer Ingelheim	GlyT1 inhibitor	CIAS	Phase III
Evenamide	Newron Pharmaceuticals	Voltage-gated sodium channel inhibitor	Schizophrenia	Phase III
SPG302	Spinogenix	Glutamatergic synapse regeneration	Schizophrenia	Phase II
Pomaglumetad methionil	Denovo Biopharma	mGlu2/3 agonist	Schizophrenia	Phase II
KYN-5356	Kynexis Therapeutics	KAT II inhibitor	CIAS	Phase I
Cholinergic signalling				
Xanomeline/trospium chloride	Bristol Myers Squibb	M_1/M_4 mAChR agonist	Schizophrenia AD psychosis	Approved Phase III
ANAVEX3-71	Anavex Life Sciences	SIGMAR1/M_1 mAChR	Schizophrenia	Phase II
Emraclidine	Cerevel/Abbvie	M_4 mAChR PAM	Schizophrenia AD psychosis	Phase II Phase II
NBI-1117568	Neurocrine Biosciences	M_4 mAChR agonist	Schizophrenia	Phase III
RL-007	Recognify Life Sciences	GABA/acetylcholine modulator	CIAS	Phase II
Neuroplasticity				
Zagociguat	Tisento Therapeutics	Soluble guanylate cyclase stimulator	Schizophrenia	Phase I
BI 409306	Bayer	Phosphodiesterase 9 inhibitor	Schizophrenia	Phase II
Serotonin/dopamine modulation				
Ulotaront	Otsuka	TAAR1 inhibitor	Schizophrenia	Phase III
Ralmitaront	Roche	TAAR1 inhibitor	Schizophrenia	Phase II
Reducing inflammation, oxidative stress and obesity				
N-acetylcysteine	Thorne	Glutathione precursor	Schizophrenia	Phase II
Metformin[a]	Nurx	Antihyperglycemic agent	Overweight in schizophrenia	Phase II
Semaglutide[b]	Novo Nordisk	Glucagon-like peptide receptor agonist	Prediabetes and obesity in schizophrenia	Phase II

AD, Alzheimer's disease; CIAS, cognitive impairment associated with schizophrenia; GABA, gamma-aminobutyric acid; GlyT1, glycine transporter 1; KAT II, kynurenine aminotransferase II; mAChR, muscarinic acetylcholine receptor; mGlu, metabotropic glutamate receptor; PAM, positive allosteric modulator; SIGMAR1, sigma non-opioid intracellular receptor 1; TAAR1, trace amine-associated receptor 1. [a]Approved for type 2 diabetes. [b]Approved for type 2 diabetes and obesity.

Therapeutic strategies in development

The advances in the understanding of the neuropathology and genetics of schizophrenia have provided targets for the development of novel drugs or for re-purposing existing drugs to correct pathologic processes responsible for core symptoms of schizophrenia without directly interacting with the dopamine receptors. Functional MRI and electroencephalography (EEG) results along with GWAS findings point to abnormalities in synaptic neurotransmission, especially the glutamatergic, cholinergic and GABAergic neuronal systems[15]. However, dysfunction of a component of a neural circuit such as a neurotransmitter receptor disrupts downstream neuronal function that may be more clearly linked to symptoms. For example, current antipsychotic drugs block excessive dopamine receptor stimulation in the striatum, which is driven by cortico-limbic dysfunction[16]. Finally, schizophrenia is associated with more general medical morbidity and premature mortality that has recently attracted clinical interest for treatment.

Targeting glutamatergic signalling

Given the substantial representation of glutamatergic risk genes in schizophrenia, glutamatergic neurotransmission has been viewed as a promising target for drug intervention. Glutamate is the primary excitatory neurotransmitter in the brain and accounts for up to 80% of corticolimbic synapses. Its synaptic effects are mediated by two classes of receptors: glutamate-gated cation channels and a family of G protein-coupled receptors designated metabotropic glutamate receptors (mGluRs). There are three major forms of glutamate-gated cation channels. The AMPAR is a sodium ion (Na^+) channel gated by glutamate and mediates excitatory postsynaptic currents. As this depolarization leads to opening of the NMDAR channel, the AMPAR is intimately involved in NMDAR function. The subunits comprising the AMPARs are encoded by four genes, *GRIA1–4*, that form tetramers composed of two dimers[32,33]. *GRIA3* has a rare highly penetrant coding variant associated with schizophrenia[25].

The second ionotropic glutamate receptor, the kainic acid receptor, plays a major role in synaptic plasticity. Rare allelic variants are associated with schizophrenia, autism and intellectual disability[34]. The NMDAR is a glutamate receptor that primarily transduces Ca^{2+}, which stimulates gene expression and Ca^{2+}-activated enzymatic processes[35] (Fig. 3). The receptor is a heterotetramer of subunits encoded by seven genes: *GRIN1* (GluN1), *GRIN2A–2D* (GluN2), *GRIN3A*, and *GRIN3B* (GluN3). GluN1 forms the cation channel core and notably has the binding site for the requisite co-agonists glycine or D-serine[36]. The GluN2 and GluN3 subunits contain the receptor site for glutamate[37]. One of the main functions of the NMDAR is to promote synaptic

plasticity, including long-term potentiation (LTP); stimulate neuronal differentiation during development; and, with excessive activation of extra-synaptic receptors, promote excitotoxicity. *GRIN2A* is a risk gene for schizophrenia, and highly penetrant loss-of-function *GRIN2A* mutations also markedly increase risk for developing schizophrenia[26].

There are eight mGluRs, all of which are G protein-coupled receptors[38,39]. They are divided into three groups based on their coupling to second messengers, with Group I coupled to phospholipase C and Groups II and III coupled to Gi to inhibit adenylyl cyclase. The mGluRs dimerize to form functional receptors. Their primary roles are to modulate glutamatergic neurotransmission at presynaptic and postsynaptic sites. The Group II mGluR3 is encoded by a risk gene for schizophrenia[39] and acts pre-synaptically to inhibit glutamate release[40].

Dysfunction of glutamatergic neurotransmission has been implicated in the pathophysiology of schizophrenia for more than 40 years. The initial evidence arose from the study of the psychotomimetic effects of the dissociative anaesthetics ketamine and phencyclidine (PCP), which produced a syndrome that is difficult to distinguish from schizophrenia[41,42]. Dissociative anaesthetics like ketamine are non-competitive NMDAR channel blockers. Importantly, ketamine at low doses produces negative symptoms, such as social withdrawal, and the subtle cognitive impairments characteristic of schizophrenia[43]. Furthermore, low-dose ketamine produces several physiologic abnormalities associated with schizophrenia, such as abnormal eye tracking, enhanced subcortical dopamine release, impaired prepulse inhibition, hypofrontality and abnormal event-related potentials[44–46]. Therefore, pharmacologically induced NMDAR hypofunction replicates the core clinical features of schizophrenia as well as its neurophysiologic abnormalities, providing the first evidence of the critical role of glutamatergic dysfunction in the disorder.

Studies in experimental animals indicate that NMDARs on cortical PV^+GABAergic neurons are most sensitive to dissociative anaesthetics, resulting in disinhibition of the cortical pyramidal output neurons[47]. In the methylazoxymethanol acetate neurodevelopmental rat model of schizophrenia that involves selective elimination of hippocampal GABAergic neurons in late gestation[48], the disinhibited excitatory output neurons drive subcortical dopamine release[49]. Genetically induced NMDAR hypofunction caused by knocking out serine racemase (SR), which synthesizes D-serine, also increases striatal dopamine release as monitored by in vivo dialysis[50]. These studies demonstrate that differential neuronal sensitivity to NMDAR inhibition results in dysfunction of entire neural circuits, impacting striatal dopamine release, not just the NMDAR[16], and thus likely contributing to the full spectrum of schizophrenia symptoms (Fig. 1). Furthermore, the results support the notion that psychosis is a downstream consequence of corticolimbic dysfunction and suggest that drugs targeting this corticolimbic glutamatergic dysfunction would theoretically impact not only cognitive and negative symptoms but possibly dopamine-mediated positive symptoms.

NMDARs. D-Serine is a full agonist at the glycine modulatory site (GMS) on the NMDAR, the occupancy of which is required for NMDAR function. SR is encoded by *SRR*[51], which is also a risk gene for schizophrenia. SR is expressed nearly exclusively in brain neurons[52], where it is localized in postsynaptic spines of glutamatergic and GABAergic

Box 1 | Striatal dopamine and the pathophysiology of psychosis

More than 70 years ago, chlorpromazine was discovered to be the first effective antipsychotic drug[217]. Pharmaceutical companies soon identified other phenothiazines with greater potencies that shared behavioural effects in experimental animals, supporting the notion of a common mechanism of action[218]. In 1963, Carlsson, noting the Parkinsonian side effects of antipsychotic drugs, a condition due to loss of striatal dopamine, showed that antipsychotic drugs increased the turnover of striatal dopamine, leading him to propose that antipsychotic drugs act by blocking dopamine receptors[219]. A decade later, Snyder utilized tritiated dopamine and tritiated haloperidol to label a striatal dopamine receptor, and measured the affinity of antipsychotic drugs for the dopamine receptor[220]. Snyder found a highly significant correlation between antipsychotic drug affinities for the D_2 receptor and their clinical potencies (a previously discovered dopamine-sensitive adenylyl cyclase that was blocked by chlorpromazine was designated the D_1 receptor). Snyder proposed that excessive release of dopamine caused the symptoms of schizophrenia and that antipsychotic drugs attenuate dopamine receptor stimulation, causing a reduction in psychotic symptoms. This is known as "the dopamine hypothesis of schizophrenia"[221]. Notably, the diagnostic criteria for schizophrenia in the Diagnostic and Statistical Manual of Mental Disorders, starting with the third edition[222], are heavily weighted to positive symptoms, further reinforcing the field's impression that antipsychotic drugs treat the entire condition.

Recent molecular neuroimaging studies have provided invaluable information supporting the role of dopamine in the pathophysiology of psychosis in patients with schizophrenia[223]. Based on several positron emission tomographic studies to interrogate dopaminergic neurotransmission in people with schizophrenia compared with healthy controls, it is abundantly clear that increased presynaptic dopamine synthesis and release, especially in striatal regions, underlie positive symptoms and may even predict the emergence of psychotic symptoms in high-risk individuals, who will eventually go on to develop schizophrenia[224]. A recent meta-analysis of imaging studies in patients with schizophrenia reported that presynaptic alterations in dopamine synthesis, baseline synaptic dopamine levels and dopamine release are abnormalities frequently observed in patients with schizophrenia[225]. However, similar changes in presynaptic striatal dopamine function have been observed in other psychotic disorders, including bipolar disorder[226], suggesting that the pathophysiology of increased dopamine neurotransmission is not specific to schizophrenia but rather to psychosis in general.

Research over the past two decades demonstrates that negative and cognitive symptoms are unaffected or even exacerbated[227] by antipsychotic drugs and that these symptoms correlate with the neuropathology of schizophrenia, including cortical atrophy, ventricular enlargement and loss of corticolimbic spines. Nevertheless, the unequivocal demonstration of dopamine's cause of psychosis and the D_2 receptor as the site of therapeutic effects of antipsychotic drugs is one of the few examples of research linking a psychiatric symptom to a defined neurotransmitter.

neurons. D-Serine is released by facilitated transport as an autocrine co-agonist to prime the postsynaptic NMDARs to instantly respond to synaptic glutamate[53]. With brain inflammation, SR is expressed in reactive astrocytes, facilitating excitotoxic nerve damage by activating extra-synaptic NMDARs[54,55].

The cerebrospinal fluid (CSF) and plasma levels of D-serine are decreased in patients with schizophrenia[56,57]. The amino acid tryptophan is catabolized to kynurenine and then to kynurenic acid, which is an endogenous antagonist of the GMS on the NMDAR. Several post-mortem and CSF studies have found alterations in kynurenine pathway enzymes and elevated kynurenic acid levels in schizophrenia[58–60]. Therefore, alterations in the kynurenine pathway may play a role in reduced NMDAR neurotransmission and consequently impair cognition in schizophrenia.

Given the post-mortem, genetic and pharmacologic challenge results, interventions directed at increasing NMDAR function would presumably reduce symptoms of schizophrenia. To avoid the excitotoxic consequences of direct activation of NMDARs, early clinical trials have focused on agents that directly or indirectly act at the NMDAR's GMS, because animal studies indicate that GMS agonists can attenuate PCP-induced behaviours but do not promote excitotoxicity[60]. As reviewed in Box 2, these studies, primarily with endogenous agonists, provide strong evidence in support of the hypothesis but also reveal serious limitations, such as desensitization and low potency, that undermined their utility as clinical treatments.

Kynurenic aminotransferase II inhibitors. Kynurenic acid (KYNA), a metabolite of the kynurenine pathway, which accounts for approximately 95% of tryptophan metabolism in mammals, is an endogenous inhibitor of the NMDAR at the GMS and of the α-7 nicotinic acid receptor at the binding site for galantamine[61]. Kynurenine aminotransferase II (KAT II) is the enzyme responsible for the synthesis of KYNA. Inflammation, a common occurrence in schizophrenia, provokes the expression of reactive astrocytes and augments the expression of KAT II[62]. KYNA levels have been repeatedly found to be elevated in the CSF and in post-mortem brain tissue in a subgroup of individuals with schizophrenia[63]. Notably, increasing brain KYNA in animal studies impairs cognition[63], and preclinical studies with systemically active KAT II inhibitors have shown that selective reduction of KYNA formation has pronounced pro-cognitive effects[64,65].

Given the elevation of KYNA in the brain in schizophrenia and cognitive impairments as a disabling core symptom in schizophrenia, inhibition of KAT II could be a therapeutic strategy. The centrally active KAT II inhibitor KYN-5356 has successfully completed a phase I trial (ClinicalTrials.gov ID: NCT06225115).

GlyT1 inhibitors. The glycine transporter GlyT1 is encoded by *SLC6A9* and is expressed primarily in astrocytes and glutamatergic neurons[66], in which it mediates uptake of glycine from the synaptic cleft. Given that glycine is an NMDAR-positive modulator, GlyT1 antagonists should potentiate NMDAR function in schizophrenia by increasing synaptic glycine[67]. However, GlyT1 provides glycine to astrocytes, where glycine is converted to L-serine and further metabolized in forebrain neurons to the more potent GMS agonist D-serine, perhaps undercutting the efficacy of GlyT1 inhibition[68]. Sarcosine (*N*-methylglycine) is a relatively potent, endogenous antagonist of GlyT. The first synthetic GlyT1 antagonists showing high potency was ALX-5407, with its racemic form, *N*-(3-(4-flourophenyl)-3-(4-phenylphenoxy propyl) sarcosine, named NFPS and Org 24598 (ref. 69). However, the slow dissociation of NFPS[70] resulted in neurologic side effects in preclinical studies that precluded further clinical development. Org 25935, a related GlyT1 inhibitor, advanced to clinical studies but proved ineffective in reducing negative symptoms and improving cognition in patients with chronic schizophrenia[71].

Umbricht et al. carried out a double-blind, placebo-controlled phase II study of the non-competitive GlyT1 inhibitor bitopertin, and found a U-shaped dose–response curve with an optimal dose of 30 mg day^{-1} (ref. 72). Unfortunately, the drug failed in a phase III clinical trial due to lack of efficacy, resulting in its termination[73]. PF-03463275 is an azabicyclic that is a centrally penetrant, orally active, competitive and reversible inhibitor of GlyT1 with a Ki (the concentration of the inhibitor needed to cause 50% inhibition of the enzyme) of 12 nM[74].

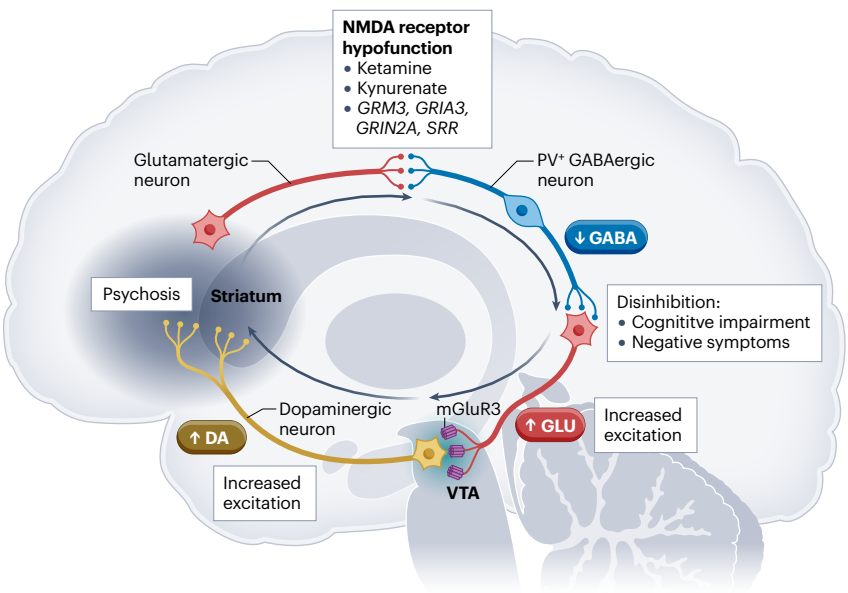

Fig. 1 | Brain circuit connecting cortical neuropathology to subcortical dopaminergic dysfunction in schizophrenia. Schizophrenia features reduced *N*-methyl-D-aspartate (NMDA) receptor function on parvalbumin-expressing (PV$^+$) GABAergic interneurons that provide recurrent inhibition to glutamatergic pyramidal neurons in the cerebral cortex. This results in disinhibition of the cortical glutamatergic pyramidal neurons and an imbalance in the excitation/inhibition ratio. The altered excitation/inhibition ratio is associated with cognitive impairments and negative symptoms. The disinhibited glutamatergic output from the temporal lobe to the ventral tegmental area (VTA) dopaminergic neurons causes increased dopamine (DA) release in the ventral striatum, resulting in psychosis. mGluR3s are expressed on glutamatergic terminals and inhibit glutamate release, thereby restoring excitation/inhibition balance. The gene encoding mGluR3 is a risk gene for schizophrenia[214], as well as the target of action of pomaglumetad, which reduces glutamate release and reduces positive, negative and cognitive symptoms in a subgroup of patients with schizophrenia[83]. GABA, γ-aminobutyric acid; GLU, glutamate; mGluR3, metabotropic glutamate receptor 3; VTA, ventral tegmental area.

Table 2 | Schizophrenia risk genes associated with neurotransmitter systems

Gene	Product	Function
Metabotropic glutamate receptors		
GRM1, GRM3	Metabotropic glutamate receptor 1 and 3	Modulate glutamate neurotransmission
Ionotropic glutamate receptors and their modulators		
GRIA1	Subunit of the excitatory glutamate AMPA receptor	Primarily responsible for excitatory postsynaptic currents
GRIN2A	Subunit of the NMDA receptor	Part of the ionotropic glutamate receptor, localized to the glutamatergic synapse
SHISA8	AMPA receptor auxiliary protein	Modulates receptor sensitization
PTK2B	Protein tyrosine kinase 2 beta	Phosphorylates AMPA and NMDA receptors, modulating their activity
PRKCB	Protein kinase C beta	Phosphorylates NMDA and AMPA receptors, modulating their function
NSF	*N*-ethylmaleimide-sensitive factor	Involved in AMPA receptor trafficking
PLK2	Polo-like kinase 2	Phosphorylates NMDA and AMPA receptors, modulating their function
PCDH17	Protocadherin-17	Interacts with GluN1 subunit of the NMDA receptor, affecting its currents
Presynaptic axon and terminal		
SNAP91	Synaptosomal-associated protein 91 kDa	Involved in the cycling of neurotransmitter storage vesicles in exocytosis
SNCA	Alpha synuclein	Modulates storage vesicle cycling in the nerve terminal
PTPRF	Receptor-type tyrosine-protein phosphatase F	Modulates the development of glutamatergic terminals
SCGN	Secretagogin	Modulates vesicular exocytosis
DOC2A	Double C2-like domain-containing protein alpha	Binds Ca^{2+} that regulates glutamate exocytosis
RIMS1	Regulating synaptic membrane exocytosis protein 1	Synaptic vesicle protein that regulates vesicular exocytosis
VPS45	Vacuolar protein sorting-associated protein 45 kDa	Involved in trafficking storage vesicles
MAPT	Microtubule-associated protein tau	Provides stability of the axon and terminal
Postsynaptic spine		
NRGN	Neurogranin	Concentrated in synaptic spines and modulates calcium availability
SHANK3	Multiple ankyrin repeat domains protein 3	Interacts with metabotropic glutamate receptors in the postsynaptic density of glutamatergic synapse
CLCN3	Voltage-sensitive chloride channel 3	Cl^--conducting channel localized to the postsynaptic density
SRR	Serine racemase	Synthesizes the co-agonist for the NMDA receptor
LRRC4B	Leucine-rich repeat-containing protein 4 (or netrin-G ligand-3)	Adhesion molecule that directly interacts with glutamatergic postsynaptic scaffolding protein postsynaptic density 95
SYNGAP1	Synaptic Ras GTPase-activating protein 1	Involved in NMDA receptor-mediated synaptic plasticity and membrane insertion of AMPA receptors
ITPR3	Inositol 1,4,5-trisphosphate (IP_3) receptor type 3	Ca^{2+}-releasing intracellular channels that are activated by IP_3
HCN1	Hyperpolarization-activated cyclic nucleotide-gated channel	Enhances and accelerates axon potentials
NLGN4X	Neuroligin-4	X-linked postsynaptic adhesion molecule at glutamatergic synapses
EXOC4	Exocyst complex component 4	Component of the exocyst, a protein complex associated with glutamate receptor trafficking and tethering at the synapse
Voltage-dependent Ca^{2+} channels		
CACNA1C, CACNA1D	Calcium voltage-gated channel subunits alpha 1C and 1D	Mediate Ca^{2+} influx on dendrites with AMPA receptor-driven depolarization
CACNB2	Calcium voltage-gated channel auxiliary subunit beta 2	Mediates Ca^{2+} influx on dendrites with AMPA receptor-driven depolarization
GABAergic neurons		
GABBR1, GABBR2	Gamma-aminobutyric acid type B receptor subunits 1 and 2	G protein-coupled receptor activated by GABA
CALB2	Calretinin	Ca^{2+}-binding protein expressed in cortical GABAergic neurons
Cholinergic neurons		
CHRNA2, CHRNA3, CHRNB4, CHRNA5	Cholinergic receptor nicotinic subunits alpha 2, alpha 3, beta 4, alpha 5	Cation channel activated by acetylcholine
CHRM3, CHRM4	Muscarinic acetylcholine receptor 2 and 3	G protein-coupled receptors activated by acetylcholine

Table 2 (continued) | Schizophrenia risk genes associated with neurotransmitter systems

Gene	Product	Function
Dopaminergic neurons		
DRD2	Dopamine D2 receptor	G protein-coupled receptor activated by dopamine
Corticotropin neurons		
CRHR1	Corticotropin-releasing hormone receptor 1	G protein-coupled receptor activated by endogenous peptides such as corticotropin-releasing hormone

Based on genome-wide association study results (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014, 2022 (refs. 213,214)). AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; NMDA, *N*-methyl-D-aspartate.

In patients with schizophrenia, the drug enhanced LTP following a cognitive task versus controls, but it did not improve cognition following cognitive training in a randomized, double-blind, placebo-controlled, within-subject, crossover study[75]. Boehringer Ingelheim's selective GlyT1 inhibitor iclepertin (BI 425809) is currently in phase III clinical trials. The drug increased CSF glycine levels by 50% at half-maximal inhibitory concentrations, and recent phase II studies in patients with schizophrenia who had cognitive impairment at baseline showed a significant improvement on a cognitive rating scale at the 10 mg and 25 mg doses[76]. However, Boehringer Ingelheim recently reported that iclepertin failed to improve cognition or performance in patients with schizophrenia in three phase III clinical trials lasting 6 months[76].

Metabotropic glutamate receptors. Pomaglumetad methionil (POMA; LY2140023) is a peptidergic prodrug that is an agonist at mGluR2/3 receptors, which are expressed on glutamatergic terminals and negatively regulate the synaptic release of glutamate. Its development was based on clinical and preclinical research showing that disinhibition of corticolimbic glutamate release disrupts the E/I ratio and increases dopamine release[77] (Fig. 1). Phencyclidine causes hyperactivity in mice that is blocked by D_2R antagonists as well as mGluR2/3 agonists, supporting the notion that increased glutamate release drives dopamine release[78]. The disinhibition of corticolimbic glutamatergic neurons by dissociative anaesthetics results from the greater sensitivity of NMDARs on PV^+GABAergic neurons to them, thus reducing pyramidal cell inhibition[16]. A mGluR2/3 agonist like POMA could not only correct the corticolimbic E/I imbalance that contributes to cognitive and negative symptoms but also reduce striatal dopamine release that causes psychosis[79]. The active metabolite of POMA, LY404039, acts primarily through the mGluR2 receptor, as mice lacking this receptor no longer show reversal of the behavioural effects of PCP[80].

In an initial phase II clinical trial comparing POMA with placebo and olanzapine in 196 in-patients with schizophrenia who had considerable psychopathology, POMA appeared to reduce positive, negative and cognitive symptoms without an adjunctive antipsychotic medication[81]. However, three subsequent (phase II and phase III) studies comprising more than a thousand participants with schizophrenia failed to replicate the effects of POMA on positive, negative or cognitive symptoms[82]. An EEG method utilizing artificial intelligence (AI) identified unique EEG patterns that are associated with clinical response to POMA with significant reductions in positive, negative and cognitive symptoms. The response is restricted to approximately 20% of the participants in the clinical trial. The modest number of responders is statistically obscured by the 80% of non-responders[83]. This finding is consistent with the aetiologic heterogeneity of schizophrenia and suggests that these genetically targeted drugs would likely affect only subgroups of *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM)-diagnosed patients.

Normalizing E/I balance. Treatment-resistant schizophrenia (TRS) affects a substantial minority of patients with schizophrenia and is associated with frequent hospitalization, high morbidity and suicide (see Nucifora et al.[84]). Currently, clozapine is the sole drug approved for TRS, but it is underutilized because of concerns over a potentially fatal side effect. In addition, approximately 30% of individuals with TRS do not respond to clozapine. Preclinical TRS models, including methylazoxymethanol acetate developmental lesions of corticolimbic GABAergic neurons[85], ketamine[86] mice[49] (which have a 70% reduction in NMDAR function[29]) and NMDAR *GRIN2A*-null mutation[87], all exhibit cortical E/I imbalance. A recent meta-analysis of ^{1}H-magnetic resonance spectroscopy studies in patients[88] provides strong evidence of E/I imbalance in schizophrenia, with elevation of limbic endogenous glutamate and reduction in GABA, consistent with studies in experimental animals.

A new chemical entity, evenamide, specifically blocks voltage-gated sodium channels (NaV), which are located on glutamatergic terminals and enhance glutamate release[89]. It does not interact with over 130 other brain targets. Therefore, evenamide normalizes excessive glutamate release and reduces hyperexcitability that occurs as a consequence of NMDAR hypofunction, without impairing basal glutamate function[90]. It reverses prepulse inhibition deficits, an abnormality characteristic of schizophrenia, in rats induced by treatment with the NMDAR antagonist ketamine[91].

In a proof-of-mechanism, double-blind, placebo-controlled, parallel-group, 4-week trial, 89 patients with schizophrenia receiving risperidone or aripiprazole suffering from breakthrough psychotic symptoms were randomly assigned to receive evenamide or placebo. Patients receiving evenamide were reported to exhibit significant improvement on the PANSS positive symptoms and Clinical Global Impressions (CGI)–Clinical Change[92]. This was followed by a 6-week, open-label study with a 46-week extension in 161 patients with TRS. Pooled results from all dose groups showed significant improvements in PANSS, with nearly 50% of participants exhibiting a greater than 20% reduction in symptoms at 1 year. Results of a recent study involving 291 patients with TRS in a 4-week, double-blind, placebo-controlled clinical trial of evenamide added to a second-generation antipsychotic revealed a significant reduction in the PANSS score ($P < 0.006$) and improvement of CGI–Severity ($P = 0.037$)[93]. Therefore, evenamide may provide a novel strategy for correcting glutamate dysregulation in schizophrenia without directly modulating NMDAR function.

Restoring glutamatergic synapses. As previously noted, loss of dendritic length and spine density on corticolimbic pyramidal neurons

is a core pathologic feature of schizophrenia that is associated with NMDAR hypofunction and excessive pruning of spines by the risk gene-encoded complement C4 (for review, see Coyle et al.[94] and Yilmaz et al.[30]). Strategies to restore glutamatergic synapses could therefore provide therapeutic benefit.

SPG302, a third-generation PEGylated (in which PEG is polyethylene glycol) benzothiazole derivative, restored synaptic density in a rat model of traumatic brain injury[95] and in the 3x transgenic mouse model of Alzheimer's disease, and also reversed the cognitive deficits in the Alzheimer's disease model[96]. SPG302 targets a regulator of F-actin-based cytoskeleton and increases spine density and their associated proteins, including PSD-95 (postsynaptic density protein 95) in vitro and in vivo. These new spines consist of synapses that exhibit a normal distribution of spine shapes[97]. Notably, the restoration of synapses in the 3x transgenic mouse Alzheimer's disease model restored glutamatergic synapse without affecting amyloid accumulation or tau pathology. SPG302 is in a phase II clinical trial in schizophrenia with the goal of restoring corticolimbic glutamatergic synapses to

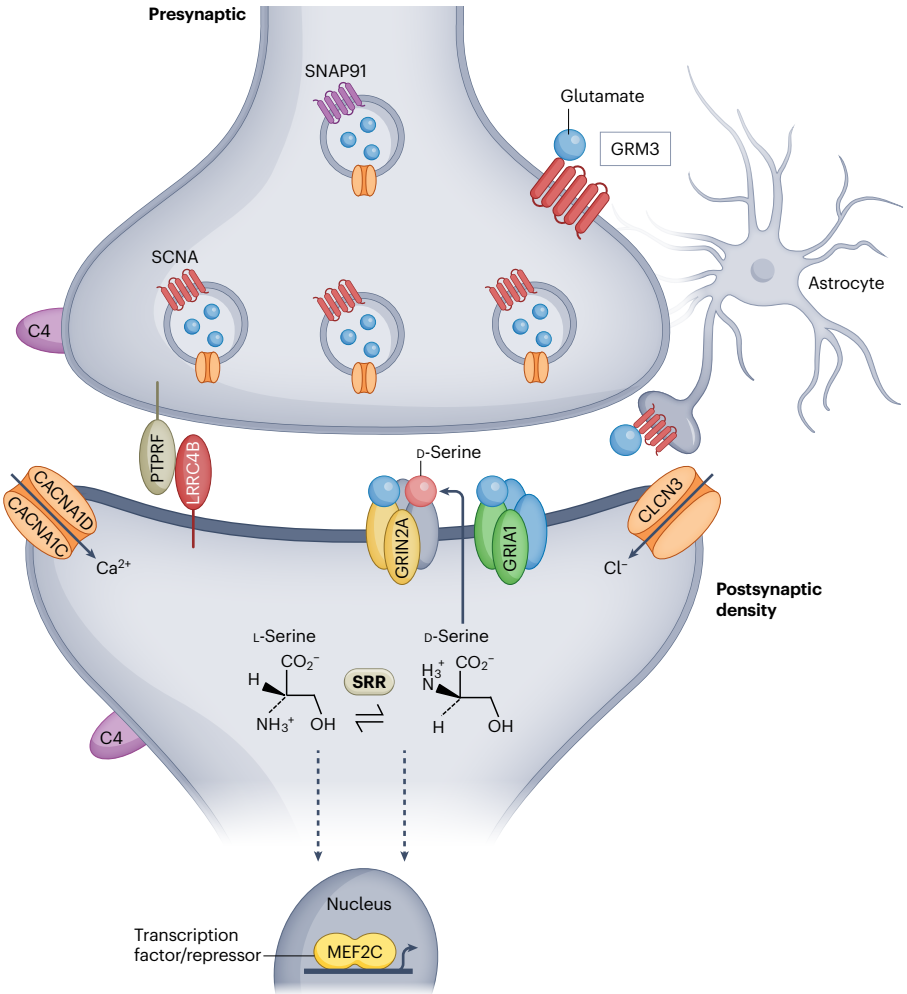

Fig. 2 | Schizophrenia risk genes are concentrated at the glutamatergic synapse. The schizophrenia risk genes discussed here, identified through genome-wide association studies, demonstrate the importance of all components of the excitatory synapse to schizophrenia. In the presynaptic terminal, synaptic vesicle trafficking is regulated by products of genes including *SNCA* (alpha synuclein) and *SNAP91* (synaptosome associated protein 91). Transsynaptic cell-adhesion molecules such as PTPRF (protein tyrosine phosphatase receptor type F) and LRRC4B (leucine rich repeat containing 4B) regulate synaptic formation, remodelling and signalling. Several ion channel subunit genes are associated with schizophrenia, including calcium channel subunits CACNA1C, CACNA1D and CACNA1G, as well as chloride ion channel subunit CLCN3. Subunits of glutamate receptors are themselves also encoded by schizophrenia risk genes, including *N*-methyl-D-aspartate receptor (NMDAR) subunit GRIN2A, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor subunits GRIA1 and GRIA3, and metabotropic glutamate receptors GRM1 and GRM3. The enzyme serine racemase (SR) converts L-serine to D-serine, the primary co-agonist of forebrain NMDARs. Complement component C4, encoded by the *C4A* and *C4B* genes, is involved in excessive pruning of excitatory synapses, resulting in the decreased density of dendritic spines observed in schizophrenia. Several nuclear factors, including the transcription factor MEF2C, regulate the expression of genes involved in glutamatergic neurotransmission. The astrocyte also plays an important role in glutamatergic neurotransmission. It takes up glutamate and synthesizes glycine, an NMDAR co-agonist and a precursor for L-serine. Astrocytic release of glutamate into the extracellular space is regulated by metabotropic glutamate receptor mGluR3, encoded by a risk gene for schizophrenia. Figure adapted with permission from Coyle, J. T., Ruzicka, W. B., Balu, D. T. Fifty years of research on schizophrenia: the ascendance of the glutamatergic synapse, Am J Psychiatry 177(12), 1119-1128 (2020)[94].

reduce cognitive deficits and negative symptoms. No studies have been reported examining the efficacy of SPG302 for restoring glutamatergic synapses in genetic models of schizophrenia.

Targeting acetylcholine receptors

Acetylcholine (ACh) was the first neurotransmitter identified in 1921 by Loewi and Dale[98]. ACh-containing, that is, cholinergic, neurons are widely distributed throughout the central and peripheral nervous systems and are involved in numerous motor and cognitive functions[99]. There are two families of ACh receptors: a large family of ligand-gated or ionotropic receptors, so-called nicotinic ACh receptors (nACHRs), and a smaller family of G protein or metabotropic receptors, designated muscarinic ACh receptors (mAChRs)[100] (Fig. 4). Based on genetic and neuropathology studies, both nAChRs and mAChRs have been implicated in the pathophysiology of schizophrenia. In general, these studies have shown reduced expression of various nAChRs or mAChRs, suggesting that receptor agonists may be of therapeutic benefit. Over the past couple of decades, several nAChR and mAChR agonists have been developed and studied as potential antipsychotic agents in people with schizophrenia.

nACHRs. Patients with schizophrenia have a high prevalence of cigarette smoking[101]. This form of nicotine self-administration has been proposed to be an attempt at self-medication[102,103]. Nicotine acts as an agonist at most nAChRs, where it can modulate local cholinergic neurotransmission. The most widely expressed subtypes in the brain are the heteromeric α4β2-subtype and the homomeric α7 nAChR[104]. Abnormal expression of α4β2 nAChRs alters cholinergic neurotransmission in neuropsychiatric disorders, including Alzheimer's disease[105] and Parkinson's disease[106]. The α5 and α7 nAChRs have been most consistently associated with schizophrenia; their allelic variants have been associated with sensory gating dysfunction and cognitive deficits[107], as well as an increased risk of developing schizophrenia[108,109]. Deletions of *CHRNA7*, the gene that encodes the Ca^{2+}-conducting α7 nAChR, are associated with schizophrenia and related psychoses[110]. Post-mortem studies have also reported decreased expression of *CHRNA7* in the hippocampus and dorsolateral prefrontal cortex of patients with schizophrenia[110,111].

Selective α7 nAChR agonists have been developed and studied as potential treatments for schizophrenia. However, they have yielded mixed results, with some[112,113] but not all[114–116] studies reporting improvement in cognitive symptoms, with little beneficial effects on positive symptoms. A recently completed large phase III trial of the α7 nAChR partial agonist encenicline (EVP-6164), failed to meet its primary clinical end point in improving cognition in patients with schizophrenia[117], thus diminishing interest in this potential mechanism. For a review of α7 nAChR agonists as potential treatments for schizophrenia, see Terry and Callahan[118] and Recio-Barbero et al.[119].

mACHRs. There are five distinct mAChRs (M_1–M_5) that make up two functional classes based on their respective G proteins and second messengers (Fig. 4). M_1, M_3 and M_5 mAChRs couple primarily through

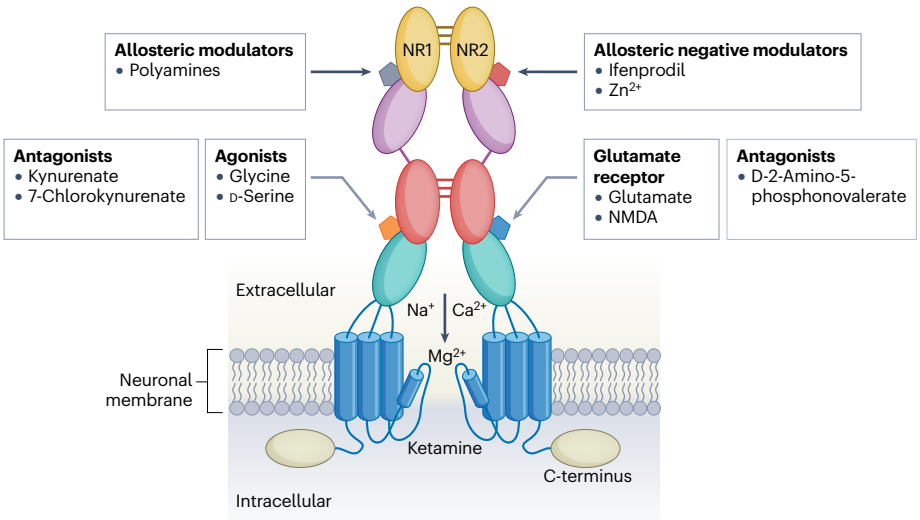

Fig. 3 | Schematic representation of the NMDA receptor. The *N*-methyl-D-aspartic acid (NMDA) receptor is an ionotropic receptor, and its activation opens a cation channel permeable to Na^+, Ca^{2+} (inward) and K^+ (outward). The influx of Ca^{2+} drives gene expression, especially expression of those genes responsible for synapse plasticity. The cation channel is blocked by Mg^{2+} at resting membrane potential, which is relieved by membrane depolarization, typically mediated by activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR). The NMDA receptor is a heterotetramer comprising combinations of three subunits: NR1, NR2 and NR3. All NMDA receptors contain two NR1 subunits and two NR2 subunits or a combination of a NR2 and a NR3 subunit. The NR1 subunit is a critical component of the channel. The channel has a binding site for dissociative anaesthetics such as ketamine and phencyclidine, which act as non-competitive inhibitors. The intracellular domain contains sites that are targets for protein kinases as well as binding sites for scaffolding proteins. The extracellular domains of NR2 and NR3 subunits contain the binding-recognition site for the neurotransmitter glutamate. The extracellular domain of NR1 contains the binding-recognition site for the co-agonists glycine and D-serine. The extracellular domains also have binding sites for negative modulators Zn^{2+} and ifenprodil, and the biphasic polyamines. The NMDA receptor has been described as a coincidence detector, as three events must occur simultaneously for the cation channel to open: depolarization of the synaptic membrane by glutamate-activating AMPARs to relieve the channel blockade by Mg^{2+}, the binding of glycine or D-serine to the recognition site on NR1, and the binding of glutamate to its recognition site on NR2 and NR3. This unique high degree of constraint on NMDA receptor function underscores its role in regulating synaptic plasticity and memory formation. D-Serine, the co-agonist in forebrain, is synthesized from L-serine by serine racemase, which is expressed in the neurons postsynaptic to the glutamatergic terminal bouton and acts as an autocrine modulator. Ca^{2+}, calcium ion; K^+, potassium ion; Mg^{2+}, magnesium ion; Na^+, sodium ion; Zn^{2+}, zinc ion.

Box 2 | Modulatory site agonists on NMDARs

Research carried out over the past three decades has provided compelling evidence that glutamatergic dysfunction, especially involving the *N*-methyl-D-aspartate receptor (NMDAR), is an important component of the pathophysiology of schizophrenia. Placebo-controlled studies of the NMDAR glycine modulatory site (GMS) agonists in schizophrenia commenced 30 years ago (see Coyle et al.[228]). These studies focused primarily on patients with chronic schizophrenia with prominent negative symptoms who were on a stable regimen of typical antipsychotics. The hypothesis was that GMS agonists would affect primarily negative symptoms and cognitive impairments, which are unresponsive to antipsychotic drugs, because these symptoms corelate with cortical atrophy and the loss of glutamatergic synapses.

Glycine. Javitt et al. pioneered double-blind, placebo-controlled studies of high-dose glycine (30–60 g day^{-1}) added to typical antipsychotics[229]. Astrocytes uniquely express 3-phosphoglycerate dehydrogenase, which converts glycine to L-serine and thus provides the precursor for D-serine synthesis in serine racemase-expressing neurons[68]. Therefore, glycine loading may reduce symptoms resulting from forebrain NMDAR hypofunction by the actions of both glycine and D-serine. In a series of modestly sized clinical trials in patients with prominent negative symptoms, investigators found significant reductions of negative symptoms and, in some cases, improvement in cognition, but no effect on positive symptoms[230,231]. The treatment increased serum glycine levels 3.5-fold and significantly increased serum L-serine levels, with clinical response inversely related to baseline serum glycine levels.

D-Cycloserine. In preclinical studies, the antitubercular drug D-cycloserine[232], a partial agonist with 60% activity at the GMS[233], readily crossed the blood–brain barrier and enhanced learning and memory in rats[234]. A dose-finding study showed a U-shaped response, with an optimal dose of 50 mg day^{-1} significantly improving cognition and reducing negative symptoms[235]. Larger studies confirmed the effect on negative symptoms but not on cognition[236,237]. However, with longer treatment, d-cycloserine lost efficacy[238], presumably due to desensitization[239]. To circumvent the loss of efficacy, once-a-week treatment was studied and found to have modest effects on negative symptoms but no effects on cognition[240,241].

D-Serine. Tsai's laboratory studied the efficacy of D-serine, as it is a full agonist at the GMS and is concentrated in the forebrain[242,243]. The first double-blind, placebo-controlled, 6-week clinical trial of D-serine (30 mg kg^{-1} day^{-1}) in patients with schizophrenia on stable doses of antipsychotic drugs showed robust reductions in positive, negative (Scale for the Assessment of Negative Symptoms (SANS)) and cognitive symptoms, and moderate improvement in a test of cognitive function at 6 weeks[244]. D-Serine plasma levels increased 40-fold. Heresco-Levy et al. replicated these findings on negative, positive and cognitive symptoms at 30 mg kg^{-1} day^{-1} of D-serine[245]. Kantrowitz et al. found robust effects at 60 mg kg^{-1} day^{-1} on Positive and Negative Syndrome Scale (PANSS) positive, negative and total subscale scores and on a score of cognitive improvement[246].

In summary, the endogenous agonists are weak, associated with NMDAR internalization[247] and desensitization[239]. Goh et al. carried out the largest meta-analysis to date by combining patients receiving glycine, D-alanine, D-serine or d-cycloserine from 31 studies and found significant reductions in SANS scores and PANSS negative subscale scores[248]. However, given the limitations of GMS agonists, the development of NMDAR-positive allosteric modulators would likely be a more effective strategy[209].

the G_q to stimulate phospholipase C to release intracellular inositol 1,4,5-trisphosphate, leading to intracellular calcium mobilization and enhanced excitatory postsynaptic currents. M_2 and M_4 mAChRs couple through $G_{i/o}$ to inhibit adenylate cyclase, leading to reduced intracellular cyclic adenosine monophosphate (cAMP), which generally suppresses excitation[120].

mAChR agonists have demonstrated encouraging antipsychotic properties and may also treat the core symptoms of schizophrenia. Interest in mAChR agonists as a potential treatment strategy for schizophrenia stems in part from the serendipitous discovery that the mAChR agonist xanomeline, originally developed for its pro-cognitive properties for Alzheimer's disease, showed rapid improvement in psychotic symptoms in a large phase II trial in people with Alzheimer's disease[121]. In vitro, xanomeline exhibits relatively equal, nanomolar-level radioligand binding affinity at all five mAChRs but with variable levels of functional signal transduction activity. At clinically relevant concentrations, xanomeline preferentially stimulates M_1 and M_4 mAChRs, although it has some very weak activity at M_2 and M_3 receptors[122]. Determination of which mAChR subtypes are involved in the behavioural actions of xanomeline has only recently been made possible with the development of mice bearing genetic deletions of one or more mAChR subtypes, as well as by using mAChR subtype-selective ligands.

The antipsychotic effects of xanomeline in Alzheimer's disease led to a small, placebo-controlled, proof-of-concept study in patients with chronic schizophrenia, which also demonstrated improvement in both positive and negative symptoms[123]. However, xanomeline was also associated with serious side effects, mostly related to cholinergic activation in the periphery (such as nausea and vomiting), that stalled further clinical development.

To mitigate the peripheral cholinergic side effects of xanomeline, investigators at Karuna Therapeutics (now Bristol Myers Squibb) combined the drug with the peripherally restricted mAChR pan-antagonist, trospium chloride[124]. Using the combination of xanomeline and trospium chloride, formerly known as KarXT, Karuna conducted three randomized placebo-controlled trials (the EMERGENT studies) in patients with acute psychosis and schizophrenia[125–127]. Treatment with xanomeline/trospium chloride met its primary end point, a reduction in PANSS total score from baseline at 5 weeks compared with placebo, as well as key secondary endpoints (such as on both positive and negative symptoms)[125–127]. Based on the results of the acute pivotal trials and chronic open label extensions, in September 2024, the FDA approved xanomeline/trospium chloride (Cobenfy; Bristol Meyers Squibb) for the treatment of schizophrenia in adults. Adverse events were generally mild to moderate in severity, mostly cholinergic in nature, and likely due to the known pharmacology of xanomeline and/or trospium chloride[125–127].

More recently, an exploratory prespecified analysis showed that xanomeline/trospium chloride monotherapy as compared with placebo improved performance on a battery of cognitive tests in a subgroup of participants with cognitive impairment[128]. Moreover, post hoc analyses of negative symptoms in the three EMERGENT clinical trials found that xanomeline/trospium chloride reduced negative symptoms in the group as a whole. When patients with prominent negative symptoms were analysed, the effect size increased substantially[128,129]. Together, these data suggest that mAChR agonists may have broad therapeutic activity on all three core symptom domains of schizophrenia. Additional prospective clinical trials in patients with predominately cognitive and/or negative symptoms and stable positive symptoms are required (see Paul et al. for a detailed review of these studies[130]).

Considerable evidence, primarily from preclinical studies, has also emerged supporting a critical role for M_4 mAChRs in mediating the antipsychotic-like properties of xanomeline and other mAChR agonists. Genetic deletion of M_4 receptors in GABAergic medium spiny neurons(MSNs) in mice, for example, almost completely blocks the antipsychotic activity of xanomeline[131,132]. Based on the macromolecular structure of the M_4 receptor, the mechanisms underlying xanomeline's rather selective activity at M_4 receptors have been characterized[133,134]. Xanomeline exhibits "efficacy-driven ligand selectivity" due largely to a differential binding pose in the active state of preferred mAChRs (that is, M_4) over others (that is, M_2) despite high similarity of the orthosteric binding pockets of these two mAChR subtypes[134].

The presynaptic and postsynaptic localizations of M_1 and M_4 mAChRs suggest neuroanatomical sites and neural circuits that may mediate the therapeutic effects of xanomeline/trospium chloride in treating the core symptoms of schizophrenia (Fig. 5). Notably, presynaptic M_4 autoreceptors reduce ACh release onto dopaminergic neurons in the ventral tegmental area, thus exerting anti-psychotic effects. In addition, in a subset of striatal MSNs that express D_1 receptors (D_1Rs), activation of M_4 autoreceptors inhibits cAMP required for D_1R-mediated signalling[135]. This suggests that M_4 mAChR agonists inhibit dopamine signalling (and psychosis), independent of altering dopamine release[136].

Although these studies may explain the effects of M_4 receptor activation on positive symptoms, activation of M_1 receptors may be important for treating cognitive and negative symptoms[137]. Excitatory M_1 receptors are located on cortical and hippocampal GABAergic interneurons, where they increase GABA-mediated inhibition of pyramidal cells and modulate gamma oscillatory frequency[138], respectively, both of which may underlie the potential pro-cognitive properties of xanomeline. Therefore, a dual M_1/M_4-preferring mAChR agonist may work on different neural circuits to more holistically treat the core symptoms of schizophrenia. Nevertheless, the predominant expression of the M_4 muscarinic acetylcholine receptor in the central nervous system and its role in regulating dopamine release in the striatum suggests that it might have antipsychotic effects but with a low risk of peripheral parasympathetic side effect[136–139]. Some drug developers are therefore pursuing M_4-preferring mAChR agonists.

Highly selective M_4 receptor allosteric agonists that bind to a site distinct from the orthosteric site, the primary binding site for ACh (see Fig. 4), have been reported to display potent antipsychotic-like activity in rodent models of schizophrenia[140–143]. Emraclidine, an M_4-receptor positive allosteric modulator, was also reported to improve positive and negative symptoms in a phase Ib clinical trial in people with schizophrenia[144]. This study, although relatively small, was nonetheless noteworthy in that, as expected, there were no reported cholinergic side effects due to stimulation of peripheral mAChRs, because M_4 receptors are mostly not expressed in the periphery. However, larger phase II studies of emraclidine in schizophrenia recently failed to demonstrate a significant drug–placebo difference. Whether these disappointing results were due to the selective M_4 allosteric mechanism of action of emraclidine or factors relating to clinical trial execution is unclear (see below).

Neurocrine Biosciences has developed an orthostatic M_4 muscarinic receptor agonist, NBI-568. This company recently reported the outcome of a phase II trial in patients with schizophrenia who were experiencing an exacerbation of symptoms. The drug was generally well-tolerated, and patients in the low-dose group showed a statistically significant reduction in symptoms (the primary end point) and in secondary endpoints, including positive and negative symptom scores. NBI-568 is currently in phase III trials.

Inidascamine is a novel neuromodulatory drug with pro-cognitive effects developed by Atai to treat cognitive impairment associated with schizophrenia. Preclinical studies show that it enhances excitatory

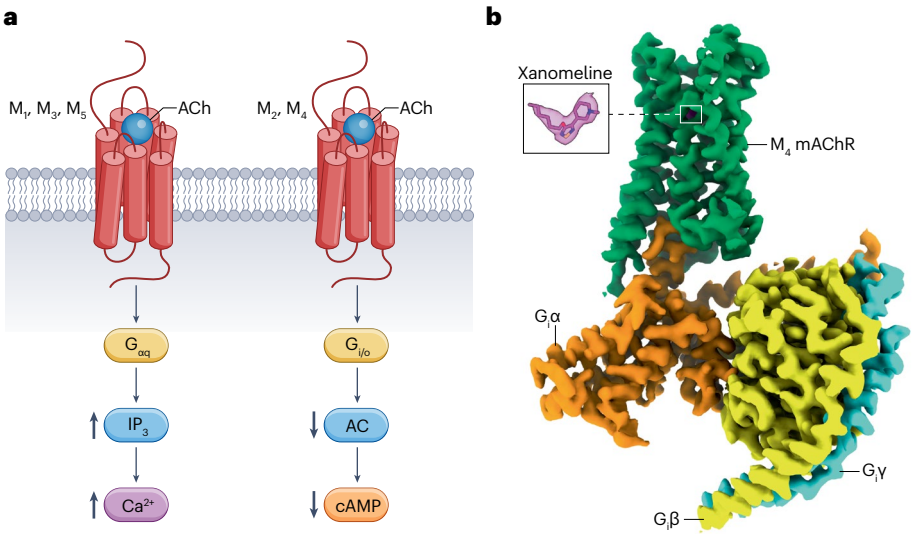

Fig. 4 | Signalling selectivity among muscarinic acetylcholine receptors. a, Muscarinic acetylcholine receptors (mAChRs) are a family of five G protein-coupled receptors (M_1–M_5) that mediate the physiological effects of the neurotransmitter acetylcholine (ACh). The M_1, M_3 and M_5 receptors are stimulatory and couple primarily to the G_q alpha subunit to stimulate phospholipase C (via inositol 1,4,5-trisphosphate (IP_3)), leading to the mobilization of intracellular calcium ion (Ca^{2+}). The M_2 and M_4 receptors are inhibitory and lower the activity of adenylyl cyclase (AC) via the $G_{i/o}$ alpha subunit to reduce cytoplasmic concentrations of cyclic adenosine monophosphate (cAMP). **b**, A consensus cryogenic electron microscopy map of the M_4 mAChR in complex with a heterotrimeric inhibitor G protein and bound to xanomeline. Adapted with permission from ref. 133 (Springer Nature Limited. All rights reserved).

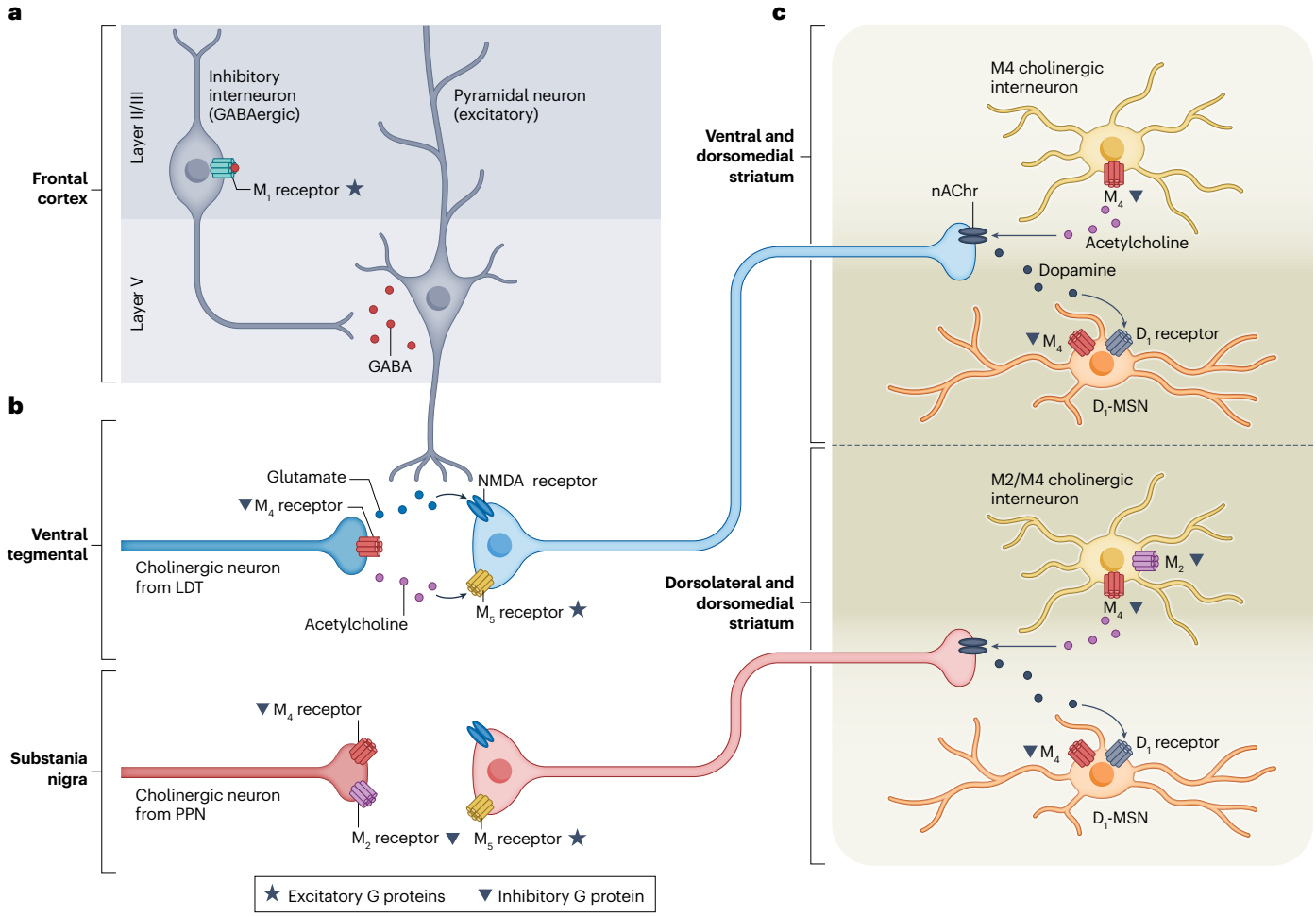

Fig. 5 | Cholinergic modulation of key neural circuits. a, Activation of M_1 muscarinic acetylcholine receptors (mAChRs) on layer II/III γ-aminobutyric acid (GABA)-ergic interneurons increases inhibitory drive onto the principal output neurons of the prefrontal cortex. Increased inhibitory tone onto layer V pyramidal neurons leads to reduced glutamatergic input to midbrain dopaminergic nuclei and subsequent decreased stimulation of *N*-methyl-D-aspartate (NMDA) receptors on the dopaminergic cell bodies[215]. Activation of M_1 mAChRs can thereby normalize excessive prefrontal cortical pyramidal neuron firing in layer V neurons. **b**, Activity of midbrain dopaminergic nuclei is also modulated by cholinergic neurons projecting from the pedunculopontine nucleus (PPN) and laterodorsal tegmental (LDT) nucleus. M_4 and M_2/M_4 autoreceptors are expressed on cholinergic projections from the LDT nucleus and the PPN, respectively. Activation of mAChR autoreceptors reduces cholinergic activity, which decreases M_5 receptor stimulation on dopaminergic cell bodies, lowering dopaminergic neuronal excitability. **c**, Dopaminergic neurons from the ventral tegmental area project to the ventral and the dorsomedial striatum, where dopamine release can be modulated by M_4-expressing cholinergic interneurons. Activation of M_4-expressing cholinergic interneurons reduces local cholinergic activity via inhibition of Ca_{v2}-type Ca^{2+} conductance and/or potassium channel opening. M_4 receptor activation inhibits acetylcholine release, which reduces activation of nicotinic acetylcholine receptors (nAChRs) localized on dopamine axons[215,216]. In the striatum, M_4 receptors on D_1-expressing MSNs (D_1-MSNs) can decrease dopamine release and D_1-MSN excitability. Dopaminergic neurons in the substantia nigra project to the dorsolateral and dorsomedial striatum. In the dorsolateral and dorsomedial striatum, M_2/M_4-expressing cholinergic interneurons control cholinergic neuronal activity and consequent dopamine release. M_4 receptors are also expressed on D_1-MSNs, where they modulate neuronal excitability and terminal dopamine release.

neurotransmission and the induction of LTP in hippocampal slices with a U-shaped dose–response curve[145]. This effect was blocked by GABA-B receptor inhibitors, although the drug does not directly interact with GABA-B receptors. It reverses cognitive deficits caused by scopolamine and reverses cognitive deficits in aged rats in the Barnes maze task[145]. In phase I and phase IIA studies, inidascamine has been found to have high bioavailability and to be well-tolerated with few side effects. Preliminary results show that it reverses cognitive impairment induced by scopolamine in healthy individuals, and it has cognitive ability-enhancing effects in patients with schizophrenia. Possible effects on negative symptoms are unclear. The combination of inidascamine with an effective antipsychotic could not only reduce disruptive positive symptoms but also ameliorate disabling cognitive impairment associated with schizophrenia.

Other biogenic amine-targeted drugs

The trace amine-associated receptor 1 (TAAR1) is a member of a larger family of G protein-coupled receptors expressed primarily in the brain

and the gastrointestinal tract[146,147]. TAAR1 is activated by a group of trace biogenic amines, including β-phenylethylamine, *p*-tyramine and tryptamine, as well as a number of psychomotor stimulants, such as amphetamine and psychedelic drugs like LSD (lysergic acid diethylamide)[148,149]. These trace amines, including TAAR1, have been implicated in the pathophysiology of schizophrenia and other neuropsychiatric disorders, including mood and substance use disorders[150]. In the central nervous system, TAAR1 has been reported to be localized both intracellularly and extracellularly at both presynaptic and postsynaptic sites. The biological significance of intracellular TAAR1 expression is unclear, although a recent report demonstrated that amphetamine (internalized via the dopamine transporter) can activate intracellular TAAR1-mediated signalling via specific G proteins, suggesting that at least some TAAR1 agonists may work intracellularly.

In rodents, TAAR1 is expressed primarily in the ventral tegmental area and dorsal raphe nucleus, areas containing dopaminergic and serotoninergic neurons, respectively, as well as the prefrontal cortex in glutamatergic neurons, which are brain regions and neurotransmitters that have all been implicated in schizophrenia[150,151]. Moreover, these trace amines have not surprisingly been shown to modulate neurotransmission mediated by dopamine and serotonin[152]. However, it is important to underscore that the expression levels and regional distribution of TAAR1 in the human brain is less clear. There are intriguing data showing that, when co-expressed with D_2Rs, TAAR1 can selectively heterodimerize with these receptors and modulate D_2R-mediated signalling[153]. Given the reported regional expression of TAAR1 in the brain, it is also not surprising that in vivo studies in rodents have shown that TAAR1 agonists regulate both dopamine-mediated and serotonin-mediated neurotransmission and behaviour[154].

The compelling biological data on TAAR1 in rodent models of psychosis have prompted the discovery of several selective TAAR1 agonists that have more recently been studied both preclinically and clinically as putative antipsychotic drugs. TAAR1 agonists developed by scientists at Roche and Sunovion have also been extensively studied in various animal models relevant to schizophrenia with encouraging results. For example, TAAR1 agonists have been shown to dose-dependently reduce hyperlocomotion induced by psychomotor stimulants, such as amphetamine and PCP, and to also have pro-cognitive effects in rodent models of memory and learning[155]. Interestingly, the TAAR1 agonist SEP-856 (also known as ulotaront) was discovered via a machine learning-enabled behavioural phenotypic screen in mice called SmartCube. The compound was found to have a behavioural signature in animal models similar to traditional antipsychotic drugs but was completely devoid of D_2R-blocking activity. It was subsequently shown to be a potent TAAR1 agonist, as well as having activity at the 5-HT1A receptor. Both receptors appear to contribute to its antipsychotic activity, at least in mice[156].

Clinical studies of the TAAR1 agonists have yielded mixed results in schizophrenia to date. The more selective partial or full TAAR1 agonists have failed to show convincing antipsychotic activity in improving either positive or negative symptoms. Although ulotaront demonstrated antipsychotic efficacy with a good safety and tolerability profile in a large phase II study in schizophrenia[157], the compound failed to separate from placebo in two recently completed pivotal phase III trials, possibly due in part to a high placebo response (NCT04072354 and NCT04092686). Therefore, although once a compelling potential non-D_2R drug target for schizophrenia, the at best mixed clinical results with TAAR1 agonists have called into question this potential mechanism and approach. The role of aetiologic heterogeneity in the failure of TAAR antagonists, in spite of promising preclinical results, remains to be determined.

Roluperidone is a novel cyclic amine under development for the treatment of negative symptoms in schizophrenia. Preclinical studies indicate that roluperidone is an antagonist with high, equipotent affinity for the sigma-2, 5-HT_{2A} and α-1A adrenergic receptors[158]. In rodents, roluperidone reverses impaired social interactions caused by chronic treatment with ketamine and drug-induced neck dystonia, which are thought to be animal models for negative symptoms. It also reduces hyperactivity induced by apomorphine and methamphetamine, which suggests antipsychotic activity (reviewed by Davidson et al.[159]). In a phase II trial in patients with schizophrenia, roluperidone significantly reduced negative symptom scale scores at 12 weeks, but positive symptom scale scores were unchanged[160,161].

Roluperidone also improved overall cognition scores as well as individual motor and verbal fluency subscores[162]. The phase III study enrolled 513 patients with prominent negative symptoms comparing the efficacy of 32 mg and 64 mg roluperidone to placebo in a double-blind study[162]. High-dose roluperidone was associated with a statistically significant improvement in negative symptom scores. In reviewing the combined studies with open-label extensions for 6 or 9 months, Davidson et al. reported continued improvement; moreover, less than 10% of patients required discontinuation of roluperidone and re-institution of antipsychotics[163]. They speculate that the low relapse rate may be due the effects of 5-HT_{2A} antagonism, a property common to antipsychotics. Therefore, roluperidone alone appears to be a promising drug for treating patients with predominantly negative symptoms or as an add-on for patients with persistent psychotic symptoms accompanying negative symptoms.

Stimulating neuroplasticity

Increasing cyclic guanosine-3′,5′-monophosphate (cGMP). As noted above, loss of glutamatergic synapses in the cortical limbic regions of the brain resulting in cortical atrophy due to NMDAR hypofunction and/or excessive pruning of glutamatergic synapses by allelic variants of complement C4m is a core neuropathologic feature of schizophrenia that is associated with negative and cognitive symptoms[28–30]. Recent research has targeted mechanisms to restore these synapses.

cGMP is a signalling molecule that has been linked to cognition and neural plasticity (for review, see Fedele and Ricciarelli[164]). In brain, guanylyl cyclase (GC) is activated by nitric oxide, a gaseous intracellular and intercellular neurotransmitter synthesized by nitric oxide synthase (NOS). GC exists in two forms: cytosolic and membrane-bound. cGMP interacts primarily with protein kinase G, cyclic nucleotide gated channels and cGMP-regulated phosphodiesterases (PDEs). The effects of cGMP are terminated by its hydrolysis by PDEs, of which three are specific for cGMP: PDE5, 6 and 9. LTP is considered to be a fundamental component of memory formation[165]. cGMP has been implicated in cognition, because silencing NOS expression and inhibiting soluble GC reduces LTP in the hippocampus and impairs memory. PDE5 and 9 inhibitors have also been shown to enhance LTP and improve memory function in experimental animals. These behavioural effects of increasing cGMP could extrapolate to cognitive improvement and possibly reduced negative symptoms in schizophrenia.

Cyclerion Therapeutics has developed zagociguat, a brain-penetrant soluble GC allosteric stimulator that works independently of NOS, thus avoiding the oxidative stress associated with excessive nitric oxide. This class of drugs reverses the memory impairments resulting from inhibiting NOS with L-N^G-nitroarginine methyl ester (L-NAME)

in rats[166]. In preclinical studies, this class of drugs has been shown to enhance functional brain connectivity and cognitive performance, and reduce inflammation. Zagociguat was shown in human studies to be brain-penetrant and well-tolerated, with a half-life of 50 hours[167], and it has progressed to a phase I clinical trial in schizophrenia (NCT04972227).

Phosphodiesterase inhibition. An alternative way to increase cGMP signalling is to reduce its catabolism by inhibiting the relevant PDE. Drugs have been developed to inhibit cGMP-specific PDE5 and PDE9. BI 409306 is a selective PDE9 inhibitor that increases brain cGMP levels, enhances LTP, and reverses working memory and long-term memory deficits in rats[168]. BI 409306 also reduces social deficits and amphetamine-induced hyper-locomotion in the maternal immune activation model of schizophrenia[169]. BI 409306 has completed a phase I clinical trial, which demonstrated good safety and tolerability[170]. In a 12-week, double-blind, placebo-controlled trial involving more than 500 patients on stable doses of antipsychotic drugs, BI 409306 was well-tolerated, but there was no significant improvement of psychopathology nor improvement in cognition[171]. Two further clinical trials were terminated because of the COVID-19 pandemic[172].

Inflammation, oxidative stress and obesity

Since its early description by Kraepelin, schizophrenia has been considered primarily a brain disorder, although growing evidence indicates that it can have systemic manifestations with adverse health consequences. Individuals with schizophrenia die on average 15–20 years earlier than unaffected peers, primarily due to suicide (approximately 5%–10%), cancer and cardiovascular disease[173]. Individuals with schizophrenia bear a disproportionate burden of cardiovascular disease risk factors, including smoking, obesity, hypertension and type 2 diabetes. The overall prevalence of substance abuse is also significantly higher than in the general population. For example, cigarette smoking is fourfold greater in patients with schizophrenia, which triples the risk for cardiovascular disease[174]. The fact that the substance abuse risk may be intrinsic to this disorder, as opposed to a consequence of a harmful social environment, is suggested by clinical studies demonstrating a spontaneous reduction in alcohol and cigarette consumption when patients are treated with clozapine[175].

Individuals with schizophrenia are at risk for developing obesity, presumably due in part to lower physical activity associated with negative and cognitive symptoms[176]. Adiposity has been exacerbated in schizophrenia by both first-generation and second-generation antipsychotic drugs, especially olanzapine and clozapine. Henderson et al. documented a mortality rate from cardiovascular diseases of 9% and a rate of new-onset diabetes of 43% during 10 years of treatment with clozapine[177]. The substantial weight gain resulting from treatment with antipsychotic drugs is associated with the development of hypertension, dyslipidaemia, insulin resistance, type 2 diabetes and metabolic syndrome[178]. This perfect storm drives two other debilitating responses: inflammation and oxidative stress. Inflammation — including elevated levels of circulating cytokines such as tumour necrosis factor and interleukin-6, as well as C-reactive protein. These may be an adaptive response, but the long-term consequences can be detrimental, contributing to the development of metabolic syndrome and insulin resistance[179].

Several studies have now shown that oxidative damage is present in some cases of schizophrenia[180,181]. Growing evidence suggests that it contributes to the declining course and poor outcome in certain patients[182]. Compared with levels in healthy individuals, total antioxidant and glutathione levels have been shown to be lower in the plasma of non-medicated people with schizophrenia as well as in patients medicated for first-episode and chronic schizophrenia[182–184]. Fast-spiking PV^+ interneurons in the prefrontal cortex and subcortical regions, including the hippocampus, thalamic reticular nucleus and amygdala, are particularly vulnerable to oxidative stress because of high oxidative metabolism[185,186]. This damage is made manifest by downregulation of presynaptic markers, including parvalbumin itself, as well as the perineural nets that enmesh this population of GABAergic neurons[187], which are markers of impaired GABAergic function. In addition, magnetic resonance spectroscopy studies have revealed decreased phospholipid levels and increased lipid peroxidation in the forebrain, leading to damage of the brain's myelinated pathways[188].

***N*-acetylcysteine.** Several clinical trials of *N*-acetylcysteine (NAC), a precursor of glutathione, one of the main cellular antioxidants, have been carried out in patients with schizophrenia in an attempt to reduce oxidative stress. NAC readily crosses the blood–brain barrier and is virtually devoid of side effects. In a proof-of-concept clinical trial, supplementation of NAC in patients with chronic schizophrenia led to improvements in negative symptoms, auditory mismatch negativity[189] and local neural synchronization measured by EEG[190], as well as decreased side effects of antipsychotics[191]. Improvement in negative symptoms and PANSS total score was replicated in two independent studies[192,193], and two studies showed improvement in cognition in patients with chronic schizophrenia[194,195]. A randomized, double-blind, placebo-controlled add-on trial with NAC was carried out by Conus et al.[196]. Patients showed improved cognition (processing speed), and a subgroup of patients with high levels of peripheral oxidative markers also showed improved positive symptoms. Moreover, in a subgroup of patients in the same study who underwent EEG studies, NAC supplementation led to improved auditory evoked potentials, known to be impaired in schizophrenia[197]. Some of these patients with chronic schizophrenia also underwent proton magnetic resonance spectroscopy, which revealed that NAC supplementation for 6 months increased glutathione levels by 23%. The results thus far, based on symptom response and biochemical improvements, hold promise of the efficacy of anti-oxidants for patients with evidence of oxidative stress[198].

Metformin. Weight gain is the dominant cause of type 2 diabetes, metabolic syndrome, and increased cardiovascular morbidity and mortality in schizophrenia. Recently, weight reduction has become an important but largely unattainable goal in this population[199]. Prior to the introduction of glucagon-like peptide-1 receptor agonists (GLP-1RAs), metformin was the lone weight-loss pharmacotherapy available. It has a strong safety profile (unlike stimulant-like appetite suppressants, which can exacerbate psychosis) and documented weight loss properties[200]. Nevertheless, a large, multisite, randomized control trial of metformin in outpatients with schizophrenia showed that only 17% of patients lost more than 5% of their body weight, leaving the vast majority still clinically obese[201].

Glucagon-like peptide-1 receptor agonists. GLP-1RAs such as liraglutide, exenatide, and the most recent addition, semaglutide, are a new class of drugs with proven efficacy in the management of diabetes and obesity as well as their complications, including metabolic syndrome in the general population[202]. What is more tantalizing is the evidence from

Glossary

Anhedonia
The inability to experience pleasure.

Cortical atrophy
The reduction of the volume of the cerebral cortex and hippocampus in schizophrenia, primarily due to loss of axons and synapses.

Corticolimbic synapses
Synapses in the cerebral cortex and limbic structures, including the hippocampus and amygdala.

Dissociative anaesthetics
Drugs like ketamine and phencyclidine that are non-competitive antagonists of *N*-methyl-D-aspartate (NMDA) receptors and cause amnesia and a feeling of disconnection from the surroundings.

Excitatory postsynaptic currents
The depolarization of the postsynaptic membrane by an excitatory neurotransmitter causing the opening of a cation channel resulting in the influx of Na^+ and Ca^{2+} ions.

Excitotoxicity
A phenomenon in which high concentrations of glutamate, especially at extra-synaptic NMDA receptors, overload the neuron with Ca^{2+}, leading to neuronal death.

Gamma oscillatory frequency
Electroencephalography-recorded oscillatory rhythms that range between 30 and 100 Hz and are associated with attention, memory and perception.

Genome-wide association study
(GWAS). A study that involves the sequencing of the genome to identify genetic variants in different individuals to determine whether the variant is associated with a particular trait. Such variants may occur in non-coding regions of the gene that could affect processing or expression.

HbA1c
Glycated haemoglobin, which is elevated in type 1 and 2 diabetes due persistent elevation of blood glucose.

Hypofrontality
The impaired ability of individuals with schizophrenia to activate the frontal cortex, as documented by functional imaging studies when the individual is attempting to perform a cognitive task.

Long-term potentiation
(LTP). A persistent enhancement of postsynaptic excitatory responses following high-frequency stimulation of the presynaptic glutamatergic input mediated by the NMDA receptor.

Methylazoxymethanol acetate
A potent but short-lived toxic alkylating agent that crosses the blood–brain barrier and kills dividing cells. Timing administration to when a group of neurons are mitotically active, such as the cortical GABAergic neurons late in pregnancy, can eliminate those neurons.

Oxidative stress
An imbalance between reactive oxygen species, such superoxide, hydroxy radical and hydrogen peroxide, and the ability of the tissue to detoxify them, resulting in cellular damage.

Partial agonist
A drug that binds to a receptor but only displays the partial activity of a full agonist. A weak partial agonist, such as the antipsychotic drug aripiprazole, has only 20% agonism, resulting in 80% antagonism.

Parvalbumin
A calcium-binding protein expressed in cortical GABAergic neurons that provide recurrent inhibition to pyramidal neurons.

Perineural nets
Extracellular matrix structures that surround the cell bodies of certain neurons, such as the cortical parvalbumin-positive GABAergic interneurons, and stabilize their synapses. Perineural nets are vulnerable to oxidative stress.

Phosphodiesterases
(PDEs). A group of enzymes that inactivate the second messengers cyclic AMP and cyclic GMP by cleaving a phosphodiester bond.

Postsynaptic density
A protein-rich band on the postsynaptic component of the glutamatergic synapse that is composed of a 95 Dalton protein (PSD-95), scaffolding proteins and glutamate receptors.

Pyramidal neurons
The major excitatory output neurons of the cerebral cortex, named after their large conical cell bodies.

Synaptic spines
The protrusions on dendrites that receive glutamatergic terminals forming excitatory synapses.

Trace biogenic amines
A group of amines structurally related to catecholamines, such as octopamine and tyramine, found in low concentrations in the brain that are agonists of the TAAR-1 receptor.

Ventral tegmental area
A midbrain area where the cell bodies of dopaminergic neurons that innervate the striatum and frontal cortex are concentrated.

individuals with no mental illness that treatment with GLP-1RAs results in reduced brain inflammation, spontaneous reduction in substance abuse (cigarettes and alcohol), possible improved cognitive function and even slowed progression of Parkinson's disease[203,204]. These behavioural effects are consistent with the widespread expression of the GLP-1 receptor in the brain[205].

Early trials with GLP-1RAs in patients with schizophrenia have demonstrated a beneficial effect on body weight, but unfortunately their effects on psychiatric symptoms, except mood, were not monitored in these studies[206,207]. Recently, the results of a large placebo-controlled double-blind randomized clinical trial with semaglutide in patients with schizophrenia receiving second-generation antipsychotic drugs were reported. The patients had pre-diabetic levels of glycosylated haemoglobin A and elevated body mass. They were treated for 30 weeks with semaglutide and exhibited significant reductions in HbA1c and body weight (−9.2 Kg), and improvement in high-density cholesterol and triglycerides. Notably, self-rated quality of life significantly improved, whereas the PANSS-6 score was unchanged[208].

Conclusions and outlook

Schizophrenia remains a very disabling disorder. Current treatments, although effective in controlling psychotic symptoms such as hallucinations and delusions, have little to no impact on the disabling negative and cognitive symptoms of the syndrome. The D_2R antagonist antipsychotic drugs are also associated with a number of problematic side effects. These tragic facts underscore the need to find better options than the current D_2R-blocking drugs that have been the mainstay treatments for schizophrenia for more than 70 years, and to pursue new approaches, ideally informed by our recent understanding of the disease biology. The recent approval of Cobenfy may signal a new era of treatment for schizophrenia without reliance on D_2R antagonists. The following are critical conclusions of our analysis.

Recent GWASs and whole-genome sequencing studies have identified more than 200 risk loci in schizophrenia, revealing the remarkable genetic heterogeneity of the disease. Thirty of these loci contain genes that are associated with the glutamatergic synapse, four with the cholinergic synapse and only one with the dopaminergic synapse.

Many of these genes encode plausible targets for drugs to potentially treat positive, negative or cognitive symptoms.

Looking to the future, it is imperative that the genetic heterogeneity of schizophrenia be addressed. It is important to recognize that individual risk genes account for less than 5% of the phenotype. Therefore, a drug targeted at a specific risk gene would predictably have a small effect on schizophrenia in general and perhaps even in that subgroup of individuals with schizophrenia who have the risk gene. The robust therapeutic effects of D_2R antagonists, albeit only on positive symptoms, likely results from the fact that they block the consequences of the disinhibited glutamatergic input to the substantia nigra and not on the effects of *DRD2* risk gene[16]. Therefore, risk genes may be more important in identifying dysfunctional neuronal circuits responsible for the negative and cognitive symptoms, which would be more effective targets for treatment.

Attempts to enhance NMDAR function with agonists acting at the GMS or by increasing synaptic glycine levels through inhibition of the glycine transporter GlyT1 to date have yielded mixed results, although some studies support this approach for potentially treating negative and, importantly, cognitive symptoms. The reason for these disappointing clinical trial results with NMDAR modulators is likely multifactorial, such as poor drug-like properties of natural products, desensitization, low potency and aetiologic heterogeneity. Allosteric NMDAR agonists may be a more productive approach[209].

The substantial loss of cortico-limbic glutamatergic synapses, which is present already at first episode but progresses over the subsequent decade[210], indicates that therapeutic strategies would likely differ from simply correcting neurotransmitter imbalance. First, greater attention must be paid to understanding the mechanisms responsible for the development and maintenance of glutamatergic spines. There is preclinical evidence that restoring NMDAR function in adulthood may reverse spine loss[211]. Second, reversal of synaptic loss in the human brain may require a much longer course of treatment than used in standard clinical trials, harkening to our experience with Alzheimer's disease[212]. Third, interventions might be necessary early in the course of the disorder, such as at first episode of psychosis or with high-risk youth prior to the onset of psychosis. This approach will require much more robust biomarkers, including polygenic risk scores, brain imaging and EEGs, to identify asymptomatic 'high-risk' individuals who are likely to convert to schizophrenia. Finally, we believe that new diagnostic criteria for schizophrenia (beyond the DSM) that emphasize negative and cognitive symptoms will be important, as these core symptoms appear to be most closely linked to the genetic risk factors, neuropathology and poor functional outcomes than the more commonly targeted positive symptoms.

The serendipitous discovery of the antipsychotic properties of the M_1/M_4-preferring mAChR agonist xanomeline in Alzheimer's disease and more recently xanomeline/trospium chloride in schizophrenia demonstrate that it is possible to treat psychosis in the absence of direct D_2R blockade and without sedation, weight gain and extrapyramidal side effects. Preliminary data also suggest that mAChR agonists like xanomeline/trospium chloride may reduce negative and cognitive symptoms.

There is a growing awareness that schizophrenia has serious medical comorbidities associated with obesity and oxidative stress that cause premature death. Many of these comorbidities can now be treated or even prevented with GLP-1RAs that not only cause substantial weight loss but also reverse brain inflammation and the associated detrimental metabolic and cardiovascular consequences of obesity. Therefore, despite decades of disappointing attempts to find more effective treatments for people living with schizophrenia, several life-altering treatments may finally be on the horizon.

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Author contributions

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Competing interests

J.T.C. is a founder of Waveform Bioscience, a member of the Scientific Advisory Board of SyneuRx and a consultant to Response Pharmaceuticals. S.M.P. is a former employee and shareholder of Karuna Therapeutics (now Bristol Myers Squibb); a cofounder and shareholder of Sage Therapeutics, Voyager Therapeutics, Rapport Therapeutics and Seaport Therapeutics; a shareholder of Alnylam Pharmaceuticals and Eli Lilly and Company; and a venture partner at Third Rock Ventures. Since the inception of this manuscript, he has had no financial interests in Cobenfy and its marketing.

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