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CME Review Article

Keeping up with the clinical advances: schizophrenia

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https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

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Released: July 25, 2019
CME credit expires: May 15, 2022

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Authors

Amanda Krogmann, BSc, is affiliated with Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry in Berlin, Germany. Ms Krogmann has no financial relationships to disclose.

Luisa Peters, BSc, is affiliated with Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry in Berlin, Germany. Ms Peters has no financial relationships to disclose.

Laura von Hardenberg, MPhil, is affiliated with Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry in Berlin, Germany. Ms von Hardenberg has no financial relationships to disclose.

Katja Bödeker, PhD, is affiliated with Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry in Berlin, Germany. Dr. Bödeker has no financial relationships to disclose.

Viktor B. Nöhles, MA, is affiliated with Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry in Berlin, Germany. Mr. Nöhles has no financial relationships to disclose.

Christoph U. Correll, MD, is affiliated with Charité Universitätsmedizin, Department of Child and Adolescent Psychiatry in Berlin, Germany; the Zucker Hillside Hospital, Psychiatry Research, Northwell Health in Glen Oaks, New York, USA; and Zucker School of Medicine at Hofstra/Northwell, Department of Psychiatry and Molecular Medicine in Hempstead, New York, USA. Dr. Correll has been a consultant/advisor to or has received

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda, and is also a shareholder of LB Pharma.

No writing assistance was utilized in the production of this article.

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This activity is provided by NEI. Additionally provided by the ASAP.

Support

This activity is supported by an unrestricted educational grant from Indivior.

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

CNS Spectrums (2019), **24**, 41-68.
doi:10.1017/S109285291900124X

REVIEW ARTICLE

Keeping up with the therapeutic advances in schizophrenia: a review of novel and emerging pharmacological entities

*Amanda Krogmann,[1,†] Luisa Peters,[1,†] Laura von Hardenberg,[1] Katja Bödeker,[1] Viktor B. Nöhles,[1] and Christoph U. Correll[1,2,3]**

[1] Department of Child and Adolescent Psychiatry, Charité Universitätsmedizin, Berlin, Germany
[2] Department of Psychiatry, The Zucker Hillside Hospital, Northwell Health, Glen Oaks, New York, USA
[3] Department of Psychiatry and Molecular Medicine, Zucker School of Medicine at Hofstra/Northwell, Hempstead, New York, USA

Schizophrenia remains one of the most severe medical diseases. Current dopamine modulating first-generation and second-generation antipsychotics target mainly positive symptoms, but not/inadequately negative and cognitive symptoms. Additional challenges include nonadherence and adverse effects, especially cardiometabolic dysregulation. This review evaluates new/emerging pharmacological treatments for schizophrenia. Therapies targeting total symptoms include cannabidiol, D_3 antagonist/5-HT_{1A} partial agonist F17464, lumateperone (ITI-007), phosphodiesterase 10A (PDE10A) inhibitors MK-8189 and TAK-063, sodium nitroprusside, and trace amine-associated receptor-1 (TAAR1) agonist RO5263397 and SEP-363856. Treatments targeting negative symptoms include the PDE10A inhibitor LuAF-11167, 5-HT2A inverse agonist pimavanserin, sigma-2/5-HT2A antagonist roluperidone (MIN-101), and d-amino acid oxidase (DAAO) inhibitor TAK-831. Agents targeting primarily cognitive dysfunction are the glycine transporter-1 inhibitor BI-425809 and cannabidiol. Therapies targeting residual positive symptoms/treatment-resistant schizophrenia include pimavanserin, dopamine D_1/D_2 antagonist LuAF-35700, and DAAO inhibitor sodium benzoate. Two new long-acting injectable antipsychotic formulations, Aripiprazole Lauroxil NanoCrystal® and the first subcutaneous injectable LAI Perseris (RBP-7000), were recently approved by U.S. Food and Drug Administration, and positive results were announced for Risperidone ISM®, each achieving therapeutic levels within 24 hours, without need for initial oral cotreatment/loading injection-strategies. Paliperidone palmitate 6-monthly intramuscularly injectable and Risperidone subcutaneously injectable TV46000 are currently under investigation. Finally, the samidorphan+olanzapine combination targets reduced weight gain liability, while maintaining olanzapine's efficacy. Most of these trial programs are still ongoing or have yielded mixed or even negative results. Thus, additional mechanisms of action and agents require study to improve schizophrenia outcomes for total/positive symptoms with reduced adverse effects, but also cognitive symptoms, negative symptoms, and treatment resistance, the areas of greatest need in schizophrenia currently.

Received 15 May 2019; Accepted 4 June 2019

Key words: Schizophrenia, psychopharmacology, randomized controlled trials, antipsychotics, phases 2 and 3.

Introduction

Schizophrenia is a still all-too-often chronic and debilitating psychiatric disorder that is characterized by a combination of positive and negative symptoms, cognitive dysfunction, affective and motor disturbances that often result in functional impairment and poor quality of life.[1,2]

Current treatment guidelines suggest long-term treatment with antipsychotic medications in conjunction with psychological interventions, for people with first episode psychosis, an acute exacerbation or recurrence of psychosis.[3] Despite pharmacologic advances in recent years, an effective treatment of schizophrenia remains an issue, as knowledge about the pathophysiology of this complex disorder is lacking.[1,4] The most challenging components of treatment effectiveness are adherence and efficacy for negative and cognitive as well as residual positive symptoms and adverse effects.[1]

Dopamine modulating antipsychotics remain the primary and only currently approved treatment for schizophrenia, and over the past years many different

*Address correspondence to: Christoph U. Correll, MD, The Zucker Hillside Hospital, Psychiatry Research, 75-59 263rd Street, Glen Oaks, New York 11004, USA. (Email: ccorrell@northwell.edu)
†The authors contributed equally to this work.
This activity is supported by an unrestricted educational grant from Indivior.

antipsychotics have been developed and tested for their efficacy and safety in reducing acute symptoms of schizophrenia and maintaining stability.[5-9] However, currently available drugs are mostly effective against positive symptoms (i.e., hallucinations, delusions, disorganized thought or speech, and bizarre behaviors). This situation leaves most patients with diverse residual symptoms relatively untreated, especially negative symptoms (lack of motivation, drive, enjoyment, social interactions) and cognitive dysfunction (deficits in attention, memory, executive functioning, grasp of social situations/interactions), which lead to poor quality of life outcomes and lifelong impairments,[10-18] as cognitive and negative symptoms persist for most of the patients' lives.[15,19] To date, there are no FDA-approved medications for negative and cognitive symptoms, and augmentation strategies have been largely disappointing so far.[20,21]

Furthermore, as at least positive symptoms in schizophrenia have primarily been associated with dopamine dysfunction, all currently available effective antipsychotics have dopamine D_2 receptor occupancy as a key feature, which is also associated with a varying degree of adverse effects, including motor impairments and prolactin abnormalities, with additional dopamine or off-target receptor activity-related effects on sedation, weight gain, metabolic disturbances and cardiovascular risk factors, morbidity and mortality.[22-29] In addition, too much dopamine blockade has been associated with secondary negative and cognitive symptoms.[20]

However, drugs with dopamine D_2 receptor occupancy have remained the only approved and effective pharmacologic treatment for schizophrenia, since its discovery in the 1950s.[16] Currently, only clozapine, which has considerable adverse effects,[30] has been found superior to other antipsychotics in treatment-resistant schizophrenia,[31] defined as a failure to at least two non-clozapine antipsychotics.[32] Thus, less side effect–prone agents in monotherapy or as augmentation are needed for patients with suboptimal positive symptom response or treatment-resistance.

Recent findings suggest that the core pathophysiology of schizophrenia may also involve dysfunction of glutamatergic, serotonergic, cholinergic, and gamma-aminobutyric acid (GABA) signaling, with an imbalance within any of these influencing the entire system.[33] Therefore, novel treatment approaches have also been focusing on molecular targets beyond the dopamine hypothesis, including glutamate, serotonin, acetylcholine, GABA, and inflammatory cytokines.[34,35]

Due to the goal of maintenance treatment[8] and long-standing problems with adherence in schizophrenia,[36] long-acting injectable antipsychotics (LAIs) have been developed and largely shown benefits for prevention of relapse, hospitalization, and mortality in patients with schizophrenia.[37-42] Novel LAI formulations have emerged, aiming to improve acceptability and avoid the need for oral cotreatment or loading strategies.

Therefore, this selective review aimed to (i) summarize the mechanisms of action and, if available, the results of novel, emerging, and currently investigated pharmacologic treatments for total, negative, and cognitive symptoms of schizophrenia, as well as residual and resistant positive symptoms, (ii) summarize the latest clinical data of newly approved formulations of LAIs, and (iii) evaluate the data for the addition of opioid receptor modulation to mitigate olanzapine-associated weight gain.

Methods

We conducted a selective review of (i) different pharmacological drug targets for the treatment of total, negative, and cognitive, as well as residual or resistant positive symptoms of schizophrenia, (ii) new FDA-approved and investigated LAIs, and (iii) samidorphan-olanzapine combination. For this purpose, we conducted in March 2019 a series of targeted literature searches in PubMed and clinicaltrials.gov for "schizophrenia" paired together with the following mechanisms of action or psychopharmacological agents: phosphodiesterase 9 inhibitor, PDE-9 inhibitor, phosphodiesterase 9 (PDE9) inhibitor, phosphodiesterase 10A (PDE10A) inhibitor, d-amino acid oxidase (DOAA) inhibitor, cannabidiol, glycine transporter-1 (GLYT1) inhibitor, dopamine D1 antagonist, dopamine D1 partial agonist, dopamine D2 antagonist, dopamine D2 partial agonist, dopamine D3 antagonist, dopamine D3 partial agonist, trace amine-associated receptor-1 (TAAR1) agonist, 5-HT2A inverse agonist, sigma-2/5-HT2A antagonist, lumateperone (ITI-007), roluperidone (MIN-101), sodium benzoate, sodium nitroprusside, LuAF-11167, LuAF-35700, BI-425809, F17464, MK-8189, RO5263397, SEP-363856, TAK-063, TAK-831, Aripiprazole Lauroxil NanoCrystal® or Aristada Initio, Doria® or risperi-done ISM®, paliperidone palmitate, risperidone extended release, TV-46000, Perseris and RBP-7000. Excluded were agents or trials evaluating patients with other psychotic disorders than schizophrenia, or mixed samples.

Results

Total symptoms of schizophrenia (including positive and negative symptoms)

Although many first- and second-generation antipsychotics are available, all modulate dopamine with or without serotonergic transmission modulation, but additional mechanisms of actions conferring efficacy, either added on separately or combined with dopamine-serotonin antagonism, are needed. Furthermore,

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

improved safety and tolerability also remains a goal. Several agents are at different stages of testing.

Cannabidiol

While tetrahydrocannabinol (THC), the major component of cannabis, is pro-psychotic, the potential antipsychotic and precognitive properties of cannabidiol for schizophrenia and its efficacy for other neuropsychiatric disorders are actively being pursued.[43–45]

In an exploratory 6-week, double-blind study, patients with schizophrenia were randomized to cannabidiol ($n = 43$) or placebo ($n = 45$) added to preexisting antipsychotics.[46] Although no differences between cannabidiol and placebo emerged regarding the Positive and Negative Syndrome Scale (PANSS) total or negative and general scale scores, cannabidiol had significantly lower PANSS positive scores at week 6. Furthermore, cannabidiol was superior to placebo in being rated as improved (Clinical Global Impressions-Improvement (CGI-I)) and as not severely unwell (CGI-Severity). However, cannabidiol was not superior to placebo on the Global Assessment of Functioning (GAF) Scale or the Brief Assessment of Cognition (BACS) (Table 2). Cannabidiol was well tolerated, with similar adverse event frequencies between cannabidiol and placebo.

F17464

F17464 is an oral, selective D_3 antagonist/5-HT_{1A} partial agonist that is developed for the treatment of schizophrenia.[47]

In a phase-II, double-blind, randomized, placebo-controlled, parallel-group 6-week trial,[48] patients ($n = 134$) with acute exacerbation of schizophrenia were randomized to 40 mg/day F17464 or placebo. The F17464 group was significantly superior to placebo in reducing the PANSS total score, PANSS positive and general subscale score, and of the PANSS Wallwork factors, which correspond to cognitive functioning. However, F17464 did not differentiate from placebo on the PANSS negative and CGI-S scores (Table 2).[48]

Adverse events were comparable to placebo. Overall, results of this phase-II study demonstrated therapeutic efficacy in improving total, positive, and PANSS-derived cognitive symptoms in acutely exacerbated schizophrenia patients, with a favorable safety profile.[48]

Lumateperone (ITI-007)

Lumateperone, also known as ITI-007, is an investigational agent with simultaneous modulation of serotonin, dopamine, and glutamate, which is being developed for the treatment of schizophrenia, bipolar depression, and other neuropsychiatric/ neurodegenerative diseases. The FDA has accepted the new drug application (NDA) for lumateperone for the treatment of acutely exacerbated schizophrenia in December 2018.

Lumateperone acts as a presynaptic partial agonist and postsynaptic antagonist at dopamine D_2 receptors with functional mesolimbic/mesocortical selectivity.[49] In addition, it has potent serotonin 5-HT_{2A} receptor antagonism, serotonin transporter inhibition, and stimulates phosphorylation of glutamatergic N-methyl-D-aspartate (NMDA) $GluN_{2B}$ receptors, likely downstream of dopamine D_1 receptor intracellular signaling.[49] Recently, the additional and unique increase of AMPA currents via the mTOR protein pathway has been described.[50]

At the therapeutic dose of 60 mg/day, lumateperone fully saturates 5-HT_{2A} receptors, at modest levels of dopamine receptor occupancies (30–40%), at least partially due to its wider separation (60-fold) between its affinity for 5-HT_{2A} receptors and D_2 receptors, compared to other second-generation antipsychotics, including risperidone (12-fold) and aripiprazole (0.18-fold).[51]

Lumateperone has been investigated in three placebo-controlled trials of acutely exacerbated schizophrenia, two of which included risperidone for assay sensitivity as an active comparator, and all conducted in the USA only.[52] In a 4-week, phase-IIb clinical trial ($n = 335$; ITI-007-005), ITI-007 showed statistically significant efficacy vs. placebo in improving schizophrenia symptoms, measured with the PANSS total score and its subscale scores at a dose of 60 mg/day (but not at 120 mg/day), and at a similar effect size as risperidone.[52] Compared to risperidone 4 mg/day, ITI-007 was superior at reducing negative symptoms, as well as on key safety and tolerability measures including prolactin, body weight, and glucose and lipid levels.[52] In a first 4-week, phase-III trial ($n = 440$; ITI-007-301), lumateperone 60 mg/day separated from placebo regarding schizophrenia symptoms both in PANSS total and CGI-S.[50] Notably, although lumateperone 40 mg/day was not superior to placebo regarding PANSS total scores, the 40 mg/day group was significantly superior regarding the CGI-S and PANSS positive subscale score (although not formally tested as the primary outcome did reach statistical significance), like the 60 mg/day group (Table 2). In a second phase-III trial lasting 6 weeks ($n = 695$; ITI-007-302), however, lumateperone 60 mg/day as well as 20 mg/day did not separate from placebo regarding schizophrenia symptoms, while risperidone 4 mg/day did (Table 2).[50] Nevertheless, although risperidone separated from placebo, it also had the greatest dropout rate, with patients dropping out early being potentially the less responsive patient subgroup, and the placebo effect was much larger than in the other two trials, making the results less reliable than in the first two trials. In terms of adverse effects, lumateperone separated on few symptoms from placebo, including only somnolence, sedation,

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

TABLE 1. Selected novel and emerging non-pharmacological and pharmacological treatments for schizophrenia

Treatment	Company	Phase	Receptor/mechanism of action	Indication	Adverse effects
Target: *total symptoms (including positive and negative symptoms)*					
Cannabidiol (add-on)	N/A	N/A	Partial cannabinoid$_1$ receptor antagonist, calcium channel modulator	Schizophrenia, other neuropsychiatric disorders	Dyslipidemia, nausea,[46] sedation[88]
F17464 (monotherapy)	Pierre Fabre Medicament	Phase-II	D_3 antagonist, 5-HT$_{1A}$ partial agonist	Schizophrenia	Insomnia, agitation, and increased triglycerides[48]
Lumateperone (ITI-007) (monotherapy)	Intracellular therapies (ITI)	Phase-III, under FDA review	5-HT$_{2A}$ antagonist, 5-HT transport inhibitor, presynaptic D_2 partial agonist and postsynaptic D_2 antagonist, D1-regulated NMDA and AMPA agonist	Schizophrenia, bipolar depression, agitation in patients with dementia, neuropsychiatric/neurodegenerative diseases	Somnolence, dry mouth, headache[131]
MK-8189 (monotherapy)	Merck Sharp & Dohme Corp.	Phase-II	PDE10A inhibitor	Schizophrenia	N/Av
RO5263397 (monotherapy)	Roche	Phase-III	TAAR1 agonist	Schizophrenia	N/Av
SEP-363856 (monotherapy)	Sunovion, Sumitomo-Dainippon	Phase-III	TAAR1 agonist	Schizophrenia	Somnolence, nausea, diarrhea, dyspepsia[71]
Sodium Nitroprusside(monotherapy)	N/A	N/A	Nitric oxide donor	Schizophrenia	N/Av[62]
TAK-063 (monotherapy)	Takeda	Phase-II	PDE10A inhibitor	Schizophrenia	Akathisia, dystonia[57]
Target: *negative symptoms* LuAF-11167 (monotherapy)	Lundbeck	Phase-II	PDE10A inhibitor	Schizophrenia	N/Av
Pimavanserin (add-on)	Acadia	Phase-II	5-HT$_{2A}$ inverse agonist	Schizophrenia, major depressive disorder, Parkinson's psychosis, psychosis in Alzheimer's disease	N/Av[76]
Roluperidone (MIN-101) (monotherapy)	Minerva Neurosciences	Phase-III	5-HT$_{2A}$ antagonist, sigma2 antagonist, alpha1-adrenergic antagonist	Schizophrenia	Headache, anxiety, insomnia, schizophrenia symptoms, asthenia, nausea, and somnolence[78]
TAK-831 (monotherapy)	Takeda	Phase-II	D-amino acid oxidase (DAAO) inhibitor	Schizophrenia, cerebellar ataxia	N/Av[57]
Target: cognitive dysfunction					
BI-425809 (add-on)	Boehringer-Ingelheim	Phase-II	Glycine-transporter-1 (GLYT-1) inhibitor	Schizophrenia	N/A[86,87]

TABLE 1. (*Continued*)

Treatment	Company	Phase	Receptor/mechanism of action	Indication	Adverse effects
Cannabidiol (add-on)	N/A	N/A	Partial cannabinoid$_1$ receptor antagonist, calcium channel modulator	Schizophrenia, other neuropsychiatric disorders	sedation[88]
Target: *residual and treatment-resistant positive symptoms*					
LuAF-35700 (monotherapy)	Lundbeck	Phase-III	$D_1 > D_2$ antagonist 5-HT$_{2A}$ antagonist 5-HT$_6$ occupancy	Treatment-resistant schizophrenia	N/Av[91]
Pimavanserin (add-on)	Acadia	Phase-III	5-HT$_{2A}$ inverse agonist	Schizophrenia, major depressive disorder, Parkinson's psychosis, psychosis in Alzheimer's disease	Headache, somnolence, insomnia[93]
Sodium benzoate (monotherapy)	N/A	N/A	D-amino acid oxidase (DAAO) inhibitor	Treatment-resistant schizophrenia	N/Av[94,95]
Target: *reducing antipsychotic non-adherence*					
Aripiprazole Lauroxil NanoCrystal® Dispersion (Aripiprazole Lauroxil $_{NCD}$; Aristada Initio)(monotherapy)	Alkermes	FDA-approved	Partial D_2 agonist Partial 5-HT$_{1A}$ agonist 5-HT$_{2A}$ antagonist	Schizophrenia	Injection pain, headache, weight gain, insomnia, dyspepsia, and anxiety[100]
Paliperidone Palmitate 6-monthly formulation (monotherapy)	Janssen	Phase-III	5-HT$_{2A}$ antagonist D_2 antagonist	Schizophrenia	N/Av
Perseris™ Risperidone s.c. injection (RBP-7000) (monotherapy)	Indivior	FDA-approved	5-HT$_{2A}$ antagonist D_2 antagonist	Schizophrenia	Injection site pain, headache, sedation/somnolence, and weight gain[111]
Risperidone extended release s.c. injection (TV46000) (monotherapy)	Teva	Phase-III	5-HT$_{2A}$ antagonist D_2 antagonist	Schizophrenia	N/Av
Risperidone ISM® (Doriafi) (monotherapy)	Laboratorios Farmacéuticos Rovi,	Phase-III	5-HT$_{2A}$ antagonist D_2 antagonist	Schizophrenia	N/Av
Target: *amelioration of adverse effects*					
Samidorphan + Olanzapine (ALKS3831) (monotherapy)	Alkermes	Phase-III, under FDA review	μ-opioid antagonist + olanzapine	Olanzapine-induced weight gain + schizophrenia	Weight gain, somnolence, dry mouth, anxiety, headache, and schizophrenia[128]

AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, N/A, not applicable; N/Av, not available, NMDA, N-methyl-D-aspartate, PDE, phosphodiesterase, s.c. , subcutaneous, TAAR, trace amine-associated.

TABLE 2. Selected novel and emerging pharmacological treatments for schizophrenia targeting total (including positive and negative) symptoms

References	Total *n*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
					Scale(s)	Statistical outcome(s)	
Cannabidiol							
McGuire et al. (2018)[46]	88	6 weeks	Cannabidiol 1000 mg/day + preexisting antipsychotic ($n=43$)	Placebo + preexisting antipsychotic ($n=45$)	PANSS positive	Treatment difference = −1.4; 95% CI = −2.5, −0.2; $p=.019$	*Positive study*: Cannabidiol was significantly superior in improving PANSS positive symptoms (CGI-I and CGI-S scores, compared to placebo). No separation from placebo on the PANSS negative and general subscale, PANSS total, GAF, and BACS.
					PANSS negative	Treatment difference =.0; 95% CI = −1.3, 1.4; $p=.965$	
					PANSS general	Treatment difference = −1.3; 95% CI = –3.2, 0.7; $p=.196$	
					PANSS total	Treatment difference = -2.8; 95% CI = −6.5, 0.9; $p=.133$	
					CGI-I	Treatment difference = -0.5; 95% CI = −0.8, −0.1; $p=.018$	
					CGI-S	Treatment difference = −0.3; 95% CI = −0.5, 0.0; $p=.044$	
					GAF	Treatment difference = 3.0; 95% CI = −0.4, 6.4; $p=.08$	
					BACS	Treatment difference: 1.31; 95% CI = −.10, 2.72; $p=.068$	
F17464							
Bitter et al. (2019)[48]	134	6 weeks	F17464 40 mg/day ($n=67$)	Placebo ($n=67$)	PANSS total	Treatment difference (SE) = −6.2 (2.5), $p=.02$	*Positive study*: F17464 was significantly superior in reducing PANSS total, as well as PANSS positive and general subscale score, and Wallwork factors of the PANSS (cognitive functioning), compared to placebo. No differences in PANSS negative and CGI-S.
					PANSS positive	$p=.03$, non-parametric test	
					PANSS negative	No statistical significance	
					PANSS general	Treatment difference (SE) = −3.6 (1.3), $p<.01$	
					Wallwork factors PANSS (cognitive function)	Treatment difference (SE) = −0.85 (0.4), $p=.03$	
					CGI-S	No statistical significance	
Lumateperone (ITI-007)							
Lieberman et al. (2016)[52]	335	4 weeks	ITI-007 60 mg/ day ($n=84$)ITI-007 120 mg/day ($n=83$)	Placebo ($n=85$) Risperidone 4 mg/day ($n=82$)	PANSS total	ITI-007 60 mg/day vs. placebo: $p=.017$, effect size = .42	*Positive study*: ITI-007 60 mg was significantly superior to placebo in reducing PANSS total and PANSS positive subscale scores and CGI-S. 120 mg did not separate from placebo.
						ITI-007 120 mg/day vs. placebo: $p=.708$, effect size = .07	
					PANSS positive	Risperidone 4 mg/day vs. placebo: $p=.013$, effect size =.44	
						ITI-007 60 mg/day vs. placebo: $p=.002$, effect size = .50	
						ITI-007 120 mg/day vs. placebo: $p=.272$, effect size = .17	
						Risperidone 4 mg/day vs. placebo: $p=.002$, effect size =.51	

TABLE 2. (*Continued*)

References	Total *n*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
					Scale(s)	Statistical outcome(s)	
					PANSS negative	ITI-007 60 mg/day vs. placebo: $p = .230$, effect size = .19 ITI-007 120 mg/day vs. placebo: $p = .319$, effect size = .16 Risperidone 4 mg/day vs. placebo: $p = .914$, effect size =.02	
					PANSS general	ITI-007 60 mg/day vs. placebo: $p = .040$, effect size = .33 ITI-007 120 mg/day vs. placebo: $p = .217$, effect size = .17 Risperidone 4 mg/day vs. placebo: $p = .003$, effect size =.48	
Vanover et al. (2018)[50]-Study ITI-007-301	440	4 weeks	ITI-007 60 mg/day ($n = 150$) ITI-007 40 mg/day ($n = 150$)	Placebo ($n = 150$)	PANSS total	ITI-007 40 mg/day vs. placebo: treatment difference: −2.6; $p = .164$ ITI-007 60 mg/day vs. placebo: treatment difference: −4.2; $p = .022$	Positive study: ITI-007 60 mg was significantly superior to placebo regarding PANSS total, PANSS positive, and CGI-S Score
					CGI-S	ITI-007 40 mg/day vs. placebo: treatment difference: effect size =.30, $p = .025$ ITI-007 60 mg/day vs. placebo: treatment difference: effect size =.39, $p = .0003$	
Vanover et al. (2018)[50]-Study ITI-007-302	695	6 weeks	ITI-007 60 mg/day ($n = 174$) ITI-007 20 mg/day ($n = 174$)	Placebo ($n = 174$) Risperidone 4 mg/day ($n = 174$)	PANSS total	N/Av	*Negative study*: Neither dose of ITI-007 separated from placebo on the primary endpoint (PANSS total), but risperidone did; a high placebo response (>15 points on the total PANSS score) was observed in this study.
MK-8189							
https://clinicaltrials.gov/ct2/show/results/NCT03055338[58]	224	4 weeks	MK-8189 titrated from 4 mg/day to 12 mg/day over 7 days and then maintained for another 3 weeks ($n = 90$)	Placebo ($n = 89$) Risperidone titrated from 2 mg/day to 6 mg/day over 7 days and then maintained for another 3 weeks ($n = 45$)	PANSS total	MK-8189 vs. placebo $p = .074$ Risperidone vs. placebo $p = .033$ MK-8189 vs. risperidone $p = .440$	*Negative study*: MK-8189 did not separate from placebo on PANSS total, but risperidone did.

(*Continued*)

TABLE 2. (*Continued*)

References	Total *n*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
					Scale(s)	Statistical outcome(s)	
SEP-363856							
Poola et al. (2018)[71]	245	4 weeks	SEP-363856 flexible dosing: 50 mg/day or 75 mg/day ($n = 120$)	Placebo ($n = 125$)	PANSS total	$p = .0001$, effect size =.45	*Positive study*: SEP-363856 was significantly superior to placebo on PANSS total and all three subscale scores, CGI-A, BNSS, and MADRS.
					PANSS positive	$p = .019$, effect size =.32	
					PANSS negative	$p = .008$, effect size =.37	
					PANSS general	$p < .001$, effect size =.51	
					CGI-S	$p < .001$, effect size =.52	
					BNSS	$p < .001$, effect size =.48	
					MADRS	$p = .02$, effect size =.32	
Sodium nitroprusside							
Hallak et al. (2013)[60]	20	4 weeks	Sodium nitroprusside 0.5 μg/kg/min for 4 h ($n = 10$)	Placebo ($n = 10$)	BPRS-18	$p < .001$, $F_{1,18} = 12.91$	*Positive study*: sodium nitroprusside was significantly superior to placebo, within 4 h, on the BPRS
Wang et al. (2018)[61]	42	4 weeks	Sodium nitroprusside 0.5 μg/kg/min for 4 h ($n = 21$)	Placebo ($n = 21$)	PANSS	No statistical significance	*Negative study*: Sodium nitroprusside failed to separate from placebo on the primary endpoint (PANSS total).
					WAIS	No statistical significance	
Stone et al. (2016)[62]	20	4 weeks	Sodium nitroprusside 0.5 μg/kg/min for 4 h ($n = 10$)	Placebo ($n = 10$)	PANSS negative	$p = .75$, effect size =.095	*Negative study*: Sodium nitroprusside failed to separate from placebo on the primary endpoint (PANSS total).
					BPRS-18	$p = .81$, effect size =.11	
					SWM	$p = .2$, effect size =.30	
Brown et al. (2019)[63]	52	2 weeks	Sodium nitroprusside 0.5 μg/kg/min for 4 h ($n = 18$) Sodium nitroprusside 0.5 μg/kg/min for 4 h + placebo ($n = 16$)	Placebo + placebo ($n = 18$)	PANSS total	$z = -.59$; $p = .57$	*Negative study*: Sodium nitroprusside failed to separate from placebo on the primary endpoint (PANSS total).
					PANSS positive	$z = -.93$; $p = .35$	
					PANSS negative	$z = -.19$; $p = .85$	
TAK-063							
Macek et al. (2019)[57]	164	6 weeks	TAK-063 20 mg/day($n = 83$)	Placebo ($n = 81$)	PANSS total	Least-squares mean difference vs. placebo (standard error) = −5.46 (3.44); $p = .115$, effect size =.308	*Negative study*: TAK-063 failed to separate from placebo on the primary endpoint (PANSS total).

BACS, Brief Assessment of Cognition in Schizophrenia; BNSS, Brief Negative Symptom Scale; BPRS-18, 18-Item Brief Psychiatric Rating Scale; CBD, Cannabidiol; CGI-I, Clinical Global Impressions Scale – Improvement; CGI-S, Clinical Global Impressions Scale – Severity; CI, confidence interval; GAF, Global Assessment of Functioning; MADRS, Montgomery-Asberg Depression Rating Scale; OR, odds ratio; PANSS, Positive and Negative Syndrome Scale; SOC, standard of care; SWM, Spatial Working Memory; WAIS, Wechsler Adult Intelligence Scale.

and fatigue (Table 1). However, these adverse effects were generally only mild or moderate, and lumateperone was associated with low and placebo-like discontinuation rates.[50]

Finally, in phase 1 of a recently completed study ($n = 302$, ITI-007-303),[53] investigating the safety of ITI-007 in an open-label setting in patients with stable schizophrenia switching from standard-of-care (SOC) antipsychotics to lumateperone, 6 weeks of treatment with lumateperone led to significant improvements in both schizophrenia symptoms and key cardiometabolic parameters, such as LDL-cholesterol and triglycerides as well as prolactin levels. After only 2 weeks of switching back to SOC antipsychotics, the safety variables that had significantly improved trended back to pre-lumateperone baseline and were not significantly improved anymore.[54] Interestingly, in this study program, lumateperone was dosed in the evening, and the already-low adverse event rates seen in the acute studies in which AM dosing had been applied were further reduced.

In phase 2 of the same study ($n = 603$, ITI-007-303)[54] patients were enrolled for a planned treatment duration of up to 1 year. As the study is ongoing, data reflect an interim data cut that includes observed cases for those subjects who have had completed each visit (300 days, $n = 184$). After 300 days of treatment, lumateperone led to significant improvements in both schizophrenia symptoms (Table 2) and key cardiometabolic parameters, such as body weight and total cholesterol, LDL-cholesterol as well as prolactin levels.[54] These results imply that patients with stable symptoms on other antipsychotics may further improve when switched to lumateperone.[54]

Overall, lumateperone represents a novel approach, with a unique mechanism of action, which seems to be promising in enhancing efficacy with a favorable safety profile.

Phosphodiesterase 10A (PDE10A) inhibitors

Phosphodiesterase 10A (PDE10A) inhibitors are expected to modulate via cAMP- and cGMP-dependent mechanisms both the dopamine D_1-direct and D_2-indirect striatal pathways and regulate the phosphorylation status of a panel of glutamate receptor subunits in the striatum.[55] Therefore, studies of PDE10 inhibitors are expected to target both dopaminergic and glutamatergic dysfunction in schizophrenia.

Several PDE10A inhibitors are currently investigated, including TAK-063 and MK-8189 for total schizophrenia symptoms.

TAK-063[56] has shown mixed results. In a phase-II, 6-week, randomized, placebo-controlled study, subjects with an acute exacerbation of schizophrenia were randomized to TAK-063 20-mg/day ($n = 83$) or placebo ($n = 81$). Although in this sample, TAK-063 failed to separate from placebo on total PANSS at study endpoint, the effect size was small (0.308) (Table 2). Consistent with previous phase-I studies, TAK-063 was well tolerated, with higher rates of akathisia and dystonia vs. placebo.[57]

In addition, one recent negative study read out for MK-8189. In a placebo- and active-controlled, 4-week study of patients ($n = 224$) with an acute exacerbation of schizophrenia, MK-8189 ($n = 90$) was compared with placebo ($n = 89$) and with risperidone ($n = 45$). At study endpoint MK-8189 did not separate from placebo or risperidone on the PANSS total score. Conversely, risperidone significantly separated from placebo on the PANSS total score (Table 2). Furthermore, MK-8189 did not separate from placebo in other secondary outcomes (adverse events and study discontinuation).[58]

Sodium nitroprusside (nitric oxide donor)

Nitric oxide may be implicated in the pathophysiology of schizophrenia, as it is a gas that mediates the release of neurotransmitters, and seems to be involved in learning, memory, and neurodevelopment.[59] As a nitric oxide donor, sodium nitroprusside may thus improve symptoms of schizophrenia.

The original randomized, double-blind, placebo-controlled study of sodium nitroprusside, conducted in Brazil, examined the effectiveness and safety of a single intravenous administration of sodium nitroprusside (0.5 μg/kg/min for 4 hours) for the improvement of positive, negative, anxiety, and depressive symptoms in 20 patients with schizophrenia who were within the first 5 years of schizophrenia and who were taking antipsychotics.[60] After the adjunctive infusion of sodium nitroprusside, a rapid improvement of symptoms was observed within 4 hours, with significant superiority of sodium nitroprusside vs. placebo on the 18-item Brief Psychiatric Rating Scale total score and subscale scores, which persisted for 4 weeks after infusion (Table 2).[60]

However, three recent studies were unable to replicate these original study results. In one study, 42 adults with schizophrenia were randomized to two placebo or sodium nitroprusside infusions (0.5 μg/kg per min for 4 h) during a 1-week interval.[61] The authors failed to find any significant effect of sodium nitroprusside vs. placebo on psychotic symptoms or cognitive functions, although sodium nitroprusside seemed relatively well tolerated. In a second study, 20 patients with a diagnosis of schizophrenia or schizoaffective disorder were randomized to an infusion of sodium nitroprusside (0.5 μg/kg per min for 4 h) or placebo and re-assessed for symptoms and cognitive performance immediately after the infusion, and 4 weeks later (Table 2).[62] Similarly, the authors failed to observe any significant advantage of sodium nitroprusside vs.

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placebo for reducing psychotic symptoms or improving spatial working memory vs. placebo. Finally, in a third, 2-week acute treatment study,[63] patients ($n = 52$) were randomized to one of three treatment sequences (sodium nitroprusside + sodium nitroprusside; placebo + sodium nitroprusside; placebo + placebo), without separation of sodium nitroprusside from placebo in this study (Table 2). Consistent with the results of the two prior studies, no differences emerged in safety or tolerability measures.[63] However, as in the original, positive study patients were younger, in an earlier illness phase and more severely ill than in the negative trials, patient features that may enhance the efficacy of sodium nitroprusside may need to be considered in future trials.[64]

Trace amine-associated receptor 1 (TAAR-1) agonists

Trace amine-associated receptor 1 (TAAR1) is a G-protein-coupled receptor that belongs to the TAAR family. Discovered in 2001, TAARs have been found in several tissues, including the central nervous system and olfactory epithelium.[65,66] TAAR1 is activated by endogenous trace amines that are structurally related to monoaminergic neurotransmitters. TAAR1 agonists include amphetamine and methamphetamine, and TAAR1 seems to be most selective to dopamine, being less responsive to the endogenous tryptamine, norepinephrine, and serotonin, although glutamatergic transmission may also be modulated. In turn, these receptor features make TAAR1 agonists attractive targets for the treatment of schizophrenia.[65,66] Currently two TAAR1 agonists are being evaluated for schizophrenia. These include SEP-363856[67,68] and RO5263397[66,69] (for which wide variations in blood levels have been described based on genotype and ethnicity).[70]

While for RO5263397, phase-II study results have to our knowledge not been publicly reported, results of a phase-IIb study of SEP-363856 have been presented as a poster.[71] In a phase-II, randomized, double-blind, placebo-controlled 4-week, flexible dose study, SEP-363856 50 mg/day or 75 mg/day ($n = 120$, modal dose=75 mg/day) was superior to placebo ($n = 125$) for PANSS total scores, PANSS positive, PANSS negative, and PANSS general psychopathology subscale score, CGI-S, Brief Negative Symptom Scale (BNSS), and the Montgomery-Asberg Depression Rating Scale (MADRS). All-cause discontinuation (approximately 20%) and intolerability-related discontinuation (<10%) were similar to placebo (Table 2). Moreover, changes in body weight, blood glucose, lipids, and prolactin levels were comparable to placebo. Adverse effects ≥2% and at a maximum 1–2.5% greater than with placebo included somnolence, nausea, diarrhea, and dyspepsia.[71]

Negative symptoms

After a positive phase-II study,[72] the bitopertin program of a GLYT-1 inhibitor was stopped due to following negative studies,[73] leaving again negative symptoms a highly desirable and sorely needed indication for the treatment of schizophrenia. Several different agents are currently investigated for this indication.

LuAF-11167

Since PDE10A inhibitors have not reliably separated from placebo in acutely exacerbated schizophrenia,[57,58] LuAF-11167 is currently being developed for the treatment of negative symptoms.[74] Since, possibly, dopamine blockade due to accompanying antipsychotic treatment in the adjunctive trial programs for acutely exacerbated schizophrenia patients may interfere with the optimized effects of a PDE10A inhibitor for negative symptoms, an ongoing study evaluates LuAF-11167 in monotherapy vs. placebo. Results are not available for this phase-II study.[74]

Pimavanserin

Pimavanserin is a 5-HT_{2A} inverse agonist approved for the treatment of psychosis associated with Parkinson's disease. In one prior study of schizophrenia patients,[75] pimvanserin added to lower risperidone doses (2 mg/day) was equally efficacious as higher risperidone doses (6 mg/day); also pimavanserin augmentation seemed to reduce EPS. Currently, the ongoing ADVANCE study is a phase-II, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of adjunctive pimavanserin for the treatment of negative symptoms of schizophrenia.[76] This 26-week study compares three doses of pimavanserin (34 mg, 20 mg, or 10 mg) plus background antipsychotic vs. placebo plus background antipsychotic, with the primary outcome measure being the Negative Symptom Scale-16 (NSA-16). Results are expected later in 2019.

Roluperidone (MIN-101)

Roluperidone, also known as MIN-101, is a cyclic amido derivative, with affinities for sigma-2, 5-HT_{2A}, and alpha1-adrenergic receptors, developed to target negative symptoms and cognitive dysfunction in schizophrenia patients. MIN-101 has low affinity for dopaminergic, muscarinic, cholinergic, and histaminergic receptors. Recent studies have shown that MIN-101 is an antagonist at sigma-2 and 5-HT_{2A}.[77,78]

Reportedly, an unpublished phase-IIa study[79] was positive for negative symptoms in schizophrenia, which was replicated in a phase-IIb trial.[78] In that 12-week study, 234 patients who had been symptomatically stable for at least ≥3 months and who had predominant negative

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

symptoms (score ≥20 on the PANSS negative subscale, baseline mean = 26.8) were randomized to roluperidone 32 mg/day or 64 mg/day or placebo. At 12 weeks, MIN-101 32 mg/day and 64 mg/day were statistically significantly superior in the PANSS negative factor score (pentagonal structure model). In addition, positive results were also reported for PANSS negative symptom, total, and activation factor scores, CGI-S, and the BNSS (Table 3).[78] In addition, roluperidone was safe, without clinically significant changes in vital signs, routine laboratory values, body weight, metabolic parameters, or neuromotor scale scores. Adverse events included headache, anxiety, insomnia, schizophrenia symptoms, asthenia, nausea, and somnolence.[78]

Results of secondary analyses from this trial also suggested that roluperidone may also have an enhancing effect on cognitive functioning.[77] The BACS token motor, verbal fluency, and composite *z* scores improved significantly vs. placebo in the 32 mg roluperidone group, but not the 64 mg/day group, although the efficacy for negative symptoms was greater for the higher dose, and although negative correlations were seen for improvements in certain cognitive symptom domains and negative symptom reduction even in the 64 mg/day group (Table 3). Thus, it is important to note that dose-related effects of roluperidone diverged between negative and cognitive symptom improvement. Moreover, results do not yet indicate whether similar results would be observed for patients with a different range of schizophrenia symptoms.[77] Nevertheless, roluperidone represents an innovative mechanism of action, which seems to be promising in improving the treatment of negative symptoms, as well as cognitive dysfunction while having a favorable safety profile. The ongoing phase-III trial program will have to confirm these initial results.[80]

TAK-831

D-serine is an endogenous ligand for the glycine modulatory binding site on the NR1 subunit of NMDA receptors in the brain, whose agonist functioning is thought to improve negative symptoms of schizophrenia.[81] Since D-serine is degraded by the flavoenzyme DAAO, DAAO inhibitors may improve NMDA functioning and negative symptoms in schizophrenia.

TAK 831 is an oral, highly selective and potent DAAO inhibitor that is undergoing phase-II testing for the treatment of negative symptoms in schizophrenia.[82] In this 12-week, placebo-controlled trial, three different doses (50 mg/day, 125 mg/day, 500 mg/day) are tested using the PANSS negative symptoms factor score as the primary outcome.

Cognitive impairment

Since the negative results for encenicline, an alpha-7 nicotinic acetylcholine receptor agonist for cognition, in schizophrenia,[83] activity in this area has slowed down considerably. Since glycine is involved in glutamatergic NMDA transmission, which seems to be relevant for both negative and cognitive symptoms in schizophrenia,[84] GLYT-1 agonists may also improve cognitive dysfunction.

BI-425809

BI 425809 is a GLYT-1 inhibitor that was well tolerated in a phase-1 study in healthy male volunteers, displaying an adverse event profile suggestive of GLYT1-inhibiting effects.[85] BI 425809 is currently undergoing phase 2 testing for cognitive dysfunction in schizophrenia.[86] In this 12-week, placebo-controlled study, four doses of once daily oral BI 425809 are evaluated for their effect on the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (MCCB) total score, with everyday functional capacity, measured by Schizophrenia Cognition Rating Scale (SCoRS), being the key secondary outcome.[86] Another 12-week, phase-II, placebo-controlled proof of concept study with the same outcomes is being planned that aims to explore the effect of oral once daily BI 425809 on cognition administration in patients with schizophrenia on stable antipsychotic treatment and adjunctive computerized cognitive training.[87]

Cannabidiol

Cannabidiol has also been investigated for the treatment of cognitive dysfunction in schizophrenia. In a 6-week, randomized, placebo-controlled, fixed-dose study targeting cognition, oral cannabidiol (600 mg/day) added on to background antipsychotics was not superior to placebo in 36 stable chronic schizophrenia patients on either the MATRICS CCB or the PANSS total score (Table 3).[88] Similarly, in another 6-week study of 88 patients with schizophrenia focusing on total PANSS that separated on positive symptoms and CGI-I and CGI-S, there was no significant benefit of adjunctive cannabidiol (1000 mg/day) for the secondary outcome of cognition measured with the Brief Assessment of Cognition in Schizophrenia.[46]

Residual and treatment-resistant positive symptoms

Residual and refractory symptoms of schizophrenia remain a major unmet need in schizophrenia. Only clozapine is indicated for this indication, and few agents are being studied in this area.

LuAF-35700

LuAF-35700 is a D_1-preferring D_1 and D_2 antagonistic investigational antipsychotic agent that is also an antagonist at serotonin 5-HT_{2A} and 5-HT_6 receptors with high

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

TABLE 3. Selected novel and emerging pharmacological treatments for schizophrenia targeting negative and cognitive symptoms

References	Total *n*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
Target: negative symptoms							
LuAF-11167							
https://clinicaltrials.gov/ct2/show/NCT02202213[74]	47	N/Av	LuAF-11167 0.25 mg/day (*n* = N/Av) LuAF-11167 0.5 mg/day (*n* = N/Av) LuAF-11167 1 mg/day (*n* = N/Av) Part A: monotherapy Part B. adjunctive therapy to risperidone	Placebo (*n* = N/Av)	N/Av	N/Av	
Pimavanserin							
https://clinicaltrials.gov/ct2/show/study/NCT02970305[76]	380	26 weeks	Pimavanserin 34 mg/day + background antipsychotic (*n* = N/Av) Pimavanserin + background antipsychotic 20 mg/day (*n* = N/Av) Pimavanserin + background antipsychotic 10 mg/day (*n* = N/Av)	Placebo (*n* = N/Av)	N/Av	N/Av	
Roluperidone (MIN-101)							
Davidson et al. (2017)[78]	234	12 weeks	Roluperidone 32 mg/day (*n* = 76) Roluperidone 64 mg/day (*n* = 79)	Placebo (*n* = 79)	PANSS negative (pentagonal structure: N1-N4; G5-G8; G13-14)	Roluperidone 32 vs. placebo: $p < .024$, effect size = .45 Roluperidone 64 vs. placebo: $p < .004$, effect size = .57	*Positive study*: Roluperidone was significantly superior to placebo on the PANSS negative factor score (pentagonal structure model). In addition, positive results were reported for secondary outcomes (PANSS negative, total and activation factor score, CGI-S, and BNSS). No difference in PANSS positive or depression scores.
Keefe et al. (2018)[77]	234	12 weeks	Roluperidone 32 mg/day (*n* = 76) Roluperidone 64 mg/day (*n* = 79)	Placebo (*n* = 79)	BACS Subscale: Tower of London	Roluperidone 32 mg *z*-score = −1.1, $p = .57$ Roluperidone 64 mg *z*-score = −1.4, $p = .57$	*Positive secondary analyses* of the primary study: results suggest a possible benefit of roluperidone on cognitive functioning in patients with stable positive and concurrent clinically significant negative symptoms.

TABLE 3. (*Continued*)

References	Total *n*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
					Token Motor	Roluperidone 32 mg *z*-score = −1.1, *p* = .04 Roluperidone 64 mg *z*-score = −1. *p* = .08	
					Symbol coding	Roluperidone 32 mg *z*-score = −2.6, *p* = .77 Roluperidone 64 mg *z*-score = −2.7, *p* = .08	
					Verbal fluency	Roluperidone 32 mg *z*-score = −1.3, *p* = .01 Roluperidone 64 mg *z*-score = −1.2, *p* = .06	
					Verbal memory	Roluperidone 32 mg *z*-score = −1.4, *p* = .09 Roluperidone 64 mg *z*-score = −1.3, *p* = .29	
					Digit sequency	Roluperidone 32 mg *z*-score = −1.3, *p* = .06 Roluperidone 64 mg *z*-score = −2.1, *p* = .82	
					BACS composite	Roluperidone 32 mg *z*-score = −2.8, *p* = .05 Roluperidone 64 mg *z*-score = −2.9, *p* = .72	

(*Continued*)

TABLE 3. (*Continued*)

References	Total *n*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
TAK-831							
https://clinicaltrials.gov/ct2/show/NCT03382639[82]	234	12 weeks	TAK-831 50 mg/day (*n* = N/Av) TAK-831 125 mg/day (*n* = N/Av) TAK-831 500 mg/day (*n* = N/Av)	Placebo (*n* = N/Av)	PANSS negative	N/Av	N/Av
Target: cognitive dysfunction							
BI-425809							
https://clinicaltrials.gov/ct2/show/NCT02832037[86]	504	12 weeks	BI-425809 4 dosing options (no further details) (*n* = N/Av)	Placebo (*n* = N/Av)	MATRICS SCoRS	N/Av	N/Av
https://clinicaltrials.gov/ct2/show/NCT03859973[87]	200	12 weeks	BI-425808 3 dosing options (no further details) + Adjunctive Computerized Cognitive Training (*n* = N/Av)	Placebo + Adjunctive Computerized Cognitive Training (*n* = N/Av)	MATRICS SCoRS PANSS	N/Av	N/Av
Cannabidiol							
Boggs et al. (2018)[88]	36	6 weeks	Cannabidiol 600 mg/day + preexisting antipsychotic (*n* = 18)	Placebo + preexisting antipsychotic (*n* = 18)	MATRICS composite Score	$F(1,32) = 1.48$, $p = .23$	*Negative study*: Cannabidiol was not significantly superior to placebo in enhancing cognitive functioning or PANSS total score.
					PANSS total	$F(3,101) = 1.66$, $p = .18$	
McGuire et al. (2018)[46]	88	6 week	Cannabidiol 1000 mg/day + preexisting antipsychotic (*n* = 43)	Placebo + preexisting antipsychotic (*n* = 45)	BACS	Treatment difference: 1.31; 95% CI = −.10, 2.72; $p = .068$	*Negative study*: Cannabidiol was not significantly superior to placebo on the BACS.

BACS, Brief Assessment of Cognition in Schizophrenia; CI, confidence interval; MATRICS, Measurement and Treatment Research to Improve Cognition in Schizophrenia; PANSS, Positive and Negative Syndrome Scale; SCoRS, Schizophrenia Cognition Rating Scale.

affinity. Due to its relatively lower dopamine D_2 occupancy, it is expected to have less antidopaminergic-related adverse effects, including EPS, prolactin elevation, dysphoria or anhedonia, and depressed mood, than most currently available antipsychotics. The FDA granted fast-track designation for LuAF-35700 in November 2015. Currently, this novel antipsychotic is in phase-III of its clinical development, evaluating two doses (10 mg/day and 20 mg/day) in the Daybreak[89] and one dose (10 mg/day) in the ANEW[90] study programs.

In the DAYBREAK study, 1098 patients who had failed at least one prior well-documented antipsychotic treatment trial without satisfactory clinical improvement were enrolled and underwent a single-blinded, prospective, 6-week treatment period with either risperidone (4–6 mg/day) or olanzapine (15–20 mg/day) to confirm antipsychotic treatment resistance. Those failing to adequately respond to prospective treatment with risperidone or olanzapine were randomized to either stay on this treatment or switch to LuAF-35700 for another 10 weeks. In a press release from on October 25, 2018, Lundbeck announced that in the DAYBREAK study LuAF-35700 was not superior, but as effective as olanzapine or risperidone for treatment-resistant patients (Table 4). The drug was well tolerated and safe at both doses.[91]

Due to these results, the ANEW was terminated that had a similar design, except for evaluating a single dose of 10 mg/day of LuAF-35700 vs. placebo and for stratifying randomization for treatment-resistant schizophrenia developing either within the first 5 years or after 10 years of the illness. Final results in a relatively small number of randomized patients are currently awaited.

Pimavanserin

Since a first augmentation study of risperidone with pimavanserin had shown that enhancing 5-HT_{2A} receptor blockade by adding pimavanserin to a sub-effective risperidone dose provided faster onset of action, and at endpoint, equal efficacy and better safety, compared to standard dose risperidone, while reducing EPS,[75] a program for schizophrenia patients with suboptimal positive symptom response was initiated.

The recently completed ENHANCE-1 study is a phase-III, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of adjunctive pimavanserin for the treatment of schizophrenia with residual positive symptoms.[92] This international, 6-week study ($n = 396$, mean age = 37.2 years) compared pimavanserin (starting dose 20 mg, with adjustments possible to 34 mg or 10 mg) plus background antipsychotic vs placebo plus background antipsychotic (risperidone = 39.1%, olanzapine = 35.7%, aripiprazole = 21.3%).[93] Despite numerical advantages, pimavanserin augmentation missed statistical separation from placebo for the primary outcome, PANSSS total score ($p = 0.0940$). A positive trend was also observed on the key secondary endpoint, the CGI-S score ($p = 0.0543$). In a pre-specified subgroup analysis by region, significant separation from placebo was seen in the European sites (>80% of the sample) both for the PANSS total score (unadjusted $p = 0.0234$), and the CGI-S score (unadjusted $p = 0.0214$). Furthermore, in the entire sample, pimavanserin reduced negative symptoms significantly more than placebo, both regarding the PANSS negative symptoms scale sub-score (unadjusted $p = 0.0474$) and the PANSS Marder negative factor score (unadjusted $p = 0.0362$).

Approximately 88% of pimavanserin and 96% of placebo patients completed the study. Additionally, pimavanserin was well-tolerated with low and similar rates of adverse events in the adjunctive pimavanserin (40.4%) and adjunctive placebo (36.9%) groups. Adverse events reported in at least 5% of patients in the pimavanserin group included headache, somnolence, and insomnia. Discontinuations due to adverse effects were low, being 2.5% for pimavanserin vs. 0% for placebo.[93]

Sodium benzoate

Not only dopaminergic hyperactivity but also NMDA receptor hypofunction has been implicated in the pathophysiology of schizophrenia, possibly especially in patients resistant to treatment with dopamine antagonizing agents.[32] In addition to NMDA partial or full agonists, NMDA functioning can be increased by raising d-amino acid levels via blockade of their metabolism. Sodium benzoate, a DAAO inhibitor and common food preservative, has this mechanism. In two placebo-controlled trials, sodium benzoate had beneficial efficacy and acceptable tolerability.[94,95]

In the first randomized, double-blind, placebo-controlled trial,[95] 52 patients with chronic schizophrenia stabilized with antipsychotics for ≥3 months were randomized to 6 weeks of add-on treatment of 1 g/day of sodium benzoate vs. placebo. Sodium benzoate produced a 21% improvement in PANSS total score, and with large effect sizes (range = 1.16–1.69). Sodium benzoate was significantly superior to placebo in the PANSS total and subscales, Scales for the Assessment of Negative Symptoms-20 items, Global Assessment of Function, Quality of Life Scale and Clinical Global Impression. In addition, neurocognition subtests improved significantly, including the domains of processing speed and visual learning (Table 4). Sodium benzoate was well tolerated without significant adverse effects.

In the second randomized, double-blind, placebo-controlled trial,[94] 60 inpatients with schizophrenia stabilized with clozapine were randomized to 6 weeks of add-

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

Table 4: Selected novel and emerging pharmacological treatments for schizophrenia targeting residual and treatment-resistant total symptoms

References	Total *N*	Trial duration	Active Group(s)	Comparison(s) Groups	Results		Comments
LuAF-35700							
https://clinicaltrials.gov/ct2/show/results/NCT02717195[89]	1098	16-weeks	LuAF-35700 10mg/day (*n* = N/Av) LuAF-35700 20mg/day (*n* = N/Av)	Risperidone 4-6mg/day (*n* = N/Av) Olanzapine 15-20mg/day (*n* = N/Av)	PANSS total	N/Av	**Negative study:** LuAF-35700 was not superior to, but as effective as risperidone and olanzapine.
https://clinicaltrials.gov/ct2/show/results/NCT03230864[90]	120	14-weeks	LuAF-35700 10mg/day (*n* = N/Av)	Risperidone 4-6mg/day (*n* = N/Av) Olanzapine 15-20mg/day (*n* = N/Av)	PANSS total	N/Av	N/Av
Pimavanserin							
https://clinicaltrials.gov/ct2/show/results/NCT02970292[92] https://www.nasdaq.com/press-release/acadia-pharmaceuticals-announces-topline-results-from-phase-3-enhance-trial-of-pimavanserin-as-20190722-00780	396	6-weeks	Pimavanserin 10mg, 20mg or 34mg/day + background antipsychotic (*n* = 193)	Placebo + background antipsychotic (*n* = 196)	PANSS total CGI-S PANSS Negative Factor Score	*p* = .0940 (European subsample, >80%: unadjusted *p* = .0234) *p* = .0543 (European subsample, >80%: unadjusted *p* = .0214) unadjusted *p* = 0.474	Negative study for the primary outcome, but trend-level significance in the entire sample as well as positive study in the preplanned subgroup analysis of the European sites (approx. 80% of the sample), both for PANNS total and for CGI-S. Also, significant separation from placebo for negative symptoms in the entire sample.
Sodium Benzoate							
Lane et al., 2013[95]	52	6-weeks	Sodium Benzoate 1000md/day (*n* = 25)	Placebo (*n* = 27)	PANSS total PANSS positive PANSS negative PANSS general SANS GAF QOLS CGI-???? HDRS Speed of Processing Verbal learning and memory Neurocognitive composite	Treatment difference (SE) = –2.1 (0.3); *p* < .001, effect size = 1.53 Treatment difference (SE) = –0.6 (0.1); *p* < .001, effect size = 1.69 Treatment difference (SE) = –0.6 (0.1); *p* < .001, effect size = 1.19 Treatment difference (SE) = –0.9 (0.2); *p* < .001, effect size = 1.16 Treatment difference (SE) = –2.0 (0.2); *p* < .001, effect size = 1.56 Treatment difference (SE) = 1.1 (0.2); *p* < .001, effect size = 1.2 Treatment difference (SE) = 1.1 (0.2); *p* < .001, effect size = 1.5 Treatment difference (SE) = –0.1 (0.02); *p* < .001, effect size = 1.21 Treatment difference (SE) = -0.13 (0.1); *p* < .001, effect size = 0.74 *p* = .03, effect size = .65 *p* = .02, effect size = .07 *p* = .04, effect size = .67	**Positive study:** Sodium benzoate was significantly superior to placebo on the PANSS total score, PANSS subscales, SANS, GAF, QOLS, CGI, and cognitive functioning.

Table 4: (*Continued*)

References	Total *N*	Trial duration	Active Group(s)	Comparison(s) Groups	Results		Comments
Lin et al., 2018[94]	60	6-weeks	Sodium Benzoate 1g/day ($n = 20$) Sodium Benzoate 2g/day ($n = 20$)	Placebo (n=20)	PANSS total	Sodium Benzoate 1g/day vs. placebo Treatment difference (SE) = −3.35 (2.38); $p = .159$ Sodium Benzoate 2g/day vs. placebo Treatment difference (SE) = −3.80 (1.35); $p = .005$	**Positive study:** Sodium benzoate was significantly superior to placebo on the PANSS total score PANSS subscales and QOLS, but mainly for the sodium benzoate 2g group only.
					PANSS positive	Sodium Benzoate 1g/day vs. placebo Treatment difference (SE) = −.59 (.70), $p = .401$ Sodium Benzoate 2g/day vs. placebo Treatment difference (SE) = −1.43 (.52), $p = .006$	
					SANS	Sodium Benzoate 1g/day vs. placebo Treatment difference (SE) = −3.90 (1.73); $p = .024$ Sodium Benzoate 2g/day vs. placebo Treatment difference (SE) = −3.40 (1.54); $p = .027$	
					QOLS	Sodium Benzoate 1g/day vs. placebo Treatment difference (SE) = 2.70 (1.53); $p = .078$ Sodium Benzoate 2g/day vs. placebo Treatment difference (SE) = 2.50 (0.94); $p = .008$	
					GAF	Sodium Benzoate 1g/day vs. placebo Treatment difference (SE) = 1.50 (1.03); $p = .147$ Sodium Benzoate 2g/day vs. placebo Treatment difference (SE) = 1.55 (0.82); $p = .059$	

CGI = Clinical Global Impressions Scale; GAF = Global Assessment of Functioning; HDRS = Hamilton Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; N/Av = Not Available; QOLS = Quality of Life Scale; SANS = Scale for the Assessment of Negative Symptoms; SE = Standard Error

on treatment with 1 g/day sodium benzoate, 2 g/day sodium benzoate, or placebo. At 6 weeks, 2 g/day sodium benzoate was associated with significantly greater improvement than placebo in PANSS total score, PANSS positive subscore, and Quality of Life Scale. Furthermore, both the 1 mg/day and 2 mg/day sodium benzoate were associated with significantly greater improvement in the Scale for the Assessment of Negative Symptoms vs. placebo (Table 4). Sodium benzoate was well tolerated without relevant adverse effects. Furthermore, as an indication of the mechanism involved in the significant results, changes of the antioxidant catalase differed among the three groups and were correlated with the improvement of PANSS total score and PANSS positive score in the sodium benzoate group.

Agents targeting antipsychotic non-adherence

Non-adherence remains a serious issue with schizophrenia as with many other psychiatric and medical disorders.[36] Although several second-generation LAIs have been approved,[96] several have required oral cotreatment for several weeks until therapeutic antipsychotic levels have been reached. Moreover, historically, all LAIs were injected deep intramuscularly. Four innovative LAI formulations have been developed to avoid the need for loading or booster injections and/or oral cotreatment. Furthermore, two LAI formulations have received recent FDA approval, one being the first subcutaneously injected LAI.

Aripiprazole lauroxil NanoCrystal® Dispersion (AL_{NCD}; Aristada Initio)

Aripiprazole lauroxil (AL) (Aristada®) is an extended-release, intramuscular long-acting injectable (LAI) aripiprazole prodrug with high dosage and considerable dosing interval flexibility (441, 662, and 882 mg monthly, 882 mg every 6 weeks, or 1064 mg every 8 weeks). However, due to being a prodrug and slow release, therapeutic drug levels are achieved only gradually, so that oral aripiprazole supplementation for 21 consecutive days is required after the first intramuscular injection.

In order to achieve faster efficacy and significantly shorten or eliminate oral supplementation during the initiation phase, a 1-day intramuscular initiation regimen for aripiprazole lauroxil (Aristada Initio™) was approved by the FDA on July 2, 2018.[97] The single injection comprises the same prodrug used in aripiprazole lauroxil but with smaller particles, known as the nanocrystalline milled dispersion of aripiprazole lauroxil. The smaller nanoparticle size enables faster dissolution of aripiprazole lauroxil, resulting in faster release of aripiprazole into plasma.[98] Simultaneous administration of the 1-day initiation regimen with all approved aripiprazole lauroxil dosing regimens is predicted to achieve the correct blood levels within 4 days.[99]

A recent phase-III, double-blind, placebo-controlled study compared a 1-day initiation regimen with the 21-day oral coverage regimen. Patients ($n = 161$) randomized to the 1-day initiation regimen received a 675 mg injection of aripiprazole lauroxil NanoCrystal® Dispersion (AL_{NCD}), a single 30 mg oral aripiprazole tablet, and then an aripiprazole lauroxil injection (441 mg or 882 mg). Subjects randomized to the 21-day oral coverage regimen received 15 mg oral aripiprazole and an aripiprazole lauroxil injection (441 mg or 882 mg) on day 1, followed by 20 days of 15 mg oral aripiprazole. The 1-day regimen groups had comparable aripiprazole exposure to the corresponding 21-day groups (Table 5). The most common side effects were injection pain, headache, weight gain, insomnia, dyspepsia, and anxiety in both therapies.[100]

Therefore, aripiprazole $lauroxil_{NCD}$ Technology can offer an alternative aripiprazole lauroxil initiation regimen that ensures therapeutic aripiprazole levels during the first 21 days of treatment[100] and has a comparably side effect profile, faster efficacy, and might positively affect adherence due to a very minimized (1 day) oral supplementation.

Paliperidone 6-monthly formulation

After developing a once-monthly and a 3-monthly intramuscular injectable formulation of paliperidone,[101] Janssen is currently conducting phase III trial for a 6-monthly formulation of paliperidone palmitate. Results are still outstanding.

Perseris™ risperidone for subcutaneous injection (RBP-7000)

Risperidone has been available since 1993 to treat schizophrenia and bipolar disorders. Risperidone blocks serotonergic 5-HT_{2A} and dopaminergic D_2 receptors with greater affinity to the 5-HT_{2A} receptor. In addition, there is a much less affinity to other receptors such as alpha-1- and alpha-2-adrenergic receptors as well as H1-histaminergic receptors.[102] Up until 2018, risperidone LAI was only available in a microsphere formulation that had to be injected deep intramuscularly every 2 weeks and that required a 21-day oral risperidone supplementation phase at the initiation of risperidone microsphere treatment.[96]

RBP-7000 (Perseris™) is a recently (July 27, 2018) FDA-approved subcutaneous LAI formulation of risperidone[103] that requires no oral supplementation and is the first antipsychotic available as a subcutaneously (intraabdominally) administered LAI.[104] The once monthly injected depot formulation uses the ATRIGEL© administration system. After injection, the delivery system solidifies upon contact with bodily fluids, and the

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

TABLE 5. Selected novel and emerging pharmacological treatments for schizophrenia targeting the amelioration of antipsychotic non-adherence and body weight gain

References	Total *N*	Trial duration	Active group(s)	Comparison(s) groups	Results		Comments
Aripiprazole Lauroxil (AL) NanoCrystal® Dispersion (Aripirpazole Lauroxil $_{NCD}$; Aristada Initio)							
Walling et al. (2018)[100]	161	3 weeks	AL 441 mg/1-day ($n = 39$) AL 882 mg/1-day ($n = 41$)	AL 441 mg/21-days ($n = 40$) AL 882 mg/21-days ($n = 41$)	N/A	N/A	*Positive study*: The 1-day regime groups had comparable aripiprazole exposure to the corresponding 21-day group.
Risperidone ISM® (Doria®)							
https://clinicaltrials.gov/ct2/show/results/NCT03160521[114,115]	438	12 weeks	Risperidone ISM 75 mg/day (n = N/Av) Risperidone ISM 100 mg/day (n = N/Av)	Placebo (n = N/Av)	PANSS total	Risperidone ISM 75 mg vs. placebo p <.0001 Risperidone ISM 100 mg vs. placebo p <.0001	*Positive study*: Risperidone was significantly superior to placebo in PANSS total and CGI-S scores.
					CGI-S	Risperidone ISM 75 mg vs. placebo p <.0001 Risperidone ISM 100 mg vs. placebo p <.0001	
Perseris™ Risperidone (RBP-7000)							
Nasser et al. (2016)[109]	337	8 weeks	RBP-7000 90 mg/day ($n = 111$) RBP-7000 120 mg/day($n = 114$)	Placebo ($n = 112$)	PANSS total	RBP-7000 90 mg vs. placebo $p = .0004$ RBP-7000 120 mg vs. placebo p <.0001	*Positive study*: RBP-7000 was significantly superior to placebo on the PANSS total, positive, and general score, as well as on the CGI-S. RBP-7000 was not superior to placebo on the PANSS negative subscale score.
					PANSS negative	RBP-7000 90 mg vs. placebo, $p = .186$ RBP-7000 120 mg vs. placebo, $p = .039$	
					PANSS positive	RBP-7000 90 mg vs. placebo, $p = .0003$ RBP-7000 120 mg vs. placebo, p <.0001	
					PANSS general	RBP-7000 90 mg vs. placebo$p$ <.0001 RBP-7000 120 mg vs. placebo, p <.0001	
					CGI-S	RBP-7000 90 mg vs. placebo, $p = .0002$ RBP-7000 120 mg vs. placebo, p <.0001	

(*Continued*)

TABLE 5. (*Continued*)

References	Total *N*	Trial duration	Active group(s)	Comparison(s) groups		Results	Comments
Target: amelioration of adverse effects							
Samidorphan + olanzapine (ALKS3831)							
Martin et al. (2018)[125]	309	week	Samidorphan 5 mg/day + olanzapine ($n = 80$) Samidorphan 10 mg/day + olanzapine ($n = 86$) Samidorphan 20 mg/day + olanzapine ($n = 68$)	Placebo + olanzapine ($n = 75$)	Body weight	Samidorphan 5 mg vs. placebo 2.8% vs. 4.1% Samidorphan 10 mg vs. placebo 2.1% vs. 4.1% Samidorphan 20 mg vs. placebo 2.9% vs. 4.1%	*Positive study*: Samidorphan was superior to placebo in reducing olanzapine-induced weight gain.
ENLIGHTEN-2[127]	538	12 weeks	ALKS3831 ($n = 266$)	Olanzapine ($n = 272$)	Body weight	ALKS3831 vs. olanzapine 4.2% vs. 6.6%, $p = .003$	*Positive study*: ALKS3831 was significantly superior to placebo in reducing olanzapine-induced weight gain.
Potkin et al. (2019)[128]	403	4-weeks	ALKS3831 ($n = $ N/Av)	Olanzapine ($n = $ N/Av) Placebo ($n = $ N/Av)	PANSS total	ALKS3831 vs. placebo, $p < .001$ Olanzapine vs. placebo, $p = .004$	*Positive study*: ALKS3831 was significantly superior to placebo in reducing PANSS total and CGI-S scores, being almost identical to olanzapine.
					CGI-S	ALKS3831 vs. placebo, $p = .002$ Olanzapine vs. placebo, $p < .001$	

CGI-S, Clinical Global Impression Scale – severity; N/Av, not available; PANSS, Positive and Negative Syndrome Scale.

resulting biodegradable implant delivers the drug for a longer period depending on the dose strength and the injection volume.[105]

Pharmacokinetic population analyses reported optimized occupancy of the dopamine D_2 receptor for RBP-7000 after repeated doses of 90 mg/day and 120 mg/day and a potentially improved side effect profile compared to oral risperidone.[106,107] An 8-week, pivotal phase-III double-blind, placebo-controlled trial in acutely exacerbated patients with schizophrenia demonstrated the efficacy, safety, and tolerability of RBP-7000 (90 mg/day and 120 mg/day).[108–110] Common treatment-related side effects were injection site pain, headache, sedation/somnolence, and weight gain. Mean subject-reported injection site pain, as measured by the Visual Analog Scale scores (0 = no pain to 100 = unbearably painful), was similar in all treatment groups following both injections, with pain scores decreasing from a mean of 27 at 1 min after the first dose to a range of 3–7 at 30–60 min postdose. Moreover, *de novo* patients were recruited, and completers from the double-blind placebo-controlled study were transferred to a 1-year open-label study in which they received monthly injections of RBP-7000 (120 mg/day). In general, the safety achieved with 12 monthly injections of RBP-7000 was comparable to that of oral risperidone (Table 5). In addition, symptoms continued to improve in completers of the placebo-controlled trial who moved on to the long-term study.[111]

RBP-7000 has fast efficacy without the need for loading or booster injections or oral cotreatment and the subcutaneous injection route, which is hoped to be associated with less injection pain improved convenience, acceptance, and adherence. However, like risperidone microspheres, RBP-7000 needs to be refrigerated; furthermore, it needs to be reconstituted, and a large bore needle (18 G 5/8-inch length needle) is required for the subcutaneous intrabdominal injection.[104]

Risperidone extended release for subcutaneous injection (TV-46000)

Currently, risperidone extended release (TV-46000) is being studied in different dose regimens administered subcutaneously in patients with schizophrenia aged 13–65 years. One placebo-controlled study evaluates the efficacy, safety, and tolerability of two dose regimens of TV-46000 as relapse prevention treatment of patients who are clinically stabilized and eligible for risperidone treatment.[112] One TV-46000 dose-controlled study evaluates the long-term safety and tolerability of two dose regimens and will last up to 80 weeks (including a 4-week screening period, 12-week oral conversion/stabilization stage, 56-week double-blind maintenance stage, and 8-week follow-up period).[113] Results are expected in the middle or end of 2020.

Risperidone ISM® or Doria®

Recently, positive topline results of the PRISMA-3 trial, a multicenter, randomized, placebo-controlled phase-III study of once-monthly intramuscular Doria® or Risperidone ISM®, were announced.[114] ISM® is a technology for the release of drugs that is based on the in-situ formation of biodegradable matrices after the administration of a liquid carrier. Due to its special characteristics, therapeutic antipsychotic blood levels are achieved without requirement of initial oral antipsychotic coadministration or initial loading or booster injections. In the PRISMA-3 study[115] of 438 acutely exacerbated patients with schizophrenia, once-monthly injections of 75 mg and 100 mg of Risperidone ISM® each showed statistically significant improvement ($p < .0001$) vs. placebo injections in the total score of the PANSS as well as in the CGI-Severity scale at 12 weeks, the pre-specified primary and key secondary efficacy endpoints (Table 5).[114] A long-term, open label study that evaluates the safety, tolerability, and durability of the long-term effects of Risperidone ISM® is under way.

Amelioration of antipsychotic-related adverse effects

The recent FDA approval of the vesicular monoamine transporter-2 (VMAT-2) inhibitors valbenazine and deutetrabenazine for the effective amelioration of tardive dyskinesia associated with antidopaminergic medications in schizophrenia[116] was the first indication of a novel mechanism molecule specifically for the management of an adverse effect of antipsychotic medications. Currently, ALKS3831 is under study to ameliorate weight gain associated with olanzapine treatment.

Olanzapine-related weight gain

Most currently available antipsychotics are associated with considerable weight gain and cardiometabolic adverse effects.[22,23,117] These adverse effects are relevant for cardiovascular morbidity and mortality,[27] and are especially prominent early on in treatment and especially with clozapine and olanzapine.[118–120] Since both clozapine and olanzapine have been associated with efficacy advantages,[120,121] mitigating the weight gain and/or metabolic burden is of high clinical importance.

Fixed-dose combination of olanzapine and samidorphan (ALKS3831)

Samidorphan is an opioid antagonist, which originally has been investigated for the treatment of addiction and which is now examined for its mitigating or preventing effect of olanzapine-induced weight gain. Samidorphan (ALKS33) binds with high affinity to human μ-, *k*-, and ∂-opioid receptors and functionally acts as an μ-opioid receptor antagonist with low intrinsic activity at *k*- and

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

∂-opioid receptors.[122] By blocking opioid receptors involved in the brain reward pathway augmentation is decreased and cravings are reduced.[123] Results of a phase-I trial in healthy volunteers indicated that combining olanzapine with samidorphan (ALKS3831) did not affect the pharmacokinetic profile of either drug.[124] Similarly, in a phase-I proof of concept study in healthy volunteers, samidorphan in combination with olanzapine was associated significantly with less weight gain than olanzapine alone.[123] In recent studies, the combination drug ALKS3831 has been investigated, comprising a flexible dose of olanzapine and a fixed dose (10 mg/day) of samidorphan.

Results of a 12-week, phase-II trial (ENLIGHTEN-1) suggested mitigating effects of ALKS3831 on olanzapine-induced weight gain in schizophrenia patients across all dose-ranges of olanzapine, with equivalent efficacy to olanzapine and with a similar safety profile, except for significantly less weight gain.[125] This study had a 1-week open-label olanzapine lead-in period, which was followed by 12 weeks of double-blind treatment with olanzapine plus placebo ($n = 75$) or olanzapine plus 5 mg ($n = 80$), 10 mg ($n = 86$), or 20 mg ($n = 68$) of samidorphan. Treatment with ALKS3831 was associated with statistically significant lower weight gain (37% lower weight gain vs. olanzapine plus placebo) (Table 5). Adverse events reported at a frequency ≥5% in any of the ALSK3831 groups and occurring at least two times more frequently than with olanzapine plus placebo included somnolence, sedation, dizziness, and constipation. Since all patients received a 1-week olanzapine monotherapy run-in treatment and since olanzapine alters metabolic glucose and lipid parameters within a week, this study was not designed to assess metabolic effects of ALKS 3831.

These positive results have recently been replicated in a 6-month study (ENLIGHTEN-2) where ALKS-3831 was associated with statistically significant advantages over olanzapine plus placebo for both primary endpoints, percentage change in body weight at 6 months and proportion of patients gaining ≥10%, as well as for the key secondary endpoint, the proportion of patients gaining ≥7%.[126] At 6 months, weight increased with ALKS3831 (n=266) by 4.21% vs. 6.59% with olanzapine (n=272), translating into a 57% lower mean percent weight change (p=0.003). Similarly, weight gain ≥10% ALKS3831 occurred in 17.8% with ALKS 3831 vs. 29.8% for olanzapine ($p = .003$, number-needed-to-treat (NNT)=9). Finally, weight gain ≥7% ALKS3831 occurred in 27.5% with ALKS 3831 vs. 42.7% with olanzapine (Table 5). For weight gain ≥2%, ≥5%, and ≥15% at six months, similar results were observed, each favoring ALKS3831. In the ENLIGHTEN-2 study, there was no significant difference between ALKS3831 and olanzapine at the end of 6 months in any of the investigated glucose and lipid metabolism parameters. However, somewhat surprisingly, the mean increases in fasting glucose, insulin, HbA1C and lipids were relatively small, which may have reduced the power to differentiate ALKS 3831 from Olanzapine. The most common adverse events with ALKS3831 were weight gain, somnolence, and dry mouth; the most common adverse events with olanzapine were weight gain, somnolence, and increased appetite.[127]

Finally, in a 4-week, phase-III, randomized, double-blind active (olanzapine monotherapy) and placebo-controlled trial in patients experiencing acute exacerbation of schizophrenia, ALKS3831 was investigated to demonstrate that addition of the centrally active samidorphan to olanzapine in ALKS3831 does not reduce olanzapine's efficacy. This study showed superior antipsychotic efficacy of ALKS3831 compared to placebo, with almost identical efficacy as olanzapine monotherapy (Table 5).[128] ALKS3831 was generally well tolerated, with a safety profile similar to olanzapine. Adverse events leading to study discontinuation included weight gain, somnolence, dry mouth, anxiety, headache, and schizophrenia. In this short, 4-week study, body weight gain was not dissimilar between olanzapine and ALKS3831. Nevertheless, the results must be seen within the study's limitations, including baseline difference between groups with regard to BMI, the acute nature of the study population, inpatient treatment, and a short duration of the trial, making it difficult to compare weight gain between the three groups, as ALKS3831 is known to exert its weight gain mitigating effect only after 3 weeks of treatment.[128]

Overall, ALKS 3831 has proven to be effective in the treatment of schizophrenia and has been associated with significantly less olanzapine-induced weight gain.[128] Questions still remain regarding the potential of ALKS3831 to also mitigate olanzapine's adverse effects on glucose and lipid parameters, and on oxidative stress and inflammation that are generally associated with significant body weight gain.

Summary and Conclusion

This targeted and selective review (i) differentiated the mechanisms of action of new and emerging antipsychotics and medications with novel mechanisms targeting total, positive, negative, and cognitive symptoms of schizophrenia, as well as residual and treatment-resistant positive symptoms, non-adherence, and olanzapine-related weight gain, and (ii) evaluated the latest clinical data on these agents inasmuch as these are already available. Successful phase-III and/or phase-II trial programs have included (i) new formulations of aripiprazole lauroxil LAI and risperidone LAI that have been able to avoid the need for oral cotreatment, as well as, in the case of the two risperidone LAI formulations, loading/booster

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

injections in the initial phases of LAI treatment,[100,111,114] leading to FDA approval of Aripiprazole Lauroxil NanoCrystal® Dispersion (AL_{NCD}; Aristada Initio) and once-monthly subcutaneously injected Perseris™ Risperidone (RBP-7000); (ii) the treatment of acutely exacerbated schizophrenia with lumateperone, a novel antipsychotic modulating dopamine, serotonin and, via D_1 agonism, glutamatergic transmission[50] that is currently being evaluated by the FDA for approval for acutely exacerbated schizophrenia, and (iii) the combination of samidorphan plus olanzapine in one pill for the reduction of body weight gain with ALKS3831 at 3 and 6 months,[123,125,126] while maintaining olanzapine's efficacy.[124,127,128]

The other selectively reviewed agents have had either suggestive or mixed or, even, negative findings, or are at different stages of phase-II or phase-III development for different symptom domains of schizophrenia. Suggestive and encouraging results exist for monotherapy with roluperidone (MIN-101) for negative symptoms,[78] and the TAAR1 agonist SEP-363856,[71] D_3 antagonist/$5HT_{1A}$ partial agonist F17464, cannabidiol, and sodium benzoate for total psychotic symptoms. Negative findings have been reported for total symptom reduction with PDE10A inhibitors (e.g., MK-8189 and TAK-063) and sodium nitroprusside given adjunctively with background antipsychotics in acutely/severely ill patients, for cannabidiol targeting cognitive dysfunction in schizophrenia, and for monotherapy with the D_1-preferring D_1/D_2-antagonist LuAF-35700 for treatment-resistant schizophrenia. The pimavanserin trial for residual positive symptoms was negative for the primary and key secondary outcome in the overall sample, but showed significant separation from placebo in the prespecified regional analysis of the European sites that had enrolled >80% of the sample, and showed significant separation from placebo for negative symptoms in the overall analysis set.[93] Relevant data are expected soon for pimavanserin augmentation of antipsychotics for predominant negative symptoms. Trials are under way, but in the early stages for the DAAO inhibitor TAK-831 given adjunctively with antipsychotics and the phosphodiesterase 10A inhibitor LuAF-11167 in monotherapy for negative symptoms, as well as the GLYT-1 inhibitor BI-425809 targeting cognitive dysfunction in schizophrenia.

Of note, the findings of lumateperone showing that the lower 40 mg dose was significantly superior to placebo for positive symptoms and CGI-S, but not for total symptoms,[50] suggest that in future studies of novel agents that have minimal adverse effects, the broad-spectrum endpoint of total PANSS may be better exchanged for the more specific PANSS positive subscale when targeting the reduction of psychotic symptoms.

Interestingly, since dopamine blockade of background antipsychotic treatment may possibly interfere with the efficacy of novel, non-dopamine receptor targeting agents that focus on the improvement of negative symptoms, two trial programs attempt the testing of monotherapy of a non-dopaminergic mechanism molecular entity. These include the phase-II - PDE-10 inhibitor LuAF-11167 trial program[74] and the $5HT2_A$/sigma 2 antagonist roluperidone (MIN-1010).[78] While data from the ongoing phase-II PDE10A inhibitor LuAF-11167 trial program are not available, roluperidone has already shown in one phase-II trial superiority vs. placebo for negative symptoms.[78] Although this superiority did not seem to have been accompanied by too many psychotic exacerbations (surprisingly both in the roluperidone and in the placebo arm), despite withdrawal of the antipsychotic for the 3-month study period (plus an up to 4-week washout period), concern remains as to the safety of both roluperidone and LuAF-11167 that may not be sufficiently antipsychotic in and of themselves to protect patients from a psychotic relapse. It will be important to observe longer-term data with each of these agents and to identify characteristics of patients with relevant levels of negative symptoms who could possibly be sufficiently stable to be switched safely to a non-dopamine targeting novel agent. These studies will need to prove that, in fact, such non-dopamine modulating agents can improve negative symptoms while maintaining positive symptom stability, despite the removal of the prior dopamine modulating antipsychotic agent that at one point was needed to reduce schizophrenia symptoms.

Even 66 years after the serendipitous discovery of chlorpromazine as the first "antipsychotic" agent, the most challenging issue in the pharmacological management of this complex and multifactorial disorder is the need for increased efficacy, reduced side effects, and exploring novel approaches to effectively treat negative symptoms, cognitive dysfunction, and residual/treatment-resistant positive symptoms, which currently remain the biggest gaps in the management of schizophrenia.[130]

Although emerging data exist, results from important trial programs are still outstanding and further high-quality trials are required to evaluate the efficacy and tolerability of novel pharmacological approaches to the management of different domains of schizophrenia. Unfortunately, to date, only limited progress has been made in the exploration of novel psychopharmacological treatment targets for schizophrenia that go beyond the D_2 hypothesis. Therefore, the need for novel treatment approaches, which target the entire range of complex symptoms in schizophrenia, remains urgent. Nevertheless, part of the limited success for the search of novel treatments for schizophrenia remains the limited understanding of the pathophysiology of schizophrenia.[1] Therefore, a better understanding of pathophysiological mechanism and biomarkers is indispensable to ensure improved drug development for schizophrenia.

https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press

Acknowledgements

We thank Jonathan M. Meyer, MD, clinical professor in the Department of Psychiatry at the University of California, San Diego School of Medicine in La Jolla, CA, for sharing a presentation given at NEI congress 2018 that contained some of the reviewed material.

Funding

No funding declared.

Disclosure

Ms. Krogmann, Peters, von Hardenberg, Dr. Bödeker, and Mr. Nöhles have nothing to disclose.

Dr. Correll has been a consultant and/or advisor to or has received honoraria from: Alkermes, Allergan, Angelini, Boehringer-Ingelheim, Gedeon Richter, Gerson Lehrman Group, Indivior, IntraCellular Therapies, Janssen/J&J, LB Pharma, Lundbeck, MedAvante-ProPhase, Medscape, Merck, Neurocrine, Noven, Otsuka, Pfizer, Recordati, Rovi, Servier, Sumitomo Dainippon, Sunovion, Supernus, Takeda, and Teva. He has provided expert testimony for Bristol-Myers Squibb, Janssen, and Otsuka. He served on a Data Safety Monitoring Board for Boehringer-Ingelheim, Lundbeck, Rovi, Supernus, and Teva. He received royalties from UpToDate and grant support from Janssen and Takeda. He is also a shareholder of LB Pharma.

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1. Phosphodiesterase 10A (PDE10) inhibitors currently being investigated, such as TAK-063 and MK-8189, are expected to target both _____ and _____ dysfunction in schizophrenia.
   A. Cholinergic, serotoninergic
   B. Dopaminergic, glutamatergic
   C. Dopaminergic, serotoninergic
   D. Histaminergic, glutamatergic

2. Which of the following investigational agent being tested as a monotherapy does not have a non-dopaminergic mechanism
   A. ALKS3831
   B. LuAF-11167
   C. MIN-1010

3. Lumateperone (ITI-007), an investigational agent for the treatment of schizophrenia, simultaneously modulates which of the following:
   A. Dopamine
   B. Glutamate
   C. Serotonin
   D. A and C
   E. B and C
   F. A, B, and C

4. RBP-7000 (Perseris), a recently FDA-approved long-acting injectable (LAI) formulation of risperidone, requires an oral risperidone supplementation after the first subcutaneous injection.
   A. True
   B. False

5. The investigational agent sodium benzoate is a ....
   A. d-amino acid oxidase (DAAO) inhibitor
   B. glycine transporter-1 (GlyT-1) inhibitor
   C. phosphodiesterase 10A (PDE10) inhibitor

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https://doi.org/10.1017/S109285291900124X Published online by Cambridge University Press