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FEATURE REVIEW

The pipeline and future of drug development in schizophrenia

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While the current antipsychotic medications have profoundly impacted the treatment of schizophrenia over the past 50 years, the newer atypical antipsychotics have not fulfilled initial expectations, and enormous challenges remain in long-term treatment of this debilitating disease. In particular, improved treatment of the negative symptoms and cognitive dysfunction in schizophrenia which greatly impact overall morbidity is needed. In this review we will briefly discuss the current pipeline of drugs for schizophrenia, outlining many of the strategies and targets currently under investigation for the development of new schizophrenia drugs. Many of these compounds have great potential as augmenting agents in the treatment of negative symptoms and cognition. In addition, we will highlight the importance of developing new paradigms for drug discovery in schizophrenia and call for an increased role of academic scientists in discovering and validating novel drug targets. Indeed, recent breakthroughs in genetic studies of schizophrenia are allowing for the development of hypothesis-driven approaches for discovering possible disease-modifying drugs for schizophrenia. Thus, this is an exciting and pivotal time for the development of truly novel approaches to drug development and treatment of complex disorders like schizophrenia.
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Introduction

Since the discovery of the antipsychotic effect of chlorpromazine more than 50 years ago,[1] the number of antipsychotic medications available for the treatment of schizophrenia has tremendously increased. With the development of the first-generation antipsychotics, or typical antipsychotics, it was for the first time possible to treat the 'positive' symptoms of schizophrenia, such as delusions and hallucinations, leading to the deinstitutionalization of the world's mentally ill. The typical antipsychotic drugs, however, are generally not thought to be effective at treating the 'negative' symptoms, such as anhedonia and lack of motivation, and cognitive dysfunction of schizophrenia and have a high burden of extrapyramidal side effects (EPS).[2]

The reintroduction of clozapine in the United States in 1989, issued in the current era of atypical or second-generation antipsychotics. Atypical antipsychotic drugs are differentiated from typical antipsychotic drugs by virtue of a relative lack of EPS and serum prolactin elevation as compared with typical antipsychotic drugs. Clozapine itself has become the 'gold standard' antipsychotic medication because of its absence of debilitating extrapyramidal side effects and its demonstrated clinical superiority in treatment-resistant schizophrenia[3] and suicidality.[4] Whether clozapine has any significant beneficial effect on negative symptoms and cognition is unclear.[2,5] Clozapine, however, is associated with its own set of serious side effects including weight gain, diabetes and an increased risk of seizures and agranulocytosis.[6]

The documented superiority of clozapine[3,7] over other antipsychotic drugs has led to an intense effort over the past 15–20 years to develop clozapine-like atypical antipsychotics that are safer and better tolerated than clozapine. As such, multiple atypical and pseudo-atypical antipsychotic drugs, including risperidone, olanzapine, quetiapine and ziprasidone have been developed. Expectations that these agents comprised a breakthrough in the treatment of schizophrenia, especially with regards to improvements in negative symptoms and cognition were initially high.[8] These expectations, however, have not been realized.[9,10] While there is evidence that most of the new medications offer, at best, modest advantages over the typical antipsychotic drugs with regard to improvement in negative symptoms, cognitive impairment and functional capacity, the improvements are not consistent among studies.[2,11,12] In addition, the

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atypical antipsychotics carry their own substantial side-effect burden, specifically weight gain and the metabolic syndrome.[13,14]

While the introduction of antipsychotic medications has had a profound effect on the treatment of schizophrenia over the past 50 years, and the atypical antipsychotic drugs have provided a larger and more diverse armamentarium of treatment options, the advances that have been made since the discovery of the antipsychotic properties of chlorpromazine have been small and incremental. Thus, enormous challenges remain in the long-term treatment of this debilitating disease and continuing with the current paradigms of drug discovery is unlikely to produce significant advances.[15,16] It is therefore important to continue to pursue diverse molecular targets for discovering new antipsychotic compounds and to devise novel paradigms for drug discovery in schizophrenia.

A fundamental barrier to the discovery and development of novel treatments for schizophrenia remains that our level of understanding of the biological processes involved in schizophrenia is not sufficient to predict the therapeutic value of novel drug targets.[16] Thus, unvalidated targets are frequently left unpursued by the pharmaceutical industry and, frequently, companies have focused on alterations of existing medications (that is, separating enantiomers or marketing active metabolites; for example 9-OH-risperidone or paliperidone),[17] finding additional compounds that hit known and validated targets ('me too' drugs; for example ORG-5222 or asenapine),[18] and on gaining approval on new indications for already marketed drugs[19] (for example clozapine for suicide in schizophrenia[4]). These methods, however, cannot continue indefinitely as the number of such possibilities is limited and thus it is critical to find new approaches to drug development. Interestingly, many of the atypicals will soon be going off patent, beginning with the launch of generic risperidone in 2007. Thus, there is significant interest and urgency within the pharmaceutical industry and among schizophrenia basic scientists and clinicians in developing safer and more-effective treatments for schizophrenia.

In this review we will briefly discuss the current pipeline of drugs for schizophrenia (Table 1) and will outline many of the strategies and targets currently under investigation for the development of new schizophrenia drugs. In addition, we will highlight the importance of developing new paradigms for drug discovery in schizophrenia and call for an increased role of academic scientists in discovering and validating novel drug targets.[15,16]

Symptom domains in schizophrenia

It has been proposed that new therapeutics in schizophrenia should target narrower ranges of symptoms rather than to try to develop the perfect 'monotherapy' for a complex disorder.[20] This proposal is grounded in the complexity of schizophrenia which is characterized by severe and variable symptoms in a number of symptom domains, including positive symptoms such as hallucinations, delusions, and disorganized thought, negative symptoms such as a lack of motivation and interest, and a blunted affective range, and symptoms of cognitive impairments in attention, working memory, and a variety of executive functions. All of the currently approved drugs for the treatment of schizophrenia, however, were developed and are most efficacious at treating the positive symptoms of the disease while the negative symptoms and cognitive impairments actually contribute disproportionately more to the long-term disability in patients with schizophrenia.[21]

It is clear that patients who exhibit significant negative symptoms have particularly poor functional capacity and quality of life[22,23] and while there was optimism that the atypicals comprised a breakthrough in the treatment of negative symptoms,[8] this prospect has not been realized to a clinically significant degree.[9,10] Despite the limitations of current medications and the morbidity associated with negative symptoms, no drug has received Food and Drug Administration (FDA) approval for an indication of negative symptoms. As such, the National Institutes of Mental Health (NIMH) has recently released a consensus statement on the negative symptoms of schizophrenia[24] highlighting that negative symptoms represent a distinct and clinically important entity that should be a focus of future drug development efforts.

In addition to negative symptoms, schizophrenia is also characterized by significant cognitive impairments. For example, patients with schizophrenia have been documented to have problems with attention, working memory and learning and a variety of executive-level functions including abstract thinking and problem solving.[25,26] Indeed, a meta-analysis of cognitive deficits suggested that indices of cognitive deficits are much better predictors of functional outcome than indices from any other symptom domain.[27] However, these cognitive deficits have been relatively unimproved by currently approved antipsychotic drugs, though some evidence exists for the superiority of atypicals such as olanzapine and risperidone over typicals.[5,28,29] Owing to the remaining need for improved treatment of the cognitive impairments in schizophrenia the National Institutes of Mental Health (NIMH) has begun a joint academic and industry initiative termed MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) to facilitate the development of better treatments targeted at cognition.[30]

Thus, while psychopharmacologic research in schizophrenia aims for the development of new antipsychotic drugs with a more rapid onset of action, lower risk of side effects and improved efficacy in the domains of negative and cognitive symptoms it is unlikely that a single drug will have the desired effect across all of these domains. Optimal treatment of

Table 1 Approximate[a] pipeline of drugs in development for schizophrenia

Primary target name[b]	*Generic name*	*Originator*	*World status*
Launched[c]			
Multiple	Clozapine	Novartis	Launched
D2, 5-HT2A	Olanzapine	Eli Lilly	Launched
D2, 5-HT2A	Quetiapine	AstraZeneca	Launched
D2, 5-HT2A	Risperidone	Johnson & Johnson	Launched
D2, 5-HT2A	Paliperidone	Johnson & Johnson	Launched
D2, 5-HT2A	Sertindole	Lundbeck	Launched
D2, 5-HT2A	Ziprasidone	Pfizer	Launched
D2 partial, 5-HT1A agonist	Aripiprazole	Otsuka	Launched
D2, D3	Nemonapride	Astellas	Launched
Phase III			
Multiple	Asenapine	Organon/Pfizer	Discontinued by Pfizer[d]
D2, 5-HT2A	Iloperidone	Titan Pharmaceuticals	Phase III
D2, 5-HT2A	Blonanserin	Dainippon	Phase III
D2 partial, 5-HT1A agonist	Bifeprunox	Solvay	Phase III
Retinoid-X-receptor activator	Bexarotene	Non-industry source	Phase III
Phase II			
Multiple	ACP-104 (NDMC[e])	Acadia	Phase II
D2, 5-HT2A	Ocaperidone	Johnson & Johnson	Phase II
D2, 5-HT2A	Lurasidone hydrochloride	Sumitomo	Phase II
D2, 5-HT1A agonist	SLV-313	Solvay	Phase II
D2, 5-HT2A, 5-HT1A	Abaperidone hydrochloride	Ferrer	NDR
D2, D3 partial	Aplindore fumarate	Wyeth	Phase II
D2, 5HT transport inhibitor	SLV-310	Solvay	Phase II
D2 partial	(−)-3PPP, Maryland	Non-industrial source	NDR
D2 agonist, 5-HT1A	SDZ-MAR-327	Novartis	NDR
D1, D2, 5-HT2A	ZD-3638	AstraZeneca	NDR
5-HT2A/2C	SR46349B	Sanofi-Aventis	Phase II
α_2AR, AChR agonist	Dexefaroxan	Pierre Fabre	Phase II
AMPA 1	Org-24448	Cortex Pharmaceuticals	Phase II
NMDA allosteric modulator	D-serine	Prestwick Pharmaceuticals	Phase II
mGluR2	Unknown	Eli Lilly	Phase II
NK3	Osanetant	Sanofi-Aventis	Phase II
Sigma1	E-5842	Esteve	NDR[f]
Nischarin	Idazoxan	Potomac Pharma	Phase II
Unspecified	TGOF02N	Fabre-Kramer	Phase II
Unspecified	Uridine, Polifarma	Polifarma	Phase II
Phase I			
D2, 5-HT1A	SSR-181507	Sanofi-Aventis	NDR
D3	AVE-5997EF	Sanofi-Aventis	NDR
D3, 5-HT1A	BTS-79018	Abbott	NDR
D4	NGD 94-1	Schering-Plough	NDR
α_7 nAChR	MEM-3454	Memory Pharmaceuticals	Phase I
Glycine transporter	ALX-5407	NPS Pharmaceuticals	Phase I
CB1	CBD cannabis derivative	GW Pharmaceuticals	Phase I
Sigma1	SSR-125047	Sanofi-Aventis	NDR
Unspecified	YKP-1358	SK Corporation	Phase I
Unspecified	CRD-101	Curidium	Phase I
Preclinical			
D2	Y-931	Mitsubishi Pharma	NDR
D2	Dopamine antags	Neurogen Corporation	NDR
D2, D1, 5-HT2A	GMC-283	Merck KGaA	NDR
D2, D3	PD-157695	Pfizer	NDR
D2, 5-HT, D4	HMR-2934	Sanofi-Aventis	NDR
D2, 5-HT1A, D3	PD-158771	Pfizer	NDR
D2, 5-HT2A, mAChR	Org-23366	Akzo Nobel	NDR
D1	D1 agonist D2 antagonist	Eli Lilly	Preclinical
D1	BSF-78438	Abbott	NDR
D1	LE-300	Sanofi-Aventis	NDR
D3	BP4.879a	Bioprojet	NDR
D3	SB-277011	GlaxoSmithKline	NDR
D3	PD-157533	Pfizer	NDR

Table 1 Continued

Primary target name[b]	*Generic name*	*Originator*	*World status*
D3	U-99194A	Pfizer	NDR
D3	PNU-177864	Pfizer	NDR
D4	PD-165167	Pfizer	NDR
D4	PD-172760	Pfizer	NDR
D4	U-99363E	Pfizer	NDR
D4	SPI-376	Spectrum Pharmaceuticals	NDR
DA antagonist, GABA agonist	BL-1020	BioLineRx	Preclinical
5-HT2C agonist	5-HT2C agonists	Pfizer	Preclinical
5-HT2C agonist	5-HT2C agonists	Wyeth	Preclinical
5-HT4	5-HT4/D2 antagonists	Johnson & Johnson	NDR
α_7 nAChR	RMG-40083	Remergent	Preclinical
α_7 nAChR	TC-5280	Targacept	Preclinical
α_7 nAChR	PNU-282987	Pfizer	NDR
α_7 nAChR	TC-1698	Targacept	NDR
Glutamate antagonist	ADX-2 series	Addex	Preclinical
Glycine transporter	GlyT-1 inhibitors, Organon	Akzo Nobel	Preclinical
Glycine transporter	GlyT-1 inhibitors, Organon-2	Akzo Nobel	Preclinical
Glycine transporter	GlyT-1 inhibitors, Organon-3	Akzo Nobel	Preclinical
Glycine transporter	SSR-504734	Sanofi-Aventis	Preclinical
Glycine transporter	SSR-103800	Sanofi-Aventis	Preclinical
Glycine transporter	Org-24461	Servier	Preclinical
Glycine transporter	GlyT-1 inhibitors, Gliatech	Merck & Co	NDR
mGluR	mGluR agonists	Taisho	NDR
mGluR2	mGluR2 agonist	Merck & Co	Preclinical
Neuregulin 1	Schizophrenia therapy	deCODE genetics	NDR
Sigma1	Sigma antagonists	Esteve	NDR
Sigma1	MS-377	Schering AG	NDR
Sigma1	NE-100	Taisho	NDR
Peptidergic receptor	ABS-201	Argolyn Bioscience	Preclinical
Unspecified	BGC-20-761	BTG	Preclinical
Unspecified	GPCR allosteric modulators	Eli Lilly	Preclinical
Unspecified	Calcineurin modulators	Galenea	Preclinical
Unspecified	R-1678	Hoffmann-La Roche	Preclinical
Unspecified	Schizophrenia therapy	Integragen	Preclinical
Unspecified	Neuroleptics	Intra-Cellular Therapies	Preclinical
Unspecified	Schizophrenia therapy	Sequenom	Preclinical
Unspecified	CDD-0304	Cognitive Pharmaceuticals	NDR
Unspecified	Neuroleptics	CuraGen	NDR
Unspecified	Neuroleptic	Orion Pharma	NDR
Unspecified	Clozapine-DHA, Protarga	Sankyo	NDR
Unspecified	P-1704	Sanofi-Aventis	NDR
Discontinued[g]			
D2	SDZ-HDC-912	Novartis	Discontinued
D2	(S)-amisulpride	Sanofi-Aventis	Discontinued
D2	Remoxipride	AstraZeneca	Discontinued
D2, 5-HT2A, 5-HT1A agonist	1192U90	GlaxoSmithKline	Discontinued
D3	RGH-1756	Gedeon Richter	Discontinued
D4	Belaperidone	Abbott	Discontinued
D4	Sonepiprazole	Pfizer	Discontinued
5-HT2A	Fananserin	Sanofi-Aventis	Discontinued
Sigma1	E-6276	Esteve	Discontinued
Sigma1	Rimcazole	GlaxoSmithKline	Discontinued
Sigma1	SR-31742A	Sanofi-Aventis	Discontinued

[a]This is an approximation of the pipeline of drugs being developed for schizophrenia, adapted from BL Roth and PJ Conn: IOM White Paper, 2006. Attempts were made to make this table as accurate as possible, though due to the scarcity of published material, the authors can accept no responsibility for the currency and accuracy of this table. Subsections of the table are in no particular order.

[b]Compounds are assumed to be antagonists at each listed target unless otherwise specified.

[c]Only includes the atypical antipsychotics.

[d]Organon may be continuing development (http://www.medicalnewstoday.com/medicalnews.php?newsid=57683).

[e]NDMC, *N*-desmethylclozapine.

[f]NDR, no development reported, compounds are listed as to their last known Phase of development.

[g]Recently discontinued compounds.

schizophrenia in the near future will likely rely on polypharmacy with individualized treatment aimed at the multidimensional nature of this disorder.

Current antipsychotics and drugs in phase III clinical trials

There are a number of theories regarding the mechanism of action of antipsychotic drugs,[16,31,32] though the precise mechanism remains incompletely understood. Briefly, it is important that all of the currently approved antipsychotic drugs have at least some affinity for the dopamine D_2 receptor and for the typicals there is a strong correlation between the therapeutic doses and their binding affinity for D_2 receptors.[33,34] In addition, positron emission tomography (PET) studies have demonstrated that antipsychotic effects are associated with a striatal D_2 receptor occupancy of 65–70%[35,36] with occupancy levels greater than 80% associated with increased risk of EPS.[36] The basis of the 'atypicality' of newer medications, likewise is incompletely understood, though a primary theory is the serotonin–dopamine antagonism theory[37] which posits that a higher ratio of serotonin 5-HT_{2A} receptor affinity to dopamine D_2 receptor affinity explains the enhanced efficacy and reduced EPS burden seen with the atypicals. This hypothesis is consistent with the atypical features of risperidone, olanzapine, quetiapine, ziprasidone and the recently approved paliperidone (9-OH-risperidone). A third class of antipsychotics are the dopamine partial agonists, with aripiprazole being the only one currently approved for clinical use.[32] It is thought that the relative lack of EPS seen with clinical use of aripiprazole is due to its functional selectivity at D_2 receptors protecting against excessive blockade of the D_2 system.[32,38,39] Thus, while the mechanism of action of currently available antipsychotics is not fully known, D_2 receptor occupancy (either by antagonism or functionally selective agonism) is important for the treatment of the positive symptoms of schizophrenia with some modulation of this D_2 blockade, likely increased dopamine transmission in the cortex and hippocampus, being important for both why atypical antipsychotics and aripiprazole have a reduced EPS burden and somewhat higher efficacy at treating negative symptoms and cognitive dysfunction.[40]

The drugs in the pipeline for the treatment of schizophrenia that are currently in Phase III clinical trials appear to have the same mechanism of action of already available agents. Asenapine (formerly known as ORG-5222; now discontinued from clinical development) and iloperidone are antagonists at D_2 and 5-HT_{2A} and many other receptors (Table 2) and bifeprunox is a D_2 partial agonist. A new drug

Table 2 Approximate K_i[a] values (in nM) for selected current and pipeline antipsychotics

Receptor	*Haloperidol*	*Clozapine*	*N-DMC*[b]	*Risperidone*	*Paliperidone (9-OH-risperidone)*	*Iloperidone*	*Asenapine (Org-5222)*
D_1	122	266	14	244	41	129	2.9
D_2	2.1	141	101	2.4	1.6	11	1.4
D_3	5.4	347	153	8	3.5	11	1.8
D_4	3.9	23	64	5.8	54	14	1.8
D_5	124	255	284	290	29	319	23
5-HT_{1A}	2067	134	14	423	617	93	32
5-HT_{2A}	83	9.3	11	0.34	1.1	1.9	0.28
5-HT_{2C}	4475	9.4	12[c]	12	48[d]	147	0.24[d]
5-HT_{5A}	2247	3857	351	206	278	NA	4
5-HT_6	5133	13	12	2057	2414	63	1.4
5-HT_7	626	37	60	5.6	2.7	112	0.72
α_{1A}	12	1.6	105	5	2.5	NA	4.4
α_{2A}	1932	90	138	151	3.9	162	8.5
M_1	>10 000	14	68	>10 000	>10 000	4898	24
M_2	>10 000	104	415	>10 000	>10 000	3311	79
M_3	>10 000	32	96	>10 000	>10 000	>10 000	39
M_4	>10 000	18	170	>10 000	>10 000	8318	>10 000
M_5	657	28	35	>10 000	>10 000	>1000	9.5
H_1	1698	1.3	3.4	20	19	12[d]	0.16
H_2	1003	153	375	120	121	NA	23

Abbreviations: 5-HT, serotonin; D, dopamine; M, muscarinic acetylcholine; H, histamine; alpha, α-adrenergic.
[a]Averaged from cloned human receptor data from the Psychoactive Drug Screening Program database (http://pdsp.med.unc.edu/pdsp.php), and references therein.
[b]*N*-desmethylclozapine.
[c]Cloned human receptor data not available, data from cloned rat receptor.
[d]Cloned human receptor data not available, data from human brain tissue.

application has been submitted for bifeprunox for treatment of schizophrenia (http://www.google.com/search?sourceid=navclient&ie=UTF-8&rls=DMUS,DMUS:2006-43,DMUS:en&q=bifeprunox+fda). A novel medication bexarotene—a retinoid-X-receptor activator is currently listed as being in Phase III clinical trials as an add-on medication for schizophrenia (http://clinicaltrials.gov/ct/show/NCT00141947?order=6). As such, with the possible exception of bexarotene, all compounds currently in Phase III clinical trials represent 'me-too' drugs that are not significantly different from currently available medications, though there is some clinical benefit to having additional drugs available as individuals may have differential responses to medications and have varying tolerance to side effects. As these drugs will not represent significant advances in the treatment of schizophrenia, this review will focus primarily on compounds at earlier stages of development.

The current 'gold standard' antipsychotic, clozapine, interestingly has relatively weak affinity for the D_2 dopamine receptors but has moderate-to-high affinity and antagonist/inverse agonist activity for many other neurotransmitter receptors, including other dopamine receptors (D_1, D_3, D_4), various serotonin receptors (5-HT_{2A}, 5-HT_{2C}, 5-HT_6, 5-HT_7), muscarinic acetylcholine receptors (M_1, M_2, M_3, M_4, M_5), and adrenergic receptors (α_1, α_2).[31] Additionally, clozapine's active metabolite, *N*-desmethylclozapine, is a potent partial agonist at dopamine[41] and muscarinic[42,43] receptors. This extremely complex pharmacological profile is thought to underlie both clozapine's superior clinical efficacy and its spectrum of serious side effects.[3] As such, much effort in antipsychotic drug development over the past two decades has been to create clozapine-like drugs that bind to fewer targets and thus reduce the side-effect burden by targeting only the appropriate receptors. As will be reviewed below, attempts thus far to target clozapine's 'magic receptor', however, have largely been unsuccessful. Indeed, it appears that the paradigm of 'one-disease one-target' that became the dominant approach in the pharmaceutical industry with the advent of molecular biological techniques, while ideal from a scientific and practical perspective, may not be suitable for complex psychiatric diseases such as schizophrenia. In recent years, a number of authors have proposed that designing selectively non-selective drugs that interact with several molecular targets (coined 'magic shotguns')[31] will lead to more effective medications for a variety of complex disorders.[31,44,45]

We will briefly review the individual molecular targets that may have a role in these 'magic shotguns' or in a polypharmacy approach targeting the various clinical symptom domains of schizophrenia (Table 3). Where available, references to key review articles are provided. In addition, we will highlight how selective compounds have generally been ineffective as monotherapy for schizophrenia. Indeed, many of the drugs in Phase I, Phase II and preclinical development for the treatment of schizophrenia represent a shift from targeting D_2 and 5-HT_{2A} receptors to targeting other monoaminergic receptors and other neurotransmitter receptors, though results in small clinical trials have generally been less than encouraging.

Additional dopaminergic approaches

In addition to the key role of dopamine D_2 receptors in antipsychotic function, compounds selective for other dopamine receptors have been explored as potential treatments for schizophrenia.

Dopamine D_1 receptors

Significant evidence exists for the importance of dopamine D_1 receptors in the pathophysiology of schizophrenia, particularly having a role in cognitive dysfunction.[46] For example, chronic blockade of D_2 receptors results in a downregulation of D_1 receptors in the prefrontal cortex and consequently produces severe impairments in working memory in non-human primates.[47] This downregulation of D_1 receptors may explain why long-term treatment with typical antipsychotic drugs may contribute to the cognitive dysfunction in schizophrenia. In fact, direct blockade of D_1 receptors with selective antagonists, predicted to have antipsychotic effects in early preclinical models, showed no antipsychotic efficacy in clinical trials and may have exacerbated symptoms in some patients.[48,49] Thus, current efforts are focused on a possible role of D_1 receptor agonists in treating the cognitive dysfunction in schizophrenia. Indeed, short-term administration of a D_1 selective agonist, ABT-431, reversed the cognitive deficits in monkeys treated chronically with a D_2 receptor antagonist.[47] Other studies have also shown cognitive enhancement with a partial agonist of the D_1 receptor and selective, full D_1 receptor agonists in non-human primates.[50,51] Thus, novel compounds targeted at stimulating D_1 receptor signaling either directly or indirectly may be of immense value in treating the cognitive deficits in schizophrenia, though some potential pitfalls may need to be overcome. First, in addition to insufficient D_1 receptor activity, excessive D_1 activity such as that resulting from acute stress may also be deleterious to cognition.[52] In addition, chronic treatment with a D_1 receptor agonist may actually lead to downregulation of the D_1 receptor potentially worsening cognition in the long term. Thus, an optimized level of D_1 receptor activation may be required to realize full cognitive benefits,[52] which may be accomplished by partial agonists or an intermittent pattern of administration.[47,53]

Dopamine D_3 receptors

D_3 receptors are structurally similar to D_2 receptors and thus most antipsychotics have relatively high affinity for these receptors.[54] As such, significant effort has been placed on investigating the potential role of the D_3 receptor as a target for drug development in schizophrenia. Indeed, a post-mortem study of

Table 3 Possible pharmacologic targets in schizophrenia

Primary symptom domains	*Potentially druggable clinical targets*	*Possible pharmacologic targets*
Positive symptoms	Hallucinations Delusions Formal Thought Disorder	Dopamine D_2 antagonists Dopamine D_2 partial agonists Dopamine D_3 antagonists/agonists Serotonin 5-HT_{2C} agonists Muscarinic M_1 agonists Glutamate modulators Cannabinoid CB_1 antagonists Neurokinin NK_3 antagonists Neurotensin NT1 agonists PDE10A inhibitors Glycine transport inhibitors mGluR2 positive modulators
Negative symptoms	Blunted Affect Anhedonia Avolition Alogia Asociality	Dopamine D_1 agonists Dopamine D_3 antagonists/antagonists Serotonin 5-HT_{2A} antagonists Serotonin 5-HT_{1A} partial agonists NMDA modulators Glycine transport inhibitors Neurokinin NK_3 antagonists Neurosteroids
Cognitive deficits	Working Memory Attention/Vigilance Verbal Learning/Memory Visual Learning/Memory Reasoning/Problem Solving Information Processing Speed Social Cognition	Dopamine D_1 agonists Dopamine D_3 agonists COMT inhibitors Serotonin 5-HT_{2A} antagonists Serotonin 5-HT_{1A} partial agonists Serotonin 5-HT_4 partial agonists Serotonin 5-HT_6 antagonists Cholinesterase inhibitors Muscarinic M_1 agonists Muscarinic M_4 agonists Nicotinic α_7 agonists and modulators Nicotinic $\alpha_4\beta_2$ agonists NMDA positive modulators AMPA positive modulators Glycine transport inhibitors mGluR2/3 positive modulators $GABA_A$ positive modulators Neurokinin NK_3 antagonists COX2 inhibitors

drug-free patients with schizophrenia demonstrated elevated D_3 receptor levels in contrast to normal D_3 receptor levels in patients treated with antipsychotic medications.[55] In addition, a D_3 receptor partial agonist was able to block the increase in locomotor activity in mice induced by *N*-methyl-D-aspartate (NMDA) glutamate receptors antagonists, such as phencyclidine or ketamine, a frequently used preclinical model of psychosis.[56] As such, multiple selective dopamine D_3 agents are currently in clinical trials for the treatment of schizophrenia. For example, A-437203 is currently undergoing Phase II trials, although clinical data are not yet available[54] as is SB-773812 (Clinical Trials @.gov identifier NCT00259870). Development of another agent, PNU-177864, which is a partial agonist at D_3 receptors appears to have been stopped due to safety concerns.[57] Thus, the potential antipsychotic efficacy of selective D_3 receptor agonism and antagonism remains unknown at this time, though some data suggest the benefit of D_3 receptor partial agonists in the treatment of Parkinson's disease and drug addiction.[58] Additional preclinical studies have also suggested a role of D_3 receptor antagonists in improving negative symptoms[59] and working memory,[60] though clinical evidence is unavailable.

Dopamine D_4 receptors

When the dopamine D_4 receptor was initially cloned it was also found that clozapine had higher affinity for this receptor than for D_2 receptors creating significant speculation that the D_4 receptor may be clozapine's 'magic receptor'.[61] Further support of a role of D_4 receptors in schizophrenia came from postmortem

studies showing higher levels of D_4 receptors in the forebrain, though these results have not been entirely consistent among studies.[62] Even so, clinical trials of D_4 antagonists have not demonstrated any appreciable efficacy in the treatment of acute schizophrenia. For example, randomized, controlled trials of L-745870 and sonepiprazole found no differences in clinical responses compared with placebo-treated patients with schizophrenia.[63,64] In addition, a trial of finanserin, a potent antagonist at both D_4 and serotonin 5-HT_{2A} receptors, also found no evidence of antipsychotic efficacy versus placebo in patients with schizophrenia.[65] These clinical trial failures have suggested that selective D_4 receptor antagonism alone is not responsible for the antipsychotic efficacy of clozapine; however, it is possible that D_4 receptor blockade in collaboration with action at other neurotransmitter receptors may be clinically beneficial. Indeed, studies of the physiological roles for the D_4 receptor are finding that D_4 receptors may play an important role in impulsivity and working memory.[62] For example, recent findings demonstrated that D_4 receptors in hippocampal neurons can decrease NMDA receptor activity[66] and inhibit glutamatergic signaling in the frontal cortex.[67] In addition, D_4 antagonists were observed to reverse phencyclidine-induced cognitive impairment in monkeys,[68] together suggesting that D_4 receptor-selective agents may be valuable in the treatment of the cognitive deficits in schizophrenia.

Catechol-O-methyltransferase

Catechol-*O*-methyltransferase (COMT) is a postsynaptic enzyme that methylates and thereby deactivates synaptically released catecholamines, particularly dopamine.[69] Historically, monoamine oxidase was considered the primary enzyme for the initial deactivation of synaptic dopamine,[70] though mounting evidence suggests that COMT may be especially important for the breakdown of dopamine, particularly in the prefrontal cortex.[71] For example, COMT knockout mice show increased baseline levels of dopamine, but not other catecholamines such as norepinephrine, specifically in the frontal cortex.[72] In addition, the COMT knockout mice also showed enhanced memory performance,[72] suggesting a potential role of COMT inhibition in improving cognition. Indeed, a selective, reversible inhibitor of COMT, tolcapone, has been reported to improve working memory in rodents[73] and has been shown to improve cognitive dysfunction in patients with advanced Parkinson's disease,[74] though use is limited due to a risk of liver failure.[75] Other COMT inhibitors are currently being investigated for treatment of the cognitive dysfunction in schizophrenia.

Interestingly, a common single-nucleotide polymorphism (SNP) in the gene encoding COMT (val108/158met) results in the transcription of a variant of the COMT enzyme with approximately 40% less enzymatic activity in humans.[76] The reduced activity associated with the met variant presumably results in greater availability of dopamine in the prefrontal cortex and, thus, may be linked to some aspects of cognition in humans. Furthermore, accumulating evidence predicts that patients with schizophrenia who have the met allele may have improved cognitive response to clozapine.[77] The potential of pharmacologic inhibition of COMT in the long-term treatment of the cognitive dysfunction in schizophrenia, however, remains to be determined.

Serotonergic approaches

As serotonin receptors have been postulated to play a critical role in the action of the atypical antipsychotic drugs, we will briefly review a few of the serotonin receptors that continue to be targets in drug development for schizophrenia.

Serotonin 5-HT_{2A} receptors

Since the report that the atypicals, as a group, bind with higher affinity to 5-HT_{2A} receptors than to dopamine D_2 receptors,[78,79] selective 5-HT_{2A} receptor antagonists have been extensively explored as putative antipsychotic drugs. Unfortunately, however, the 5-HT_{2A} selective compound M-100907, was discontinued after two Phase III trials found M-100907, although more effective than placebo, failed to reduce symptoms to the same extent as haloperidol.[80] A Phase II study of the 5-$HT_{2A/2C}$ antagonist SR46349B (eplivanserin) showed efficacy similar to haloperidol and better than placebo.[81] Thus, it is now clear that while selective 5-HT_{2A} receptor antagonists may have antipsychotic properties, they are not superior to D_2 antagonists. It is likely that the predominant role of 5-HT_{2A} receptors in antipsychotic action is to modulate dopaminergic tone, particularly along the mesocortical pathway.[82,83] However, these studies also provide insight into why compounds with more complex pharmacologic profiles are likely superior to the 'magic bullet' approach in the treatment of complex diseases such as schizophrenia.[31,45]

Serotonin 5-HT_{1A} receptors

In addition to antagonism of the 5-HT_{2A} receptor, the agonist effects of clozapine on 5-HT_{1A} receptors have been postulated to contribute to its superior efficacy.[84] Research has also demonstrated that 5-HT_{1A} receptor agonism may actually result from 5-HT_{2A} receptor antagonism suggesting that 5-HT_{1A} agonism alone may produce an atypical antipsychotic drug when coupled with weak D_2 antagonism. Indeed, aripiprazole, a D_2 receptor partial agonist, may owe some of its atypical properties to its net effect of weak D_2 receptor antagonism, 5-HT_{2A} receptor antagonism and 5-HT_{1A} receptor agonism.[32,38,85] As such, 5-HT_{1A} receptor modulation is most likely to play a role in regulating dopaminergic tone similarly to 5-HT_{2A} receptors,[83] thus contributing to atypicality. Particularly, 5-HT_{1A} receptor agonism has been suggested to enhance dopamine levels in the prefrontal cortex,[86] which may be related to the modest efficacy of many

atypicals in treating the negative symptoms and cognitive dysfunction of schizophrenia. Thus far, attempts to develop medications combining 5-HT_{1A} receptor agonism with other receptor binding activities have not full replicated the superior clinical profile of clozapine, again highlighting the need for compounds with more complex pharmacologic profiles.[31]

Serotonin 5-HT_{2C} receptors

Serotonin 5-HT_{2C} receptors are found at high densities in the ventral tegmental area and the substantia nigra, among other sites, where they tonically inhibit dopamine release.[83] Indeed, 5-HT_{2C} receptor agonists have been shown to decrease dopamine levels in the mesolimbic and mesocortical, but not nigrostriatal pathways,[83,87] suggesting that 5-HT_{2C} agonists may have antipsychotic potential without causing EPS. Interestingly, a moderately selective 5-HT_{2C} agonist was recently shown to have antipsychotic-like effects on a battery of preclinical rodent models, including inhibition of conditioned avoidance response and amphetamine-induced hyperactivity, without inducing EPS.[88] Additionally, the weight gain and metabolic syndrome seen with administration of many of the atypical antipsychotics is thought to be due in part to antagonism of 5-HT_{2C}, as well as histamine H_1 receptors (Table 2).[89,90] Indeed, 5-HT_{2C} agonists have been shown to reduce food intake and body weight in humans.[91] However, a high degree of selectivity for 5-HT_{2C} receptors is absolutely critical, as stimulation of 5-HT_{2A} receptors may exacerbate psychosis and stimulation of 5-HT_{2B} receptors is thought to be the cause of the cardiac valvulopathy seen with fenfluramine and ergot-derived dopamine agonists.[92] An additional concern is that suppression of dopaminergic neurotransmission along the mesocortical pathway may be detrimental to cognition. Overall, 5-HT_{2C} receptor agonists show promise as antipsychotic and/or anorexic agents, though a high level of receptor selectivity will be crucial.

Serotonin 5-HT_4 receptors

Serotonin 5-HT_4 receptors are found at high densities in the hippocampus, frontal cortex and amygdala, suggesting a role of these receptors in cognitive functions.[93] Indeed, 5-HT_4 receptors have been shown to be markedly decreased in patients with Alzheimer's disease[94] and 5-HT_4 receptor agonists have shown promise in the improvement of cognitive function by enhancing cholinergic transmission in the hippocampus,[93] and are thus being developed for the treatment of Alzheimer's disease. Interestingly, a recent study showed that the activation of 5-HT_4 receptors in a neuronal culture inhibited the secretion of β-amyloid peptide and enhanced neuronal survival.[95] While 5-HT_4 receptor-selective agonists are mostly being studied for their role in the treatment of Alzheimer's disease, they may also be of benefit in the treatment of the cognitive dysfunction in schizophrenia.

Serotonin 5-HT_6 receptors

As several atypical antipsychotics, including clozapine and olanzapine exhibit high nanomolar affinity for 5-HT_6 receptors,[96] significant efforts have been made to understand its possible role in schizophrenia and other neuropsychiatric disorders.[97] Studies in rodents have suggested a role for 5-HT_6 receptors in the control of cholinergic neurotransmission,[98] and the selective 5-HT_6 receptor antagonist SB-271046 has been shown to improve memory retention in the water maze test of spatial learning and memory.[99] Thus, 5-HT_6 receptors may have an important future role in the treatment of cognitive deficits in neuropsychiatric illnesses such as Alzheimer's disease and schizophrenia.

Other monoaminergic approaches

α_2 adrenergic receptors

In the prefrontal cortex, α_2 adrenergic receptors appear to play an important role in cognitive functioning.[100] Indeed, treatment with the α_2 adrenergic receptor agonists clonidine and guanfacine has been shown to improve cognitive performance in small trials of patients with schizophrenia.[101,102] In addition, patients randomized to risperidone plus guanfacine showed significant improvement on tasks of working memory and attention compared with patients receiving typical antipsychotics plus guanfacine.[102] Thus, α_2 adrenergic receptor activity is likely to be important in the development of new drugs for schizophrenia that can improve cognition. Complicating the picture, however, is the fact that clozapine and other atypicals have potent antagonist properties at α_2 adrenergic receptors,[103] which may contribute to the atypicality of atypicals by preferentially enhancing dopaminergic transmission in the frontal cortex over subcortical dopaminergic pathways.[104] Indeed, combined treatment of a selective α_2 adrenergic receptor antagonist with a typical antipsychotic drug has been reported to produce a profile of antipsychotic activity similar to clozapine.[105] Thus, balancing α_2 adrenergic receptor activity to achieve both antipsychotic and pro-cognitive efficacy may be challenging.

Cholinergic approaches

Acetylcholine is known to play an important role not only in motor function, but also in various domains of cognition, particularly attention, learning, and memory.[106] Indeed, cholinergic dysfunction has been shown to be central to the pathophysiology of Alzheimer's disease and has also been postulated to contribute to the cognitive deficits of various neuropsychiatric disorders, including schizophrenia.[107] Cholinesterase inhibitors, such as donepezil and rivastigmine, are currently the main pharmacologic approach to the treatment of Alzheimer's disease and have been shown to slow the cognitive decline in this neurodegenerative disease.[108] As such, it has been proposed that cholinesterase inhibitors may also be useful in the treatment of the cognitive dysfunction in

schizophrenia.[109] Indeed, there have been multiple small randomized-controlled trials of cholinesterase inhibitors in patients with schizophrenia, though results have been disappointing.[110] In addition to cholinesterase inhibitors, significant efforts are underway to explore the modulation of various subtypes of both muscarinic and nicotinic acetylcholine receptors in the treatment of schizophrenia.

Muscarinic acetylcholine receptors

Of the five known muscarinic acetylcholine receptors (M_1–M_5), the M_1 receptor has been most closely linked to cognition and schizophrenia.[111] For example, decreased M_1 receptor binding has been reported in postmortem studies of the prefrontal cortex, hippocampus, and striatum from patients with schizophrenia,[111] suggesting that M_1 receptor agonism might by beneficial in treating the cognitive dysfunction in schizophrenia.[111] Indeed, the salutary actions of clozapine on cognition have been hypothesized to be due in part to action at M_1 receptors.[112] However, studies have variably reported clozapine to be both an agonist and an antagonist at M_1 and other muscarinic receptors.[111] Interestingly, the major active metabolic of clozapine, *N*-desmethylclozapine, has been reported to be a potent M_1 agonist that preferentially binds to M_1 receptors versus clozapine[113] although more comprehensive studies fail to demonstrate selectivity of *N*-desmethylclozapine for M_1 receptors.[42] In addition, *N*-desmethylclozapine has high affinities for 5-HT_{2A} and 5-HT_{2C} receptors, and is a partial $D_{2/3}$ receptor agonist,[41,43] suggesting that this metabolite of clozapine may also have antipsychotic and cognition-enhancing properties. Indeed, *N*-desmethylclozapine (ACP-104) and other M_1 receptor agonists are in clinical trials as potential treatments of the cognitive dysfunction in schizophrenia.

Xanomeline, a non-selective muscarinic agonist with potent actions at a variety of non-muscarinic GPCRs including 5-HT_{1A} and 5-HT_{2A} receptors[114] improved cognition and psychotic-like symptoms in Alzheimer's disease, but was discontinued due to poor tolerability.[115] The relatively non-selective actions of xanomeline at a number of GPCRs (http://pdsp.med.unc.edu/pdsp.php) should engender caution among schizophrenia researchers for embracing positive data from xanomeline studies as being specifically indicative of a role for M_1 receptors in schizophrenia. Indeed, as muscarinic receptor subtype selectivity has been difficult to attain, allosteric modulators of muscarinic receptors are being extensively developed and explored as potential therapeutic agents.[116] Overall, evidence suggests that selective M_1 receptor agonists or positive allosteric modulators could be useful in treating various symptom domains in schizophrenia, though the roles of the other muscarinic receptor subtypes are less clear.

Nicotinic acetylcholine receptors

It is well known that the smoking rates in individuals with schizophrenia are significantly higher than in the general population and some have suggested that these individuals may be 'self-medicating' with nicotine.[117] Indeed, nicotine administration has been shown to improve various measures of cognition and may ease some of the side effects of antipsychotic medications.[117] Thus, considerable research has explored the potential use of nicotinic agents for the treatment of schizophrenia, specifically selective agonists and antagonists at various subunits of the nicotinic acetylcholine receptor. For example, the α_7 nicotinic receptor subtype modulates auditory gating, a process known to be deficient in schizophrenia[118] and agonists at α_7 receptors such as 3-2,4-dimethoxybenzylidene anabaseine (DMXB-A) can normalize the auditory gating deficits in rodents.[119] Moreover, DMXB-A had a positive effect on a cognitive battery in a small proof-of-concept trial in humans,[120] and additional clinical trials of α_7 receptor agonists are underway. However, long-term use of α_7 agonists may induce the desensitization of nicotinic receptors, leading to a limited duration of efficacy.[118]

It has also been suggested that $\alpha_4\beta_2$ nicotinic receptors are involved in cognition, and agonists of $\alpha_4\beta_2$ receptors such as RJR 2403 can produce significant and long-lasting improvement of memory in rats.[121] Thus, nicotinic $\alpha_4\beta_2$ receptor agonists may be of therapeutic benefit for the treatment of the cognitive deficits in schizophrenia. In addition, allosteric modulators of nicotinic receptors are being explored as therapeutic agents. For example, galantamine is a positive allosteric modulator of nicotinic receptors in addition to being an acetylcholinesterase inhibitor.[118] The allosteric interaction of galantamine with nicotinic receptors can enhance the channel activity induced by a receptor agonist, either endogenous acetylcholine or theoretically a co-administered subtype-selective agonist.

Glutamatergic approaches

Since the 1950s, the *N*-methyl-D-aspartate (NMDA) glutamate receptor antagonists phencyclidine (PCP) and ketamine were known to produce a large range of schizophrenia-like symptoms including psychotic symptoms, negative symptoms, and cognitive dysfunction.[122] Thus, it has been hypothesized for decades that some deficiency in NMDA function might play a role in the pathophysiology of schizophrenia[122] and that drugs that can augment NMDA receptor activity may have therapeutic potential in schizophrenia. It is also important to note that a competing hypothesis suggests that a hyperactivity, not deficiency, of glutamatergic neurotransmission is involved in the psychopathology of schizophrenia, leading to seemingly contradictory pharmacologic approaches being explored.[122] Below, we briefly review various approaches being explored for modulating NMDA receptor neurotransmission and discuss approaches aimed at other glutamatergic mediators.

NMDA glutamate receptors

NMDA glutamate receptors are ligand-gated ion channels with a primary glutamate binding site and an allosteric glycine binding site.[122] Interestingly, the opening of the NMDA channel appears to require both glutamate and glycine binding and can be modulated by multiple substances, including Mg^{2+}, polyamines, and protons, at various allosteric sites.[122] Thus, there are multiple potential sites to target for enhancing NMDA receptor activity; however, direct agonists of the glutamate binding site of the NMDA receptor may not be clinically feasible due to the risk of excess excitation causing neurotoxicity and seizures. Therefore, the allosteric sites on the NMDA receptor complex, particularly the glycine binding site have been targeted for development of pharmacotherapy in schizophrenia.

Compounds that target the glycine site of the NMDA receptor complex have been studied in multiple small clinical trials and include the amino acids glycine, D-cycloserine, D-serine, and D-alanine.[123] In most of these studies, the test compound was administered along with either a typical or atypical antipsychotic, and there appears to be significant benefits in reducing negative symptoms and cognitive impairment in patients with schizophrenia.[123] Of the four agents, D-cycloserine has been the least efficacious, likely due to it being a partial agonist that acts as an antagonist at high doses. Interestingly, when used concurrently with clozapine, glycine[124] and D-serine[125] have been reported to be ineffective while D-cycloserine seemed to worsen symptoms,[126] possibly because clozapine may already enhance glycine and glutamate neurotransmission. Overall, agonists at the glycine allosteric site of the NMDA glutamate receptor hold promise in the treatment of the negative and cognitive symptoms of schizophrenia, possibly as an augmentation of currently existing antipsychotics.

Glycine transporter

Another strategy being explored to boost NMDA activity at the glycine allosteric site is to increase synaptic glycine by inhibiting the glycine transporter. The use of glycine transport inhibitors would have the advantage of avoiding the very high doses of glycine and D-serine that are needed. Indeed, preclinical data suggest that inhibition of glycine reuptake represents a feasible approach to enhance NMDA receptor activity and possibly be therapeutic in schizophrenia.[122] For example, selective, high-affinity inhibitors of the glycine transporter, including Org-24598,[127] *N*-[3-(4′-fluorophenyl)-3-(4′-phenylphenoxy)propyl]sarcosine[128] and SSR-504734 have been found to reverse PCP-induced hyperactivity and dopaminergic hyperreactivity in rodents.[127,128] Clinical trials to date, however, have only studied the low potency glycine transport inhibitor sarcosine (*N*-methyl glycine). In a clinical trial of sarcosine added to the stable antipsychotic regimen of patients with schizophrenia, there was a highly significant reduction in negative symptoms, along with smaller but significant reductions in positive and cognitive symptoms.[129] Interestingly, a subsequent study with patients on clozapine, found no improvement of symptoms with the addition of sarcosine, a result similar to studies with the NMDA glycine site agonists.[130] These results strongly suggest a role of glycine transport inhibitors in the treatment of schizophrenia, though results of trials with selective, high-potency inhibitors are anticipated.

Metabotropic glutamate receptors

Agents acting at metabotropic glutamate receptors (mGluR) are currently in preclinical development. Specifically, there are two main groups of mGluRs being studied in schizophrenia, Group I receptors include mGluR1 and mGluR5 and Group II receptors include mGluR2 and mGluR3.[131] Group I receptors increase presynaptic glutamate release while Group II receptors inhibit presynaptic glutamate release, however, agonists at each are being explored as potential treatments in schizophrenia demonstrating the duality of glutamatergic hypotheses in the pathophysiology of schizophrenia.[132,133] Indeed, both approaches have shown efficacy in preclinical models of schizophrenia,[122] however, development of selective agents at mGluR subtypes has been an issue. Allosteric modulators of mGluRs hold promise as therapeutic agents and several groups have recently developed highly selective allosteric potentiators of these receptors.[133,134] These selective allosteric modulators of mGluRs compounds may prove beneficial in the treatment of schizophrenia and preliminary positive results with an mGluR2 agonist in Phase II trials have been reported (http://newsroom.lilly.com/ReleaseDetail.cfm?ReleaseID=221389).

Other ionotropic glutamate receptors

Another glutamatergic approach to drug development in schizophrenia has been the development of compounds that stimulate AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and kainate glutamate receptors. AMPA receptors help to activate NMDA receptors while NMDA receptors are required for proper incorporation of AMPA receptors into the postsynaptic membrane, a process involved in synaptic plasticity.[135] Direct AMPA receptor agonists rapidly desensitize AMPA receptors limiting their therapeutic utility, therefore, allosteric potentiators of AMPA receptor function, a class of compounds termed ampakines, are being studied as potential treatments for schizophrenia.[135] Ampakines can enhance glutamatergic transmission, facilitating long-term potentiation, learning and memory in rodents and may avoid the desensitization frequently seen with direct AMPA agonists.[135] In a clinical trial of schizophrenic patients on clozapine, coadministration of the ampakine CX-516 yielded significant improvements in memory and attention;[136] however, a trial of CX-516 as monotherapy in schizophrenia showed no clear beneficial effects.[137] Importantly, higher potency ampakines are currently under

clinical development as both monotherapy for schizophrenia and adjunctive treatment for cognitive dysfunction, though results of trials are not yet available. An initial trial with Org24448 has been planned for cognition enhancement in schizophrenia (NCT00425815) though progress has not yet been reported for this compound.

In apparent contrast to the postulated utility of positive allosteric modulators of AMPA receptors as antipsychotics, preclinical data also paradoxically suggest that AMPA receptor antagonists may have antipsychotic efficacy. For example, the AMPA receptor antagonist, LY-326325 was shown to attenuate amphetamine-induced stereotypy[138] and suppress conditioned avoidance response in rats.[139] In addition, administration of the AMPA/kainate receptor antagonist, LY-293558, partially reversed the impairment of working memory induced by subanesthetic doses of ketamine in rats[140] suggesting a possible utility of AMPA antagonists in the treatment of the cognitive deficits in schizophrenia, though further research is indicated.[40] Overall, it remains unclear if modulation of AMPA receptors by agonists, antagonists or allosteric modulators such as ampakines has therapeutic value in the treatment of schizophrenia although this is a highly active area of research.

Other approaches

Cannabinoid receptors

A recent meta-analysis demonstrated a statistically significant correlation of prior cannabis use and the development of schizophrenia[141] adding to a large amount of evidence implicating the endogenous cannabinoid system in schizophrenia.[142] The endogenous cannabinoid system contains at least two cannabinoid receptors, the CB_1 and CB_2 receptors. A selective CB_1 receptor antagonist, SR-141716 showed activity in preclinical models of antipsychotic efficacy,[143,144] however, in a recent clinical trial, SR-141716 failed to demonstrate antipsychotic efficacy versus placebo.[81] Whether further clinical trials with cannabinoid receptor antagonists in schizophrenia are warranted is debatable.

Neurokinin receptors

Neurokinin 1 (NK_1) and neurokinin 3 (NK_3) receptors have been explored as potential targets for neuropsychiatric drug development.[145–147] NK_1 receptor antagonists may have efficacy in the treatment of depression, though a recent clinical trial of the NK_1-selective antagonist, aprepitant, for depression did not show efficacy versus paroxetine.[148] NK_3 receptor antagonists, however, have been investigated as potential antipsychotic agents as NK_3 receptors appear to regulate midbrain dopaminergic function.[149] As such, several NK_3 receptor antagonists, including osanetant and talnetant, have been in development as potential treatments for schizophrenia. In a recent clinical trial, osanetant showed statistically significant improvement in positive symptoms and global assessment versus placebo and was similar to haloperidol;[81] however, an informal report of a follow-up study indicated negative results and the compound was discontinued.[149] No clinical trial data have been published to date on talnetant and trials in schizophrenia appear to have been discontinued; thus whether NK_3 receptor antagonists may serve as novel antipsychotics either as monotherapy or as augmentation for the treatment of negative symptoms or cognition remains to be determined.

Neurotensin receptors

Neurotensin (NT) is a neuropeptide that, for decades, has been implicated in the pathophysiology of schizophrenia as it is closely associated with, and modulates dopaminergic and other neurotransmitter systems.[150] Indeed, significant preclinical data suggested a potential use of NT receptor agonists as novel therapeutic agents for the treatment of schizophrenia.[150] For example, administration of NT agonists, such as PD-149163, can reverse amphetamine-induced effects on hyperactivity and prepulse inhibition without inducing catalepsy.[151] Thus, NT receptor agonists likely have potential in the treatment of schizophrenia; however, there have been no published clinical trials of NT agonists. Interestingly, there is also seemingly contradictory evidence indicating that NT antagonists may have antipsychotic potential as there may be pathologically increased NT tone in schizophrenia.[150] A recent clinical trial, however, showed no antipsychotic efficacy of a potent and selective NT_1 receptor antagonist, SR-48692, compared with placebo.[81] Thus, NT antagonists may not be useful for the treatment of schizophrenia; however, clinical trials of NT agonists are needed to explore this novel treatment strategy for schizophrenia.

Additional approaches

A number of other approaches for the development of novel therapeutics for the treatment of schizophrenia have been described including, cyclooxygenase-2 (COX2) inhibitors, phosphodiesterase 10A (PDE10A) inhibitors, neurosteroids, and secretin. COX-2 inhibitors such as celecoxib have been hypothesized to improve cognitive performance by reducing inflammatory processes in the central nervous system.[152] Indeed, in one small trial, there was some significant benefit with the addition of celecoxib to risperidone.[153] PDE10A is a recently identified phosphodiesterase expressed at high levels in the brain and PDE10A inhibitors have been shown to antagonize the effects of both amphetamine and phencyclidine in rodents suggesting antipsychotic potential.[154] Secretin is a gastrointestinal peptide that has poorly defined roles in the brain, however, recent studies have suggested a possible therapeutic benefit in autism and transient improvement of symptoms in schizophrenia,[155] though repeated intravenous administration is likely to limit therapeutic potential.

Neurosteroids, such as dehydroepiandrosterone (DHEA),[156] pregnenolone[157] and their derivatives have been implicated in neuroprotection and enhancement of NMDA receptor neurotransmission suggesting therapeutic potential in schizophrenia,[40] possibly by actions at sigma1 receptors.[156,157] Indeed, a double-blind study of DHEA as an adjunct to antipsychotic treatment in chronic schizophrenic patients with prominent negative symptoms suggests some efficacy at improving negative symptoms, especially in women,[158] though further studies are needed.

Moving towards the future

As is apparent from the preceding sections, most of the current strategies for developing novel compounds for the treatment of schizophrenia have not been successful. All currently available medications target D_2 dopamine receptors—a paradigm that has dominated drug development for the past 20 years—and many have been identified by activity in preclinical models that were devised based on pharmacologic manipulation (such as psychostimulant-induced behaviors). Indeed, these models have helped identify additional antagonists at dopamine D_2 and serotonin 5-HT_{2A} receptors, and are helping to identify novel neurotransmitter approaches to modulate dopamine. In addition, the development of highly selective agents for various neurotransmitter receptor targets has been and will continue to be extremely valuable in the elucidation of brain physiology and the understanding of the pathophysiology of complex disorders such as schizophrenia; however, future drug discovery approaches will have to be truly revolutionary and based on a better understanding of the pathogenesis of the disease. Interestingly, we are in an era of increased knowledge and enormous spending in biomedical research but a dearth of advances in therapeutics. This decrease in the introduction of fundamentally new drugs into clinical practice is evidence of attempts to make a fundamental shift in the basic paradigms used for drug discovery. Thus, this is an exciting and pivotal time for the development of truly novel approaches to drug development and treatment of complex disorders like schizophrenia. Below, we will discuss some of the exciting advances in our understanding of the pathophysiology of schizophrenia, will highlight some novel strategies currently being explored for drug development, and will stress the need for an increased role of academic scientists in target identification and validation.

Models of the pathophysiology of schizophrenia

A major critique of current drug discovery approaches for schizophrenia is that adequate treatments cannot be developed because the underlying causes of major mental illnesses remain incompletely understood.[21,31,159] Indeed, while there have been enormous advances in our understanding of the basic biological processes contributing to many human diseases, a detailed understanding of the processes underlying schizophrenia and other complex mental disorders remains elusive. With the sequencing of the human genome and the development of genomics-based technologies, there are unprecedented opportunities for gaining fundamental new insights into these complex diseases.[160] Currently, at least three highly overlapping hypotheses of the underlying pathophysiology of schizophrenia drive drug discovery efforts.[16]

The first hypothesis, and the one that accounts for all of the current antipsychotic medications and the vast majority of compounds in the pipeline, is the *signal transduction hypothesis*, which posits that basic alterations in receptor-medicated signal transduction induces schizophrenia-like psychopathology. Therefore, normalizing the altered signaling with medications targeting receptor and post-receptor molecules should be efficacious in treating schizophrenia.[122,161] Indeed, targeting these neurotransmitter receptor sites has, to this point, been the predominate focus of psychopharmacological research, and this strategy has led to significant advances in our understanding of the pathophysiology of schizophrenia and brain function as a whole. Future efforts, however, should move beyond the current strategies of solely targeting the synaptic neurotransmission at the receptor level to the development of agents that can affect more diverse cellular functions including intracellular signaling pathways and the mechanisms involved in synaptic plasticity.

Second, *the molecular-genetic hypothesis* posits that strong effects of susceptibility genes underlies the pathophysiology of schizophrenia,[162] and suggests that targeting drugs at these genes or their associated anatomic and functional pathways might yield novel and more effective treatments for schizophrenia.[163,164] Indeed, significant progress has been made in recent years on elucidating various susceptibility genes in schizophrenia, including dysbindin, neuregulin 1, COMT, DISC1, and others.[165] Interestingly, many of these genes appear to be related to the control of synaptic plasticity and glutamate transmission (particularly NMDA receptor function) (Figure 1). These recent breakthroughs in genetic studies of schizophrenia begin to allow for hypothesis-driven approaches for developing actual disease-modifying drugs for schizophrenia. In addition, individualized treatment strategies could be developed that are focused on subgroups of schizophrenic patients with specific susceptibility alleles.

A third hypothesis, *the neural network hypothesis*, proposes that schizophrenia results from the strong effects of altered neuronal integration. This hypothesis predicts that drugs that fundamentally reset the tone of networks of neuronal interactions will prove efficacious in treating schizophrenia.[159,166] Indeed, significant evidence exists suggesting that schizophrenia is a neurodevelopmental disorder associated with abnormal connectivity resulting from defects in synaptic pruning and migration of neurons.[167] Thus, if alterations in synaptic pruning are the primary

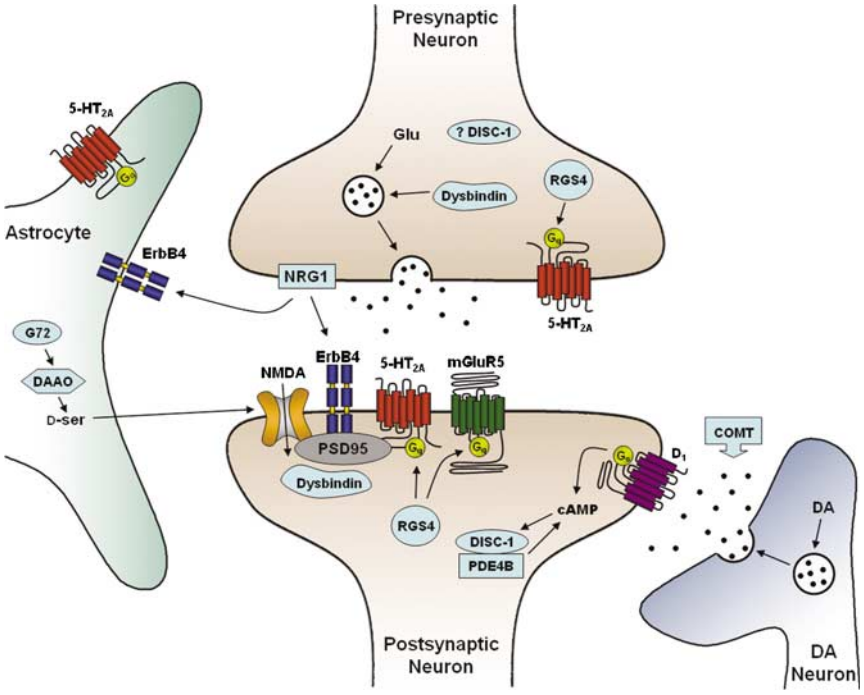

Figure 1 Hypothetical roles of schizophrenia genes at a glutamatergic synapse. Pictured is a hypothetical schematic of various putative schizophrenia susceptibility gene products and how they may affect neurotransmitter signaling at a glutamatergic synapse. The schizophrenia genes include: DISC-1 (disrupted in schizophrenia-1), Dysbindin, NRG1 (neuregulin-1), RGS4 (regulator of G protein signaling 4), COMT (catechol-*O*-methyltransferase), PDE4B (phosphodiesterase 4B), G72, and DAAO (D-amino acid oxidase). Other abbreviations are: Glu (glutamate), DA (dopamine), NMDA (*N*-methyl-D-aspartate glutamate receptor), 5-HT_{2A} (serotonin receptor 2A), mGluR5 (metabotropic glutamate receptor 5), D_1 (dopamine receptor 1), ErbB4 (ErbB-type tyrosine kinase receptor B4), cAMP (cyclic adenosine monophosphate), G_q/G_s (G proteins), PSD95 (postsynaptic density protein 95), D-ser (D-serine). Adapted from Harrison and Weinberger[162] and Roth.[16]

process underlying the pathophysiology of schizophrenia, possibly due to inherited genetic alterations in genes such as DISC1 or dysbindin, then effective treatment strategies should target the underlying deficits (Figure 1). In addition, successful treatment of schizophrenia may then require early recognition and treatment during or even before an obvious prodromal stage. However, if the underlying defects are due to abnormal migration of cortical neurons and subsequent dysregulation of cortical development, it may be impossible to ameliorate such deficits via simple pharmacological approaches.

Challenges of future drug discovery

While there has been significant progress in our understanding of the underlying pathophysiology of schizophrenia, a great deal of additional research is needed before we can begin the systematic development of drugs that may address the root cause of the disease. Thus, before our full understanding of those causes, the development of novel drugs with superior efficacy and improved side-effect profiles is still essential. It has been suggested that 'selectively non-selective' drugs, or 'magic shotguns,' can already be developed and may fill a clinical need for improved therapeutics.[31,44] Indeed, genomics-based screening approaches are being used to identify novel drug candidates based on their ability to either mimic the gene expression 'signature' of gold-standard drugs like clozapine, or based on their ability to normalize the expression of genes that are altered in schizophrenia.[45] Alternatively, high-throughput behavioral screenings may prove useful for the identification of novel medications for schizophrenia,[45] though hurdles exist in finding animal behavioral models with good predictive value.

Indeed, while current preclinical models for schizophrenia are quite effective at predicting whether a candidate molecule will have 'atypical' properties, they are less able to predict overall efficacy and are completely unable to predict greater efficacy than currently available antipsychotics. In addition, none of the available animals models accurately predict the propensity of various antipsychotic drugs to induce weight gain and associated side effects, although some of this can be predicted based on knowledge of *in vitro* receptor pharmacology.[90] Moreover, in terms of the negative and cognitive symptom domains in schizophrenia, none of the commonly used animal models are highly predictive, although preclinical memory models may be useful for predicting ability to enhance cognition. This lack of predictive, reliable

and efficient animal models has severely hindered progress in discovering novel therapeutics for schizophrenia, highlighting a need for increased collaboration between scientists in academic settings and industry. Thus, we advocate that academic-based scientists should be more aggressively involved in contributing to the drug discovery process, particularly by focusing on target validation[15] (Figure 2). This challenge will require increased collaboration with the pharmaceutical industry as well as priority by the NIMH to fund such endeavors.

Conclusions

In the past 20 years, new therapies for schizophrenia have primarily emerged from a quest to discover new drugs that lack the extrapyramidal side effects of the typical antipsychotic drugs. While the atypical antipsychotics have probably been of some benefit to patients, due to their somewhat improved therapeutic margin and efficacy at treating the negative symptoms of schizophrenia, this modest benefit has been tempered by their own troublesome side-effect profiles, including weight gain and diabetes—likely due to off-target actions at therapeutically irrelevant receptors.[90,168] Thus, we have reached a significant bottleneck in the drug discovery process due to incomplete understanding of the mechanisms of action of the currently available antipsychotics as well as poorly defined pathophysiology for this complex and likely heterogeneous disorder. Interestingly, as many of the atypicals will soon go off patent, there is increased urgency within the pharmaceutical industry to develop new, novel treatments for schizophrenia.

We predict that the future of pharmacologic treatment of schizophrenia will likely start with the continued use of polypharmacy and augmentation strategies aimed at treating the multiple symptom domains of schizophrenia. This may be followed by the development of selectively nonselective single compounds that can target multiple domains at once while simultaneously decreasing side effects, eliminating potential pharmacokinetic interactions and improving medication compliance.[31,45] The long-term goal, of course, will be to develop 'cure therapeutics'[164] which will likely require a substantial shift in the current paradigm of drug development and significant advances in our understanding of the pathophysiology of schizophrenia. Thus, it is important to continue to pursue diverse molecular targets and increase efforts at validating novel targets. Indeed, recent breakthroughs in genetic studies of schizophrenia have provided renewed excitement for the development of drugs at novel targets that may target underlying disease processes. This shift in our approach to drug development will require considerable contributions from academic-based researchers as well as bold and potentially risky endeavors by the pharmaceutical industry.

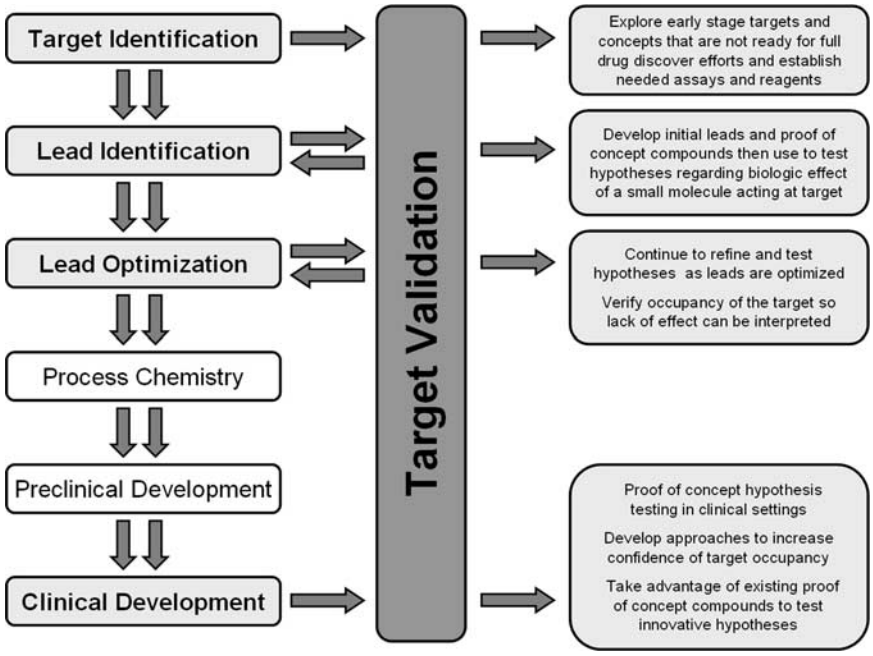

Figure 2 Continuous target validation in academia. Identifying and validating novel targets is a significant rate-limiting step in new drug development which has led to few new drugs with truly novel mechanisms of action. Thus, increased research in the academic setting is needed to identify selective compounds for novel targets that may be used for testing hypotheses at these targets and for proof of concept experiments. Continuous validation of targets by academic scientists at each step in the drug development process, including proof of concept experiments in the clinical setting, may facilitate the development of fundamentally new therapeutics for schizophrenia. Adapted from BL Roth and PJ Conn: IOM White Paper, 2006.

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