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REVIEW

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Investigational dopamine antagonists for the treatment of schizophrenia

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ABSTRACT

Introduction: Schizophrenia is a debilitating illness with a chronic impact on social function and daily living. Although various antipsychotics are available, there are still many challenges and unmet needs. Thus, many compounds with diverse mechanisms have been investigated, but all approved antipsychotics still require interactions with dopamine D_2 receptors.

Areas covered: We searched for investigational drugs using the key words 'dopamine' and 'schizophrenia' in American and European clinical trial registers (clinicaltrials.gov; clinicaltrialsregister.eu). Published articles were searched in PubMed, Embase, Medline, PsycINFO, Cumulative Index to Nursing and Allied Health Literature (CINAHL), the Web of Science and the Cochrane Central Register of Controlled Trials Library.

Expert opinion: The prospect of developing a dopamine antagonist is hopeful. Brexpiprazole and cariprazine, which were agents listed as 'investigational dopamine antagonists,' just received FDA approval. Novel agents such as BL 1020, ITI-007, and JNJ-37822681 have solid published data available, and agents such as L-THP, Lu AF35700, S33138, and SB-773812 are under vigorous investigation. However, the expected benefits of the newly developed antagonists may not be great because they offer little enhanced efficacy for negative symptoms, cognition and functional outcomes.

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Schizophrenia; Investigational antipsychotics; Phase II; agonist; antagonist; dopamine

1. Introduction

Schizophrenia, which affects approximately 1% of the population, is a debilitating illness with a chronic impact on social function and daily living [1]. It is characterized by the presence of positive, negative, and cognitive symptoms [2]. Although various antipsychotics are available, there are still many challenges and unmet needs [3]. More than 30% of patients do not respond to multiple antipsychotics, and they are regarded as having treatment-resistant schizophrenia [4].

The serendipitous emergence of typical antipsychotics, drugs that block dopamine D_2 receptors, has resulted in the partial treatment of schizophrenia. These typical antipsychotics are especially helpful in improving patient's positive symptoms, including delusion and hallucination [5]. Beyond treating positive symptoms, functional recovery has become an important goal in the treatment of schizophrenia. Several studies have suggested that negative symptoms, cognitive deficits, and extrapyramidal symptoms (EPS) largely account for the functional disability of schizophrenia [6]. In contrast to typical antipsychotics, atypical antipsychotics exert more balanced effects on dopaminergic and serotonergic receptors. By doing so, these atypical antipsychotics have replaced typical antipsychotics, with the aim of enhancing positive symptom control, improving negative symptoms, and decreasing neuroleptic-induced side effects, such as EPS [7]. However, no clear evidence has shown that atypical antipsychotics are more effective or are better tolerated than typical antipsychotics, and this assumption has become increasingly challenged even as atypical prescriptions have increased [8,9]. Currently, available atypical antipsychotics are also associated with undesirable side effects, including weight gain, diabetes, metabolic disturbances, and cardiovascular illnesses [10,11]. Therefore, novel antipsychotic agents are needed to diversify treatment options to improve symptoms, safety, and tolerability for long-term treatment of patients with schizophrenia.

Several imaging studies have shown that schizophrenia is associated with dopamine hyperactivity in the anterodorsal region of the caudate nucleus and that this hyperactivity is specifically coupled to positive symptoms [12,13]. Revisions to the dopamine hypothesis, the modified dopamine theory, further posit increased presynaptic dopamine function in the striatum with decreased dopamine function in the frontal cortex [14,15]. However, evidence from genetic, brain imaging, clinical, and pharmacologic studies have illustrated that schizophrenia is in fact a heterogeneous group of disorders [16,17]. Thus, no single molecular event can provide a complete solution to the complex pathophysiology of schizophrenia [18]. Additional research has identified other neurotransmitter systems in addition to dopamine that

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Article Highlights

- Schizophrenia is a debilitating illness with a chronic impact on social, vocational, and daily living functioning. Numerous potential agents having diverse mechanism of action were investigated. However, dopamine D_2 blocking agents still remained the only approved and effective drug class for schizophrenia and related psychotic disorders.
- The prospect of developing a clinically useful novel agent that generates a dopamine blockade is promising. Although ABT-925 failed to show its superior efficacy over placebo, BL-1020, ITI-007, and JNJ-37822681, have solid published data showing their efficacy and the potential to provide enhanced safety than the currently available atypical antipsychotics. Other agents such as L-THP, Lu AF35700, S33138, and SB-773812 are currently under vigorous investigation.
- These potential agents may broaden pharmacological options for clinicians in the future. Unfortunately, expected benefits from these agents are likely to be small because they may offer little enhanced efficacy for negative symptoms, cognition, and functional outcomes.
- More in-depth exploration of extra-dopaminergic mechanisms is necessary. Paradoxically, deeper understanding about atypical antipsychotics, such as clozapine, and better insight regarding dopamine theory will be required to develop a more efficacious and safe antipsychotics.
- Agents with diverse mechanisms of action beyond dopamine are being investigated, with positive prospects. However, much as 'all roads lead to Rome,' all the studied agents to date lead to alteration of dopamine receptors. Thus, the development of agents with dopamine antagonist properties will continue, unless a drug having a truly extra-dopaminergic mechanism, with its mechanism of action fully explained, is developed.

functions in the pathology of schizophrenia. Moreover, symptoms not responsive to current treatments likely involve neurotransmitter systems other than dopamine. In order to design antipsychotics with mechanisms extending beyond dopamine, diverse potential agents targeting glutamate receptors [19], promoting neuroprotection and decreasing neuroinflammation [20,21], enhancing cholinergic transmission [22], attenuating secondary messengers [23], modulating cannabinoid receptors [24], improving gamma-butyric acid (GABA) transmission [25], and regulating serotonin receptors [26] have been tested. However, none of these potential agents has yet been successfully developed for the treatment of schizophrenia. In fact, since their discovery in the 1950s, all known approved antipsychotic agents exert their effects through modulating dopamine transmission [27,28]. Even the most recent FDA-approved antipsychotics, including brexpiprazole [29] and cariprazine [30], target dopamine receptors, although they are not selective dopamine antagonists and have affinity for several serotonergic receptors. Thus, the purpose of this article is to provide a current review of investigational drugs for the treatment of schizophrenia with dopamine antagonism actions. Our primary aim is to forecast the clinical role of dopamine antagonist agents in the treatment of schizophrenia by focusing on their clinical results.

2. Data search

We initially searched for investigational drugs using the keywords 'dopamine' and 'schizophrenia' in American and European clinical trial registers (clinicaltrials.gov; clinicaltrialsregister.eu). Published articles were also identified from PubMed, Embase, Medline, PsycINFO, Cumulative Index to Nursing and Allied Health Literature, the Web of Science, and the Cochrane Central Register of Controlled Trials Library using the same terms. Reference lists from identified articles and reviews were used to find additional studies. No language restrictions were utilized. Agents that had received FDA approval and studies that were terminated due to safety concerns were excluded from our review. Published clinical trials were prioritized because they provide more organized data than unpublished trials. The data searches and verification were handled by lead authors (C-U Pae and C Han) and independently reassessed by coauthors (S-J Lee and S-M Wang).

3. Investigational dopamine antagonists with published clinical trials

3.1. ABT-925

ABT-925 is the only selective D_3 antagonist that has been tested in patients with schizophrenia [31]. ABT-925 has an approximately 100 times higher *in vitro* affinity for dopamine D_3 receptors than D_2 receptors [32]. Only one randomized, double-blind, placebo-controlled study (DBRPCT) has been performed to assess safety, tolerability, and clinical effects in patients with schizophrenia [31]. The study contained 155 patients, and they were randomized to ABT-925 50-mg, 150-mg, and placebo-treatment groups. Patients included were 18–65-year-old schizophrenia or schizoaffective disorder patients with an acute exacerbation of prominent 'active phase' symptoms, as defined by the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision criteria. The inclusion criteria were a Positive and Negative Syndrome Scale (PANSS) total score of 60 or greater and a score of 4 or greater ('moderate') for at least 2 of the 5 PANSS-positive symptoms.

The results showed no mean difference in PANSS scores among the three treatment groups. In fact, no significant differences between ABT-925 and placebo were observed for any end points. ABT-925 was generally safe, and the adverse event (AE) rate was similar among the three groups. A study using position emission tomography (PET) showed that D_3 receptor occupancy was less than 60% for both ABT-925 50 and 150 mg doses. This study also suggested that the dose of ABT-925 should be higher than 450 mg in order to achieve a sufficient level of D_3 receptor blockade [33]. Thus, the doses of ABT-925 used in the DBRPCT might have been too low. Similarly, the low doses might have been the reason for the ABT-925 50 and 150 mg doses having similar safety profiles and EPS propensity compared with placebo.

A unique *post hoc* analysis was conducted among the same population to investigate the effects of the S9G genotype on responses to ABT-925 [34]. Among 155 patients included in the DBRPCT [33], DNA samples from 117 patients were reanalyzed for the Ser9Gly D_3 receptor polymorphism. The results showed significant genotype-by-treatment interaction, with a higher mean change of PANSS total scores from baseline to end point in patients treated with 150 mg ABT-925 who carried the Gly allele. These results suggested that a

subpopulation of patients with a DRD3 G allele could respond better to 150 mg ABT-925 than patients with a DRD3 SS genotype.

3.2. BL-1020

BL-1020 is a first-in-class GABA-enhanced antipsychotic. It is an ester of the typical antipsychotic perphenazine and the key inhibitory brain neurotransmitter GABA. It blocks dopamine D_2 receptors with a high affinity for serotonin 5-HT_{2A} and histamine H_1 receptor interactions [35]. It also has an agonistic property for $GABA_A$ but not for $GABA_B$ receptors. A significant involvement of abnormalities in GABAergic function in schizophrenia has been demonstrated in numerous studies [36]. Rigorous studies have indicated that augmenting GABA function via an antipsychotic may lead to improved tolerability of dopamine antagonist medications [37]. Animal studies have suggested that the addition of GABA contributed to the precognitive outcomes associated with BL-1020 [38].

An understanding of dopamine, serotonin, glutamate, and GABA function in schizophrenia is needed to understand BL-1020's putative mechanism of action. Its D_2 receptor antagonism from perphenazine will directly decrease dopamine secretion in the mesolimbic pathway, leading to improvement of positive symptoms [39]. Although perphenazine may induce or worsen negative symptoms by blocking dopamine secretion in the prefrontal cortex, BL-1020's $GABA_A$-stimulating property may overcome this and improve positive, negative, and cognitive symptoms of schizophrenia. First, $GABA_A$ stimulation will inhibit glutamate neurons in the cortico-brainstem glutamate pathway. The hypoactive glutamate neurons will be less able to activate mesolimbic dopamine neurons, leading to improvement of positive symptoms. Second, the hypoactive glutamate neurons will not be able to activate GABA interneurons, which are located between glutamate neurons and the mesocortical dopamine neurons. GABA interneurons will be disinhibited, causing increased activation of mesocortical dopamine neurons and resulting in increased dopamine secretion in the prefrontal cortex. The increased dopamine in the prefrontal cortex will improve negative and cognitive symptoms of schizophrenia (Figure 1) [40]. Thus, the combination of GABA with perphenazine may substantially ameliorate the negative symptoms induced or worsened when perphenazine is used alone. Furthermore, the GABA component may enhance efficacy for the overall treatment of schizophrenia, including improvement in positive, negative, and cognitive symptoms. Like other atypical antipsychotics, 5-HT_{2A} antagonism will theoretically contribute to lowering the risk of EPS and prolactinemia.

The above hypothesis was investigated in a 6-week DBRPCT [41]. A total of 363 patients with chronic schizophrenia were randomized to receive BL-1020 (10 or 20–30 mg), placebo, or risperidone (2–8 mg). The results showed that the 20–30-mg BL-1020 dose was significantly better than placebo and equal to risperidone in improving PANSS (P = .02 vs. placebo) and Clinical Global Impression (CGI) (P < .001 vs. placebo) scores. However, the 10-mg BL-1020 dose was not superior to the placebo. In addition, the 20–30-mg BL-1020 dose improved cognitive function, as measured by the Brief Assessment of Cognition in Schizophrenia Scale, more significantly than the placebo (P = .009, effect size = .50), risperidone (P = .019, effect size = .43), or the 10-mg BL-1020 dose (P = .013, effect size = .42). In terms of safety, the prevalence of EPS and akathisia was similar in the 20–30-mg BL-1020 and the risperidone treatment groups, but it was significantly higher than in the 10-mg BL-1020 and placebo groups. The 20–30-mg BL-1020 treatment group showed significantly greater increases in prolactin

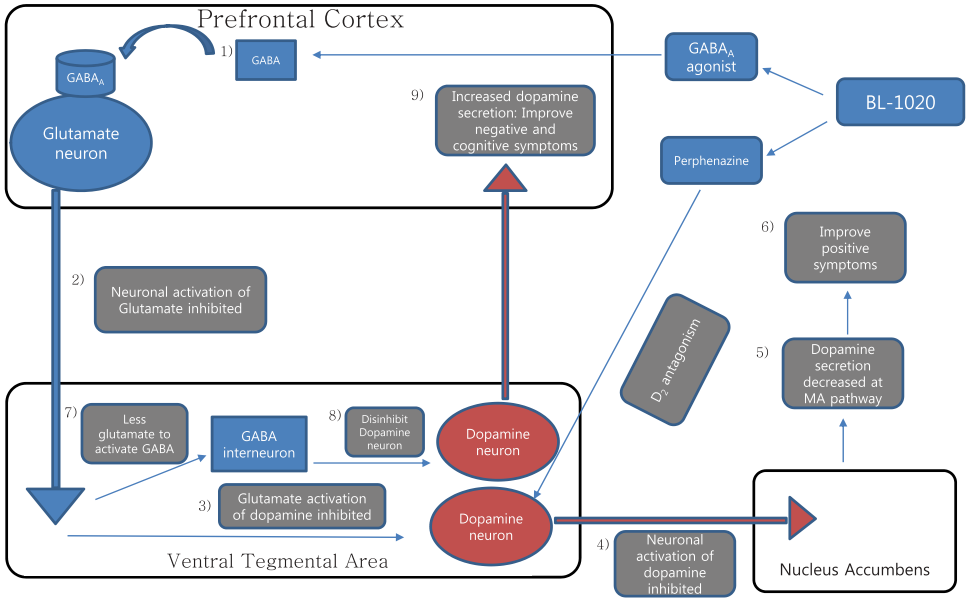

Figure 1. Mechanism of action for BL-1020 in negative and cognitive symptoms [38–40]. BL-1020 is a conjugate of perphenazine, a classical antipsychotic with D_2 receptor antagonist, and inhibitory brain neurotransmitter GABA. Positive symptoms of schizophrenia can be improved by direct inhibition of mesolimbic dopamine neuron via D_2 receptor antagonist property of perphenazine. BL 1020's $GABA_A$ agonist property will improve both positive and cognitive symptoms of schizophrenia. 1-2) $GABA_A$ agonist will inhibit glutamate neuron of cortio-brainstem glutamate pathway. 3-4) Hypoactive glutamate neuron will not be able to activate mesolimbic dopamine neurons, 5-6) leading to improvement of positive symptoms. 7) The hypoactive glutamate neuron will not able to activate GABA interneuron, 8) GABA interneuron's action will be disinhibited 9) causing increased activation of mesocortical dopamine neuron leading to improved cognition.

level than placebo, but the prolactin increase was much higher ($P < .0001$) for risperidone (mean change = 45.74 ± 44.96) than for 20–30 mg BL-1020 (mean change = 8.43 ± 38.89).

A subsequent DBRPCT (phase II/III study), called CLARITY (NCT 01363349), was conducted to further investigate the short-term (6-week) and long-term (6-month) pro-cognitive and antipsychotic effects [42]. The primary outcome measure was the MATRICS Consensus Cognition Battery (MCCB) normative composite score. MCCB is a neuropsychological test that comprises 10 measures of 7 different cognitive areas [43]. However, the investigating company, BioLineRx LTD, opted to discontinue the CLARITY study in March 2013 because an interim analysis showed that 'the trial would not meet the prespecified primary efficacy end point' [44].

A PET study showed that 32 mg of BL-1020 resulted in an average D_2 receptor occupancy of 44% at 4–6 h, and PK–PD data suggested that once-daily 32 mg BL-1020 administration will result in D_2 receptor occupancy between 50% and 70% [45]. Although the optimal dose of BL-1020 remains to be determined, more than 30 mg may be needed to show therapeutic effects. Therefore, an open-label multicenter, 6-week, sequential cohort study (NCT00480571) is presently ongoing to determine the safety and tolerability of two higher dose ranges (20–40 and 30–50 mg/day) of BL-1020 [46]. One additional phase II DBRPCT, NCT00722176, is still ongoing. NCT00722176 is a 6-week extension of the study by Geffen et al. [41]. Patients who completed the 6-week treatment period were eligible to continue an optional 6-week extension of the double-blind treatment [47].

3.3. Lumateperone (ITI-007)

Lumateperone (ITI-007) is currently in late-stage development for acute schizophrenia, bipolar depression, and behavioral disturbances in patients with dementia [48]. ITI-007 has a unique action involving multiple receptors. At low doses, it exhibits high-affinity serotonin 5-HT_{2A} receptor antagonism. At medium doses, it exhibits serotonin transporter (SERT) blockade and dopamine D_1 and unique dopamine D_2 presynaptic partial agonism, with postsynaptic antagonism activity selectively in the mesolimbic/mesocortical area [49]. This regional selectivity allows for the functional blockade of dopamine without increasing dopamine turnover, theoretically resulting in antipsychotic efficacy without motor side effects. It also increases the phosphorylation of mesolimbic GluN2B NMDA channel subunits. Thus, by acting through serotonergic-, dopaminergic-, and glutamatergic-signaling systems with regional selectivity, ITI-007 is expected to improve positive, negative, and cognitive symptoms of schizophrenia (Figure 2).

In a DBRPCT, 335 acutely psychotic adults with schizophrenia received ITI-007 (60 and 120 mg), placebo, and risperidone (4 mg) treatments [50]. ITI-007 at 60 mg was superior to placebo and equal to risperidone in improving the PANSS total score (Table 2). Secondary analyses further illustrated improvements in negative and depressive symptoms with 60 mg ITI-007. *Post hoc* analysis further showed that 60 mg ITI-007 significantly ($P < .001$, effect size = .6) improved prosocial behavior, as defined by a reduction in the PANSS prosocial factor. In terms of safety, both doses of ITI-007 were well tolerated with low discontinuation and AEs. More importantly, the metabolic profile, including prolactin, fasting glucose, total cholesterol, and triglyceride levels, was significantly better than for risperidone. No significant prolongation in corrected QT intervals or increase in heart rate was observed with ITI-007, suggesting a safe cardiovascular profile. Interestingly, the higher dose of ITI-007 (120 mg) was not as therapeutically effective as the lower dose of ITI-007 (60 mg). The authors could not determine an apparent reason and could only speculate that a higher frequency of side effects, specifically somnolence/sedation, might be the cause. Somnolence and sedation effects were mostly mild, but the occurrence of somnolence/sedation might have had

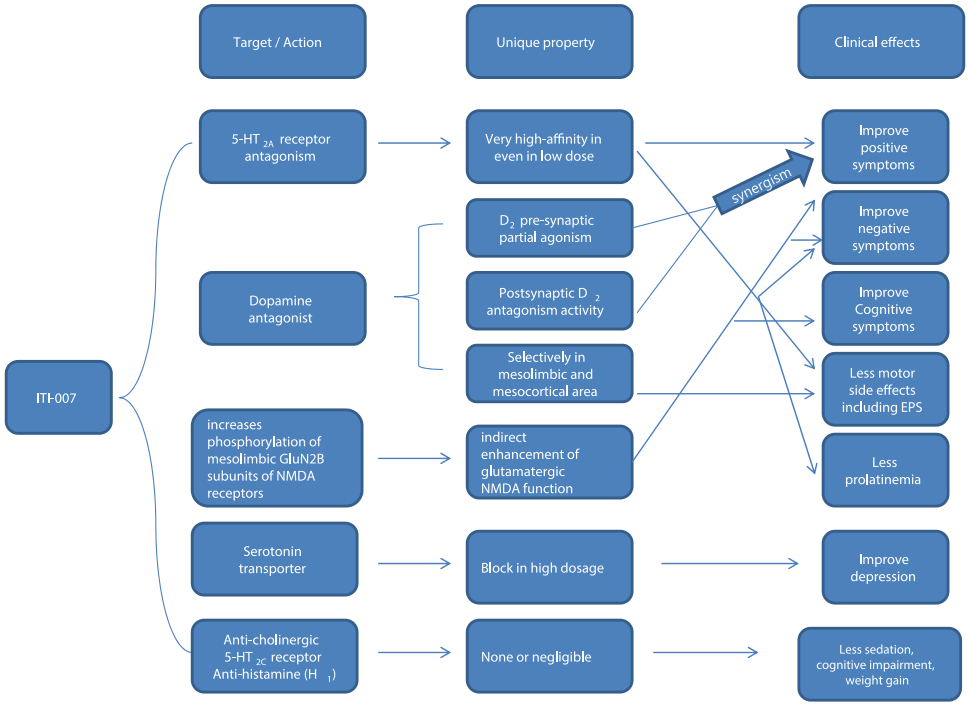

Figure 2. Mechanism of action for ITI-007 [49–50].

to a negative impact when patients underwent PANSS scoring. In addition, the higher dosage of ITI-007 resulted in higher D_2 receptor occupancy, which might have resulted in EPS. EPS may have masked ITI-007's effects on negative symptoms. In line with this hypothesis, the results showed that 60 mg reduced the severity of symptoms in a PANSS-negative symptom subscale (effect size = .34) for subgroups with prominent negative symptoms at baseline, whereas the improvement in negative symptoms with 120 mg was negligible (effect size = 0). The balance between presynaptic and postsynaptic reactions might be optimal at a dose of 60 mg [48] due to a unique synergy of presynaptic partial dopamine D_2 agonism and postsynaptic D_2 antagonism that could have been reduced with the higher dosage of ITI-007.

Two phase III trials were subsequently conducted, and both studies used dosages of ITI-007 lower than 60 mg. The first study, which investigated efficacy of ITI-007 at 60 and 40 mg, demonstrated superiority of ITI-007 at 60 mg over placebo at week 4 (LS mean change from baseline on PANSS total score [ITI-007 = −14.5 points, placebo = −10.3, effect size = −.30, P = .022]) [51]. ITI-007 at 60 mg also demonstrated improved social functioning as measured by improvement in the Personal and Social Performance Scale compared to placebo. In terms of safety, the numbers needed to harm for ITI-007 60 mg versus placebo for somnolence, sedation, and fatigue were 8, 16, and 25, respectively [52].

The second phase III study, which included risperidone at 4 mg as an active comparator, compared the efficacy of ITI-007 at 20 and 60 mg and placebo in schizophrenia. Again, ITI-007 at 60 mg improved symptoms of schizophrenia, but statistical superiority over placebo was not shown because of a high placebo response (Figure 3). Notably, both ITI-007 at 20 and 60 mg were less likely to increase triglycerides, cholesterol, and prolactin than risperidone. Moreover, in pooled analyses of all three of the above studies, the mean change of PANSS scores from baseline to end point for ITI-007 at 60 mg was significantly different from the placebo, and this significant difference was observed as early as day 8 (Figure 4) [53].

3.4. JNJ-37822681

JNJ-37822681 is a highly selective D_2 receptor antagonist characterized by a rapid dissociation rate from the D_2 receptor. Unlike many other atypical antipsychotics, it lacks affinity for serotonergic, histaminergic, and adrenergic receptors [54]. As an alternative to the 'balanced serotonin 5-HT_2A-dopamine D_2' hypothesis, rates at which agents dissociate from D_2 receptors have been suggested to better distinguish atypical from typical antipsychotics [55]. Furthermore, rapid dissociation from the D_2 receptor was hypothesized to reduce the risk of EPS and other metabolic side effects [56].

This hypothesis was tested in a DBRPCT [57]. Efficacy and safety of JNJ-37822681 were evaluated in patients with an acute exacerbation of schizophrenia by randomizing them to JNJ-37822681 (20, 40, or 60 mg in two divided doses), olanzapine (15 mg once daily), or placebo (for 6 weeks followed by olanzapine for 6 weeks) treatments. Although the total duration of the study was 12 weeks, its primary efficacy measure was a mean change of the PANSS total score from baseline to week 6. The results showed that all three JNJ-37822681 groups were equally effective as olanzapine and were more effective than placebo in improving the PANSS total score. Interestingly, 60 mg JNJ-37822681 showed significant improvement over placebo for mean change in the PANSS total score after day 3 (P < .05). In terms of safety, insomnia, akathisia, somnolence, and agitation were more frequent in JNJ-37822681-treated groups than in the placebo- and olanzapine-treated groups. A detailed analysis suggested that EPS-related AEs of JNJ-37822681 at 20 mg were comparable to that of olanzapine, but the rate increased dose dependently with the highest incidences observed in the JNJ-37822681 60 mg group. On the other hand, metabolic parameters were not worsened in all JNJ-37822681 groups, whereas the olanzapine group showed significant changes versus placebo for triglyceride, low-density lipoprotein cholesterol, very low-density lipoprotein cholesterol, and free fatty acid levels. *Post hoc* analysis showed that mean weight

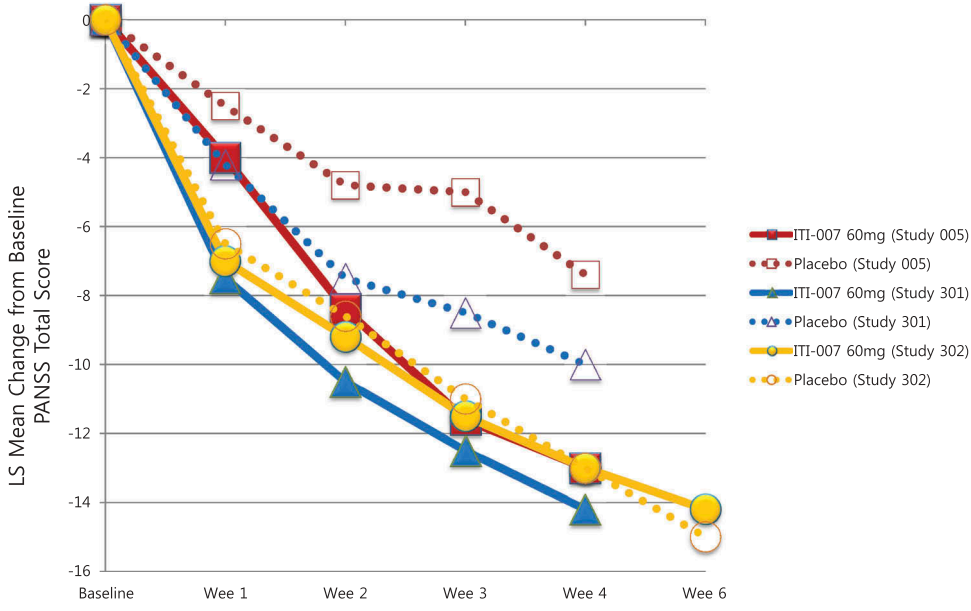

Figure 3. High placebo affect for study trial ITI-007-302 (Adapted from [53]). In all 3 studies, ITI-007 60mg improved symptoms of schizophrenia with a similar trajectory and magnitude of improvement. However, the placebo response was high in trial ITI-007-302. Thus, the separation between ITI-007 60mg and placebo was not observed.

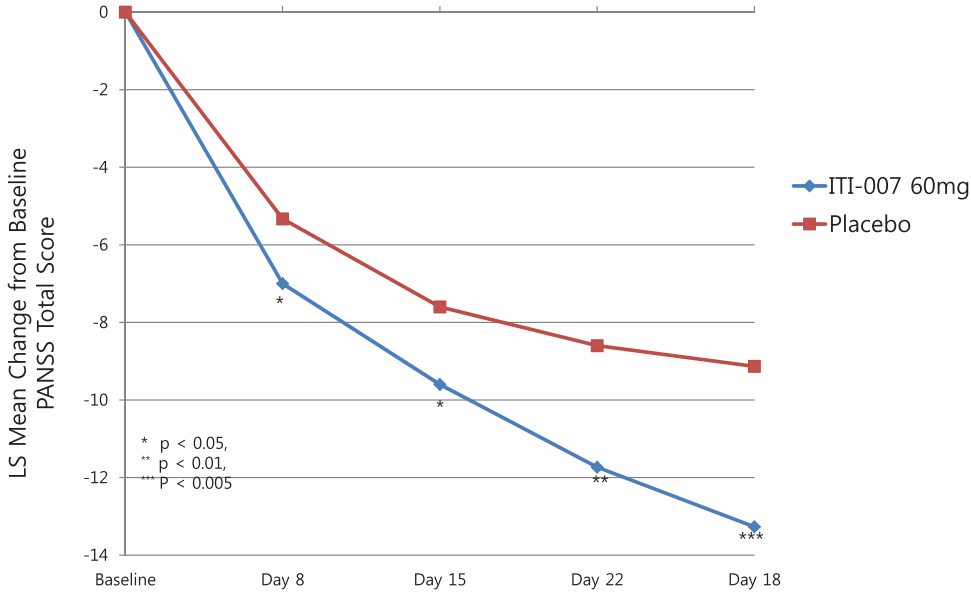

Figure 4. Pooled data for ITI-007 60mg across 3 trials (ITI-007-005, ITI-007-301, ITI-007-302) using analysis of covariance (ANCOVA) with last observation carried forward (Adapted Reprinted from [53]).

changes at week 12 were −.3, +.3, +.8 kg for the JNJ-37822681 20, 40, and 60 mg doses, respectively, and the mean changes were significantly less ($P < .001$) than those observed in the olanzapine group (+2.7 kg) [58].

A summary of receptor profiles of published clinical trials including BL-1020, ITI-007, and JNJ-37822681 is provided in Table 1. Table 2 summarizes randomized, controlled, double-blind studies of investigational dopamine antagonists with published data for the treatment of schizophrenia.

4. Agents without published clinical trials

4.1. L-tetrahydropalmatine

Levo-tetrahydropalmatine (L-THP) is an alkaloid found in several different plant species which was traditionally used in Chinese herbal medicine [59]. It has robust anti-inflammatory properties including TNF-alpha and Intercellular Adhesion Molecule (ICAM) inhibition, antiprotozoal activity, and an antipsychotic-like pharmacological profile of D_1, D_2, and D_3 receptor antagonism [60,61]. It was originally investigated in the treatment of substance abuse disorders such as cocaine addiction [62,63]. Since its high affinity for D_1 versus D_2 receptors distinguishes it from typical antipsychotics, and its D_1-to-D_2 ratio resembles that of clozapine, a randomized clinical trial is currently being conducted for the treatment of schizophrenia (NCT02118610) [64].

4.2. Lu AF35700

In order to understand Lu AF35700, its relationship with Zicronapine must first be addressed. Zicronapine is a D_1, D_2, and 5-HT_{2A} receptor antagonist. Two phase II trials of zicronapine (3, 5, 7, 10 mg) compared its efficacy with that of placebo and olanzapine. The results showed that 7 and 10 mg Zicronapine were comparable to olanzapine and were more efficacious than placebo [65]. However, Lundbeck decided to remove zicronapine from its development portfolio due to the development of Lu AF35700, which has a better drug-ability profile than zicronapine [66]. Lu AF35700 has a novel pharmacological profile with predominant D_1 vs. D_2 dopamine receptor occupancy and high 5-HT_6 receptor occupancy [67]. Because of its lower D_2 receptor occupancy, Lu AF35700 is hypothesized to have a better side-effect profile than other current antipsychotics, including a lower risk of causing EPS, prolactin elevation, dysphoria/anhedonia, and depressed mood. Lu AF35700 has already demonstrated tolerability in a safety trial. A completed but unpublished phase I study investigated safety, tolerability, pharmacokinetic, and pharmacodynamic properties of Lu AF35700 in patients with schizophrenia [68]. Another phase I trial is recruiting patients to investigate the effects of Lu AF35700

Table 1. Binding affinities (K_i values in nM)[a] of investigational dopamine antagonists for the treatment of schizophrenia.

Receptors	ITI-007 [49]	JNJ-37822681 [55]	BL-1020 [46]
D_1	52	>3000	100
D_2	32	158 (132–190)	66
D_3		1159	48
D_4			124–384
5-HT_{1A}			685
5-HT_{2A}	.5	2896	211
5-HT_{2C}	173	>4000	
5-HT_6			323
5-HT_7			51
$Alpha_1$	73	>5000	1770
$Alpha_2$			227
H_1	>1000	4931	473
M_1			1500
SERT	62		
NERT	>1000		
DAT	>1000		
$GABA_A$			3740

D_1: Dopamine D1 receptor; D_2: dopamine D2 receptor; D_3: dopamine D3 receptor; D_4: dopamine D4 receptor; 5-HT_{1A}: $serotonin_{1A}$ receptor; 5-HT_{2A}: $serotonin_{2A}$ receptor; 5-HT_{2C}: $serotonin_{2C}$ receptor; 5-HT_6: $serotonin_6$ receptor; 5-HT_7: $serotonin_7$ receptor; $Alpha_1$: a_1 adrenoreceptor; $Alpha_2$: a_2 adrenoreceptor; H_1: $histamine_1$ receptor; M_1: $muscarine_1$ receptor; DAT: dopamine transporter; $GABA_A$: gamma-aminobutyric acid receptor A; NERT: norepinephrine transporter; SERT: serotonin transporter.

Table 2. Investigational dopamine antagonists with published randomized-controlled double-blind studies for the treatment of schizophrenia.

Drug	Author (year)	Duration (weeks)/ Study phase	Dosage (mg/day)	*N*	PANSS		Safety and other results
					Baseline	Mean change (from baseline to end point)	
ABT-925	Redden (2011) [31]	6	50 150 PBO	52 54 47	NA NA NA	−6.7 (2.54) −7.6 (2.41) −7.4 (2.38)	No specific adverse event was significantly higher for either of the ABT-925 dose groups than for placebo group Secondary efficacy measures BPRS and CGI were also not significant among three groups
BL-1020	Geffen (2012) [41]	6/Phase II	10 20–30 RPR 2–8 PBO	90 89 91 93	97.7 (11.1) 97.7 (10.3) 99.5 (12.1) 98.5 (11.4)	−.7[a] −6.6[a]* −9.4[a]**	Cognitive function improvement: BL-1020 20–30 mg > PBO, RPR, and BL-1020 10 mg in BACS EPS: BL-1020 20–30 mg = RPR > BL-1020 10 mg, PBO Prolactin increase: RPR > BL-1020 20–30 mg > PBO
	NCT 01363349 (study not published) [41]	6/Phase II and III	15–35 RPR 2–6	133 136	Baseline MCCB 8.7 (13.66) 8.2 (13.86)	End point MCCB 13.5 (12.92) 12.5 (13.68)	Study terminated by its company, BioLineRx LTD, because interim analysis showed that the trial would not meet the prespecified primary efficacy end point
	NCT00722176 (study not published) [41]	6/Phase II	10 20–30 RPR 2–8 PBO	NA	NA	NA	Extension of the study by Geffen et al. The study is still ongoing, so results not yet available
ITI-007	Lieberman (2016) (ITI-007-005) [50]	4/Phase II	60 120 RPR 4 PBO	84 83 82 85	95.1 (11.1) 85.3 (15.4) 92.7 (12.5) 91.9 (10.9)	−13.2 (1.69) * −8.3 (1.68) −13.4 (1.72) * −7.4 (1.68)	TEA risk: ITI-007 120 mg > ITI-007 60 mg = PBO = RPR EPS: ITI-007 60, 120 mg = PBO < RPR Metabolic parameter: PBO = ITI-007 60, 120 mg > RPR in prolactin, fasting glucose, total cholesterol, triglycerides
	ITI-007-301 (NCT02282761, study not published) [51]	4/Phase III	40 60 PBO	150 150 150	NA	NA	ITI-007 60 mg > PBO in primary efficacy measure, LS PANSS change from baseline to end point and in PSP Safety: ITI-007 60 mg vs. placebo (somnolence: 17.3% vs. 4.0%; sedation: 12.0% vs. 5.4%; fatigue: 5.3% vs. 1.3%) ITI-007 40 mg > PBO in CGI (secondary outcome) at week 4
	ITI-007-302 (NCT02469155, study not published) [53]	6/ Phase III	20 60 RPR 4 PBO	NA NA NA NA	NA	NA	Total of 696 patients included. ITI-007 60 mg did not separate from placebo because of very high placebo response in PANSS Safety: ITI 20 mg and 40 mg less likely increased triglycerides, cholesterol, and prolactin than RPR
JNJ-37822681	Schmidt (2012) [57]	6	20 40 60 OZP 15 PBO	99 103 98 93 99	90.2 (10.39) 90.2 (10.88) 90.9 (10.78) 90.3 (11.02) 91.0 (11.15)	−18.4 (1.93)** −17.7 (1.87)** −20.0 (1.93)** −22.9 (1.88)** −6.4 (2.04)	Insomnia, akathisia, somnolence, agitation more frequent in JNJ-37822681 than in PBO or OZP Metabolic parameter: PBO = JNJ-37822681 > OZP in triglycerides, LDL cholesterol, VLDL cholesterol and free fatty acids

*$P < .05$; **$P < .01$.
[a]Results reflect difference in PANSS total LS mean score from placebo according to ANCOVA.
BACS: Brief Assessment of Cognition in Schizophrenia;EPS: Etrapyramidal symptom;LS: least square;MCCB: MATRICS Consensus Cognition Battery;OZP: olanzapine; PANSS: Positive and Negative Symptom Scale; PBO: placebo; PSP: Personal and Social Performance Scale; RPR: risperidone; TEA: treatment-emergent adverse event.

on electrical activity in the heart as measured via electrocardiogram in patients with schizophrenia or schizoaffective disorder after 6 weeks of treatment [69].

A phase III clinical trial is currently recruiting participants [70]. This study will be composed of 1000 patients to determine the efficacy and safety of Lu AF35700 at 10 and 20 mg in patients with treatment-resistant schizophrenia, with olanzapine and risperidone as comparators. Depending on the results of this phase III trial, Lu AF35700 may become the first new pharmacotherapy, after clozapine, for patients with treatment-resistant schizophrenia.

4.3. S33138

S33138 has a preferential antagonism of D_3 versus D_2 receptors with modest antagonist properties for 5-HT_{2A}, 5-HT_7, and α_{2C} receptors [71]. Its preferential blockade of D_3 over D_2 receptors may lead to the improvement of cognitive function

and frontocortical cholinergic transmission. An animal model study showed that S33138 improved cognitive performance in several rats and primates following procedures generating cognitive impairment [72]. A phase II clinical trial investigating the safety and efficacy of S33138 versus risperidone in schizophrenic patients has been ongoing since 2005, but no detailed results are yet available.

4.4. SB-773812

SB-773812 is a moderate antagonist of D_2 receptors and a high-affinity antagonist for D_3 and 5-HT_{2A} receptors. It has no affinity for histamine H_1, muscarinic M_{1-4}, D_1, adrenergic 1B, and adrenergic 1–3 receptors [73]. Along with S33138, SB-773812 is also speculated to have efficacy for cognitive and negative symptoms of schizophrenia while minimizing side effects commonly observed with other antipsychotics (i.e. sedation, weight gain, and EPS). Pharmacokinetics of SB-773812 has been investigated in healthy volunteers [74]. A phase I study further investigated safety, tolerability, and pharmacokinetics of SB-773812 in schizophrenic patients for 28 days in in-patient settings [75]. Although the results are neither posted nor published, the phase I study may have demonstrated its safety as a phase II study was conducted soon after. The phase II trial studied SB-773812 60 mg, olanzapine 15 mg, and placebo treatments in subjects with acute schizophrenia for 12 weeks. The trial is completed, but results are not yet available [73].

5. Conclusion

The biggest unmet need in the treatment of schizophrenia is the restoration of functions requiring improvement in cognitive function and the reduction of negative symptoms [76]. However, no novel antipsychotics have been able to provide better efficacy in the treatment of schizophrenia [77]. Extensive research is ongoing to overcome this obstacle and provide a breakthrough in the treatment of schizophrenia by developing antipsychotics with targets beyond dopamine receptors. As a result, several promising candidates with novel or additional mechanisms of action are currently under development [19,78]. However, antipsychotic substances with primary actions outside the dopamine system have not yet been approved for clinical practice. Hence, targeting dopamine antagonism remains a primary clinical and research focus for the treatment of schizophrenia.

The prospect of developing a clinically useful novel agent that generates a dopamine blockade is promising. Brexpiprazole and cariprazine, which were agents listed as 'investigational dopamine antagonists,' have just received FDA approval. A DBRPCT study for ABT-925 failed to show superior efficacy of 50 and 150 mg ABT-925 over placebo in all efficacy measures. However, three other agents, including BL-1020, ITI-007, and JNJ-37822681, have solid published data showing their efficacy and the potential to provide enhanced safety than the currently available atypical antipsychotics. Other agents such as L-THP, Lu AF35700, S33138, and SB-773812 are currently under vigorous investigation. Among these, Lu AF35700 is specifically being studied for its effects on treatment-resistant schizophrenia. Thus, it may become the first new pharmacotherapy, after clozapine, for patients with treatment-resistant schizophrenia if the phase III trial shows positive results. Development of the above agents, which have a variety of antidopaminergic mechanisms of action, is expected be to successful, which may broaden pharmacological options for clinicians. However, expected benefits from these agents are likely to be small because they may offer little enhanced efficacy for negative symptoms, cognition, and functional outcomes.

6. Expert opinion

A century ago, large public institutions for serious mental illness, tuberculosis, and leprosy prevailed. Among these, only mental illness, especially schizophrenia, remains unchanged in prevalence and disability [28,79]. Greater innovation in the treatment of schizophrenia is needed to overcome this persistent issue. Thus, more in-depth exploration of extra-dopaminergic mechanisms is necessary. To date, no agents have proven to have better efficacy than clozapine. A deeper understanding of clozapine and its mechanism of action will be required. Thus, two parallel waves will be expected in the development of novel antipsychotics. One wave will be the development of agents targeting receptors other than dopamine, and the other will be agents derived from the modified dopamine hypothesis.

Regarding the dopamine hypothesis, it was initially considered that only positive symptoms of schizophrenia could be explained by the dopaminergic hyperactivity theory. However, recent studies have increasingly examined the possible role of dopamine in negative and cognitive symptom domains as well [80]. Moreover, numerous studies have highlighted interactions between alternative neurochemical models of schizophrenia with dopamine [81]. Release of dopamine in the prefrontal cortex and striatum can be modulated through NMDA-stimulated GABA-release and $GABA_B$-receptor activity, which further suggested connections between the modified dopamine hypothesis and extra-dopaminergic theories of schizophrenia [82]. Likewise, most of the agents described above have mechanisms of actions in addition to dopamine antagonism. Thus, they are not considered selective dopamine antagonists. A class of drugs having antagonism selectively at dopamine receptors, namely, benzamides, has been extensively tested in the past. Many of them failed to demonstrate efficacy in schizophrenia (metoclopramide) or had to be withdrawn due to substantial side effects (remoxipride). One of the only effective substituted benzamide drugs widely used in the market is amisulpride. In this respect, the development of ABT-925 and JNJ-37822681 is significant because, unlike other investigational dopamine antagonists discussed here, their mechanisms of action are highly selective for dopamine receptors.

The D_3 receptor has been proposed as a therapeutic target in schizophrenia because it is expressed in mesencephalic, limbic, and cortical areas relevant to psychotic and cognitive symptoms of schizophrenia [32]. However, high homology between the D_3 and D_2 receptors has been an obstacle in the development of selective D_3 antagonists. Amisulpride is an atypical antipsychotic widely

used in Europe and Asia that preferentially binds to dopamine D_2 and D_3 receptors in the limbic rather than striatal structures. Theoretically, this may lower the risk of inducing EPS compared with typical antipsychotics. In *ex vivo* binding studies, amisulpride was twofold more selective for D_3 receptors than for D_2 receptors [83]. ABT-925 is unique because it has an approximately 100-fold greater *in vitro* affinity for D_3 receptors than D_2 receptors. Unfortunately, a DBRPCT study failed to demonstrate efficacy of 50 and 150 mg doses of ABT-925 relative to placebo in all outcome measures. An optimal balance between D_3/D_2 receptors, rather than high selectivity for D_3 receptors, might be important in the treatment of schizophrenia. For example, amisulpride selectively antagonizes presynaptic D_2/D_3 receptors at low doses, resulting in enhanced dopamine transmission and thereby possibly improving negative symptoms. Higher doses block postsynaptic D_2/D_3 receptors, resulting in inhibition of dopamine transmission and thereby possibly improving positive symptoms [84]. Similarly, the recently approved cariprazine has only slightly greater (10-fold) preference for D_3 receptors compared to D_2 [30]. Thus, one can speculate whether the favorable clinical efficacy of cariprazine results from interactions with D_2 or D_3 receptors [85]. The 50 and 150-mg doses were likely too low to illustrate ABT-925's role in the treatment of schizophrenia, as another study showed that D_3 receptor occupancy was less than 60% for both ABT-925 50 and 150 mg doses. To truly investigate its therapeutic role in schizophrenia, higher dosages of ABT-925 (i.e. 450 mg) should be used to achieve a sufficient level of D_3 receptor blockade in the brain.

The development of JNJ-37822681 is significant because, unlike other investigational dopamine antagonists, its main action is classical: it is a highly selective dopamine D_2 receptor antagonist. Its unique feature is a rapid dissociation rate from the dopamine D_2 receptor, which may reduce the risk of EPS and other metabolic side effects. The fact that akathisia was more frequent in JNJ-37822681 40 and 60 mg treatments than in olanzapine (15 mg) contradicted the 'rapid dissociation' theory. The rapid dissociation property might be reduced with higher JNJ-37822681 doses. Thus, subsequent studies should also investigate lower doses of JNJ-37822681. Similarly, dose-finding studies are needed for BL-1020. Although BL-1020's therapeutic effect was demonstrated in a DBRPCT with positive outcomes in cognitive functions, its effect in cognitive function was not replicated in the CLARITY study. Thus, higher doses of BL-1020 may be needed; a subsequent trial is presently ongoing to determine the safety and tolerability of two higher dose ranges (20–40 and 30–50 mg/day) of BL-1020.

Among investigational drugs discussed in this review, Lumateperone (ITI-007) is the closest to receiving FDA approval. It is in late-stage development for not only schizophrenia but also for bipolar depression and behavioral disturbances in patients with dementia. ITI-007 has multiple sites of action, including at the serotonin 5-HT_{2A} receptor, SERT, dopamine D_1 and dopamine D_2 receptors, and the mesolimbic GluN2B NMDA calcium channel. The multiple mechanisms of action of ITI-007 might have complementary synergistic effects, leading the agent to have low AEs, a better metabolic profile, and less cardiogenic effects than risperidone. In an initial DBRPCT, doses of 60 and 120 mg were used because a PET study conducted in healthy volunteers showed striatal D_2 receptor occupancy of approximately 50% and 70% for ITI-007 60 and 120 mg doses, respectively [86]. Finding an optimal D_2 occupancy dose before undertaking the phase II trial might be one of the important reasons that ITI-007 has become more promising than other investigational drugs.

Intensive research has been done in the past several decades to investigate the influence of genetic variations on antipsychotic agent dosages, treatment efficacy, and safety [87]. Pharmacogenetic testing may add predictive value for the selection of antipsychotic drugs and optimal doses according to the patient's genetic profile. Future drug development may be aimed at achieving personalized medicine: finding schizophrenic patients with the right genetic variants to maximize a drug's therapeutic effect and minimize drug-induced side effects. However, pharmacogenetic-based personalized medicine remains a challenge because many diverse genetic variants may interact with each other in combination with environmental factors. Despite this, many studies of pharmacogenomics in schizophrenic patients still rely on a few polymorphisms [88].

Agents with diverse mechanisms of action beyond dopamine are being investigated, with positive prospects. Countless other novel agents targeting alpha 7 nicotinic receptor, neuroprotection and neuroinflammation, cholinergic transmission, secondary messengers, cannabinoid receptors, and serotonin receptors are being investigated. However, much as 'all roads lead to Rome,' all the studied agents to date lead to alteration of dopamine receptors, either in the form of agonist/partial agonist or antagonist activity. Thus, the development of agents with dopamine antagonist properties will and should continue, unless a novel agent with an extra-dopaminergic mechanism, with its mechanism of action fully explained, is developed.

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