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REVIEW ARTICLE

Progress and Pitfalls in Developing Agents to Treat Neurocognitive Deficits Associated with Schizophrenia

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Abstract
Cognitive impairments associated with schizophrenia (CIAS) represent a central element of the symptomatology of this severe mental disorder. CIAS substantially determine the disease prognosis and hardly, if at all, respond to treatment with currently available antipsychotics. Remarkably, all drugs presently approved for the treatment of schizophrenia are, to varying degrees, dopamine D_2/D_3 receptor blockers. In turn, rapidly growing evidence suggests the immense significance of systems other than the dopaminergic system in the genesis of CIAS. Accordingly, current efforts addressing the unmet needs of patients with schizophrenia are primarily based on interventions in other non-dopaminergic systems. In this review article, we provide a brief overview of the available evidence on the importance of specific systems in the development of CIAS. In addition, we describe the promising targets for the development of new drugs that have been used so far. In doing so, we present the most important candidates that have been investigated in the field of the specific systems in recent years and present a summary of the results available at the time of drafting this review (May 2022), as well as the currently ongoing studies.

1 Introduction

Schizophrenia is regarded as one of the most serious of all psychiatric disorders [1], with a uniform lifetime risk of about 1% worldwide [2]. Considering broader diagnostic criteria, the lifetime rate of schizophrenia and related categories is even higher, with a range between 2 and 3% [3]. Thereby, life expectancy in schizophrenia is reduced by 13–15 years [4] and some reliable estimates suggest a suicide rate of around 5% [5].

Like most psychiatric disorders, schizophrenia is a syndromic concept. The diagnosis is made clinically, based on symptoms, examination of the mental state, and the use of operational criteria as defined by the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [6] or the International Classification of Diseases [7]. Both classifications assign schizophrenia to the spectrum of psychotic disorders, mainly pointing out positive and negative symptoms of the disease [8]. The statement that cognitive deficites were recognized as a central component of schizophrenia since the early days of modern psychiatry, as seen in the texts of Kraepelin and Bleuler originates from the publication Elvevag et al. [9]. Extensive scientific evidence has since supported the major role of cognitive impairments associated with schizophrenia (CIAS), particularly as they contribute significantly to the disability of affected individuals and are generally highly resistant to the available therapy options [10].

Thereby, the scope of the CIAS is wide ranging. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative [11] defined the following seven cognitive domains mainly impaired in schizophrenia: speed of processing, attention-vigilance, working memory, verbal learning, visual learning, reasoning and problem solving, and social cognition [12–14]. Large studies indicate that cognitive performance in patients with schizophrenia is one to two standard deviations lower than in age-matched control subjects [15]. Mostly normal cognitive profiles have been reported only in a small proportion of patients with schizophrenia, but even they perform below

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Key Points

Current efforts to address cognitive impairments associated with schizophrenia are primarily based on interventions in non-dopaminergic systems.

Among the numerous compounds currently under investigation, the development of the selective glycine transporter inhibitor BI 425809 and the TAAR1 agonist ulotaront (SEP-363856) is the most advanced. Both compounds have been granted a breakthrough therapy designation by the US Food and Drug Administration.

Other substances in advanced stages of development are the combined muscarinergic agonist/antagonist formulation KarXT, the serotonin $5HT_{2A}$ receptor antagonists roluperidone (MIN-101) and pimavanserin, the selective 5-HT_6 receptor antagonist AVN-211 as well as the dopamine-serotonin system stabilizer RP5063 (brilaroxazine).

Finally, the large phenotypic heterogeneity of the schizophrenia symptomatology implies an associated high neurobiological diversity that can only be adequately addressed by individualized treatment approaches.

the expectations that would result from their family's level of education [16] and show weaknesses in information processing speed [17].

Cognitive impairments are detectable in all stages of schizophrenia and prior to the onset of psychosis [18, 19], as well as in subjects with an increased familial or clinical risk [20]. They represent an essential predictive factor of functional outcome in terms of social, occupational, living status [21–25], medication adherence, and ability to self-manage medication [26–28], as well as relapse prevention [29]. Additionally, the global neurocognition is strongly interconnected with social cognition, which is tightly linked with real-life functioning [30, 31].

1.1 Neurobiological Basis of CIAS

Current understanding of the neurobiological basis of CIAS includes extensive, albeit multifaceted, evidence. Several studies reported an association between CIAS and cortical thickness in different brain regions [32, 33], with most robust findings within the fronto-temporal regions, which are generally known to be mainly involved in cognition [34] and thereby not directly linked to overall symptom severity [35]. Moreover, successful cognitive performance also requests a synergistic interaction with reward circuits, in which dysfunctions have also been shown in schizophrenia [34]. Furthermore, CIAS are associated with abnormalities of functional connectivity within and between regions comprising the cortico-cerebellar-striatal-thalamic loop and the task-positive and task-negative cortical networks [36]. Additionally, individuals with poor social and neurocognitive performance could be differentiated from those with normal performance by greater resting-state connectivity in the mirror neuron and mentalizing systems [37].

In the multifactorial context, the interaction between genetic and environmental factors is a central element of the etiology of schizophrenia [38], while numerous genes are also known to be associated with CIAS. Most of them encode proteins that participate in neurotransmission [38] and/or are involved in the modulation of various neurocircuitry as well as synaptogenesis and neuroplasticity [39].

From a neurochemical perspective, which is crucial when it concerns the development of new medications, CIAS has been linked to imbalances in neurotransmitters such as glutamate, gamma-aminobutyric acid (GABA), dopamine, acetylcholine, and histamine [40]. Accordingly, several promising categories of substances targeting those systems have been identified for further drug development, including nicotinic partial agonists, muscarinic agonists, glutamate enhancer, GABA-A partial agonists, GABA-B antagonists, serotonin (5HT) antagonists, histamine agonists, and phosphodiesterase inhibitors [41]. In recent years, several additional mechanisms have also been addressed, including neuropeptides, immunomodulatory and anti-inflammatory agents, and genetic-based approaches [42, 43].

2 Current Approaches for the Treatment of CIAS

Currently, the treatment of schizophrenia relies primary on antipsychotics, whose effectiveness in mitigating the positive symptoms is undisputed [44]. Thereby, antipsychotics seem to be much less effective against CIAS. Some earlier studies and meta-analyses attributed certain pro-cognitive superiority to the second-generation antipsychotics as compared with treatment with first-generation antipsychotics [45–47], but this view has been gravely questioned by the results of the CATIE [48] and EUFEST [49] studies and refuted by some other meta-analyses [50, 51]. Nevertheless, a large meta-analysis that included 54 randomized double-blinded trials enrolling 5866 patients and 14 drugs reported a certain advantage for individual substances in specific cognitive domains without finding overall superiority [51]. It should be mentioned here that some recently approved antipsychotics were not included in this meta-analysis.

Cariprazine is a potent dopamine D_3- and D_2-receptor partial agonist [52, 53] that received approval from the US Food and Drug Administration (FDA) for the treatment of

schizophrenia in September 2015. Currently available data indicate a potentially pro-cognitive effect of cariprazine [54] that may be attributed to the preferential D_3 receptor affinity [55].

The most recently approved innovative antipsychotic lumateperone acts as a potent 5-HT_{2A} receptor antagonist, a D_2-receptor presynaptic partial agonist, and a post-synaptic antagonist, as well as a D_1-receptor-dependent modulator of glutamate and a serotonin reuptake inhibitor [56, 57]. Data from the few available studies suggest that lumateperone is not only effective for positive and negative symptoms but also for CIAS [58]. However, similar to cariprazine, the evidence base for the pro-cognitive effects is currently too small to make a reliable assessment. Consequently, further, and manufacturer-independent investigations are required. Summing up, despite indications that some pharmacological treatments may be beneficial in various cognitive domains, there is currently no specific drug for CIAS that has been approved by any regulatory agency worldwide [59].

3 New Psychopharmacological Approaches for the Treatment of CIAS

In the following sections, we first provide a brief overview of the available evidence on the importance of specific systems in the development of CIAS. In addition, we describe the targets for the development of new drugs that have been used so far. In doing so, we present the most important candidates that have been investigated in the field of the specific systems in recent years and present a summary of the results available at the time of drafting this review (May 2022), as well as the currently ongoing studies. All contents are briefly summarized in Table 1. For the overview of ongoing studies with specific substances, entries in the most well-known register of clinical studies, ClinicalTrials.gov (https://clinicaltrials.gov), were searched, and the announcements of the companies developing the specific substances were also reviewed.

4 The Glutamatergic System

The involvement of the glutamatergic neurotransmission in the etiology and pathophysiology of schizophrenia is supported by a growing body of evidence at several levels [60]. The first related intervention was documented more than seven decades ago with encouraging results after the use of glutamic acid for the treatment of catatonic symptoms [61]. However, comprehensive evidence suggests that the symptoms of schizophrenia are not simply a consequence of a glutamate deficit. Currently, the central role of glutamatergic disbalance and the hypofunction of the glutamatergic *N*-methyl-D-aspartate receptors (NMDA-Rs) are acknowledged as the key factors [62].

In general, glutamate is the major excitatory neurotransmitter in the brain, with glutamatergic neurons utilizing between 60 and 80% of total brain metabolic activity [63]. Glutamatergic neurotransmission occurs through two classes of receptors, metabotropic glutamate receptors (mGluRs) and ionotropic glutamate receptors. Metabotropic glutamate receptors are members of the G-protein-coupled receptor superfamily classified into three groups (I, II, and III) and differentiated into eight different receptor types [64]. Ionotropic glutamate receptors are named after the agonists originally found to selectively activate them: a-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) [65]. The stated complexity of glutamatergic neurotransmission implies a large number of presynaptic, postsynaptic, and regulatory proteins that represent suitable targets for drug development [66, 67].

4.1 Targeting the NMDA-Rs

N-methyl-D-aspartate receptors are glutamate-gated cation channels that play a vital role in synaptic transmission, neuroplasticity, and cognitive functions [68]. The application of non-competitive NMDA-R antagonists (as phencyclidine or ketamine) induces symptoms comparable with positive, negative, and cognitive symptoms in schizophrenia [69–71]. Thereby, it is likely that the downstream availability of glutamate increases owing to the involvement of GABAergic interneurons and the activation of AMPA receptors (AMPA-Rs) [62, 72].

The NMDA-R is a heterotetrametric complex composed of seven possible subunits: GluN1, GluN2A-GluN2D, and GluN3A-GluN3B3 [73]. Uniquely amongst ligand-gated ion channels, it requires two obligatory co-agonists, binding at the glutamate-binding site (GluN2) and the glycine-binding sites (GluN1 or GluN3) [65, 74]. *N*-Methyl-D-aspartate receptors can also be allosterically modulated by various other substances [75] acting as positive negative allosteric modulators (PAMs) or negative allosteric modulators. Positive allosteric modulators cause an increase of the response and negative allosteric modulators cause a decrease of the response elicited by the endogenous ligands acting at the orthosteric sites [76]. Additionally, the NMDA-R is redox sensitive, and its activity may be potentiated by glutathione, which is a major antioxidant and redox regulator that protects cells against oxidative stress [77]. Thus, a glutathione deficit is found to be related to an NMDA-R hypofunction and synaptic plasticity impairment [78]. The complex binding properties of the NMDA-R enable several different approaches in order to modulate the glutamatergic neurotransmission, which will be presented below.

Table 1 Brief overview of the main targets for the development of new drugs, the most important candidates that have been investigated in the field of the specific systems in recent years, and a summary of the results available at the time of drafting this review (May 2022), as well as the currently ongoing studies

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Glutamatergic system						
Modulation of the glutamatergic neurotransmission through NMDA-R						
Direct co-activation of the NMDA-R via GlyMS	Glycine	0.14–0.8 g/kg/day	Add on	Well tolerated in low dosages High-dose glycine can result in unwanted adverse effects, such as nausea and sensorimotor gating deficits [68]	Heterogeneous results [83, 84] Negative overall evaluation by two reviews suggesting that none of the three agents is a generally effective therapeutic option for treating negative symptoms or cognitive impairments in schizophrenia [68, 85]	
	D-Cycloserine	25–250 mg/day	Add on	Generally unfavorable benefit-risk ratio [68]	Positive reports indicating beneficial effects of higher dosages of D-serine on some cognitive parameters and neuroplasticity [86, 87]	
	D-Serine	Up to 60 mg/kg (~4 g/day)	Add on	Well tolerated in low dosages High concentrations can lead to peripheral neuropathies, such as oxidative damage, neurotoxicity, and renal toxicity [68]		NCT04140773 NCT05046353
Indirect co-activation of the NMDA-R via glycine reuptake inhibition by GlyT-1 inhibition`	Sarcosine	1–2 g/day	Add on	Well tolerated without dropouts because of severe adverse reactions or death [92]	Insufficient evidence for positive effects on cognitive impairment associated with schizophrenia despite the evidence of positive effects on overall symptomatology [91, 92]	
	Bitopertin	5–60 mg/day	Add on	Generally well tolerated; common AEs (incidence ≥5%) included somnolence, dizziness, and headache [94] Reduction in mean hemoglobin levels in some patients [95]	No evidence for positive effects on cognitive impairment in schizophrenia despite the evidence of positive effects on negative symptoms [94, 95]	

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
	BI 425809	10–25 mg	Add on	Generally well tolerated; most commonly reported AEs: headache, back pain, nausea, vomiting, and neck pain [96–98]	Positive results from a phase I study [96, 97] Improved cognition after 12 treatment weeks in one phase II study [98] BTD for BI 425809 for the treatment of CIAS was granted in May 2021 by the FDA [99]	NCT03859973 NCT04846868 (CONNEX-1) NCT04846881 (CONNEX-2) NCT04860830 (CONNEX-3) NCT05211947
	PF-03463275	40–60 mg	Add on	Not reported	Lack of attenuation of any ketamine-induced effects but improvement of working memory accuracy in healthy control subjects and increased long-term potentiation in patients with schizophrenia, indicating an increase in neuroplastic capacity during cognitive remediation and other rehabilitative treatment [101] However, the substance was not listed in Pfizer's pipeline released in February 2022 [103]	NCT01911676
Indirect modulation of NMDA-R function by reducing the D-serine metabolism through an inhibition of the flavoenzyme DAO	Sodium benzoate	1–2 g/day	Add on	Well tolerated; only mild AE: weight gain, insomnia, tachycardia, concentration impairments [105, 106] Classified as 'generally recognized as safe' by the FDA [111]	Heterogeneous results showing positive effects on neurocognition and positive and negative symptoms in patients with chronic schizophrenia [108] as well as on quality of life [109] but also a lack of beneficial effects on cognition [107, 108]	NCT01908192 NCT03094429 ACTRN12621000327886

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
	TAK-831 (luvadaxistat)	50–500 mg	Add on	Generally well tolerated; only mild AEs were reported: headache, insomnia, and weight gain [113]	Positive phase II study: beneficial effects on cognition in participants with schizophrenia with luvadaxistat 50 mg vs placebo but not with luvadaxistat 125 mg or 500 mg [113]	NCT05182476
Direct positive allosteric modulation of NMDA-R receptors	CAD-9303	3–1000 mg	Add on	Not reported	Under development by Cadent Therapeutics (in the meantime, part of Novartis) to address the negative and cognitive symptoms of schizophrenia (one completed phase I study, no results posted up to now [NCT04306146])	
Enhancement of NMDA-R activity via redox/glutathione sensitive site by increasing the glutathione levels	*N*-Acetylcysteine	600–3600 mg/day	Add on	Well tolerated; no significant side effects; beneficial metabolic effects [124]	Positive evidence for significant cognitive improvements following N-acetylcysteine treatment reported in a comprehensive systematic review [123] particularly regarding working memory [124]	NCT02505477 NCT05142735 NCT03149107 NCT04013555
Non-competitive NMDA-R antagonism	Memantine	Up to 20 mg/day	Add on	Well tolerated; no significant side effects [130, 131]	Heterogeneous results Two comprehensive meta-analyses reported adjunctive therapy with memantine to have a beneficial effect, mainly on negative symptoms, but also on neurocognitive functions [130, 131]	NCT04857983 NCT03860597 NCT04789915
	AVP-786 (d6), a combination of dextromethorphan hydrobromide and ultra-low-dose quinidine sulfate	34/4.9 mg twice a day	Add on	Generally well tolerated; most frequent AEs: dry mouth, diarrhea, dizziness headache, and nasopharyngitis [133]	A promising treatment option for Alzheimer's disease, including agitation [133] Trend-like beneficial effects on cognition in schizophrenia (NCT02477670)	NCT03896945

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Modulation of the AMPA-R activity						
Allosteric potentiators of AMPA receptors (AMPAkines)	BIIB104 (PF-04958242)	0.15–0. 5 mg/twice a day	Add on	Well tolerated [139]	Reduction in ketamine-induced impairments in immediate recall and the 2-Back and spatial working memory tasks in 29 healthy male subjects [139]	NCT05152485 NCT05148481 NCT04079101 NCT03745820
	CX-516	900 mg three times daily	Add on	Generally well tolerated with more fatigue, insomnia, and epigastric discomfort compared with placebo treatment [140]	Beneficial effects on memory and attention in patients treated with clozapine in a pilot trial [140] Negative results in a later larger study with CX-516 as an add-on to a standard antipsychotic treatment [141]	
Modulation of the mGlu-R activity						
mGlu-R- 2/3 agonist	Pomaglumetad methionil (LY2140023 monohydrate, prodrug of the mGlu 2/3 agonist, LY404039)	80–160 mg/day	Monotherapy	Well tolerated; AEs with highest incidence: gastrointestinal symptoms and headache [154–156]	Despite an earlier study showing positive effects [153], the substance did not significantly improve symptoms of schizophrenia compared to a placebo [154–156], which led to the cessation of the LY2140023 drug development program Hints that the substance was more effective in certain populations, including early-in-disease patients [157] Encouraging results from a pharmaco-MRI study in healthy controls [158]	

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
mGlu-R-2 selective PAMs	JNJ40411813/ ADX71149	100–450 mg/day	Add on	Well tolerated; most common AEs: headache, dizziness, and fatigue [160].	A generally good tolerability demonstrated in two randomized, double-blind phase I studies [160] Trend towards a reduction of cognitive deficits in attention and episodic memory precipitated by smoking withdrawal in a subpopulation of healthy volunteers, but without a statistical significance [160]	
	AZD8529	40–80 mg/day	Monotherapy/add on	Well tolerated; most common AEs: headache, akathisia, sedation, anxiety, and increased appetite [161]	No improvement of symptoms in schizophrenia in a proof-of-principle study [161] Increased activation in task-activated fronto-striatal regions, as a hint that the substance may be beneficial for an important subset of individuals with schizophrenia [152]	
Cholinergic system						
Increase of the acetylcholine concentration						
AChE-Is	Donepezil	5–10 mg/day	Add on	Well tolerated. No significant differences between patients receiving AChE-I and placebo regarding occurrence of AEs [166]	Weak evidence for a beneficial effect of the use of AChE-Is in combination with antipsychotics on a few domains of mental state and cognition [166] and working memory [168] Lack of evidence [169, 170] Evidence for a small positive effect of galantamine [171] as well as of the galantamine-memantine combination compared with placebo [172]	
	Rivastigmine	3–12 mg/day	Add on			
	Galantamine	6–24 mg/day	Add on			

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Enhancement of cholinergic neurotransmission via activation of muscarinic receptors						
Muscarinic agonists	Xanomeline	25–75 mg	Monotherapy	Frequent AEs, mostly associated with the gastrointestinal system [173]	Positive effect on psychotic symptoms and cognitive effects in patients with schizophrenia [173]	
	KarXT (xanomeline + trospium chloride)	50/20 mg to 125/30 mg twice a day	Monotherapy/add on	Generally well tolerated; most common AEs: constipation, nausea, dry mouth, dyspepsia, and vomiting [176]	Positive results regarding improvement of psychotic symptoms originating from a phase II study [176] Trends towards improvement in cognition in an exploratory analysis in cognition [177]	NCT04659161 NCT04659174 NCT04820309 NCT05145413 NCT04738123 NCT05304767
Selective agonist of muscarinic M_1 receptors	*N*-Desmethylclozapine (norclozapine) [ACP-104]	100–200 mg twice a day	Monotherapy	Generally well tolerated; most common AEs: increased salivation, tachycardia, and dyspepsia, which were noted to be dose related [181]	Lack of efficacy showed in a phase IIb trial [181]	
PAM of M_1 receptors	ACP-319	Not reported	Not reported	Not reported	Early development for the improvement of cognitive function and other neuropsychiatric symptoms in patients with CNS disorders [182]	
PAM of M_4 receptors	CVL-231 (emraclidine)	10–30 mg/day	Monotherapy	Well tolerated; most common AEs gastrointestinal, similar to placebo [183]	Positive top-line results for CVL-231 in a phase Ib clinical trial in patients with schizophrenia [183]	NCT05106309 NCT04787302 NCT05245539 NCT05227703 NCT05227690 [352]

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Enhancement of cholinergic neurotransmission via activation of nACh-Rs						
Selective alpha7-nACh-Rs partial agonist	Encenicline (EVP-6124)	1–2 mg	Add on	Generally well tolerated; most frequent AE: mild constipation negative [194]	Positive effects of encenicline on cognition in schizophrenia were observed in studies with a small number of participants [192, 193], but the results from two 6-month, randomized, double-blind, placebo-controlled, parallel-dosing, phase III studies were negative [194], and further investigations of this drug were terminated [195]	
	ABT-126	25 or 75 mg	Add on	Generally well tolerated; most frequent AEs: diarrhea, dizziness, headache, nausea, fatigue, and nasopharyngitis [196, 197]	Pro-cognitive effects limited to non-smokers in a phase II study [196] A lack of beneficial effects on cognition in light smokers [197]	
Positive allosteric modulators of the alpha7-nAChRs	AVL-3288	10–30 mg	Add on	Not reported	Some promising effects on cognition in schizophrenia in preclinical and first clinical studies, but a lack of positive effects in a larger phase Ib study [200]	
	JNJ-39393406	200 mg	Add on	Well tolerated [201]	Absence of a cognitive improvement in schizophrenia [201]	

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Serotonergic system						
Modulation of 5-HT_{2A} receptors						
Partial inverse agonist and antagonist at serotonergic 5-HT_{2A} receptors	Pimavanserin	10–34 mg	Add on	Generally well tolerated; most frequent AEs: headache and somnolence [212]	Enhancement of the efficacy of low-dose risperidone [210] Add on to clozapine reduced therapy-refractory hallucinations and delusions after several months of treatment [211] Significant improvement of the negative symptoms, but not of the general symptoms in a large phase II study in stable outpatients with schizophrenia [212]	NCT03121586 NCT04531982
Antagonist 5-HT_{2A} receptors and at sigma-2 receptors	Roluperidone (MIN-101)	32–64 mg/day	Monotherapy	Generally well tolerated; most frequent AEs: headache, anxiety, insomnia, nausea, somnolence, and agitation	Statistically significant efficacy in reducing negative symptoms and good tolerability in a phase IIb study in 244 stable patients with schizophrenia [213] In a post hoc analysis: some pro-cognitive effects of MIN-101 that correlated significantly with the improvement of negative symptoms [214] Improvement of negative symptoms (marginally missing statistical significance), and statistically significant improvements in the Personal and Social Performance Scale total score under roluperidone 64 mg/day (phase II study, $n = 513$) [215] After a type C meeting with the FDA, Minerva Neurosciences announced in April 2022 further steps towards a new drug application (FDA) for roluperidone as a monotherapy for patients diagnosed with schizophrenia with moderate-to-severe negative symptoms and stable positive symptoms [216]	

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Modulation of other 5-HT receptors						
Selective 5-HT_6 receptor antagonist	AVN-211	4–8 mg	Add on	Well tolerated [218]	Pro-cognitive effects (attention improvement) as an add-on to antipsychotic medication in a pilot 4-week trial in patients with schizophrenia [217] One later study on a larger sample showed positive sex-related effects on the positive and negative symptoms favoring female individuals [218], but without benefits on cognition	According to the pharmaceutical manufacturer (Avineuro), there are ongoing phase II/III clinical trials with AVN-211 (AVISETRON) [221]
	ANV-322, AVN-101	Not reported	Not reported	Not reported	Early development, precognitive effects in animal models [219, 220]	According to the manufacturer, ready to enter phase II clinical trials for treating diseases associated with cognitive dysfunction [221]
Dopaminergic system						
Targeting dopaminergic D_1 receptors						
PAM at the D_1 receptors	Mevidalen (LY-3154207)	25–200 mg/day	Add on	Dose-proportional increases in blood pressure, pulse, and activation [226]	Some pro-cognitive effects originating from preclinical experiments [223] A lack of beneficial effects on cognition in Lewy body dementia [226]	
	ASP4345	3–150 mg	Add on	Generally well tolerated; most frequent AEs: headache and somnolence [227]	Pro-cognitive effects shown in a phase I study [227] Further development stopped because the primary endpoint of the assay was not reached [228]	
Selective dopamine D_1/D_5 receptor partial agonist	PF-06412562 (CVL-562)	1–45 mg/day	Add on	Generally well tolerated with only mild-to-moderate side effects including tiredness, headache, nausea, vomiting, and dizziness [230]	No clinical benefit relative to placebo on assessments of cognition or reward processing in symptomatically stable patients over a 15-day treatment period [230] Hints of a beneficial effects if cognition following an inversed U-shape relationship [231, 232]	NCT04457310

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Activity on serotonergic, dopaminergic, and α-adrenergic receptors, with a significantly higher affinity to the D_1 than for the D_2 receptor	Lu AF35700	10–20 mg/day	Add on	Generally well tolerated [233]	No significant difference from placebo an add-on to treatment with an atypical antipsychotic in a recent phase III study (NCT03230864) [233]	
Targeting dopaminergic D_3 receptors						
Preferential D_3- vs D2-receptor antagonism and partial agonism at $5HT_{1A}$ receptors	F17464	20–40 mg/day	Monotherapy	Generally well tolerated; most frequent AEs: insomnia, agitation, and increased triglycerides [237]	Pro-cognitive effects demonstrated in a phase II study [237]	
Dopamine-serotonin system stabilizer						
Dopamine-serotonin system stabilizer with an optimum balance of potent partial agonist activity at the dopamine D_2, D_3, D_4, serotonin 5-HT_{1A} and 5-HT_{2A} receptors, and antagonist activity at the serotonin 5-HT_6 and 5-HT_7 receptors	RP5063 (brilaroxazine)		Monotherapy	Generally well tolerated; most frequent AEs: insomnia and agitation [238, 239]	Trends toward cognitive improvement in a phase II trial [238] Improved social functioning and cognition [239]	NCT05184335
Endocannabinoid system						
Cannabinoid 1 receptor antagonism	Cannabidiol	300–1280 mg/day	Add on or monotherapy	Generally well tolerated; most frequent AEs: mild sedation, mild transient, GI discomfort, and hyperlipidemia	Two systematic reviews found some evidence for the potential of cannabidiol in alleviating psychotic symptoms and cognitive impairment in patients with a variety of conditions [255, 256] A lack of clinical evidence for beneficial effects of cannabidiol against cognitive impairments was stated from other systematic reviews [257–260]	NCT02926859 NCT04605393 NCT02088060 NCT02504151 NCT03608137 NCT04700930 NCT04411225 NCT02492074 NCT04105231

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Phosphodiesterase inhibition						
Phosphodiesterase 4 inhibitors	Roflumilast	100 µg and 250 µg	Add on	Not reported	Cognitive-enhancing effects in both animal studies [268] and in healthy human participants [269, 270] Improvement of some EEG biomarkers with 250 µg of roflumilast has been reported [271], as well as a significant improvement in verbal memory [272]	
PD10A inhibitors	TAK-063	20 mg	Monotherapy	Generally well tolerated; most frequent AEs: akathisia, somnolence, dyspepsia, headache, and nausea [276]	Pro-cognitive effects in preclinical studies [274, 275] Negative results from a phase II study [276] In one additional neuroimaging study on healthy male participants, TAK-063 attenuated ketamine-induced changes in functional MRI signals were found in multiple regions of the brain during the resting state and working memory tasks [277]	
	MK-8189	4–24 mg	Monotherapy	Generally well tolerated; most frequent AEs: diarrhea, akathisia, nausea, and headache [278]	Negative phase II study results (NCT03055338) [278]	NCT04624243 NCT04506905
Phosphodiesterase 9 inhibitors	BI 409306	10–100 mg/day		Generally well tolerated; most frequent AEs: eye disorders, nasopharyngitis, diarrhea, insomnia, nausea, and headache [280]	Lack of significant effects on cognitive function in patients with schizophrenia in a phase II trial [280]	NCT03230097

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Modulation of TAAR1						
Agonism at TAAR1 and serotonin 5-HT_{1A} receptors	Ulotaront (SEP-363856 or SEP-856)	50–75 mg/day	Monotherapy	Generally well tolerated; most frequent AEs: somnolence, agitation, nausea, diarrhea, and dyspepsia [289]	Positive results from randomized controlled trials regarding positive and negative symptoms [288] Positive results from the 26-week, open-label extension study regarding PANSS total and CGI [289] Positive evidence regarding pro-cognitive effects from preclinical studies [290] BTD by the FDA for the treatment of patients with schizophrenia in in May 2019 [291] [286]	NCT04109950 NCT04038957 NCT04865835 NCT04825860 NCT04072354 NCT04092686 NCT04115319
Modulation of the upstream glutamate system by blockage of voltage-gated blocking sodium channels						
Voltage-gated sodium channel blocker	Evenamide (NW-3509)	30–50 mg/day	Add on	Generally well tolerated; two patients taking evenamide discontinued treatment because of AEs (atrial fibrillation and seizure)	Positive results from a phase II study [301] Pro-cognitive effects shown in animal studies [300]	EudraCT Number: 2020-006062-36 (phase II/III)
Anti-inflammatory and immunomodulatory approaches						
Broad-spectrum antibiotic from the tetracycline family	Minocycline	50–200 mg	Add on	Generally well tolerated; most frequent AEs: nausea, headache, dizziness, anorexia, vomiting, tooth discoloration and visual disturbances, skin discoloration, vertigo, and psychosis [314] Some concerns were raised regarding a possible antibiotic-resistance [353]	Beneficial effects on the cognitive domains of visual learning, executive function and attention [310] More beneficial in first-episode psychosis or early-phase schizophrenia [315] Negative results regarding negative symptoms and cognitive impairments in patients with recent-onset psychosis [314]	

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
Downregulation of the key inflammatory cytokines tumor necrosis factor-alpha, interleukin-16, and interleukin-12	Davunetide	5–30 mg	Add on	Well tolerated [315]	Some pro-cognitive effects; more beneficial in first-episode psychosis or early-phase schizophrenia [315]	
Interleukin-6 receptor antibody	Tocilizumab	3-monthly infusions of 8 mg/kg	Add on	Generally well tolerated and all adverse events were mild [320]	Positive effects on cognitive impairments in schizophrenia, open-label pilot trial [320] Negative results from a larger randomized controlled trial ($n = 36$) [321]	NCT02874573
Anti-interleukin-6 chimeric monoclonal antibody	Siltuximab	Three infusions of 11 mg/kg in 3-week intervals	Add on	Not reported	Preclinical evidence [319]	NCT02796859
Further approaches						
Neurosteroids and neuroactive steroids	Pregnenolone	50–200 mg/day	Add on	Well tolerated	Significant reduction in the deficits in visual attention, sustained attention, and executive functions [334] Improvement in functional capacity and communication [336] More beneficial in first-episode psychosis or early-phase schizophrenia [310]	
	Dehydroepiandrosterone	200 mg/day	Add on	Well tolerated	Significant improvement in cognitive functions of visual sustained attention and visual and movement skills [335]	

Table 1 (continued)

Acting mechanism	Substances	Dosage	Usage	Safety aspects	Current findings regarding the effects on cognition	Ongoing investigations
	Oxytocin	10–48 IU/day up to 40 IU twice daily intranasal	Add on	Well tolerated	A comprehensive meta-analysis that included 17 studies showed a small significant effect on theory of mind in patients with neurodevelopmental disorders (including schizophrenia) [341] Additionally, positive effects of oxytocin have been reported on emotional recognition [342] and higher-order social cognition [343] but also on working memory [344] and verbal fluency [345] in schizophrenia. However, there is also a relatively high proportion of studies with negative results [346], although review articles mainly confirm the positive effect of oxytocin on social cognition and some other symptoms in schizophrenia [346–348]	NCT03900754 NCT04177719 NCT03245437

AChE-I acetylcholinesterase inhibitor, *AEs* adverse events, *AMPA-R* a-amino-3-hydroxy-5-methyl-4-isoazolepropionic acid receptors, *BTD* breakthrough therapy designation, *CGI* Clinical Global Impression, *CNS* central nervous system, *DAO* D-amino acid oxidase, *EEG* electroencephalogram, *FDA* US Food and Drug Administration, *GlyMS* glycine modulatory site, *GlyT-1* glycine transporter 1, *mGlu-R* metabotropic glutamate receptors, *MRI* magnetic resonance imaging, *nACh-Rs* nicotinic acetylcholine receptors, *NMDA-R* N-methyl- D-aspartate receptors, *PAM* positive allosteric modulator, *PANSS* Positive and Negative Syndrome Scale, *RCT* randomized controlled trial, *TAAR1* Trace Amine-Associated Receptor 1, *VGSCs* voltage-gated sodium channels

4.1.1 Interventions on the Glycine Modulatory Site

Glycine binding on the glycine modulatory site is necessary for NMDA-R activation [79] and for the opening of the channel subunit once the receptor has been activated by a glutamatergic agonist [80]. Apart from glycine, other D-amino acids such as D-serine, D-cycloserine, and D-aspartate also exhibit co-activator properties [81]. The use of these co-agonists to enhance the NMDA-R-mediated neurotransmission and improve negative symptoms and CIAS [82] has so far produced mixed results [83, 84] as summarized in two comprehensive reviews, which yielded a negative overall evaluation [68, 85]. However, it is worth mentioning that the negative results tend to come from studies with lower doses, while studies with a higher dosage of D-serine (60 mg/kg [~4 g/day]) showed beneficial effects on some cognitive parameters and neuroplasticity [86, 87].

The search for ongoing studies at ClinicalTrials.gov revealed solely two active entries with D-serine. The first study (NCT04140773) examines the effects of a high dose of D-serine (2 g/day) on CIAS in early stages of disease, while in the second study (NCT05046353), D-serine (120 mg/kg) will be administered in addition to a cognitive remediation program along with a stabile antipsychotic.

4.1.2 Glycine Reuptake Inhibitors

One other promising mechanism to enhance NMDA-R function is to increase the availability of the necessary co-agonist glycine (or D-serine) through the inhibition of glycine reuptake from the synapse. Two plasma membrane transporters for glycine have been identified. Thereby, the glycine transporter type 1 (GlyT-1) is widely distributed throughout the brain [88] and thus a potential target for the development of new therapeutic agents.

One of the first compounds that gained large attention was sarcosine (*N*-methylglycine), a non-selective inhibitor of glycine transport [89] and a NMDA-R glycine site co-agonist [90]. Clinical trials with sarcosine revealed partly conflicting results. Two comprehensive meta-analyses confirmed positive effects of sarcosine combined with first-generation antipsychotics and second-generation antipsychotics (with the exception of clozapine) on clinical symptoms overall, but not on cognitive functions [91, 92].

Bitopertin, a potent selective GlyT-1 inhibitor, showed antipsychotic-like activity in modulating both glutamatergic and dopaminergic neurotransmission in animal models [93]. In humans, bitopertin significantly reduced negative symptoms in a phase II proof-of-concept trial, but its effects on cognition were negative [94]. An absence of significant effects on cognition was also found in three subsequent phase III trials conducted over 24 weeks [95].

After promising phase I results with BI 425809, a potent selective GlyT-1 inhibitor [96], a large multicentric phase II study (sponsored by Boehringer Ingelheim) was launched in 2019 (NCT03859973) [97]. This still ongoing study investigates the benefit of combining BI 425809 with adjunctive computerized cognitive training over 12 weeks treatment in patients with schizophrenia. In the meantime, the results from one other phase II, randomized, double-blind, placebo-controlled, parallel-group trial were published, showing BI 425809 (dosages of 10 and 25 mg) to have a statistically significant benefit over placebo in terms of cognition during 12 weeks of treatment [98]. In May 2021, the company announced that the FDA has granted BI 425809 a breakthrough therapy designation for the treatment of CIAS [99]. With this status, the substance is eligible for intensive guidance from the FDA on the drug development program and priority review [100]. The company also announced the initiation of the CONNEX trial program, consisting of three phase III clinical trials (NCT04846868, NCT04846881, and NCT04860830) with 586 patients in each study. The estimated completion date of all three trials is May 2024. One additional study is designed as a follow-up for the CONNEX program (NCT05211947) to examine the long-term safety of BI 425809 once daily during 1 year.

One further GlyT-1 inhibitor, PF-03463275 [101], showed positive effects on cognition in an animal model [102]. Results from a study in healthy controls and in patients with schizophrenia indicated an increase in neuroplastic capacity during cognitive remediation and other rehabilitative treatment [101]. One active, but not recruiting, phase II study with PF-03463275 was also found on ClinicalTrials.gov (NCT01911676). However, the substance was not listed in the Pfizer pipeline released in February 2022 [103].

4.1.3 Indirect Modulation of NMDA-R Function by Reducing the D-Serine Metabolism

One of the main regulators of the cellular D-serine level and release is the flavoenzyme D-amino acid oxidase (DAO), which thus has the potential to modulate the function of NMDA-Rs and to contribute to their hypofunction in schizophrenia [104]. Increased DAO activity leads to decreased D-serine levels, which may subsequently lead to NMDA-R hypofunction [68]. Accordingly, at least two DAO inhibitors are in advanced clinical investigation as potential novel drugs for schizophrenia treatment, including sodium benzoate and TAK-831.

The add-on of sodium benzoate (which is widely used as a preservative and a food pickling agent) showed beneficial effects on neurocognition, positive and negative symptoms in patients with chronic schizophrenia [105] as well as on

quality of life [106]. In addition, adjunctive treatment with the combination of sodium benzoate (1g/day) plus sarcosine (2 g/day), but not sarcosine alone, improved the Positive and Negative Syndrome Scale (PANSS) total score, PANSS-positive score, and quality of life in patients with schizophrenia without positive effects on cogitation [107]. However, adjunctive use of benzoate in early psychosis did not reveal significant differences in any subscales of the PANSS or any secondary measures [108].

ClinicalTrials.gov lists two actively regrouting phase II/III studies [sponsored by SyneuRx International (Taiwan) Corp.] evaluating the safety and efficacy of sodium benzoate for schizophrenia in adolescents (NCT01908192; estimated completion June 2023) and as an add-on therapy with clozapine for residual symptoms of refractory schizophrenia in adults (NCT03094429; estimated completion June 2026). One further study (Australian New Zealand Clinical Trials Registry ACTRN12621000327886) investigates the optimal dosing in treatment-refractory schizophrenia. In this study, the participants will receive dosages between 1 and 4 g/day [109]. Concerning safety issues, the authors point out that sodium benzoate was classified as 'Generally Recognized As Safe' by the FDA and allowed in a concentration up to 1% in medicines [110]. Further, the joint committee by the Food and Agriculture Organization of the United Nations and the World Health Organization has suggested an acceptable daily intake up to 5 mg/kg of body weight [111], reporting that on a daily intake of 250–500 mg/kg body weight clinical signs of toxicity are rare.

Interestingly, in one other study involving patients with behavioral and psychological symptoms of dementia, it was shown that following 6 weeks of treatment with 250–1500 mg/day of sodium benzoate the effects on cognitive performance significantly surpassed the placebo in women but not in men [112]. There are no studies so far that would report such sex differences in schizophrenia.

The second most promising selective inhibitor of DAO is TAK-831 (or Luvadaxistat), currently under development by Neurocrine Biosciences and Takeda Pharmaceutical Company Limited for the treatment of Friedreich's ataxia and cerebellar ataxia and as an adjunctive therapy for cognitive impairment and negative symptoms of schizophrenia. The (preliminary) results of the study NCT03382639 with 228 participants provided as an conference abstract [113] reported cognitive improvements with luvadaxistat 50 mg versus placebo but not with luvadaxistat 125 mg or 500 mg [113]. A ClinicalTrials.gov search conducted in May 2022 revealed one ongoing phase II study (NCT05182476) with luvadaxistat that will involve 308 patients until February 2024.

4.1.4 PAMs of the NMDA-Rs

In recent years, a number of direct PAMs or negative allosteric modulators at several newly recognized binding sites of NMDA-Rs have been identified [114]. Their main advantage is a greater subtype selectivity [74]. However, there are currently only a few reports on their clinical use.

To date, the most studied substance from this group is CAD-9303. Cadent Therapeutics (now part of Novartis [115]) started a phase I study in February 2020 (NCT04306146) in a cohort of 103 participants (healthy controls and patients with schizophrenia). The aim of the study includes an assessment of the effects on sensory and cognitive functions. According to the last available update (December 2021), the overall study status is completed, but results are yet to be posted.

4.1.5 Targeting the Redox/Glutathione-Sensitive Site of the NMDA-R

In addition to the glycine modulatory site, the NMDA-R contains a well-characterized redox/glutathione sensitive site that is modulated by the oxidized form of glutathione [116]. Decreased glutathione levels have been reported in patients with schizophrenia in cerebrospinal fluid, the prefrontal cortex [117], and the caudate region (post-mortem) [118], as well as in spectroscopic investigations [119]. Further findings also suggest a link between decreased glutathione levels and cognitive impairment [120].

A large body of evidence indicates that agents able to improve glutathione levels also ameliorate the effects of oxidative stress in various preclinical models of schizophrenia [121]. Accordingly, the glutathione precursor *N*-acetylcysteine (NAC) is particularly associated with putative neuroprotective properties that act against neurotoxic effects of the disease processes in psychotic disorders [122]. Significant pro-cognitive effects of NAC have been reported in a comprehensive systematic review [123] and a meta-analysis [124]. Regarding the ongoing research with NAC, ClinicalTrials.gov lists four active entries: NCT02505477, NCT03149107, and NCT05142735 (investigating effects of NAC on psychosis-like symptoms and cognition in persons with a clinical high risk for schizophrenia), and NCT04013555 (examines the pro-cognitive effects of NAC combined with tryptophan).

4.1.6 NMDA-R Antagonism

Abnormally high extracellular levels of glutamate have the potential to induce neuronal dysfunction and degeneration [125]. This process is referred to as excitotoxicity [126]. In

schizophrenia, the disruption in glutamatergic signaling may result in an excitotoxic effect secondary to excessive stimulation of non-NMDA glutamate receptors (i.e., AMPA-R and kainate) [127]. Additionally, preclinical data suggest that an excitotoxic effect may occur as a result of a paradoxical increase in glutamatergic activity following NMDA-R hypofunction [128]. Thus, a number of approaches that aim to reduce this glutamatergic overactivity have been investigated in recent decades.

The question of a possible benefit of concomitant off-label treatment with memantine, a non-competitive NMDA-R antagonist approved for the treatment of moderate-to-severe Alzheimer's disease [129], has so far yielded different, sometimes contradictory results. However, two meta-analyses reported adjunctive therapy with memantine to have a beneficial effect, mainly on negative symptoms, but also on neurocognitive functions [130, 131]. ClinicalTrials.gov lists three active studies investigating the pro-cognitive effect of memantine in schizophrenia: NCT04857983 (memantine augmentation of targeted cognitive training in schizophrenia), NCT03860597, and NCT04789915.

Another interesting modulation approach at the NMDA-R is the combination of deuterated (d6)-dextromethorphan hydrobromide (an uncompetitive NMDA-R antagonist) and ultra-low-dose quinidine sulfate (increases the dextromethorphan concentration by cytochrome P450 2D6 inhibition), which is currently being investigated under the name AVP-786 [132]. This oral formulation appears to be a promising treatment option for Alzheimer's disease, particularly for agitation [133]. ClinicalTrials.org lists two phase II studies designed by Avanir Pharmaceuticals to investigate the effects of AVP-786 on negative symptoms in schizophrenia (NCT02477670 and NCT03896945). The first study has been completed. The results regarding the cognitive measures state a nonsignificant trend-like group difference in the mixed-model analysis ($p = 0.074$). No further details are given.

4.2 Targeting the AMPA-R

The ionotropic post-synaptic AMPA-Rs are broadly expressed throughout the brain and mediate the majority of the fast excitatory synaptic transmission [134]. Numerous investigations indicate that the modulation of AMPA-R function could be crucial for the short-term and long-term modification of synaptic efficacy and thus for synaptic plasticity [135]. A class of compounds that bind to an allosteric site on the AMPA-Rs to prevent a receptor deactivation are known as allosteric potentiators of AMPA-Rs or AMPAkines [136]. AMPAkines have been shown to alleviate cognitive deficits in animal models of schizophrenia [137]. In this regard, several PAMs of AMPA-Rs are currently under development by Cortex Pharmaceuticals (CX516, CX614, CX691, also known as ORG24448 and farampator, CX717, CX1739), Eli Lilly (LY451395), Organon (ORG26576), Pfizer (PF-04958242), Servier (S18986 and S47445), GSK (GSK729327), and Takeda (TAK-137, TAK-653) and have entered clinical studies. However, up to now, none has achieved regulatory approval [138].

The most advanced investigations concern BIIB104 (PF-04958242), which was shown to significantly reduce ketamine-induced impairments in immediate recall and the 2-Back and spatial working memory tasks without significantly attenuating ketamine-induced psychotomimetic effects in 29 healthy male subjects [139]. Three other phase I studies were conducted by Biogen to evaluate the safety of BIIB104 as well as one phase II trial to evaluate the efficacy in subjects with CIAS (NCT03745820). In April 2022, all studies were announced as completed, the presentation of the results is still awaited. The second most promising AMPAkine CX-516 has been shown to have beneficial effects on memory and attention in patients treated with clozapine [140] in a pilot trial but the results in a later larger study were negative [141].

4.3 Targeting mGluRs

Metabotropic glutamate receptors are G-protein-coupled receptors with eight subtypes grouped in three classes: group I (mGluR-1, mGluR-5), group II (mGluR-2, mGluR-3), and group III (mGluR-4, mGluR-6, mGluR-7, and mGluR-8) [64]. In the context of drug discovery efforts, several allosteric modulators that target subtypes within each of the three groups have been investigated as potential drugs for the treatment of positive, negative, and cognitive symptoms associated with schizophrenia [142]. Preclinical studies have so far yielded numerous promising substances from these categories, most of which have yet to be tested for clinical applicability.

From group I, mGluR-5 has been considered an appealing therapeutic target because of its interaction with NMDA-Rs through structural and functional connections [143, 144]. Positive allosteric modulators of mGluR-5 have been shown to enhance long-term plasticity in the hippocampus and have pro-cognitive and antipsychotic-like effects in different animal models [145, 146]. However, the clinical transfer of these promising results has been thwarted by preclinical toxicology issues, possibly related to excessive NMDA-R activation [147].

The presynaptic mGluR-2,3 (group II) are prominently expressed in limbic brain regions and are crucial for the regulation of the excessive glutamate release [148]. Activation of mGluR group II by orthosteric agonists has been shown to enhance the function of NMDA-Rs [149] and regulate the long-term potentiation and depression in the prefrontal cortex and the hippocampus [150, 151]. Following positive

preclinical studies with mGluR-2 PAMs [152], the first promising substance from this category that reached clinical trials was pomaglumetad methionil (LY2140023 monohydrate, a prodrug of the mGluR-2/3 agonist, LY404039), developed by Eli Lilly and Company. Despite an earlier study showing positive effects [153], the substance did not significantly improve symptoms of schizophrenia compared to a placebo [154–156], which led to the cessation of the LY2140023 drug development program. However, an additional explorative analysis revealed higher efficacy in certain populations, including early-in-disease patients [157]. In a later study, Mehta and colleagues reported a reduction in the ketamine-evoked, blood-oxygen-level-dependent, magnetic resonance imaging signal relative to a placebo in healthy controls treated with LY2140023, as well as with the alanine prodrug of the selective orthosteric mGluR-2 agonist 2812223 [158].

With regard to the mGluR-2 selective PAMs, to date, two substances have progressed to clinical trials: JNJ40411813/ADX71149 and AZD8529 [159]. A generally good tolerability of JNJ40411813/ADX71149 has been demonstrated in two randomized, double-blind, phase I studies [160]. JNJ40411813 was shown to reduce the increase in positive and negative symptom scores induced by a low dose of (S)-ketamine and had a trend towards a reduction in cognitive deficits in attention and episodic memory precipitated by smoking withdrawal in a subpopulation of healthy volunteers. However, statistical significance was not obtained [160]. Currently, ClinicalTrial.Gov lists one ongoing study with JNJ40411813, which focuses on the treatment of epilepsy rather than schizophrenia (NCT04836559).

The second substance, AZD8529 (developed by AstraZeneca), did not improve symptoms in schizophrenia in a proof-of-principle study [161] either. However, in one later study, despite not producing significant group-average effects on symptoms or cognitive accuracy, AZD8529 was shown to increase activation in task-activated fronto-striatal regions, leading the authors to conclude that the substance may be beneficial for an important subset of individuals with schizophrenia [152].

With respect to mGluR-3, some investigations indicate their neuroprotective effects [162]; thus, the hypothesis has emerged that enhancement of mGluR-3 signaling may provide pro-cognitive benefits in addition to ameliorating some of the neuroinflammatory pathology seen in schizophrenia [159, 163]. Nevertheless, none of the preclinical substances investigated seem to have achieved the level of a clinical trial so far.

Concerning the mGluR group III, preclinical studies suggest that mGluR-4, mGluR-7, and mGluR-8 may be potential targets to normalize glutamatergic tone within the brain in patients with schizophrenia [64]. However, the research regarding these receptors is still in its early stages, and clinical studies are yet to be conducted [164].

5 The Cholinergic System

Central cholinergic dysfunction has long been associated with schizophrenia, making the cholinergic system an interesting target for the development of new drugs [41]. The investigated approaches include acetylcholinesterase inhibitors, muscarinic agonists, and agonists and potentiators of nicotinic receptors.

5.1 AChE-Is

To date, three acetylcholinesterase inhibitors (AChE-Is) [donepezil, rivastigmine, and galantamine] have been approved for the symptomatic treatment of mild-to-moderate Alzheimer's disease [165]. The main acting mechanism of AChE-I includes the inhibition of the enzyme acetylcholinesterase, which consecutively results in a reduced degradation and in an increased level and duration of action of the neurotransmitter acetylcholine [166].

A comprehensive base of evidence proves that cholinergic projections to the cortex and basal forebrain play an important role in compromised cognitive constructs in schizophrenia [167]. However, investigations of the potential pro-cognitive effects of AChE-Is in schizophrenia have yielded very heterogeneous results that are also reflected in the mixed results of different meta-analyses, stating weak evidence for the beneficial effect of AChE-Is in combination with antipsychotics in a few domains of mental state and cognition [166, 168] but also a lack of such evidence [169, 170]. Additionally, a small-sized positive effect of galantamine has been reported [171] and attributed mainly to its additional activity as a PAM of the nicotinergic alpha-7 receptors. Furthermore, some evidence emphasizes the effectiveness of the synergistic action of a galantamine-memantine combination [172].

5.2 Muscarinic Agonists and PAMs

One of the first promising substances from the category of muscarinic agonists was xanomeline, which showed positive effects on psychotic symptoms and cognition in patients with schizophrenia [173], as well as in preclinical models [174]. However, the occurrence of dose-dependent cholinergic adverse events mediated by stimulation of peripheral muscarinic cholinergic receptors has limited its widespread use. Therefore, a co-formulation of xanomeline and the muscarinic receptor antagonist trospium chloride (which only minimally, if at all, penetrates the blood–brain barrier)

has been developed [175]. This co-formulation is being further investigated as KarXT by the pharmaceutical company Karuna Therapeutics. Findings from a double-blind phase II trial indicate a greater decrease in the PANSS total score in patients with schizophrenia treated over 5 weeks with KarXT compared with placebo [176]. A specific effect on cognitive symptoms was not reported in this publication. However, based on a separate exploratory analysis, the company announced trends towards improvement in cognition [177].

KarXT is currently under development for schizophrenia and Alzheimer's disease psychosis. The Clinical.Trials.gov search (May 2022) revealed six active phase III studies (NCT04659161, NCT04659174, NCT04820309, NCT05145413, NCT04738123, NCT05304767) designed to investigate the safety, tolerability, and efficacy of KarXT in adult patients with schizophrenia. The estimated primary completion dates range from May 2022 to December 2024. For all six studies, the inclusion of over 1600 participants are estimated.

In addition to xanomeline, the development of some additional selective muscarinic agonists with high muscarinic M_1-receptor potency and very low activity at M_3 receptors has been reported [178]. The clinical implication of these substances, however, does not seem to have been identified yet.

When discussing the muscarinic agonists, the bidirectional modulation of muscarinergic receptors by clozapine and its metabolite should also be mentioned. Clozapine itself acts as a competitive mAChR antagonist in striatal tissue [179]. In contrast, its primary metabolite, *N*-desmethylclozapine (norclozapine), is a robust agonist of muscarinic M_1 receptors and also potentiates the NMDA-R activity [180]. The single formulation of norclozapine was investigated by ACADIA Pharmaceuticals as ACP-104 and reached a phase II study (NCT00490516). Despite some initial positive results, the phase IIb trial was discontinued because of a lack of efficacy [181], and the substance is currently not listed in the pipeline of the company. Instead, another compound, ACP-319 (PAM of M1 receptors), is in an early-stage clinical program and has been referred to as a novel approach to improving cognitive function and other neuropsychiatric symptoms in patients with brain disorders [182].

Cerevel Therapeutics is developing the substance CVL-231 (emraclidine), which is a PAM of the cholinergic M_4 receptor subtype. In June 2021, the company announced positive results for CVL-231 in a phase Ib clinical trial in patients with schizophrenia [183]. CVL-231 20 and 30 mg reduced positive and negative symptoms significantly stronger than placebo after a 5-week treatment period. In January 2022, Cerevel announced details of the phase II program in schizophrenia with two phase II studies (NCT05227703 and NCT05227690). Each trial will enrol 372 patients with schizophrenia with acute exacerbation or relapse of psychotic symptoms. Data from both trials are expected in the first half of 2024 [184]. ClinicalTrials.gov further lists three phase I studies with CVL-231 (NCT05245539, NCT04787302, and NCT05106309).

5.2.1 nACh-Rs

Nicotinic acetylcholine receptors (nACh-Rs) in the brain, belonging to the superfamily of the neurotransmitter-gated ion channels, play a crucial neuromodulatory role in the central nervous system [185]. There are two families of central nACh-Rs: the heteromeric nACh-R and the homomeric nACh-Rs, assembled from a single subunit type, typically alpha7 (alpha7-nAChRs) [186].

A number of different findings, including genetic studies, underpin a nicotinic dysfunction in schizophrenia. The smoking rates in schizophrenia range up to 70% [187], which is higher than in any other psychiatric disease. Diminished expression of alpha7-nAChRs has been reported in several regions of human post-mortem brain tissue, particularly in the hippocampus [188, 189]. Thus, different nicotinic therapies have been investigated in schizophrenia. Thereby, several compounds showed promising results in preclinical trials, as well as in early phase I and II clinical trials. However, none of them has translated to a successful phase III clinical trial [190, 191].

One of the most promising substances was the alpha7-nAChR partial agonist encenicline (EVP-6124). Some positive effects of encenicline on cognition in schizophrenia were observed in studies with a small number of participants [192, 193], but the results from a phase III study were negative [194], and further investigations of this drug were terminated [195].

Another substance on which high expectations were placed following initial studies was the selective alpha7-nAChR partial agonist, ABT-126. In a phase II study, ABT-126 significantly improved cognition in the intent-to-treat population. Further analysis of subgroups revealed that the beneficial effect (Cohen d effect size >0.8) was limited to non-smokers and had no effects in smokers [196]. As the majority of patients with schizophrenia smoke, a larger study was designed to evaluate the effects of ABT-126 in light smokers. After 12 weeks of additional treatment with 25 or 75 mg of ABT-126, neither dosage group outperformed the placebo in any cognitive domain [197]. A translational meta-analysis of rodent and human studies [198] did not reveal any statistically significant effects of alpha7-nAChR agonists on overall cognition or in any of eight cognitive subdomains in humans; but, in contrast, large effect sizes were seen in multiple behavioral tests of cognition in rodents.

5.2.2 PAMs of the alpha7-nAChRs

Compared to the direct agonists, PAMs of the alpha7-nAChRs have the major advantage that they are only active in the presence of acetylcholine and therefore less likely to cause desensitization [199]. The first auspicious compound from this category, AVL-3288, showed some promising effects on cognition in schizophrenia in preclinical and initial clinical studies but failed to evoke positive effects in a larger phase Ib study [200]. One other alpha7-nAChR PAM, JNJ-39393406, also failed to improve cognition in schizophrenia [201].

Overall, a comprehensive meta-analysis [202] found no evidence of the effectiveness of substances targeting the alpha7-nAChRs as an add-on treatment for cognitive deficits in schizophrenia. Moreover, only a small beneficial effect on negative symptoms was reported.

6 The Serotonergic System

Hypotheses regarding the involvement of serotonergic neurotransmission in schizophrenia originated in the early 1950s. Among others, it could be shown that d-lysergic acid diethylamide, which has a high structural similarity to serotonin and is a potent agonist at the 5-HT_{2A} receptors [203], can induce transient positive psychosis-like symptoms, particularly in people with a genetic predisposition for psychosis [204] and in people with schizophrenia itself [205].

Multiple serotonin receptors have been implicated in schizophrenia, including 5-HT_{1A}, 5-HT_{2C}, 5-HT_3, 5-HT_6, and 5-HT_7 receptors [206]. Nevertheless, the most relevant findings concern the 5-HT_{2A} receptors. The 5-HT_{2A} receptors are widely expressed on the dendrites of glutamatergic pyramidal neurons and GABAergic interneurons throughout the cortex, and their activation regulates both glutamatergic and dopaminergic neurotransmission [207]. Most second-generation antipsychotics exhibit a relatively high serotonin 5-HT_{2A} antagonism in addition to a relatively low D_2-receptor antagonism [208].

6.1 Substances Targeting the 5-HT_{2A} Receptors

Pimavanserin is a partial inverse agonist and antagonist at 5-HT_{2A} receptors, approved by the FDA in April 2016 for hallucinations and delusions in patients with Parkinson's disease [209]. In patients with chronic schizophrenia, the addition of pimavanserin enhanced the efficacy of low-dose risperidone [210]. Furthermore, the addition to clozapine reduced therapy-refractory hallucinations and delusions [211]. In one large phase II study, pimavanserin significantly improved negative symptoms in stable outpatients with schizophrenia [212] but the improvement in the PANSS total and in general symptom scores was not significant.

Clinical.Trials.gov search lists ten active studies with pimavanserin, including two phase III trials evaluating the effects of additional administration of pimavanserin in patients with schizophrenia (NCT03121586, NCT04531982). Both studies (estimated completion date March 2024/March 2023) are sponsored by Acadia Pharmaceuticals.

One further promising substance from the category of 5-HT_{2A} receptor antagonists is roluperidone (MIN-101), which is additionally an antagonist at sigma-2 receptors [213]. Roluperidone monotherapy demonstrated statistically significant efficacy in reducing negative symptoms and good tolerability in a phase IIb study in 244 stable patients with schizophrenia [213]. Results of a post hoc analysis suggested a possible benefit on cognitive performance that correlated significantly with the improvement of negative symptoms [214]. In a large phase III study (NCT03397134, sponsored by Minerva Neurosciences; $n = 513$), monotherapy with roluperidone (64 mg/day) improved negative symptoms in the modified intent-to-treat dataset marginally missing statistical significance, whereas improvements in the Personal and Social Performance Scale total score were statistically significant [215]. The only cognitive endpoint in this study (verbal fluency) did not change significantly. Minerva Neurosciences announced in April 2022, after a type C meeting with the FDA, further steps towards a new drug application (FDA) for roluperidone as a monotherapy for patients diagnosed with schizophrenia with moderate-to-severe negative symptoms and stable positive symptoms [216]. Other 5-HT_{2A} receptor antagonists and related compounds (SR46349B [eplivanserin], fananserin, ritanserin) have not shown very promising results in the available studies [207].

6.2 Substances Targeting 5-HT6 Receptors

AVN-211, a selective 5-HT_6 receptor antagonist, showed some beneficial antipsychotic and pro-cognitive effects (attention improvement) as an add-on to antipsychotic medication in a pilot 4-week trial in patients with schizophrenia [217]. One later study on a larger sample showed positive effects on positive and negative schizophrenia symptoms, favoring female individuals [218], without benefits for cognition. The website of the pharmaceutical manufacturer (Avineuro) lists AVN-211 (Avisetron) in the current pipeline, but details on additional studies were not available. Furthermore, the pipeline of Avineuro includes the substance AVN-322, a highly selective 5-HT_6 receptor antagonist with a high binding affinity and high potency to functionally block the receptor [219]. According to the manufacturer, AVN-322 showed pro-cognitive effects in an animal

model [219, 220] and is ready to enter phase II clinical trials for treating diseases associated with cognitive dysfunction [221]. However, ClinicalTrials.gov does not list any active study with these compounds.

7 Novel Approaches Targeting the Dopaminergic System

In general, there are five dopamine receptor subtypes: D_1 receptor, D_2 receptor, D_3 receptor, D_4 receptor, and D_5 receptor. All dopamine receptors belong to the G-protein coupled receptor family: D_1 receptor and D_5 receptor (D_1-like family) stimulate cyclic adenosine monophosphate (cAMP) signaling pathways, whereas D_2 receptor, D_3 receptor, and D_4 receptor (D_2-like family) inhibit this signalization [222].

7.1 Targeting Primarily D_1 Receptor

The D_1 receptor shows relatively high expression in mesocortical projections to the prefrontal cortex, a brain area of key importance for higher cognitive functions, including working memory, attention, and executive function [223, 224]. After promising preclinical investigations, the central acting and potent D_1-receptor PAM mevidalen (LY-3154207) has been investigated in human studies and showed acceptable safety and tolerability [223] as well as positive effects on enhancing wakefulness in in sleep-deprived healthy volunteers [225]. The substance was investigated for the treatment of cognitive deficits in Lewy body dementia and Parkinson's disease (NCT03305809), where it improved motor symptoms but had no beneficial effects on cognition [226]. There is currently no registered study relating to schizophrenia.

The examination of one other D_1 PAM ASP4345 in a phase I study revealed potential improvement in psychomotor function and visual attention and suggested improvement in information processing [227]. However, the development was stopped [228] after the add-on of ASP4345 to a stable treatment with antipsychotics failed to improve cognitive impairments in patients with schizophrenia (NCT03557931) [229].

The selective D_1/D_5 receptor partial agonist PF-06412562 failed to show a clinical benefit relative to a placebo on assessments of cognition or reward processing in symptomatically stable patients with schizophrenia over a 15-day treatment period [230]. However, in a later investigation in healthy volunteers, higher doses of PF-06412562 improved reversal learning only in individuals with low baseline working memory [231], indicating an inverted U-phenomenon relationship [232]. Based on this insight, an academia-sponsored study was initiated in collaboration with Cerevel Therapeutics in order to examine the effects of PF-06412562 (now renamed as CVL-562) on working memory neural circuits in patients with early-episode schizophrenia and to establish neuroimaging biomarkers of the D_1/D_5 targets (NCT04457310) [232]. One further compound, Lu AF35700, with high affinity for serotonergic, dopaminergic, and alpha-adrenergic receptors and thereby a significantly higher affinity to the D_1 receptor than for the D_2 receptor, did not outperform placebo as an add-on to treatment with an atypical antipsychotic in a phase III study (NCT03230864) [233].

7.2 Targeting D_3 Receptors

D_3 receptors are expressed in brain regions controlling reward, emotions, and motivation [234]. Furthermore, ample evidence suggests that D_3 receptors are associated with cognitive functioning and that a D_3-receptor blockade may enhance cognitive performance in healthy individuals and treat cognitive dysfunction in individuals with a neuropsychiatric disorder [235]. Several selective D_3-receptor antagonists have been described as having pro-cognitive effects in animal models [236]. The compound F17464, which demonstrates preferential D_3 versus D_2 receptor binding and partial agonism at $5HT_{1A}$ receptors, showed beneficial effects on social deficits and cognition in different animal models and was well tolerated in healthy human volunteers [234]. Additionally, it improved positive and negative symptoms, as well as cognitive functions, in a phase II study [237]. However, there are currently no ongoing trials with F17464 registered at ClinicalTrials.gov.

7.3 Dopamine-Serotonin System Stabilizer

The most relevant representative of this category so far is RP5063 (brilaroxazine), which shows potent partial agonistic activity at the D_2, D_3, D_4, and the 5-HT_{1A} and 5-HT_{2A} receptors, and antagonist activity at the 5-HT_{2B}, 5-HT_{2C}, 5-HT_6, and 5-HT_7 receptors, as well as a moderate affinity for the serotonin transporter [238]. RP5063 showed robust efficacy and safety in a phase II trial (NCT01490086), and trends towards cognitive improvement (nonsignificant). In April 2021, the developing company, Reviva Pharmaceuticals, announced full details of this study, reporting that endpoints for safety and efficacy in 234 patients were met as the substance mitigated positive and negative symptoms and improved social functioning and cognition [239]. According to the website of Reviva Pharmaceuticals, two phase III studies with RP50603 are currently in preparation [240]. One phase III study was registered at ClinicalTrials.gov in January 2022 (NCT05184335), aiming at an inclusion of 402 patients with schizophrenia who will receive the fixed dose of brilaroxazine or placebo. The data acquisition should be completed by December 2023.

8 The Endocannabinoid System

The endocannabinoid system comprises two G-coupled receptors referred to as the cannabinoid 1 receptor and the cannabinoid 2 receptor [241]. Cannabinoid 1 receptors are located throughout the central nervous system [242], while cannabinoid 2 receptors are primarily located on immune cells [243] and have low densities in the brain [244]. Acute administration of the main psychoactive component of cannabis delta-9-tetrahydrocannabinol, which acts as a cannabinoid 1 receptor partial agonist, produces robust cognitive deficits [245].

The second most prevalent bioactive constituent of the *Cannabis sativa* plant is cannabidiol (CBD), which does not convert to delta-9-tetrahydrocannabinol in the human body [246]. Evidence from preclinical studies suggested that CBD had potential therapeutic benefits from anti-inflammatory to neuroprotective, analgesic, and antioxidant effects [247]. It also appears to have antipsychotic properties [248, 249] and a protective effect against acute cognitive deficits produced by delta-9-tetrahydrocannabinol [250]. The exact acting mechanism of CBD still remains unknown, but evidence suggests that its activity at cannabinoid receptors is limited, as over 65 other molecular targets for CBD have been identified [251].

Several controlled clinical trials performed in order to investigate the clinical effect of CBD in schizophrenia yielded mixed results [249, 252–254]. Two systematic reviews found some evidence for the potential of CBD in alleviating psychotic symptoms and cognitive impairment in patients with a variety of conditions [255, 256], while a lack of clinical evidence for the beneficial effects of CBD against cognitive impairments was stated from other systematic reviews [257–260]. In April 2022, ClinicalTrials.gov listed nine active phase II clinical trials with CBD (NCT02926859, NCT04605393, NCT02088060, NCT02504151, NCT03608137, NCT04700930, NCT04411225, NCT02492074, and NCT04105231) investigating the effects of CBD on cognition in schizophrenia.

9 PDE Inhibitors

Nucleotide phosphodiesterases (PDEs) are ubiquitously distributed enzymes that play a major role in cell signaling by hydrolyzing cAMP and cyclic guanosine monophosphate [261]. Cyclic adenosine monophosphate and cyclic guanosine monophosphate are secondary messengers of many receptors whose hypofunctions are involved in the cognitive deficits associated with schizophrenia (such as dopamine or glutamate and many PDE subfamilies). Thus, the inhibition of PDEs is considered a promising mechanism for treatment of schizophrenia [262]. The inhibition of the breakdown of cAMP and cGAMP can alter synaptic plasticity [263] and postsynaptic signaling [264]. Currently, from the 11 known PDE families, the subtypes 4 and 10 are the most studied for the treatment of CIAS [265].

Phosphodiesterase 4 interacts with the gene Disrupted in schizophrenia 1 (DISC1), which is involved in neurogenesis and whose malfunction is related to schizophrenia [266]. One promising inhibitor of PDE4, roflumilast, currently used to treat chronic obstructive pulmonary disorder [267], showed cognitive-enhancing effects in both animal studies [268] and in healthy human participants [269, 270]. In patients with schizophrenia, significant improvements of some electroencephalogram biomarkers with 250 µg of roflumilast have been reported [271], as well as a significant improvement in verbal memory [272]. ClinicalTrials.gov lists more than 30 active studies for different somatic (asthma, bronchiectasis, chronic obstructive pulmonary disease, psoriasis) conditions, as well as for major depressive disorder and Alzheimer's disease with roflumilast. However, no further studies relating to schizophrenia were registered in April 2022.

The second intensively studied group of PDE inhibitors are PDE10A inhibitors. Up to now, these efforts have resulted in 12 reported clinical candidates and four clinically validated PDE10A PET ligands [273, 274]. Following positive preclinical studies [275], which indicated efficacy in the treatment of positive and cognitive schizophrenia symptoms, the selective PDE10A inhibitor TAK-063 was investigated in a phase II study (20 mg/day, $n = 83$). Despite not meeting the primary endpoint, the authors stated that the results might be suggestive of antipsychotic activity [276]. In one additional neuroimaging study on healthy male participants, TAK-063 attenuated ketamine-induced changes in functional magnetic resonance imaging signals in multiple regions of the brain during the resting state and working memory tasks [277]. However, the exact implication of this result is still unclear.

One other promising PDE10A inhibitor, MK-8189, currently under development by the pharmaceutical company Merck Sharp & Dohme Corp, yielded negative results regarding the PANSS total score (NCT03055338) [278]. In April 2022, ClinicalTrials.gov listed one active trial with MK-8189 in schizophrenia (NCT04624243 [phase IIb]), aiming to include 576 participants until March 2023. Results of one other completed phase I study were still not available (NCT04506905).

In addition to PDE4 and PDE10 inhibitors, there are some other novel approaches to develop inhibitors of PDE9 and PDE1B for the treatment of cognitive dysfunction in schizophrenia [279]. Earlier, the PDE9 inhibitor BI 409306 failed to improve cognitive function in schizophrenia patients in

a phase II trial [280]. Despite this negative result, a new, industry-sponsored, proof-of-concept trial has been set up to investigate the change in everyday functional capacity and cognition in patients with attenuated psychosis syndrome treated with BI 409306 versus a placebo (NCT03230097) [281].

10 Modulation of the TAAR1

Trace Amine-Associated Receptor 1 (TAAR1) is a G-protein-coupled receptor activated by trace amines and is expressed in multiple regions of the mammalian brain. It is known to be particularly present in limbic and monoaminergic areas, allegedly involved in mood, attention, memory, fear, and addiction [282]. Intensive investigations have shown that TAAR1 acts as a rheostat of dopaminergic, glutamatergic, and serotonergic neurotransmission, and thus could be considered a novel therapeutic target for schizophrenia, depression, and addiction [283]. Preclinical studies have revealed the ability of TAAR1 agonists to modulate dopaminergic tone, presumably via functional physical interaction of TAAR1 with D_2 receptors and potentially also with the dopamine transporter [284, 285].

Ulotaront, a.k.a SEP-363856 or SEP-856 [286], discovered by Sunovion Pharmaceuticals in collaboration with PsychoGenics [287], exhibits a complex mechanism, including an agonism at TAAR1 and 5-HT_{1A} receptors [287]. In a placebo-controlled clinical trial including 245 patients with acute exacerbation of schizophrenia, 4-week treatment with flexible-dosed SEP-363856 (50 or 75 mg daily) improved the PANSS total score significantly more than the placebo [288]. The results of the 26-week open-label extension study [289] revealed a continuous reduction in the PANSS total score and in the Clinical Global Impression-Severity score, with a relatively high completion rate and absence of extrapyramidal-related adverse effects. While neither publication specifically addresses the effects of SEP-363856 on CIAS, preclinical studies indicate a benefitial effect of the substance on cognitive deficits in a psychosis animal model [290]. Ulotaront was granted a breakthrough therapy designation by the FDA for the treatment of patients with schizophrenia in May 2019 [291, 286].

In April 2022, the ClinicalTrials.gov search revealed ten completed and seven active studies related to SEP-363856 in schizophrenia (NCT04109950, NCT04038957, NCT04865835, NCT04825860, NCT04072354, NCT04092686, NCT04115319). The estimated completion date for the ongoing studies ranges between September 2021 and March 2025. Furthermore, although some of the studies are designated as being completed, they are not yet published, and it is expected that these results will provide further insight into the effectivnes of SEP-363856 in the near future.

11 Modulation of the Upstream Glutamate System by Blockage of VGSCs

One new drug category, known as voltage-gated sodium channel (VGSC) blockers, has been developed based on emerging evidence suggesting that hippocampal hyperactivity and NMDA-R dysfunction create an imbalance in the excitatory/inhibitory neurocircuitry of mesolimbic dopaminergic and glutamatergic neurons, thus increasing synaptic activities in the prefrontal cortex [292]. Additionally, increased intrinsic hippocampal activity is hypothesized to be a characteristic feature of schizophrenia that is broadly associated with cognitive dysfunctions [293]. The generation and propagation of excitatory signals are essentially regulated by VGSCs [294]. Furthermore, a growing body of evidence showed a tight association between the schizophrenia pathogenesis and the gene expression and function of VGSCs [295, 296]. In this context, some evidence confirms the benefits of VGSC blockers (e.g., lamotrigine) as an add-on therapy to antipsychotics [297, 298].

Evenamide (NW-3509) is a VGSC blocker that inhibits the synaptic release of glutamate, thereby reducing hyperexcitability in both the prefrontal cortex and the hippocampus [292]. Beneficial effects of evenamide monotherapy [299], including some pro-cognitive effects [300], were demonstrated in various animal models of psychosis. In a clinical setting, the add-on of evenamide to a stable dose of risperidone or aripiprazole was shown to be well tolerated and outperformed placebo [301] in a phase II, double-blind, 28-day, placebo-controlled clinical trial with 90 patients. The developing company (Newron Pharmaceuticals) announced the results of a further phase II study (NCT04461119) in April 2021 [302], stating a confirmation of the safety of the substance. The initiation of another phase II/III study (EudraCT Number: 2020-006062-36 [303]) was announced in September 2021 [304]. The results are expected in the fourth quarter of 2022.

12 Anti-Inflammatory and Immunomodulatory Approaches

The role of inflammation and immune dysregulation in the pathophysiology of schizophrenia has been intensively investigated in recent decades. Several findings indicate that a multitude of genetic and environmental factors confer an increased risk for schizophrenia by converging to alter immune processes, which are known to play an essential

role in shaping brain development [305]. Moreover, subclinical inflammation seems to correlate with higher levels of cognitive impairment, underlining the possible utility of anti-inflammatory agents [306–308]. Additionally, based on genetic, transcriptomic, and functional studies, dysregulation in the complement system, which mediates innate immunity, has been reported in patients with schizophrenia [309].

A broad range of anti-inflammatory strategies has emerged to address immune dysregulation in schizophrenia, but results have been inconsistent. In the context of CIAS, the most frequently studied, broadly effective anti-inflammatory substances include aspirin, celecoxib, davunetide, erythropoietin, oestrogen, minocycline, *N*-acetylcysteine, omega-3 fatty acids, pregnenolone, and selective estrogen receptor modulators [310].

With respect to cognitive performance, Cho and colleagues reported in their meta-analysis significant beneficial effects for minocycline (a broad-spectrum, second-generation, tetracycline semisynthetic antibiotic approved for the treatment of acne vulgaris, some sexually transmitted diseases, and rheumatoid arthritis [311]) and pregnenolone [310] (neurosteroid [312] able to suppress the activity of interleukin [IL]-6 and tumor necrosis factor [TNF]-alpha [313]). However, this meta-analysis has not included the negative results for minocycline from a later large randomized controlled trial with 207 patients [314].

In the second meta-analysis, Çakici and colleagues reported the beneficial effects of minocycline, davunetide, and NAC on cognition, whereby effects were more pronounced in first-episode psychosis or early-phase schizophrenia [315]. Davunetide is an intranasal drug presently under development for the treatment of Alzheimer's disease and progressive supranuclear palsy [316], which downregulates the key inflammatory cytokines TNF-alpha, IL-16, and IL-12 [317]. *N*-Acetylcysteine has anti-inflammatory properties and can modulate immune functions during the inflammatory response by inhibiting TNF-alpha, IL-1β, and IL-6 [318]. *N*-Acetylcysteine additionally influences glutamatergic neurotransmission. This mechanism and findings regarding the efficiency of NAC are discussed in more detail above.

In addition to non-specific anti-inflammatory agents, monoclonal antibodies against pro-inflammatory cytokines are receiving increasing attention in the search for new therapeutics in the context of improving understanding of the involvement of specific cytokines in schizophrenia. In particular, IL-6, TNF-alpha, and interferon-γ may represent new therapeutic targets [319].

Tocilizumab, a specific IL-6 receptor antibody developed and approved for rheumatoid arthritis, improved cognition in a small open-label pilot trial [320], while a larger randomized, double-blind, placebo-controlled clinical trial (NCT02034474) was negative [321]. According to ClinicalTrials.gov, one phase I study investigating tocilizumab in schizophrenia is still active (NCT02874573). Another anti-IL-6 chimeric monoclonal antibody, siltuximab (approved for the treatment of multicentric Castleman's disease, a rare blood disorder [322]) is being tested as an adjunct to antipsychotic medications in schizophrenia (NCT02796859).

Indications of positive effects of the recombinant human interferon-γ-1b originate from two case reports [323]. Significant alterations in the levels of TNF-alpha have been demonstrated in in vivo and in vitro studies on schizophrenia [324]. Thus, some approaches follow the usage of TNF-alpha inhibitors as an adjuvant compound for schizophrenia treatment, after some promising preclinical investigations [325].

13 Further Approaches

Increasing evidence suggests a possible role of neurosteroids (steroids synthetized in the brain) and neuroactive steroids (steroids produced by an endocrine gland and subsequently reach the brain through the bloodstream) in the pathology and symptomatology of schizophrenia [326]. Both categories are often referred to simply as neurosteroids [326]. In general, neurosteroids act through genomic mechanisms, with a consecutive influence on protein synthesis, but they also exhibit other different fast-occurring non-genomic mechanisms [327], including among others the modulation of neuronal excitability in the brain via the GABA neurotransmitter system [328]. Their further targets are the NMDA-Rs, as well as nicotinic, muscarinic, serotonergic, adrenergic, and sigma-1 receptors [328]. Additionally, evidence suggests that neurosteroids have neuroprotective effects in both central and peripheral nervous systems by attenuating excitotoxicity, brain edema, inflammatory processes, oxidative stress, and neural degeneration [329]. Furthermore, they accelerate and improve neurogenesis and myelination [329, 330].

Evidence suggests that particularly pregnenolone and dehydroepiandrosterone appear to be a promising treatment option with some beneficial effects on cognition in schizophrenia [326], which was mainly demonstrated in animal models, where positive effects have been shown on learning and memory [331–333]. In clinical studies, an amelioration of cognitive deficits under treatment with pregnenolone and dehydroepiandrosterone has been shown in isolated smaller studies [334–336], but the overall evidence is sparse. ClinicalTrials.gov currently does not list any further studies with pregnenolone and dehydroepiandrosterone in the indication schizophrenia.

Another therapeutic approach includes the application of intranasal oxytocin, a neuropeptide mainly produced in the hypothalamic nuclei that acts within the brain as a neurotransmitter and neuromodulator [337]. Oxytocin is well

known to influence social attachment [338] and promote parental nurturing and social bonding [339]. Accumulating evidence also indicates its important role in human social cognition [340]. A comprehensive meta-analysis that included 17 studies showed a small significant effect on theory of mind in patients with neurodevelopmental disorders (including schizophrenia) [341]. Additionally, positive effects of oxytocin have been reported on emotional recognition [342], higher-order social cognition [343] but also on working memory [344] and verbal fluency [345] in schizophrenia. However, there is also a relatively high proportion of studies with negative results [346], although review articles mainly confirm the positive effect of oxytocin on social cognition and some other symptoms in schizophrenia [346–348], stating that it is a promising candidate for the development of new treatment options. ClinicalTrials.org lists three active studies where the effects of oxytocin on clinical or neuroimaging feature will be investigated (NCT03900754, NCT04177719, NCT03245437).

14 Conclusions

Cognitive impairment represents a central element of the symptomatology of schizophrenia that can be barely, if at all, alleviated by the currently available antipsychotics [15]. Remarkably, despite past efforts to develop alternative approaches [349] and rapidly growing evidence suggesting the immense significance of systems other than the dopaminergic system in the genesis of cognitive impairments, all drugs currently licensed to treat schizophrenia are D_2/D_3-receptor blockers [62]. Accordingly, current efforts directed to meeting the needs of patients with schizophrenia are primarily based on interventions in other non-dopaminergic systems.

Among the numerous compounds currently under investigation, the development of the selective GlyT1 inhibitor BI 425809 [97–99] and the TAAR1 agonist ulotaront (SEP-363856) [288–291] is the most advanced. The breakthrough therapy designation granted for both substances by the FDA enables regulatory monitoring of the approval process. The designation was established to expedite the development of promising drugs intended to treat serious or life-threatening conditions in cases where preliminary clinical evidence suggests substantial superiority over existing options and the products showed exceptional results for patients [100].

For BI 425809, the breakthrough designation was specifically granted for the treatment of CIAS, following positive results from a phase II study, which showed a statistically significant benefit for cognition during 12 weeks of treatment [98]. The completion of the ongoing phase III studies is expected until May 2024. Thus, in the case of positive results, BI 425809 could be the first substance to be explicitly approved for CIAS.

Ulotaront (SEP-363856), a promising first in class TAAR1 agonist, was found to significantly reduce global symptoms in schizophrenia [288, 289]. Evidence for positive effects on cognition has so far emerged only from preclinical studies [290] and the results of ongoing clinical trials may provide further insights in this regard.

Moreover, current evidence regarding the pathophysiology of CIAS suggests that interventions in the glutamatergic system may be highly promising [60, 62]. Thereby, the highly complex receptor system involved in glutamatergic neurotransmission opens up a broad diversity of possible approaches. In addition to BI 425809, existing research suggests that the DAO inhibitor TAK-831 (Luvadaxistat) [113], the direct NMDA-R PAM CAD-9303 [115] as well as AMPAkines, acting as allosteric potentiators of AMPA-Rs (represented by BIIB104 [PF-04958242] [139]) show some potential as future drugs to alleviate CIAS.

Another substance in the advanced stages of development is the combined muscarinergic agonist/antagonist formulation KarXT. Following the recently reported positive effects of KarXT on the PANSS total score [176] and the pronounced trends towards improvement in cognition in an exploratory analysis [177], the results of several ongoing clinical trials are awaited. Regarding other substances targeting the cholinergic system, promising results have been reported from the early development of two selective muscarine receptor PAMs ACP-319 [182] and CVL-231 [183, 184], targeting the M_1 and M_4 receptors, respectively.

In the field of modifications of serotonergic neurotransmission, the most promising results were reported for the $5HT_{2A}$ receptor antagonist roluperidone (MIN-101) [214–216], pimavanserin (already approved by the FDA for hallucinations and delusions in patients with Parkinson´s disease) [209, 211, 212] and the selective 5-HT_6 receptor antagonist AVN-211 [217, 218]. The efficacy of pimavanserin and AVN-211 are currently being intensively investigated in large clinical trials. The search for a suitable intervention within the dopaminergic system away from D_2/D_3 antagonism also continues, but so far without unequivocal evidence of sufficient effectiveness [225–237].

One other related innovative drug category includes the dopamine-serotonin system stabilizer, represented by RP5063 (brilaroxazine). In a recent study, RP5063 was shown to reduce positive and negative symptoms and improve social functioning and cognition in patients with schizophrenia [239]. It remains intriguing whether these results can also be confirmed in the ongoing larger phase III study, the results of which are expected in December 2023.

Among the substances that have been known for some time or are already on the market, the available study results indicate some potential pro-cognitive effects for the

glutathione precursor NAC [123, 124, 315] and memantine [130, 131]. Broad evidence suggests that the use of neurosteroids (particularly pregnenolone and dehydroepiandrosterone) may be favorable for cognition [326, 334, 335]. Moreover, the use of oxytocin seems to show positive effects, particularly by improving social cognition. However, it remains to be seen whether the existing references and level of interest are sufficient to generate more evidence and obtain approval of those substances for the treatment of schizophrenia. Furthermore, following the increasing recognition of the significant role of inflammation and immunological dysregulation in the development of schizophrenia, a growing number of compounds are also being explored in this area [306–311], although these approaches are currently at early stages of development.

Finally, the research of new pharmacological agents for the treatment of CIAS must not disregard the high phenotypic heterogeneity of the symptomatology. This is inevitably accompanied by a high neurobiological diversity that can only be adequately addressed by individual treatment approaches. This implies that a more targeted development of substances that might have a positive effect on cognition in certain subgroups of patients might be a more successful strategy than striving for substances to be effective in all patients. Furthermore, in view of the enormous complexity of schizophrenia, psychopharmacological treatment requires supplementation by psychotherapeutic interventions for a sufficient treatment success. Thus, increasing efforts are focused on developing behavioral training-based interventions (cognitive remediation [350]) in addition to pharmacological treatments for CIAS. In the meantime, several promising approaches are emerging [351], and some of the substances discussed here are now being studied in combination with such interventions. Alongside the pursuit of more personalized intervention, this could be the right way forward for urgently needed progress in the treatment of CIAS.

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