Cariprazine, a selective dopamine D₃ receptor partial agonist with unique features to treat schizophrenia negative and cognitive symptoms

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INTRODUCTION
Schizophrenia is a complex psychiatric disorder with positive and negative symptoms, as well as with impaired cognitive functions. Negative symptoms affect 15-60% of patients with schizophrenia [1]. For the treatment of schizophrenia symptoms several different antipsychotics were developed in the past five decades which all target mainly through dopamine D₂ receptor subtype either as antagonists or partial agonists. Recently a new D₂/D₃ receptor partial agonist, cariprazine, was approved by EMA and FDA for the treatment of schizophrenia and for manic or mixed episodes associated with bipolar I disorder (FDA).  

STUDY OBJECTIVE
To explore the role of dopamine D₃ receptors in the treatment of schizophrenia and investigate the hypothesis that negative and cognitive symptoms of schizophrenia can be improved by targeting dopamine D₃ receptors.

METHODS
Data from non-clinical in vitro receptor binding studies, in vivo animal behavioral studies, PET studies in patients with schizophrenia and the clinical trial in predominant negative symptom patients were analyzed and compared to provide evidence how the D₃ receptor occupancy correlates with the improvement of negative and cognitive symptoms of schizophrenia.  

RESULTS
In vitro Dopamine Receptor Binding Profile (Figure 1)
Overall, in the receptor binding assays cariprazine showed high affinity (Ki= 0.09 nM) and selectivity (8.1-fold) for recombinant human D₃ versus D₂ receptors with partial agonist activity at both [2]. Other antagonists – partial agonists (aripiprazole, brexiprazole) [3, 4] or antagonists (e.g. risperidone) [5] – showed high affinity and selectivity for D₂ versus D₃ receptors.

Figure 1 Dopamine Receptor Subtype Fingerprint of Atypical Antipsychotics

Affinities Related to D₃ Receptor

Dopamine Receptor

Aripiprazole

Brexiprazole

Cariprazine

D₂

D₁

D₃

In vivo Dopamine Receptor Occupancy (Figure 2)
In a human PET study, based on the investigated doses (1mg, 3mg, 12mg) strong and dose-dependent occupancy at both D₂ and D₃ receptor subtypes were seen after 2 weeks of cariprazine treatment in patients with schizophrenia [6]. These data (3.43–5.75-fold higher affinity for D₃ versus D₂ receptors) confirmed cariprazine’s in vivo D₃ receptor selectivity. Although all other antipsychotics have significant binding affinity for D₂ and D₃ receptors in vitro, they do not show appreciable D₂ receptor occupancy in vivo [7, 8, 9].

Figure 2 Human [¹¹C]-(+)PHNO PET Occupancy Data at D₂ and D₃ Dopamine Receptors

CONCLUSIONS
The in vitro and in vivo animal and human studies seem to confirm the hypothesis that cariprazine, the newly marketed antipsychotics, showing high affinity for dopamine D₂ receptors and balanced in vivo occupancy of both dopamine D₂ and D₃ receptors can be used for the improvement of negative and cognitive symptoms of schizophrenia.

Animal Behavioral Studies (Figure 3)
Chronic Unpredictable Stress (CUS) [10]  
In an in vivo animal behavioral model of negative symptoms, chronic unpredictable stress (CUS) was used to induce anhedonia in mice. In this model, cariprazine significantly attenuated CUS-induced anhedonia in wild-type but not in D₃ receptor knockout mice.

As cognitive deficits are related to negative symptoms of schizophrenia, cariprazine was also investigated in models for cognitive deficit. In this model, cariprazine completely reversed the phencyclidine-induced impairment of executive function in the wild-type but not in the D₃ knockout mice.

Figure 3 Animal Models of Anhedonia (A) and Cognitive Deficit (B) in Wild-Type and Dopamine D₃ Receptor Knockout Mice

Clinical Efficacy (Table 1)
Effect in Negative and Cognitive Symptoms [12]  
In a clinical trial 461 patients with predominant negative symptoms of schizophrenia were double-blind treated with risperidone (n=231) or cariprazine (n=230). The least squares mean difference (LSMD) in change from baseline to Week 26 was statistically significant in favor of cariprazine versus risperidone in PANSS-Factor Score for Negative Symptoms (PANS-FSNS; LSMD=− 1.49; P<0.002) and personal and social performance total scores (PSP; LSMD=− 4.63; P<0.001). LSMD from baseline in the Meltzer cognitive factor score was also significantly greater for cariprazine versus risperidone at weeks 18 and 26 (both weeks, P<0.05).

Table 1 LSMD Changes of PANS-FSNS, PANSS Single Items, PSP & Meltzer Cognitive Factor Score

<table>
<thead>
<tr>
<th>Outcome Measures</th>
<th>Definition</th>
<th>Cariprazine (n=230)</th>
<th>Risperidone (n=231)</th>
<th>Mean Difference</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PANNS-FSNS</td>
<td>Marder negative factor</td>
<td>-8.90</td>
<td>-7.44</td>
<td>-1.46</td>
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<td>N1</td>
<td>Blunted affect</td>
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<td>-1.1</td>
<td>-0.289</td>
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<td>N2</td>
<td>Emotional withdrawal</td>
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<td>-1.00</td>
<td>-0.244</td>
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<td>N3</td>
<td>Poor rapport</td>
<td>-1.30</td>
<td>-1.06</td>
<td>-0.243</td>
<td>0.007</td>
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<td>N4</td>
<td>Passive/apathetic social withdrawal</td>
<td>-1.53</td>
<td>-1.30</td>
<td>-0.227</td>
<td>0.016</td>
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<td>N6</td>
<td>Lack of spontanity and flow of conversation</td>
<td>-1.45</td>
<td>-1.30</td>
<td>-0.152</td>
<td>0.123</td>
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<tr>
<td>G7</td>
<td>Motor retardation</td>
<td>-1.12</td>
<td>-1.01</td>
<td>-0.109</td>
<td>0.229</td>
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<td>G16</td>
<td>Active social avoidance</td>
<td>-0.86</td>
<td>-0.69</td>
<td>-0.17</td>
<td>0.042</td>
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<td>PSP</td>
<td>Personal &amp; Social Performance</td>
<td>14.30</td>
<td>8.66</td>
<td>5.63</td>
<td>&lt;0.001</td>
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<tr>
<td>Cognitive subcale</td>
<td>Meltzer cognitive factor – Week 18</td>
<td>-2.78</td>
<td>-2.33</td>
<td>-0.448</td>
<td>0.049</td>
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<td>Meltzer cognitive factor – Week 26</td>
<td>-3.13</td>
<td>-2.60</td>
<td>0.533</td>
<td>0.028</td>
<td></td>
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</tbody>
</table>

REFERENCES
5. PDSK K Database, 2018.

DISCLOSURES & FUNDING STATEMENT
Studies were funded by Gedeon Richter Plc. and Allergan. Dr. Laszlovzsky, Dr. Barabas, Mr. Kiss, Dr. Szatmári, Dr. Németh are employees of Gedeon Richter Plc., Mr. Adham and Dr. Earley are employees of Allergan.