Targeting the dopamine receptor in schizophrenia: Investigational drugs in Phase III trials

Naren P. Rao, MBBS, MD[1,2]

Gary Remington, MD, PhD, FRCPC[1,3,4]

[1]Centre for Addiction and Mental Health (CAMH), Toronto, Canada

[2]Centre for Neuroscience, Indian Institute of Science, Bangalore, India

[3]Campbell Family Mental Health Research Institute, CAMH

[4]Dept. of Psychiatry, University of Toronto, Toronto, Canada

Corresponding author:

Dr. Gary Remington

Centre for Addiction and Mental Health (CAMH)

250 College Street

Toronto, Canada M5T 1R8

Phone: (416) 535-8501 ext. 4864

Fax: (416) 979-4292

E-mail: gary.remington@camh.ca

Abstract

Introduction: The 1950s heralded modern psychopharmacology, including chlorpromazine as the first in a long line of compounds that would come to be called 'antipsychotics'. Soon after, it was established that these drugs effected their response through blockade of dopamine and, in particular, the D_2 receptor. This information in hand, drug development turned to synthesizing highly selective D_2 antagonists (e.g., haloperidol), although evidence failed to substantiate clinical superiority for these agents versus their low potency counterparts. With its low binding affinity for the D_2 receptor and unique clinical profile, clozapine challenged, but did not negate, our longstanding emphasis on dopamine or integral role of D_2 blockade in antipsychotic activity. Dopamine continues to represent a critical line of investigation in drug development for schizophrenia, although much of the work now focuses on its potential in other symptom domains.

Areas covered: We searched for investigational drugs using the key words 'dopamine,' 'schizophrenia,' and 'Phase 3' in American clinical trial register (clinicaltrials.gov), published articles using National Library of Medicine's PubMed database, and supplemented results with a manual search of cross-references and conference abstracts. We excluded drugs which are already FDA approved and restricted to drugs in phase 3. We provide a brief description of drugs targeting dopamine receptors (agonists/partial agonists/antagonists).

Expert opinion: Drug development confirms ongoing interest in dopaminergic compounds for the treatment of schizophrenia, although the nature of the focus has changed considerably. There remains interest, albeit diminished, in developing better *antipsychotic* compounds, the D_3 receptor garnering much of the attention more recently. The greatest enthusiasm currently centres around dopamine's role in negative and cognitive symptom domains. With theories conceptualizing hypodopaminergic activity underlying these deficits, considerable effort is focused on drug strategies that will enhance dopamine activity. Finally, a small body of research is investigating dopaminergic compounds vis-à-vis side effect treatments. In domains beyond psychosis, however, dopamine arguably is not seen as so central, reflected in considerable research following other lines of investigation.

Keywords: dopamine receptor, dopaminergic, Phase III, schizophrenia

Article Highlights:

- The dopamine hypothesis has remained central to any discussion regarding the pathogenesis and treatment of schizophrenia.
- Dopamine continues to represent a critical line of investigation in drug development for schizophrenia, although much of the work now focuses on its potential in negative and cognitive symptom domains.
- While enthusiasm for developing better *antipsychotic* medication by means of dopamine receptor antagonism remains, it is being overshadowed by current interest in improving negative and cognitive symptoms.
- As the focus of schizophrenia research has shifted from *clinical* to *functional* recovery, majority of investigational drugs in phase 3 trials identify either negative symptoms or cognition as a treatment target.

Introduction

1.1 Schizophrenia

Schizophrenia is a severe,and often debilitating, psychiatric illness that routinely is first observed in late adolescence/early adulthood[1, 2]. Clinical features vary among individuals, and they encompass aheterogenousgroup of symptoms and signs that can be subgrouped into three major domains: positive (delusions, hallucinations), negative (apathy, amotivation, blunted affect etc.), and cognitive (impaired memory, attention, executive functions, etc.). The etiopathogenesis of schizophrenia remains elusive despite a half century of systematic research [3], although it was soon after the introduction of antipsychotics in the early 1950's that dopamine receptors and its blockade was first posited as the mechanism of action of antipsychotics. It remains to this point that all drugs effective in treatment of schizophrenia target dopamine receptors, anddopamine receptors continue to be targets in new drug development research [4]. In this review we summarise the evidence for targeting dopamine receptors in schizophrenia, specifically focusing on drugs in Phase III trials.

1.2 Dopamine hypothesis of schizophrenia

While other theories have been forwarded, the dopamine hypothesis has remained central to any discussion regarding the pathogenesis and treatment of schizophrenia. Over the last few decades, the hypothesis has evolved from general dopaminergic hyperactivity [5, 6] to regional dopamine differences (subcortical hyperdopaminergia and cortical hypodopaminergia) [7] to dopamine dysregulation as the final common pathway [8]. The initial model hypothesized general hyperactivity of the dopaminergic system, predominantly based on pharmacological studies indicating dopamine neurotransmission as the target of antipsychotic action [9-12]. Later, this model was revised to incorporate the advances arising from imaging and animal studies [13-15],with the recent revision positioning dopamine dysregulation as the final common pathway, implicating a complex interplay of factors that may play a contributory role[8].

1.3 Implication for clinical symptoms

Although chlorpromazine's antipsychotic properties were discovered in the early 1950s [16], it took several more decades to establish that it was the dopamine blocking properties of these drugs, and more specifically D_2 blockade, that accounted for their antipsychotic effects [17, 18]. With this information in hand, it was possible to move from the low potency conventional antipsychotics like chlorpromazine, with their heterogeneous receptor binding profiles, to the development of highly selective D_2 antagonists, such as haloperidol and pimozide. Clozapine's unique pharmacological profile (e.g. low affinity for the D_2 receptor), in combination with evidence regarding its superior efficacy in treatment resistant schizophrenia, fostered the search for other 'atypical' antipsychotics and non-dopaminergic mechanisms (e.g. serotonergic, glutamatergic and α-adrenergic) that might account for their different clinical profile[19-21]. While different lines of investigation were pursued (e.g. selective serotonin 5-HT_2 antagonism), current thinking has come full circle and reiterated the position that at least some degree of D_2 receptor blockade is necessary for antipsychotic activity [22]. Accordingly, the dopamine receptor continues to represent a key target in schizophrenia drug discovery, and the next section reviews related investigational drugs in phase III trials.

2. The dopamine system

2.1 Dopamine receptor subtypes

Dopamine receptors are classified into five distinct receptor subtypes (D_1 to D5) based on their structural and pharmacological properties. These G protein coupled receptors are grouped into either D_1 class (D_1, D_5) or D_2 class (D_2, D_3, D_4) dopamine receptors. The D_1 class and D_2 class receptors have distinct properties: a) D_1 class receptors stimulate cyclic Adenosine Monophosphate (cAMP) production by Adenylyl cyclase while D_2 class receptors result in inhibition of Adenylyl cyclase; b) D_1 receptors are located on postsynaptic target neurons, whereas D2 receptors are located on both pre- and postsynaptic neurons and, thus, have autoreceptor function as well; and, (c) splice variants are seen in D_2, but not D_1, receptors as only the D_2 class have introns in their genes. These receptors are located in high or low density at different locations throughout the central nervous system (CNS) [23] (Figure 1)

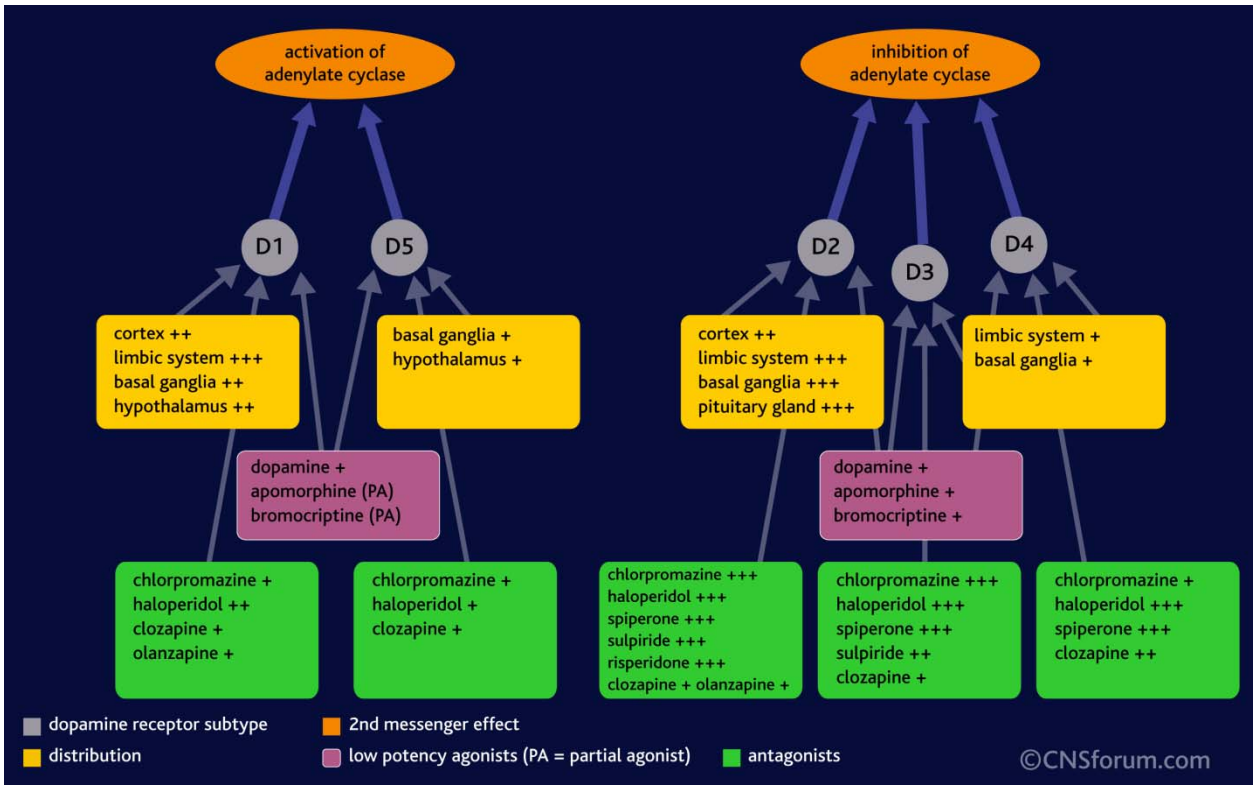

Figure 1: Subtypes of dopamine receptors and their location, specific agonists and antagonists (Adapted from CNS Forum, http://www.cnsforum.com/imagebank/item/DA_rcpt_subtypes/default.aspx)

2.2 Physiological functions of dopamine and its receptors

Dopamine is critically involved in a number of vital functions including locomotion, reward and reinforcement, affect, cognition (memory, learning, attention, impulse control, decision making, motor learning etc.), sleep, reproductive behavior and regulation of food intake. Further to this point, considerable effort has been directed toward characterizing the function(s) of individual dopamine receptor subtypes in this regard. It is important to note that although these receptors are distinct and grouped into different subfamilies, more than one receptor subtype is involved in a single function and they interact and influence each other, as well as other neurotransmitters, through their downstream effects.

D_1, D_2 and D_3 subtypes are involved in the control of motor activity, while the role of D_4 and D_5 in the control of locomotion is minimal. The location of receptor significantly influences the effect of receptor stimulation; as noted, the D_1 receptors are located postsynaptictallywhereas D_2 and D_3 receptors are located at both pre- and postsynaptic locations. D_1 has a stimulatory effect on motor activity, but D_2 and D_3 activation depends on the concentration of the dopamine or its agonist. At lower concentrations dopamine stimulates presynaptic autoreceptors, resulting in decreased activity, but at higher concentrations it stimulates postsynaptic receptors, resulting in behavioral activation. D_3 receptors predominantly exert an inhibitory action on locomotion [24, 25].

The D_1receptor is believed to play a critical role in higher cognitive functions and predominates the frontal cortex. D_2receptors are primarily located in subcortical structures and are implicated, in particular, with the positive symptoms of psychosis. In addition, they also function as autoreceptors. Both D_1 and D_2 receptors have been identified as critical in reward and reinforcement. D_3receptors are predominantly located in the ventral striatum and are believed to play an important role in motivation, whereas D_4receptors are present in the prefrontal cortex (PFC) and hippocampus, but not striatum [26]. D_5 receptors are primarily located in the hippocampus and entorhinal cortex [27].

2.3 Downstream effects of dopamine receptor stimulation: dopamine receptor signaling

Dopamine receptors constitute 7-transmembrane domain receptors and belong to a large family of G-protein coupled receptors. Binding of dopamine to receptor activates G-protein, which induces a sequence of intracellular events [28-30]. Though G-protein coupled signalling is regarded as the common mechanism of dopamine receptors, studies have implicated G-protein independent signalling events as well [31, 32].Depending on receptor subtype, stimulation of G-protein can either stimulate or inhibit cAMP production; D_1 class stimulate, while D_2 class inhibit CAMP production (Figure 2) . The activity of G protein mediated signaling is modulated by proteins termed arrestins and regulators of G protein signaling (RGS), proteins which play an important role in the desensitization/internalization of receptors [23, 33-36]. There is growing appreciation that these downstream signalling mechanisms, especially the Akt/GSK-3 signalling cascade, play an important role in psychiatric disorders and, as a result, are targets for novel psychotropic drugs [37, 38].

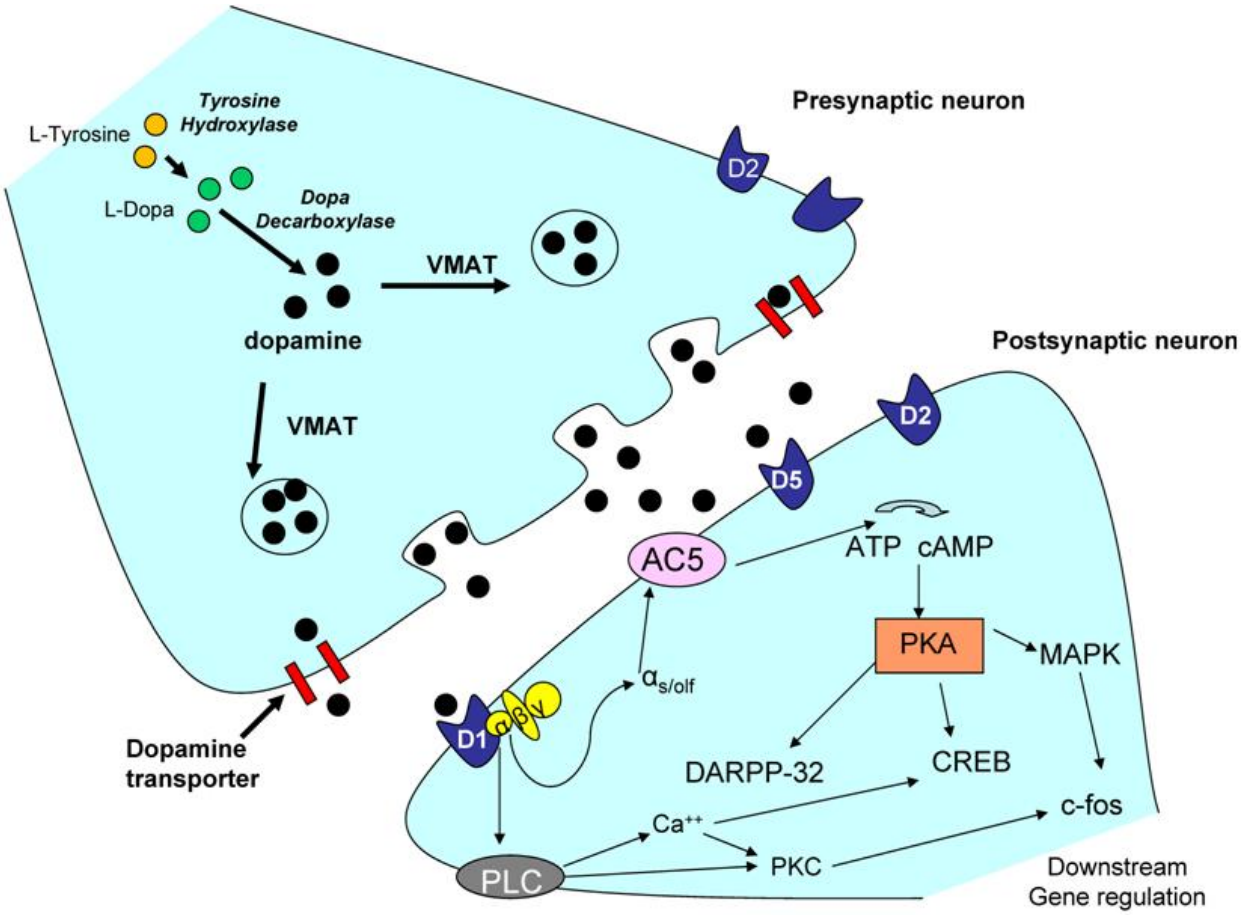

Fig2: Representative dopamine synapse. The signaling pathways in the postsynaptic neuron are only representative of D1-like receptor signaling (which increases cAMP). D2-like receptors are known to have an opposite effect on cAMP activity and, thus, slightly different downstream signaling cascades. Abbreviations: AC5 - adenylatecyclase 5; ATP - adenylyl tri-phosphate; CREB - cyclic AMP response element binding protein; DARPP-32 - dopamine and cyclic AMP-regulated phosphoprotein; D1 - dopamine receptor 1; MAPK - mitogen-activated protein kinase; PKA - protein kinase A; PKC - protein kinase C; PLC - phospholipase C; VMAT -- vesicular monoamine transporter; c-fos - downstream early gene. Adapted from *Int J BiolSci* 2010; 6(2):133-150.

3. Rationale for targeting dopamine receptors in schizophrenia

3.1 Neuroimaging and postmortem evidence

Studies have examined dopamine receptors in schizophrenia using in vivo imaging (Positron Emission Tomography, PET; Single Photon Emission Computed Tomography, SPECT) as well as postmortem samples. Postsynaptic $D_{2/3}$ receptor density has been extensively examined in both post-mortem and *in vivo* studies, with meta-analyses reporting small elevations in receptor density; however, it is also acknowledged that these results can be confounded by previous medication use [39-42]. Amphetamine-induced dopamine release and depletion paradigm studies have also demonstrated increased striatal dopamine release [43-45] and elevated baseline dopamine activity [46-49]. Most of the aforementioned studies examined striatal dopamine receptors using raclopride, a predominantly D_2 selective ligand. Recently, the role of the D_3 receptor in schizophrenia has been investigated using [^{11}C] (+)-4-propyl-9-hydroxynaphthoxazine (PHNO), a radiotracer with higher affinity for D_3 versus D_2 receptors,with no differences reported between patients and controls [50]. A limited number of studies have examined distribution of cortical D_1 receptors using the radiotracers [^{11}C] (+) 8-chloro-5-(7-benzofurany1) 7-hydroxy-3-methy1-2,3,4,5-tetrahydro-lH-3-benzazepine (NNC 112) NNC 112 and [^{11}C] 7-chloro-3-methyl-1-phenyl-1,2,4,5-tetrahydro-3-benzazepin-8-ol (SCH 23390); however, results are inconsistent, possibly due to differences in the radiotracers or differences in study population [51-53]. Some post-mortem studies have reported increased density of D_2 receptors in brains of individuals with schizophrenia, though these abnormalities could be attributed to antipsychotic medication exposure [54-56]. Similar inconsistent findings are reported in studies evaluating D_1, D_3 and D_4 receptor densities in post-mortem tissue [26, 57-59]. Taken together, though, studies do demonstrate dopaminergic abnormalities in schizophrenia.

3.2 Dopamine's role beyond psychosis: negative and cognitive symptoms

The initial dopamine hypothesis posited schizophrenia to be a disorder of general dopaminergic hyperactivity [5, 6],addressing the*antipsychotic* action of what were then termed 'neuroleptics'[60], but not the negative and cognitive symptom domains. Over the years attention has increasingly focused on these other features and, not surprisingly, has also examined putative role of dopamine. Evidence favouring dopamine's involvement can be summarised as follows: (i) both animal and human studies have identified dopamine as critically involved in motivation,

reward and cognition [61-69] ENREF 20; (ii) cognitive deficits and apathy are commonly seen in patients with Parkinson's disease, a disorder of dopamine dysfunction [70]; (iii) dopamine modulating drugs like methylphenidate and levodopa improve these symptoms [[71-73]]; (iv) functional magnetic resonance imaging (fMRI) studies during cognitive challenges quite consistently demonstrate decreased task-related activity [74-76] in dopamine receptive fields like dorsolateral prefrontal cortex (DLPFC) and anterior cingulate cortex (ACC) in patients with schizophrenia [77-89]; and, (v) PET imaging studies with a D_1 receptor radioligand demonstrate cortical dopamine dysfunction in schizophrenia [90, 91]. Summarizing, it is now widely accepted that both negative symptoms and cognitive deficits are best understood as features of hypo- rather than hyperdopaminergic activity [56, 92-94].

4. Drugs Targeting Dopamine Receptors in Phase III trials

4.1 Dopamine receptor antagonists

- **BL-1020**

  BL-1020 is a γ-aminobutyric acid (GABA)-enhanced molecule with combined dopamine antagonism and GABA agonism. In a recently completed phase II, randomized trial, 363 patients received BL-1020 in one of two doses (10, 20 mg), placebo, or risperidone (2-6 mg). BL-1020 was significantly better than placebo for treatment of positive symptoms, and superior to both placebo and risperidone for treatment of cognitive deficits [95]. However, the manufacturer BiolineRx, a biopharmaceutical development company, discontinued the Phase III trial after an interim analysis as the drug did not meet pre-determined primary efficacy end point thresholds [96].

- **Blonanserin**

  Blonanserin, developed in Japan by Sumitomo Pharmaceutical, is a D_2, D_3, and 5-HT_{2A} receptor antagonist. It has low affinity for 5-HT_{2C}, adrenergic α_1, histamine H_1 and muscarinic M1 receptors, but relatively high affinity for 5-HT_6 receptors [97, 98]. In earlier, randomized clinical trials, blonanserin proved superior to placebo, with equal efficacy to

haloperidol and risperidone, for positive symptoms, in addition to superiority versus haloperidol in terms of negative symptoms [99-102]. In one open-label trial, blonanserin had moderate effect on cognitive symptoms in first episode, but not chronic,patients with schizophrenia[103].

- **Zicronapine**

  Zicronapine's pharmacological profile includes D_1, D_2 and $5HT_{2A}$ receptor antagonist properties. In twophase II trials, multiple doses of zicronapine (3, 5, 7, 10 mg) were compared to placebo and olanzapine; zicronapine 7 and 10mg were more efficacious compared to placebo, and comparable with olanzapine[104]. A phase III clinical trial is complete but results are pending (Table 1).

4.2 Dopamine receptor agonist/partial agonists

- **Cariprazine**

  Cariprazine is a D_3 preferential D_2/D_3 receptor partial agonist [105] currently being evaluated for relapse prevention in schizophrenia (Table 1). It also has affinity for $5HT_{2B}$ and $5HT_{1A}$ receptors. In a multicentre, double-blind, randomized trial 73 participants received cariprazine in one of three doses (1.5, 3, 4.5 mg), risperidone 4 mg, or placebo. Cariprazine was well tolerated, significantly improved PANSS as well as Clinical Global Impression–Severity (CGI-S) scores versus placebo, and was comparable to risperidone [106]. The half-life of its metabolite, didesmethyl-cariprazine is longer than that of cariprazine, which may allow for the development of a once-weekly oral formulation [107]. Two short-term phase III trials involving schizophrenia were recently completed. In one, 617 subjects were randomized to cariprazine 3 or 6 mg/day, aripiprazole 10mg/day or placebo. In the second, 446 subjects were randomized to cariprazine 3-6 mg/day, cariprazine 6-9 mg/day or placebo. Both studies reported significant improvement in PANSS scores withcariprazine treatment compared to placebo. Common adverse events reported includedakathisia, insomnia, headache, restlessness and extrapyramidal symptoms [108].A new drug application has been filed [96].

- **Bromocriptine**

  Bromocriptine is a dopamine receptor agonist presently usedin gynecology for treatment of hyperprolactinemia [109]. Recently it has also been examined in psychiatry, in this case

forantipsychotic-induced hyperprolactinemia.In one open-label study, bromocriptinesignificantly decreased hyperprolactinemia secondary to antipsychotic treatment with no worsening of psychotic or extrapyramidal symptoms (EPS)[110]. Asecond open-label trial for the same indication is currently registered, although the status is not known (Table 1).

- **Bifeprunox**

  Bifeprunox is a partial agonist at D_2 and 5-HT_{1A} receptors. It also has high affinity for D_3 and D_4 receptors, although it is relatively devoid of $5HT_{2A}$, α_1, α_2, muscarinic, and histaminergic receptor binding. In a phase II double-blind, placebo-controlled study, 589 patients were administered bifeprunox in one of three doses (5, 10, 20 mg), placebo or risperidone 6 mg. Bifeprunox 20 mg produced significant reductions in PANSS scores compared to placebo, but did not match risperidone [111]. Later trials of bifeprunox were terminated, and the drug was rejected by US FDA.

4.3 Other mechanisms (non-receptor mediated dopaminergic action)

- **Lisdexamfetamine**

  Lisdexamfetamine is a prodrug of amphetamine, a drug indicated in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) [141]; the inactive prodrug is converted to l-lysine and therapeutically active d-amphetamine [142]. It was recently examined in a Phase II multicentre, open-label study that included a randomized, double-blind, placebo-controlled withdrawal phase as an adjunct to antipsychotic treatment. Lisdexamfetamine was administered (20-70 mg/day) to 92 schizophrenia patients with predominantly negative symptoms and significantly decreased scores on the Scale for the Assessment of Negative Symptoms (SANS-18), the negative symptom subscale of the Positive and Negative Syndrome Scale (PANSS), andthe total and general psychopathology scores, without worsening of positive symptoms [112]. A phase III trial was registered but withdrawn for non-safety related business prioritization reasons.

4.4 Existing drug in alternate formulation

- **Inhaled loxapine**

Loxapine, an antipsychotic used worldwide, is well established in the treatment of schizophrenia. It manifests D_2 antagonistic activity in line with other first generation antipsychotics, in addition to $5HT_{2A}$ antagonism although not of the magnitude assigned to 'atypicality'. Intramuscular loxapine is used in both the acute and maintenance treatment of schizophrenia. In a recent study loxapine was delivered by inhalation using a novel Staccato delivery system to people with schizophrenia and agitation;a total of 344 individuals were recruited in a phase III, randomized, double-blind, placebo-controlled, parallel-group study comparing inhaled loxapine (5 or 10 mg) versus placebo. Both doses significantly reduced agitation versus placebo, as assessed by the Positive and Negative Syndrome Scale–Excited Component (PANSS–EC) 2 h after first dose [113].The effect size for the PANSS-EC at 2 h was 0.45 for the 5 mg dose and 0.60 for the 10 mg dose, arguing for the 10 mg dose [114]. Common adverse events included sedation, dysgeusia and dizziness. Serious adverse effects, namely wheezing/bronchospasm, was reported in three participants, and neck dystonia/oculogyric crisis in one participant.

5. Conclusion

A half century after it was implicated in the pathophysiology of schizophrenia and the action of antipsychotics, dopamine continues to garner considerable attention in terms of drug development. However, the landscape has changed considerably, in part because of developments in our understanding regarding dopamine but also because of changes in how we conceptualize schizophrenia. The former is reflected in drugs like blonanserin and zicronapine, which focus beyond the notion of highly selective D_2 blockade, albeit for different reasons. Interest in the D_3 receptor is largely premised on its possible involvement in psychosis [115], whereas the D_1 receptor is of interest for its putative role in other domains such as negative symptoms and cognition. To this last point, it is fair to say that enthusiasm for developing better *antipsychotic* medication remains, but is being overshadowed by current interest in improving these other features. This is clearly reflected in Table 1, where 5 of the 8 drugs under investigation (blonanserin, BL-1020, cariprazine, zicronapine, lisdexamfetamine) identify either negative symptoms or cognition as a treatment target. Such a transition is very much in line with the field, which has increasingly shifted its focus from *clinical* to *functional* recovery [116].

Drugs that block dopamine and the D_2 receptor have proven to be at least reasonably effective antipsychotic drugs, but they fall considerably short in terms of efficacy in treating the other features of schizophrenia. Notably, this holds true for the newer antipsychotics as well, including clozapine [117, 118].

6. Expert opinion

It is interesting to track the direction schizophrenia drug development has taken from the standpoint of what has evolved clinically. At the time high potency conventional antipsychotics were taking over the market, psychiatry really only conceptualized schizophrenia as a disorder of *psychosis*. It was these individuals who filled institutions, and the discovery of neuroleptics was critical to the deinstitutionalization process that had begun post-World War II [119]. It was not until the 1980's that the notion of two symptom domains (positive and negative) gathered momentum and, notably, at that time it was postulated that negative symptoms were representative of underlying morphological changes not particularly amenable to pharmacological treatment.

Clozapine's reintroduction in the early 1990's in many countries, including the United States [120], generated a series of new drugs that collectively claimed 'atypical' status, generating a level of excitement and optimism that the field had not witnessed in decades. Indeed, a kind of therapeutic nihilism had grown through the 1980's as it became apparent that selective D_2 antagonists were not going to be the panacea hoped for based on existing theory. In this context, and given how unique clozapine seemed both clinically and pharmacologically, it is not surprising that expectations were high for what these new drugs might do. Earlier evidence that they led to improvement in both negative and cognitive symptoms was rapidly embraced, but over the next decade tempered considerably with later reports acknowledging that benefits in these domains were modest at best [117, 118]. At the same time, the initial notion that these drugs effected greater and broader efficacy was linked in particular to their higher serotonin 5-HT_2 versus D_2 binding profile [121], a model so popular that by the late 1990's the need for D_2 blockade was even being called into question [122].

The fallout of these events has led us to an interesting spot. It turns out that we have not built better *antipsychotics* with the exception of clozapine, and its clinical superiority seems confined to a specific subpopulation, that is treatment resistant schizophrenia (TRS). Moreover, we are left not knowing why it is superior to all other antipsychotics in this regard. Two widely held hypothetical models to explain atypicality have focused on serotonin-dopamine [121] and transient D_2 binding [123], both of which are unable to account for clozapine's greater efficacy in TRS. Atypicals mirroring clozapine on one or even both levels simply haven't delivered a similar clinical profile.

In getting to this point though, we have learned much more about schizophrenia. It is no longer conceptualized as a disorder of only psychosis; in fact, in many ways psychosis has taken a back seat to other symptom domains. More specifically, the enthusiasm to fully tap the benefits of these new and purportedly better medications led to increased expectations regarding functional recovery, and reports were soon implicating the negative and cognitive symptoms as the rate limiting features of the illness [124]. Unfortunately, as this message was crystallizing it was also becoming increasingly apparent that the drugs generating this research were falling short of initial expectations.

In looking at the drugs in Table 1, we can see pieces of this story. The search for better *antipsychotic* drugs continues, but remains built upon D_2 binding. As an aside, the search for therapeutic agents effecting their response through other mechanisms continues; for example, there is considerable interest in glutamatergic drugs [125], although recent excitement generated regarding an mGlu2/3 receptor agonist [126] has since been tempered by follow-up data [127] . What is most noteworthy from the standpoint of dopamine is the search for its role in these other symptoms, in combination with the notion that this will come through *increasing* dopaminergic activity. This categorically flies in the face of the old axiom that drugs acting in this fashion (e.g. L-dopa) are contraindicated in individuals with psychosis [128]. Additionally, it is fair to say that dopamine does not have the same foothold with respect to these other symptoms that is holds regarding positive symptoms. In that sense, the field is much more open to the possibility that systems beyond dopamine may play important roles in these other domains.

What is less clear is whether we can pharmacologically impact negative symptoms and cognitive deficits in a way that translates to meaningful clinical improvement, regardless of mechanism(s)

of action. In addition, and particularly relevant to drugs enhancing dopamine, is the clinical reality that they must be administered in the context of concomitant D_2 antagonism. We already see this scenario played out in the form of the partial dopamine agonist, aripripazole, which because of its uniqueness has been identified as the first 'third generation' antipsychotic [129]. At least to date, evidence has not been forthcoming that it has produced gains in these other features of schizophrenia that would set it apart from other atypicals. In going down this road, what we are beginning to see, however, is a shift away from the development of single drugs that attempt to do all things. Instead, as reflected in this review, drugs are being developed that may well be specific to a single domain, setting the stage for polypharmacy, with choice of agent and combinations shaped by the specific clinical profile of the particular individual - a step closer to personalized medicine.

Table1: List of investigational drugs targeting dopamine receptors in Schizophrenia

Drug name	Pharmacology	Identifier	Current Status	Sponsor	Primary target
Inhaled loxapine	D_2 antagonist	NCT00628589 NCT00721955	Completed	Alexza Pharmaceuticals, Inc.	Agitation
Blonanserin	$D_{2/3}$-$5HT_2$ antagonist	NCT01516424	Recruiting	Sumitomo Pharmaceutical (Suzhou) Co., Ltd.	Positive, negative
BL-1020	DA antagonist with GABA modulation	NCT01363349	Terminated	BioLineRx, Ltd.	Cognition
Bromocriptine	Dopamine Agonist	NCT00315081	Unknown	University Hospital, Bonn	Risperidone-induced hyperprolactinemia
Cariprazine	D_2/D_3 partial agonist; 5HT antagonist	NCT01412060 NCT01104779 NCT01104766 NCT01104792	Recruiting Completed Completed Completed	Forest Laboratories	Positive, negative symptoms
Zicronapine	D_1, D_2& $5HT_{2A}$ receptor antagonist	NCT01295372	Completed	H. Lundbeck A/S	Postitive, negative symptoms
Bifeprunox	D_2 partial agonist	NCT00366704	Terminated	Pfizer	Weight gain
Lisdexamfetamine	Amphetamine precursor	NCT01234298 NCT01760993 NCT01760993 NCT01738698 NCT01760889	Withdrawn	Shire Development LLC	Negative symptoms

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