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Review Article

Strategies for pharmacotherapy of schizophrenia

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CONTENTS

Abstract

Schizophrenia is a debilitating syndrome consisting of several symptom dimensions (positive and negative symptoms; cognitive and mood disturbances) with a large unmet treatment need. Until now, the primary focus has been on the development of single drugs for treating all symptoms. It is now realized that the pathophysiologies of the symptom dimensions are very different, requiring drugs acting through different mechanisms. Furthermore, even within each symptom dimension the pathophysiology may vary considerably. However, it may still be possible to develop a single drug with efficacy for broad symptomatology. Some examples of novel strategies are given, *e.g.,* dopamine D_2 antagonists with additional actions on specific serotonin (5-HT) receptor subtypes (5-HT_6 receptors for example), 5-HT_{2C} agonists, phosphodiesterase (PDE10) inhibitors, NK_3 antagonists and $mGlu_{2/3}$ agonists. However, it has recently become more common to attempt to develop adjunct treatments to dopamine D_2-antagonist antipsychotics, particularly for improvement in cognitive deficits, which are considered the main determinant of functional outcome. This review describes various strategies to improve cortical function, which is believed to be suboptimal in patients with cognitive deficits and negative symptoms. These include drug actions on dopamine, 5-HT, norepinephrine, nicotinic and muscarinic receptor subtypes, as well as various glutamatergic drug targets.

Introduction

Schizophrenia is a chronic and debilitating mental disorder that affects approximately 1% of the global population (1). The etiology and pathophysiology of schizophrenia remain unknown, although it is widely accepted that a combination of genetic and environmental factors are responsible, at least in part, for triggering the disease (2). In general, schizophrenia is characterized by four separate symptom domains, namely positive, cognitive, negative and affective symptoms, including delusions, hallucinations and thought disorder (*positive symptoms*), poor attention, memory impairments and executive function deficits (*cognitive symptoms*), blunted affect, aphasia, anhedonia and avolition (*negative symptoms*), as well as depression and suicidality (*affective domain symptoms*). Currently, the diagnosis of schizophrenia (using the DSM IV) is largely dependent on the emergence of positive symptoms leading to psychosis, and as such, the majority of marketed antipsychotic drugs (APDs) have predominantly targeted positive symptoms. However, with recent findings indicating a correlation between cognitive (and to a lesser extent negative) symptoms and occupational/social functioning (3-5), attention is now turning towards also targeting these symptom domains to address a major and currently unmet need in the treatment of this disease. Specifically, the MATRICS (Measurement and Treatment Research to Improve Cognition in Schizophrenia) initiative has driven clinical research and regulatory considerations toward treating the cognitive deficits, and more recently the negative symptoms, of schizophrenia (see http://www.matrics.ucla.edu/). There has also been an increase in the focus on various aspects of cognition preclinically, resulting in the successful development of several animal models (6-11) to facilitate the evaluation and development of procognitive drugs. In this review, we will outline many of the strategies and targets currently under investigation for the development of novel schizophrenia pharmacotherapies.

Existing APDs (Fig. 1) are divided into classical or first-generation APDs (preferential dopamine [DA] D_2 antagonists with haloperidol [**1**] as prototype), and second-generation or atypical APDs, broadly defined with a separation between positive symptom efficacy *versus* extrapyramidal symptom (EPS) dose and exemplified by clozapine (**2**), risperidone (**3**), olanzapine (**4**), ziprasidone (**5**), sertindole (**6**), quetiapine (**7**) and amisulpride (**8**). More recently, third-generation APDs have been devel-

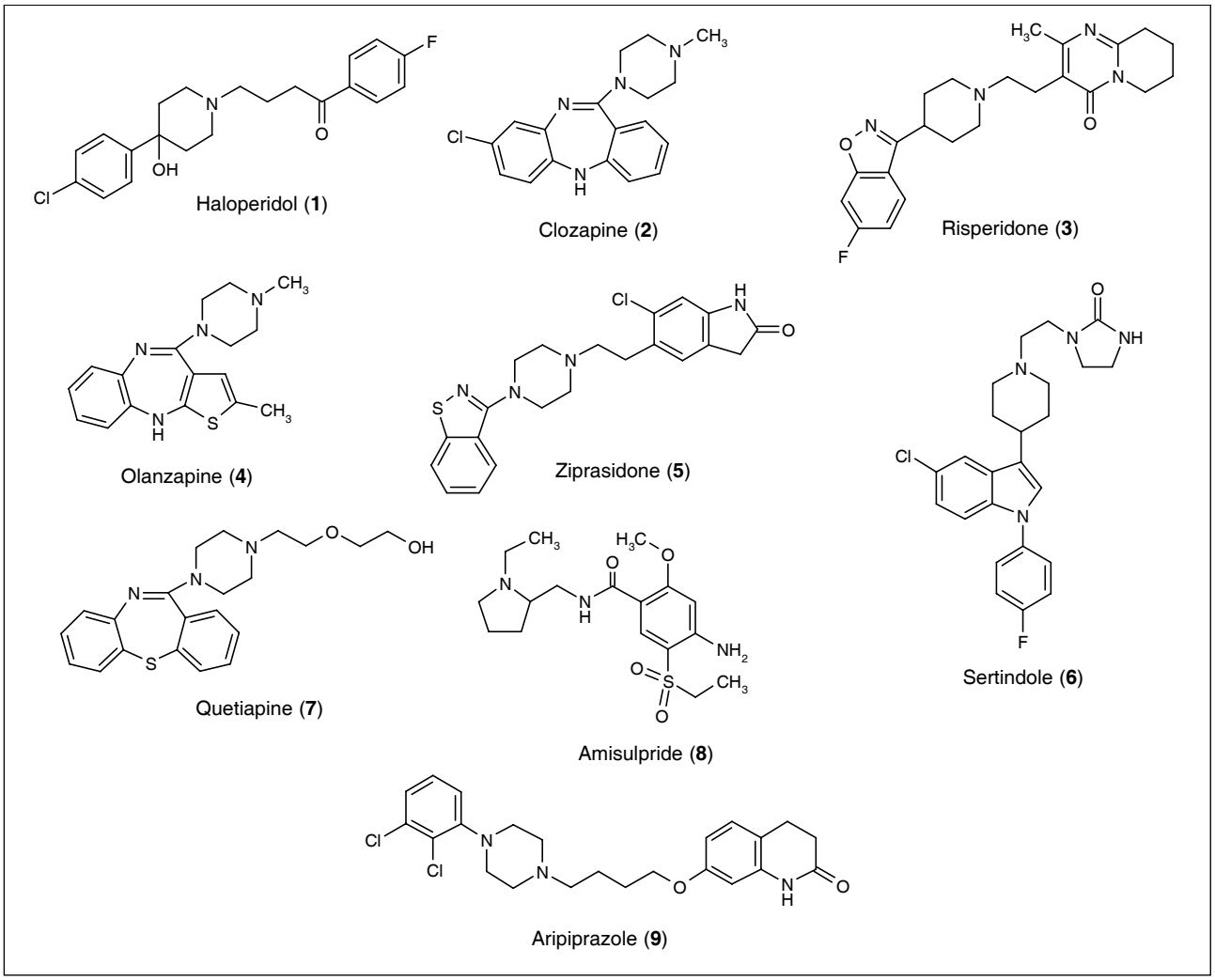

Fig. 1. Marketed dopamine D_2 antipsychotics.

oped (partial DA D_2 agonists, with aripiprazole [**9**] as the only marketed representative to date) (12). All APDs with documented efficacy on positive psychotic symptoms (*i.e.*, obtained in controlled clinical trials) have partial agonist or antagonist activity on DA D_2/D_3 receptors, except for tachykinin NK_3 antagonists and metabotropic glutamate receptor $mGlu_{2/3}$ agonists, but the effects of these novel drug classes have so far only been shown in phase II trials and require better documentation (13-15).

All second-generation APDs, except benzamides (*e.g.*, amisulpride), have parallel effects on DA D_2, 5-HT_{2A} and α_1-adrenoceptors, but variable effects on several other drug targets. However, the balance between D_2 antagonism and other receptor effects differs markedly among available drugs. Accordingly, each individual drug will have a different pharmacological profile and, in theory, different efficacy (on the various symptom dimensions) and adverse effect profile. The main feature of second-generation APDs is their so-called limbic selectivity, which is reflected by a more potent effect on limbic (mediating efficacy on positive symptoms) *versus* nigrostriatal DA function (mediating EPS). Briefly, this class of compounds has marked differences in limbic selectivity, ranging from high (clozapine, sertindole) to intermediate (olanzapine, ziprasidone) to minor (risperidone) (16, 17). With knowledge of the desired receptor profile, it is theoretically possible to optimize the profile of an APD in a so-called magic shotgun, multitargeted drug or "selective nonselective DA antagonist" (18, 19). The advantage of this approach is that the effect of the drug only depends on the relative potencies for and efficacies at the different targets in question, and that the effect is not complicated by putative pharmacokinetic (PK) differences, which are likely if adjunct treatments are given. However, in practice, it has proven very difficult to obtain magic shotguns with the right balance between wanted (on all symptom dimensions) and unwanted target effects, as structure–activity relationships (SAR) toward optimization of multiple targets, including physicochemical properties, PK, metabolic and safety characteristics, are very challenging. Furthermore, schizophrenia patients present large symptom variability, adding to the complexity of designing

a magic shotgun: This suggests that pharmacotherapy in the future should be tailored more individually by adjusting the balance between effects on various symptom dimensions (and accordingly on drug targets).

The consequence of this is that instead of a broadly acting monotherapy, it may be more feasible to choose an add-on or co-medication strategy (20) in which a known APD is combined with an appropriate dose of an additional drug influencing, *e.g.,* cognitive impairment, negative symptoms or enhancing the effect of the APD on positive symptoms. In this way, schizophrenia is not seen as a homogeneous disease entity, but rather as a conglomerate of various symptoms, each with separate pathophysiological and etiological characteristics (*e.g.,* genetic, neurodevelopmental).

Disease biology of schizophrenia

The development of novel APDs relies heavily on knowledge of the pathophysiology of the symptom dimensions affected. For positive symptoms, the main treatment focus will likely continue to be on reducing a hyperresponsive subcortical DA system in the striatum and limbic areas (21, 22). For negative and particularly cognitive symptoms, the main focus has recently been to optimize the function of a hypofunctioning prefrontal cortex. In populations of schizophrenia patients, this brain region has been shown to be less activated during performance of various cognitive tasks, the so-called "hypofrontality" syndrome. This is consistent with hypofunctioning prefrontal DA projections in schizophrenia (23). Even though positive symptoms are worsened on amphetamine challenge, negative symptomatology (24) and cognitive functioning (25, 26) appear to improve. Thus, data support an abnormal regulation of brain DA systems in schizophrenia with "opposite" dysfunctions of, *e.g.*, mesolimbic and mesocortical DA projections. Consequently, rather than blocking DA D_2 receptor transmission generally, the treatment of schizophrenia should aim at normalizing/stabilizing a dysregulated mesocortico-limbic DA system.

In addition to DA, glutamate neurotransmission is also thought to be dysregulated in the frontal cortex. The main evidence points to a glutamate hypofunction (21, 27), although the recent demonstration of APD activity for an $mGlu_{2/3}$ agonist (that *inhibits* glutamate release) has raised questions on the functional status of glutamate in schizophrenia (15, 28). However, it should be emphasized that, so far, only effects of the $mGlu_{2/3}$ agonist on positive symptoms have been shown, effects normally considered dependent upon drug activity in subcortical brain regions.

Several neurotransmitter systems and receptor subtypes modulate cortical DA and glutamate function. In this respect it must be emphasized that DA, and perhaps glutamate, function does not necessarily follow a linear concentration–effect relationship. Rather, an inverted U-shaped functional model has been developed defining an optimum functional level. Both lower and higher DA function accordingly leads to poorer outcome on cognitive responses (29, 30). Seen from a systems biology perspective, effects on cortical DA and glutamate cannot be discussed in isolation, and it has been shown *in vitro* that several neurotransmitters indirectly enhance glutamatergic function in the frontal cortex (particularly the NMDA receptor subtype). This is most likely mediated by increased extracellular DA, which in turn stimulates D_1 receptors, leading to enhanced NMDA function (*e.g.,* $5\text{-}HT_{2A}$ antagonism, α_2-adrenoceptor antagonism, M_1 agonism) (31-36).

Future monotherapy antipsychotics

A recent addition to the DA D_2 family of APDs has been the development of third-generation APDs with partial D_2-agonist activity. So far, only aripiprazole has reached the market, while another agent, bifeprunox (**10**) (Fig. 2), is in phase III development (37). Partial agonists are predicted to stabilize a dysfunctioning DA system, inhibiting transmission in synapses with high tonus and increasing function in those with low activity. The net functional activity of the partial agonist is assumed to depend on the intrinsic D_2 receptor activity of each individual drug (38). This class of compounds is well tolerated with respect to neurological side effect potential, and the clinical efficacy on positive symptoms does not seem to differ markedly from first- or second-generation APDs, although the potential has not yet been established in patients with prominent negative symptoms and cognitive deficits.

A new strategy for affecting DA function more selectively attempts to identify compounds that target differential DA signaling pathways, *e.g.*, adenylate cyclase- and ERK (extracellular signal-regulated kinase)/GSK-3 (glycogen synthase kinase-3)/GIRK (G protein-activated inward rectifier potassium channel)/arrestin-coupled pathways (39). This strategy may to some extent be linked to the third-generation partial agonists, where the term "functional selectivity" has been proposed to explain part of the profile of aripiprazole (40). Although evidence for the importance of different signaling pathways appears solid, its impact on drug discovery has yet to be validated. One compound (ITI-007, structure not published) in early development has been claimed to target DA signaling, although no documentation is available in the public domain (http://www.intracellulartherapies.com/index.htm).

The multitarget monotherapy strategy (also called "DA D_2 plus") is still pursued by many companies. Examples of compounds with similar profiles as marketed drugs are paliperidone (major metabolite of risperidone), iloperidone (development on hold following receipt of nonapprovable letter from the FDA) and asenapine (under FDA review) (41, 42). However, the results of the CATIE clinical trial were disappointing in the sense that the first-generation APD perphenazine and all investigated second-generation drugs had similar efficacy on positive symptoms, and mainly differed in adverse effect profiles (43). Thus, it is questionable whether novel drugs from

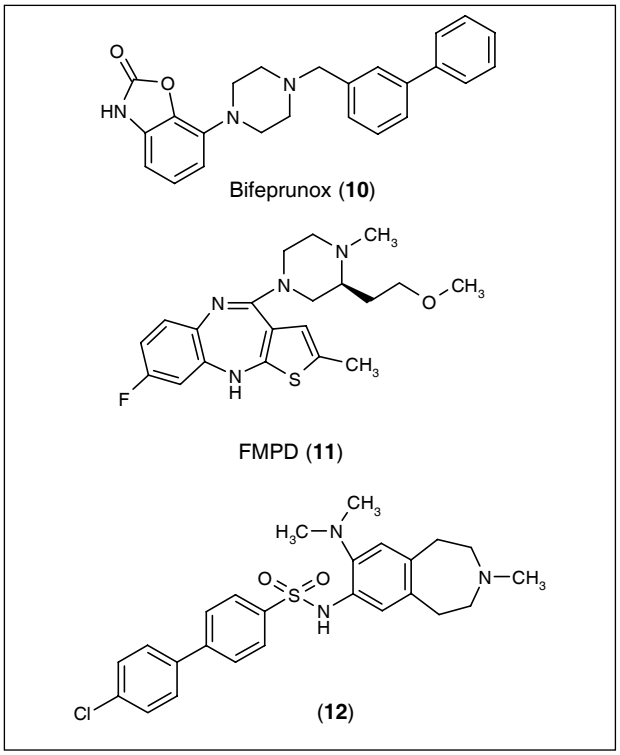

Fig. 2. Putative novel dopamine D_2 antipsychotics.

this class will lead to breakthroughs. As future drugs will have to compete with generic versions of today's drugs, they will need to have sufficient superiority in order to gain market access. Hence, compounds with various levels of improvement have been pursued, either having similar efficacy as today's drugs, but with attempts to build in superiority in terms of adverse effect spectrum (neurological, metabolic, cardiovascular and endocrine), or drugs having a genuine improvement in efficacy due to balanced effects on targeted receptors leading to clinically relevant efficacy on positive as well as cognitive symptoms. Innovative examples include the identification of an olanzapine analogue, FMPD (**11**) (Fig. 2) (44), with reduced histamine H_1-blocking activity as compared to olanzapine itself, in order to reduce weight gain potential, although this compound has apparently not been taken into further development. Another example is a series of "DA D_2/5-HT_6 plus" antagonists represented by compound **12** (Fig. 2) with the potential to treat both positive and cognitive symptoms (45, 46). GlaxoSmithKline's phase II candidate GSK-773812 (unpublished structure) belongs to this category. Its pharmacological profile is displayed on the company's home page (see http://www.gsk.com/index.htm). In our view, most of these compounds are unlikely to produce more than incremental improvements in outcome compared with presently available drugs.

Alternative monotherapy strategies are to identify non-DA targets with broad effects on several symptom dimensions (Fig. 3). Examples of such targets have been suggested to include phosphodiesterase PDE10 inhibitors with putative effects on positive symptoms and cognitive impairment, exemplified by TP-10 (**13**) and MP-10 (PF-2545920, **14**) (47-50), and AMPAkines, which enhance glutamatergic function, exemplified by farampator (**15**) (51-53). However, most predictions on these targets are based on findings from preclinical models. For AMPAkines, the main evidence suggests mainly an effect on cognitive deficits (54), and accordingly their use in combination with APDs (see later). Finally, novel non-DA mechanisms targeting primarily positive symptoms and perhaps affective symptoms have also attracted recent interest, *e.g.*, NK_3 antagonists (*e.g.,* osanetant [**16**], talnetant [**17**]) (14), 5-HT_{2C} agonists (*e.g.,* vabicaserin [**18**]) (55) and $mGlu_{2/3}$ agonists (*e.g.*, LY-404039 [**19**] and its corresponding prodrug LY-2140023 [**20**]) (15, 56).

Adjunct treatment strategies

Two different strategies can be chosen: to treat separate symptom dimensions with different drugs *or* to enhance the efficacy/tolerability ratio for a single dimension with combination treatment. The first option is the most commonly used, in part because animal models able to identify partial responses on, *e.g.*, positive symptoms, are not available. Seen from a medicinal chemistry perspective, it is easier to optimize compounds with a selective action on one target than to optimize for two or more targets in parallel. Furthermore, as explained earlier, it gives psychiatrists more flexibility to use adjunct treatments for individual symptom dimensions. Another advantage of developing combination treatments is that the clinical development program can be slightly simpler (and thus cheaper), because a novel treatment or placebo is added on top of stable treatment with an existing drug. This eliminates the need for ethically controversial placebo treatments which are required for novel monotherapies by regulatory bodies in most countries. On the downside, one must be aware that add-on treatments may not work in combination with all antipsychotics, *e.g.,* it is not rational to add a muscarinic agonist to an antipsychotic with antimuscarinic activity.

As mentioned previously in the "Disease biology of schizophrenia" section, the aim is to normalize a hypofunctioning cortex and demonstrate parallel improvement in models of cognitive performance and/or negative symptoms, while at least maintaining efficacy on positive psychotic symptoms. It has been known for several years that second-generation APDs differ from classical first-generation drugs (prototype haloperidol) in their effects on DA and acetylcholine output in the frontal cortex *versus* subcortical DA areas (striatum and nucleus accumbens). Preferential D_2 antagonists mainly enhance subcortical DA output in the striatum and nucleus accumbens, while most second-generation APDs also have marked effects in the cortex (57-59). Many studies have been conducted to dissect the receptor mechanisms involved, using the preferential DA D_2 antagonist haloperidol given alone and in combination with selective receptor ligands. In particular, 5-HT receptor subtypes,

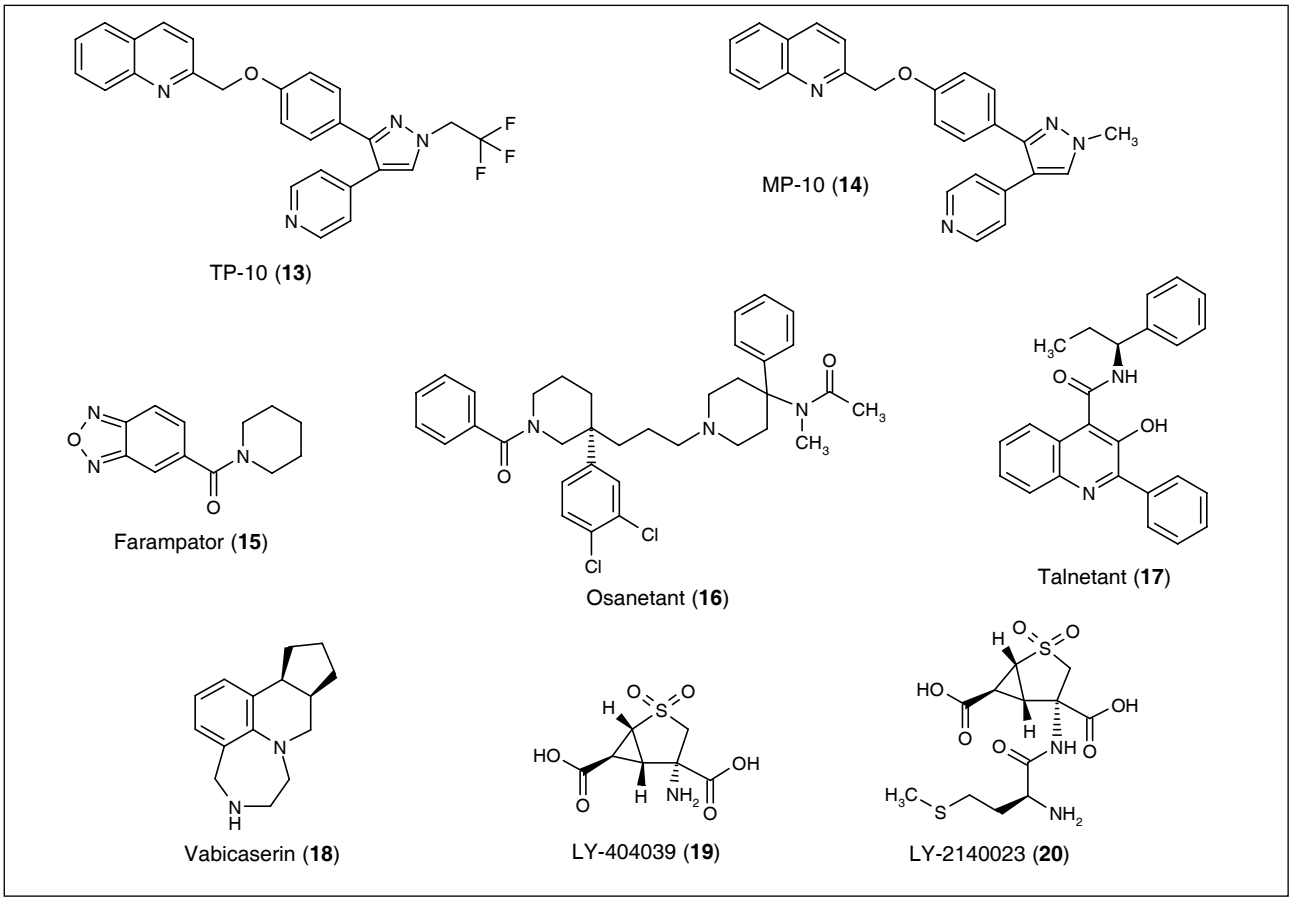

Fig. 3. Putative non-dopamine antipsychotics.

and also adrenergic mechanisms, have been studied. In the following sections, various targets influencing cortical functioning in particular will be reviewed, although modification of the effects of D_2-antagonist APDs will also be mentioned (see Table I for an overview).

Dopaminergic mechanisms

The dopamine D_2 receptor has already been discussed in detail, but all APDs are mixed D_2/D_3 and often also D_4 ligands (16, 17). However, the development of selective D_3 and D_4 receptor ligands has been a focus for several years, as these subtypes have an attractive limbic/cortical expression pattern. Several D_4 antagonists have been described and a few have been evaluated in phase II monotherapy trials with disappointing results, notably L-745870 (**21**) and sonepiprazole (**22**) (Fig. 4) (60-62). However, L-745870 was subsequently shown to be a partial D_4 *agonist*, complicating the interpretation of the clinical outcome. None of the antagonists have been studied in combination treatment with other APDs. Preclinical evidence suggests some antipsychotic potential, as well as potential for treating cognitive deficits, with D_4 antagonists or partial agonists (63-67).

A few selective D_3 antagonists have been described, but no clinical trials have been published. A preferential D_3 *vs.* D_2 antagonist, S-33138 (**23**) (Fig. 4) (68, 69), is presently in phase II development. Preclinical evidence does not support efficacy on psychotic symptoms for a selective D_3 antagonist on its own, but it may enhance the efficacy of D_2 antagonism and at the same time reduce EPS potential (69-71). The potential for D_3 antagonists in treating cognitive impairment has not been established. Interestingly, there is preclinical evidence that D_3 antagonists reduce drug craving, suggesting that targeting this receptor may be of value in treating comorbid drug abuse (72, 73).

The DA D_1/D_5 receptor subfamily has a very different neurobiology in comparison with the $D_2/D_3/D_4$ subfamily. As an alternative to increasing DA output in the frontal cortex, D_1 receptor agonists have attracted interest for the treatment of cognitive disturbances, with the effect likely mediated through enhancement of NMDA receptor function (36). Unfortunately, it has proven difficult to develop compounds with drug-like characteristics. Dihydrexidine (**24**) (Fig. 4) has reached early clinical studies, but can only be administered by the parenteral route (74, 75).

Serotonergic mechanisms

As 5-HT_{2A} antagonism is a commonly shared mechanism within second-generation APDs and has been

Table I: Putative link between mechanism and treatment of schizophrenia based on preclinical data.

Mechanism	Positive symptoms		Cognitive deficits	Monotherapy (M) or add-on (A) therapy	Other	Ref.
	Monotherapy	Enhance D_2 antagonist				
Dopaminergic						
D_1 agonism	NE	NE	↑	A		74, 75
D_3 antagonism	NE/(↑)	↑	NE	A	Drug abuse treatment	68-71
D_4 antagonism	NE/(↑)	NE	↑	M/A		63, 67
Serotonergic						
5-HT_{1A} agonism	NE	↑	↑	A	Reduce EPS, reduce weight gain, affective symptoms	88-90, 95
5-HT_{2A} antagonism	(↑)	↑	(↑)	A	Affective symptoms	6, 76, 79, 80
5-HT_{2C} antagonism	NE	↓	NE	A	Affective symptoms	93, 94
5-HT_{2C} agonism	↑	NE	NE	M	Weight loss, affective symptoms	93-96
5-HT_6 antagonism	NE	NE	↑	A	Reduce weight gain ?	6, 97, 101, 105, 137
Adrenergic						
Norepinephrine reuptake inhibition	NE	↑	↑	A	Affective symptoms	106
α_2 antagonism	NE	↑	↑	A		33, 110
α_1 antagonism	(↑)/NE	↑	NE	?	Orthostatic hypotension	112
Cholinergic						
M_1 agonism	NE /(↑)	NE	↑	A		117
M_4 agonism	(↑)	NE	?	?	Lack of tools	117
Nicotinic α7 agonism	NE	NE	↑	A		119
Nicotinic $\alpha 4\beta 2$ agonism	NE	NE	↑	A		119
Glutamatergic						
$mGlu_{2/3}$ agonism	↑	NE	NE	M		15, 56, 131
$mGlu_5$ positive modulation	(↑)	NE	↑	A		130
GlyT1 inhibition	NE	↑	↑	A	Toxic target ?	126-128, 132, 135
D-Serine/D-cycloserine	NE	↑	↑	A		52, 126, 132, 133
AMPAkines	(↑)	↑	↑	A		52, 54, 134
Miscellaneous						
NK_3 antagonism	↑	NE	NE	M		14
PDE10 inhibition	↑	NE	↑	M		47-50
H_3 antagonism	NE	↑	↑	A		123-125

↑, Positive effect; (↑), conflicting evidence; ↓, opposing effect; NE, no evidence; EPS, extrapyramidal symptoms.

hypothesized to be the main driver of "atypicality" (*i.e.*, improved efficacy without increase in EPS potential), this target has been one of the most thoroughly studied (76). Furthermore, selective 5-HT_{2A} antagonists (*e.g.,* M-100907 and eplivanserin) have been investigated for their antipsychotic potential as monotherapy. They have shown signs of efficacy on positive symptoms of schizophrenia, but efficacy has apparently not been sufficient to lead to applications for market approval (77, 78). Accordingly, 5-HT_{2A} antagonists show no or limited efficacy on their own in animal models of psychosis (79) and in microdialysis studies. However, in combination with a D_2 antagonist (mainly haloperidol), a marked increase in cortical DA and acetylcholine output has been demonstrated, suggesting that 5-HT_{2A} antagonism is functionally more effective in conditions with elevated DA neuronal feedback activity caused by D_2 receptor blockade (79, 80). This strategy has recently been used in a clinical trial of the 5-HT_{2A} antagonist pimavanserin (**25**) (Fig. 4) (81) in combination with a low dose of risperidone or haloperidol. Full details have not yet been published, but the initial trial suggested that pimavanserin enhances the efficacy of a threshold dose of risperidone to a level obtained with an optimum risperidone dose, without enhancing side effects

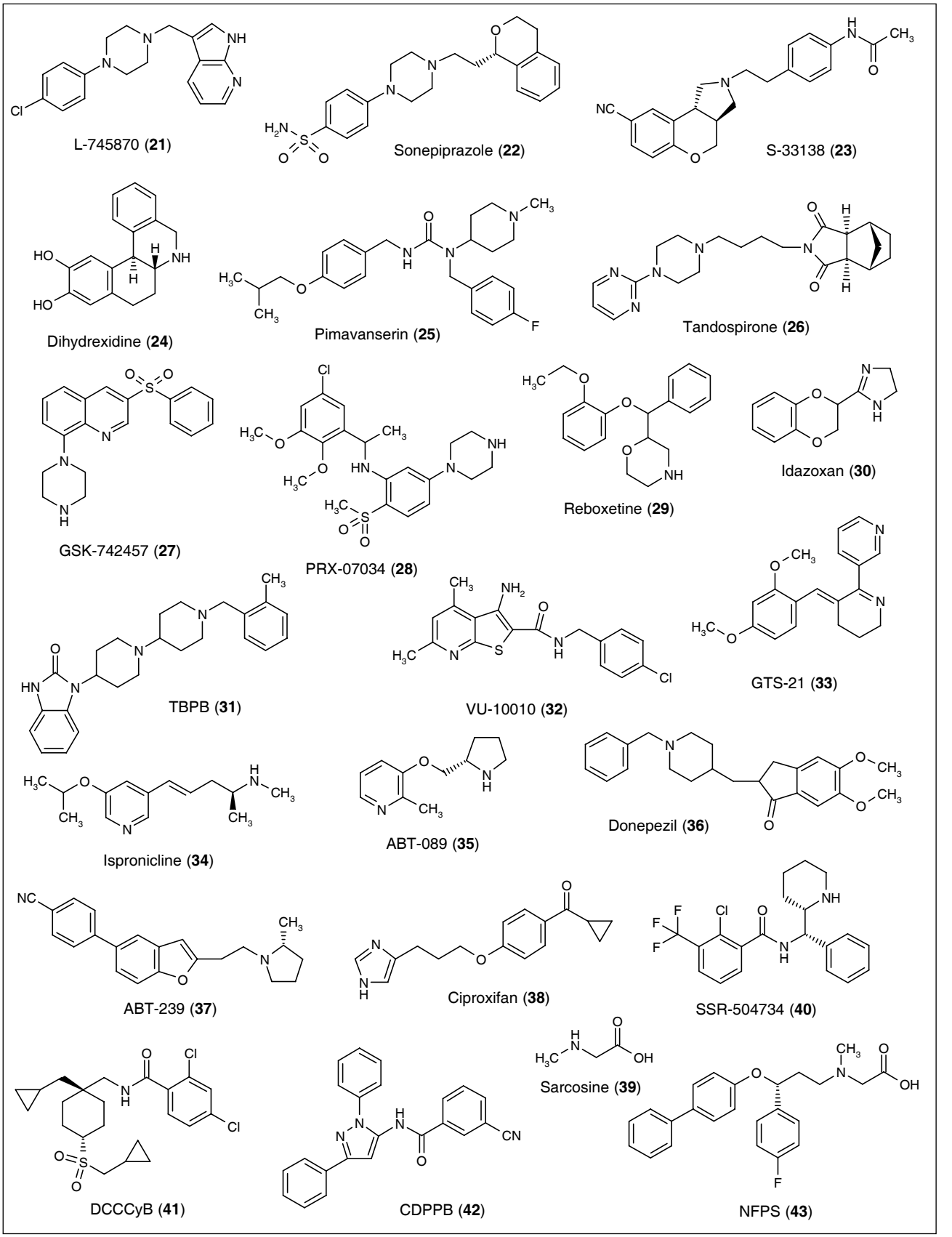

Fig. 4. Putative ligands for combination with dopamine D_2 antipsychotics.

(http://www.acadia-pharm.com/programs/schizophrenia.htm). Whether this improvement is sufficient to gain market access remains to be established.

Although most second-generation APDs improve cognitive impairment in schizophrenia to only a limited extent (*e.g.*, risperidone, clozapine, olanzapine) (82-84), the efficacy of these compounds and M-100907 has been demonstrated after acute treatment in a rat model relevant for this indication, *e.g.,* subchronic dosing with phencyclidine (PCP), followed by at least 1-week washout. These rats show specific impairment in working and episodic memory, measured as operant reversal learning and novel object recognition, respectively (8, 85, 86). On the contrary, acute treatment with risperidone, clozapine and olanzapine (for olanzapine also after repeated treatment), as well as a selective 5-HT_{2A} antagonist, did not show significant efficacy in another PCP-impaired frontal cortex-mediated response: attentional set shifting. This response is modeling executive function, an important cognitive dimension impaired in schizophrenia (6). It should, however, be mentioned that a preliminary 7-day drug treatment study in a similar model indicated efficacy for clozapine and risperidone (87). No preclinical or clinical cognition studies of 5-HT_{2A} antagonists in the presence of DA antagonism (in order to mimic clinical combination treatment) have, to our knowledge, been published.

A few APDs have moderate affinity for (and partial agonist activity at) 5-HT_{1A} receptors (*e.g.*, clozapine, ziprasidone and aripiprazole), although the level of occupancy of the 5-HT_{1A} receptor is still uncertain within a clinically relevant dose range, partly due to lack of suitable tracers for detecting the occupancy of agonists. Partial agonists potentially enhance efficacy in animal models of positive symptoms (*e.g.,* conditioned avoidance response), reduce EPS potential and enhance cortical DA output (88, 89). So far, only a limited number of studies have been conducted in animal models of cognition, but a small clinical trial suggested cognitive improvement after a combination of APD (lacking 5-HT_{1A} activity) with the 5-HT_{1A} agonist tandospirone (**26**) (Fig. 4) (90-92). Furthermore, 5-HT_{1A} agonism may reduce the potential for weight gain of second-generation APDs.

Recently, 5-HT_{2C} receptors have attracted more interest. Several APDs have potent 5-HT_{2C}-antagonist activity (*e.g.,* clozapine, olanzapine, sertindole), and selective blockade of this receptor in the DA cell body regions is followed by increased DA output in nucleus accumbens and frontal cortex when given alone (93) or in combination with haloperidol (80). This may have a positive functional outcome in frontal cortex, but a negative impact in nucleus accumbens, as functional D_2 antagonism in models of positive symptoms may be reduced (94). Apparently no efficacy differences have been observed between 5-HT_{2C}-antagonistic APDs compared to APDs lacking 5-HT_{2C} activity; thus, 5-HT_{2C} antagonism does not seem to have negative consequences for efficacy in the presence of D_2 antagonism. No clinical studies have been published with selective 5-HT_{2C} antagonists in schizophrenia and limited information on the preclinical effects on cognition is available. Finally, 5-HT_{2C} antagonism may contribute to weight gain induced by several second-generation APDs (95).

More recently, selective 5-HT_{2C} *agonists* have been shown to have activity in animal models of positive psychotic symptoms (*e.g.,* conditioned avoidance response) in the absence of EPS (catalepsy), as well as parallel decreases in DA output in striatum and nucleus accumbens. Based on inhibitory effects on DA neuronal firing, it has been suggested that this target has the potential for faster onset of action, although this requires confirmation in humans. Furthermore, 5-HT_{2C} agonists show a positive response in animal models of anxiety/depression and reduce food intake. The effect in models of cognition remains to be investigated in detail, but it has been observed that a 5-HT_{2C} agonist enhances prepulse inhibition (PPI), a measure of sensory gating (94, 96). One compound, vabicaserin (**18**) (Fig. 3) (55), is in phase II development, although no clinical results have yet been communicated.

The 5-HT_6 receptor has attracted great interest during the last decade. It is abundant in DA-rich CNS regions, as well as in the cortex/hippocampus, and has primarily been studied in relation to cognition. The second-generation APDs have variable affinities for 5-HT_6 receptors: high affinity has been demonstrated for sertindole, clozapine and olanzapine, while risperidone in particular lacks 5-HT_6 affinity. Selective antagonists at 5-HT_6 receptors have in a few studies been shown to increase acetylcholine and glutamate output in the cortex and hippocampus, while effects on DA output in frontal cortex are variable. One study has shown an increase, while another showed an increase only after combination with haloperidol or risperidone (97-100). In cognition models, 5-HT_6 antagonists reverse deficits induced by antimuscarinic drugs (scopolamine), which is consistent with an indirect procholinergic effect (101). Interestingly, sertindole has recently been shown to have a superior profile in schizophrenia-relevant cognition models; like other second-generation APDs, it reversed the subchronic PCP-induced impairment in working and episodic memory tests (85, 86), but it also exhibited high efficacy in the attentional set-shifting task (6) and superior efficacy in reversing acute PCP-induced deficits in the Morris water maze (102). This effect was similar to that observed with a selective 5-HT_6 antagonist (6). It is not clear why sertindole showed better efficacy than clozapine and olanzapine, since these drugs also have high 5-HT_6 receptor affinities. A possible explanation is that clozapine and olanzapine, but not sertindole, have additional anticholinergic effects, which may counteract the efficacy induced by 5-HT_6 receptor blockade (17, 103). There are no clinical studies comparing the cognitive effects of sertindole with other second-generation APDs, but sertindole has shown marked efficacy in a haloperidol-referenced study, particularly on measures of executive function (104).

There is no evidence that selective 5-HT_6 antagonists have antipsychotic potential as monotherapy (105), but

due to the beneficial profile of selective 5-HT_6 antagonists in cognitive models, this target is a good candidate for developing add-on treatments for cognitive disorders, including schizophrenia. Some 5-HT_6 antagonists are in early clinical development for cognitive disorders, *e.g.*, GSK-742457 (**27**) and PRX-07034 (**28**) (Fig. 4).

Adrenergic mechanisms

DA output in the frontal cortex is also influenced after manipulation of adrenergic tonus. An increase in cortical DA function is observed after selective blockade of the norepinephrine transporter, *e.g.,* by treatment with reboxetine (**29**) (Fig. 4) (106, 107). This target is not commonly affected by second-generation APDs, although recent studies suggest that it may contribute to the profile of quetiapine through a major metabolite (108).

Blockade of α_2-adrenoceptors (*e.g.*, with idazoxan [**30**] [Fig. 4]) (109) also increases cortical DA output, although only in the presence of D_2 antagonism. Furthermore, it enhances the efficacy of a D_2 antagonist in a model of positive symptoms, without influencing EPS potential (110). Also, it enhances cortical glutamate function, as well as reversing MK-801-induced cognitive deficits (33). A small clinical trial of adjunct idazoxan treatment to APDs suggested improvements in efficacy, but no larger follow-up studies have been published (111). Among second-generation APDs, risperidone has reasonably high α_2-adrenoceptor affinity (17, 103). A drawback for targets generally increasing the output of norepinephrine is the potential for peripheral adverse effects due to increased sympathetic tone (*e.g.,* increase in blood pressure).

All second-generation APDs have potent α_1-adrenoceptor-blocking activity. The general consensus is that this effect may contribute to efficacy in models of positive symptoms, thus contributing to an increased therapeutic index with respect to EPS (112). No efficacy on cognitive deficits has been suggested. Also, α_1-adrenoceptor blockade gives rise to unwanted peripheral side effects, *e.g.,* orthostatic hypotension.

Cholinergic mechanisms

Antimuscarinic or low partial agonist activity at muscarinic receptors is present in some first- and second-generation APDs (*e.g.*, clozapine and olanzapine) (17, 103). This is a very effective means to mitigate EPS, but there are several central (cognitive) and peripheral side effects associated with blockade of muscarinic receptors (113). Conversely, muscarinic agonists have for several years been known to improve cognitive responding, although the field has been slowly progressing due to: 1) close receptor homology between muscarinic receptor subtypes at ligand binding sites, leading to nonselective agonists having parasympathetic (peripheral) side effects; and 2) lack of compounds with satisfactory PK properties. Some recent developments, however, have led to renewed interest in this area. The development of allosteric/ectopic agonists (*e.g.,* TBPB [**31**]) (114) or positive allosteric modulators (PAMs, *e.g.,* VU-10010 [**32**]) (115) (Fig. 4) has increased the opportunity to identify subtype-selective compounds (116), although only limited evidence has yet been published. The M_1 and M_4 receptors have attracted the most interest for the treatment of schizophrenia, and the main evidence suggests that M_1 stimulation can improve cognition, while M_4 stimulation may mediate effects in models of positive symptoms (34, 117). Furthermore, the des-methyl metabolite of clozapine (DMC) has been shown to have significant M_1-agonist activity and was in phase II development, until it was recently shown to be ineffective in schizophrenia monotherapy (35, 118; Acadia Web site).

Nicotine has for a long time been known to improve cognitive performance (*e.g.,* attention and sensory gating function), and most schizophrenia patients are heavy smokers. With the characterization of nicotine receptor subunits, it is now possible to design compounds without the cardiovascular actions of nicotine. Several nicotinic agonists selective for the $\alpha 7$ subunit, such as GTS-21 (**33**) (Fig. 4), and for $\alpha 4\beta 2$ subunits, such as ispronicline (**34**) or ABT-089 (**35**) (Fig. 4), show procognitive activity in preclinical studies and some are in early clinical development for cognitive disorders (119).

Finally, acetylcholinesterase inhibitors (*e.g.*, donepezil [**36**] [Fig. 4]) (120), which are mainly used for the symptomatic treatment of Alzheimer's disease, deserve some comment. As they enhance cholinergic activity, they may also have a place in the treatment of schizophrenia, including cognitive deficits. However, this treatment approach has shown disappointing clinical results, perhaps because of a nonselective cholinergic enhancement (centrally and peripherally; stimulating all receptor subtypes present in the vicinity of released acetylcholine), and accordingly show too narrow a tolerability range (121).

Histamine H3 antagonists

A few histamine H_3 antagonists, exemplified by ABT-239 (**37**) (Fig. 4) (122), are in development with enhancement of cognition as the target effect. Broad procognitive effects have been demonstrated along with neurochemical evidence for increased extracellular acetylcholine in cortex and hippocampus, but not in striatum (123, 124). Some evidence for a synergistic interaction with the motor depressant effects of haloperidol has been shown with ciproxifan (**38**) (Fig. 4) (125). No clinical results are yet available for this class of compounds.

Glutamate targets

A variety of ways to enhance glutamate function have been described, primarily through the NMDA receptor subtype: glycine/NMDA agonists including the endogenous compounds glycine and D-serine (126), glycine transporter 1 (GlyT1) inhibitors such as sarcosine (**39**), SSR-504734 (**40**) and DCCCyB (**41**) (126-129), and

$mGlu_5$ positive modulators such as CDPPB (**42**) (130) (Fig. 4), but also enhancers of AMPA receptor function such as AMPAkines (farampator [**15**] [Fig. 3]) (53) and last but not least $mGlu_{2/3}$ agonists such as LY-404039 (**19**) and its prodrug LY-2140023 (**20**) (Fig. 3) (15, 56), have generated great interest.

The NMDA enhancers and AMPAkines are considered to have potential mainly for improving cognitive deficits and negative symptoms, while it is more uncertain if they have sufficient effect on positive symptoms as monotherapy. However, animal data suggest that some of these compounds have efficacy on their own in animal models of positive symptoms, or can enhance the effect of antipsychotics in these models. Cognitive improvement has been demonstrated with D-serine, GlyT1 inihibitors and $mGlu_{2/3}$ agonists (131-133), while limited data are available for AMPAkines in schizophrenia-relevant animal models of cognitive deficits (54). Clinically, there are mixed positive and negative cognitive data for D-serine, glycine, sarcosine and AMPAkines (53, 126).

In animal models of positive symptoms, D-serine and the AMPAkine CX-516 have shown a lack of inhibitory effect on conditioned avoidance response, but enhanced the efficacy of clozapine, olanzapine and risperidone (52). Furthermore, the inhibitory effects of APDs on methamphetamine-induced hyperactivity were facilitated, while cataleptogenic activity was unaffected (134). The GlyT1 inhibitors SSR-504734 (**40**) and NFPS (ALX-5407, **43**) (Fig. 4) have efficacy on their own in some models of psychosis (*e.g.*, PCP- and amphetamine-induced hyperactivity; facilitation of prepulse inhibition of startle response and clozapine-like c-fos activation) (128, 135). However, no effects on conditioned avoidance response have been observed (Olsen and Didriksen, unpublished observations). The $mGlu_5$ positive modulator CDPPB (**42**) also has efficacy on amphetamine-induced hyperactivity, but characterization in psychosis models is as yet limited (130). The $mGlu_{2/3}$ agonist LY-404039 (**19**) (Fig. 3) has also shown efficacy in a conditioned avoidance response (56). Clinical proof of concept for positive symptoms has been obtained for the $mGlu_{2/3}$ agonist, and there are several clinical trials of glycine and D-serine with variable outcome, mostly as combination studies (126). One caveat for $mGlu_{2/3}$ agonists has been raised recently, as affinity for the high-affinity state of DA D_2 receptors has been claimed (136). Clinical results with selective GlyT1 inhibitors are still awaited.

Summary and conclusions

This review has attempted to give an overview of different trends in the treatment of schizophrenia. A major point is the acceptance that effective treatment needs to cover the various symptom dimensions, and that this is very difficult to achieve with monotherapy. This has stimulated interest in developing separate treatments for different symptom dimensions. It is still early, but we feel confident that this strategy will lead to improvements in pharmacotherapy in the future, and we believe that effective treatments will pave the way for regulatory acceptance of subindications in schizophrenia. This said, there are also some promising developments within monotherapy treatments, including optimized drugs targeting multiple monoamines and drugs acting on novel targets. It will be exciting to see whether large clinical trials will confirm the promise offered by results from animal models and from small clinical trials. We have not included discussion of novel targets arising from genomic strategies, as these were outside the scope of this article, and these targets are at an even earlier stage of discovery and development. However, this strategy is very important to pursue, as it may lead to a better understanding of this complex disease.

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