I BLOCKED D2 AND ALL I GOT WAS THIS LOUSY SIDE EFFECT: WHAT TO DO WHEN D2 ISN'T ENOUGH
Learning Objectives

• Evaluate the evolving data on the neuropathology of schizophrenia

• Differentiate the mechanisms of action and corresponding clinical profiles of antipsychotics

• Evaluate the mechanisms and latest clinical data on new and emerging antipsychotics
Challenges of Treating Schizophrenia

• Chronic, severe, and debilitating brain disorder resulting in positive and negative symptoms, mood/affective impairments, and cognitive dysfunction
Schizophrenia Marketplace: Drug Development Areas for Unmet Needs

Drugs that treat negative symptoms

Drugs that enhance cognition

Drugs that provide improved options for treatment resistant patients

Drugs with enhanced safety profiles

Drugs that increase compliance

Dopamine Pathways Relevant to Schizophrenia Symptoms

The Dopamine Hypothesis of Schizophrenia

Hyperactivation of both the mesolimbic and nigrostriatal pathway is thought to underlie the positive symptoms of schizophrenia.

Hypoactivation of the mesocortical pathway is thought to underlie both the negative and cognitive symptoms of schizophrenia.

Efficacy: Beyond D2 Hypothesis

• Schizophrenia has been primarily associated with dopamine dysfunction
  - All effective treatments directly target the dopamine D2 receptor

• Core pathophysiology may also involve dysfunction of glutamatergic, serotonergic, cholinergic, and gamma-aminobutyric acid (GABA) signaling
  - Imbalance within any of these may influence the entire system
  - Novel treatment development is focusing on targets beyond dopamine, including glutamate, serotonin, acetylcholine, GABA, and inflammatory cytokines

## Beyond the D2 Hypothesis: Novel Treatment Targets for Schizophrenia

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Target</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dopamine</td>
<td>Dopamine stabilizers</td>
<td>Improve medication adherence</td>
</tr>
<tr>
<td>Glutamate</td>
<td>NMDA, AMPA, or metabotropic receptors</td>
<td>Improve negative symptoms and cognitive impairments</td>
</tr>
<tr>
<td>Serotonin</td>
<td>5HT1A agonists, 5HT2C antagonists and agonists, 5HT3 antagonists,</td>
<td>Reduce EPS; Improve negative symptoms, mood and cognitive impairments;</td>
</tr>
<tr>
<td></td>
<td>5HT6 and 5HT7 antagonists, 5HT reuptake inhibitors</td>
<td>Potential treatment for different phases of the illness</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>α-7 nicotinic and M1 muscarinic agonists and positive allosteric</td>
<td>Nicotinic agonists for cognitive symptoms; Muscarinic agonists for positive symptoms</td>
</tr>
<tr>
<td></td>
<td>modulators</td>
<td></td>
</tr>
<tr>
<td>GABA</td>
<td>Selective GABA-A agonists, GABA-B antagonists, and allosteric modulators</td>
<td>Augmentation of psychosis treatment</td>
</tr>
<tr>
<td>Inflammation</td>
<td>Cytokines</td>
<td>Possibly the early period of psychosis</td>
</tr>
<tr>
<td>Phosphodiesteras</td>
<td>PDE 4A inhibitors</td>
<td>Activates cAMP/PKA signaling, leading to potentiation of D1 receptor in vivo</td>
</tr>
</tbody>
</table>
Why aren't negative symptoms sufficiently improved with dopamine 2 antagonists?

Why aren't negative symptoms sufficiently improved with dopamine 2 antagonists? (cont.)

- substantia nigra
- striatum
- VTA
- nucleus accumbens
- DLPFC
- VMPFC
- hypothalamus
- pituitary
- thalamus

mesolimbic reward circuits

Overview of the Dopamine Synapse

In the striatum

VMAT2

D2/3 autoreceptor

DA

D1 D2 D3 D4 D5

In the prefrontal cortex

VMAT2

DA

D1 D1 D1 D1 D1

Functional Output of Cortical Dopamine and Cognition

Dopamine levels (PFC)

- Dopamine receptor activity too low
- Dopamine receptor activity too high

Cognitive performance

Activity optimal

Blocking D1

Blocking D3

Dopamine Receptor Affinities

K (nM) for dopamine

Dopamine receptor

D1 D2 D3 D4 D5

1 10 100 1,000 10,000

Higher Affinity

D1 and D3 vs. D2 Receptor Affinity

• It’s not about an antipsychotic’s relative affinities for D1 and D3 receptors compared to D2 receptors

• At antipsychotic doses, and in the presence of dopamine…it’s about an antipsychotic’s relative affinity for dopamine receptors compared to dopamine’s affinity for those receptors

• The one with the highest affinity “wins”
Cariprazine binding affinity for D2 (0.49 nM)

Blonanserin binding affinity for D2 (0.14 nM)

Brexpiprazole binding affinity for D2 (0.3 nM)

Cariprazine binding affinity for D2 (0.49 nM)

Lurasidone binding affinity for D2 (0.66 nM)

Paliperidone binding affinity for D2 (1.4 nM)

Asenapine binding affinity for D2 (1.7 nM)

Aripiprazole binding affinity for D2 (2.3 nM)

Risperidone binding affinity for D2 (3.7 nM)

Ziprasidone binding affinity for D2 (4.75 nM)

Iloperidone binding affinity for D2 (8.3 nM)

Olanzapine binding affinity for D2 (30.8 nM)

Clozapine binding affinity for D2 (147 nM)

Quetiapine binding affinity for D2 (437 nM)

DA binding affinity for D2 (K_i = 540 nM)

1 order of magnitude higher affinity than DA

2 orders of magnitude higher affinity than DA

3 orders of magnitude higher affinity than DA

1 order of magnitude lower affinity than DA

2 orders of magnitude lower affinity than DA

3 orders of magnitude lower affinity than DA

1 order of magnitude lower affinity than DA

2 orders of magnitude lower affinity than DA

3 orders of magnitude lower affinity than DA
Cariprazine binding affinity for D3 (0.09nM)
Blonanserin binding affinity for D3 (0.49nM)
Brexpiprazole binding affinity for D3 (1.1nM)
Asenapine binding affinity for D3 (1.8nM)
Paliperidone binding affinity for D3 (2.6nM)
Aripiprazole binding affinity for D3 (4.6nM)
Risperidone binding affinity for D3 (7.3nM)
Ziprasidone binding affinity for D3 (7.3nM)
Iloperidone binding affinity for D3 (10.5nM)
Lurasidone binding affinity for D3 (15.7nM)
Olanzapine binding affinity for D3 (38.1nM)
Clozapine binding affinity for D3 (310nM)
Quetiapine binding affinity for D3 (394nM)

DA binding affinity for D3 (Ki =60nm)

3 orders of magnitude higher affinity than DA
2 orders of magnitude higher affinity than DA
1 order of magnitude higher affinity than DA
1 order of magnitude lower affinity than DA
2 orders of magnitude lower affinity than DA
3 orders of magnitude lower affinity than DA

1 order of magnitude lower affinity than DA
2 orders of magnitude lower affinity than DA
3 orders of magnitude lower affinity than DA

1 order of magnitude higher affinity than DA
2 orders of magnitude higher affinity than DA
3 orders of magnitude higher affinity than DA
Summary:
Antipsychotic Binding at Dopamine Receptors

- brexpiprazole
- paliperidone
- aripiprazole
- risperidone
- ziprasidone
- iloperidone
- lurasidone
- quetiapine
- asenapine
- olanzapine
- clozapine
- cariprazine
- blonanserin

# Dopaminergic Antipsychotics in Development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Mechanism</th>
<th>Status</th>
<th>Company</th>
<th>Clinical Trial</th>
</tr>
</thead>
<tbody>
<tr>
<td>AMG579 OMS643762</td>
<td>PDE 10A inhibitor PDE10A inhibitor</td>
<td>Phase 2</td>
<td>Amgen</td>
<td>NCT01952132</td>
</tr>
<tr>
<td>DAAO1-1</td>
<td>DAAO catalyzes D-serine and glycine</td>
<td>POC ongoing</td>
<td>NCT01390376</td>
<td></td>
</tr>
<tr>
<td>Eltoprazine</td>
<td>5-HT1A/1B agonist</td>
<td>POC ongoing</td>
<td>NCT01266174</td>
<td></td>
</tr>
<tr>
<td>L-DOPA</td>
<td>Dopamine stabilization</td>
<td>POC ongoing</td>
<td>NCT01636037</td>
<td></td>
</tr>
<tr>
<td>Stepholidine</td>
<td>D2 antagonist/D1 agonist/5HT1A agonist</td>
<td>POC ongoing</td>
<td>University of Toronto</td>
<td></td>
</tr>
<tr>
<td>YKP1358</td>
<td>D2/D3/5HT2A antagonist</td>
<td>Phase 2</td>
<td>SK Bio-Pharmaceuticals</td>
<td></td>
</tr>
</tbody>
</table>
Beyond D2: Drugs in Development

• Lu AF35700
• Lu AF11167
• Pimavanserin
• Lumateperone (ITI-007)
• Xanomeline
Beyond D2: Lu AF35700

• Lu AF35700 has a novel pharmacological profile with predominant D1 vs. D2 dopamine receptor occupancy and a high occupancy of 5-HT2A and 5-HT6 serotonin receptors

• Relatively low dopamine D2 receptor occupancy is expected to result in reduced burden of adverse events, such as EPS, prolactin elevation, dysphoria/anhedonia, and depressed mood

• In 2015, the FDA granted Fast Track designation for Lu AF35700

Fellher et al. Pipeline Plus 2017;42(2):130-134.
Lu AF35700 Results From Phase III Trial on Patients With Treatment-Resistant Schizophrenia (TRS)

697 patients with TRS randomly assigned for 10 wks daily treatment

- 10mg Lu AF35700 (n=235)
- 20mg Lu AF35700 (n=232)
- Continued treatment with risperidone or olanzapine (n=230)

October 2018: Announcement that first phase of the study did not meet the primary endpoint primary endpoint: no significant difference between Lu AF35700 and risperidone/olanzapine from baseline to week 10 in the PANSS total score
Patients who had not responded to clozapine (n=10)

34mg/d pimavanserin for 4-8 weeks

Patients who had not responded to non-clozapine antipsychotics (n=10)

• All 10 patients with refractory hallucinations/delusions demonstrated marked response to pimavanserin, with continuation of response for several months of follow-up

• Improvements in negative symptoms and social functioning were also observed

Lumateperone (ITI-007)

- **5-HT2A Receptor Antagonist**
  - Improves sleep quality
  - Reduces anxiety and hostility
  - Enhances antipsychotic and antidepressant activity

- **Dopamine Phosphoprotein D2 Modulator (DPPM)**
  - D2 Pre-synaptic partial agonist and post-synaptic antagonist
  - Antipsychotic efficacy for positive symptoms
  - Reduced agitation

- **Serotonin Reuptake Inhibitor**
  - Antidepressant activity

- **Glutamatergic Phosphoprotein Modulator**
  - D1/GluN2B Modulation
  - Antipsychotic efficacy for negative and positive symptoms
  - Improved cognition and affect
  - Rapid acting improved anti-depressant activity

**PHARMACOLOGY PREDICTS ROBUST EFFICACY ACROSS A BROAD RANGE OF SYMPTOM DOMAINS AND PREDICTS HIGHLY FAVORABLE SAFETY/TOLERABILITY PROFILE**

Relatively low dopamine D2 receptor occupancy

---

Comparison of ITI-007 D2 Occupancy to Other Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose range</th>
<th>Mean D₂RO in Caudate and Putamen</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ITI-007</td>
<td>60 mg/day</td>
<td>~ 40%</td>
<td>Present results</td>
</tr>
<tr>
<td>Clozapine</td>
<td>75–900 mg/day</td>
<td>48–61%</td>
<td>Farde et al. [2]; Kapur et al. [39]; Tauscher et al. [31]</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>150–750 mg/day</td>
<td>30–62%</td>
<td>Gefvert et al. [30]; Kapur et al. [32]; Tauscher et al. [31]; Tauscher-Wisniewski et al. [33]</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40–160 mg/day</td>
<td>56 to &gt;59%</td>
<td>Mamo et al. [43]; Vernaleken et al. [44]</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4 mg/day</td>
<td>72–81%</td>
<td>Kapur et al. [38, 39]; Nyberg et al. [3]; Tauscher et al. [31]</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5–60 mg/day</td>
<td>61–80%</td>
<td>Nyberg et al. [45]; Kapur et al. [39, 46]; Tauscher et al. [31]</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40–80 mg</td>
<td>&gt;65%</td>
<td>Wong et al. [5]</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>1.5–3 mg/day</td>
<td>69 to &gt;90%</td>
<td>Reviewed by Citrome [42]</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10–30 mg</td>
<td>88–90%</td>
<td>Yokoi et al. [6]; Mamo et al. [7]</td>
</tr>
</tbody>
</table>
## Lumateperone (ITI-007) Efficacy and Tolerability

<table>
<thead>
<tr>
<th>Properties</th>
<th>Risperidone</th>
<th>ITI-007</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Receptor binding</strong></td>
<td>12-fold difference in affinities for 5-HT2A and D2 receptors</td>
<td>60-fold difference in affinities for 5-HT2A and D2 receptors</td>
</tr>
<tr>
<td><strong>Negative symptom efficacy</strong></td>
<td>Reduces negative symptoms</td>
<td>Superior to risperidone at reducing negative symptoms, including social function, and depressive symptoms in patients with comorbid schizophrenia/depression</td>
</tr>
<tr>
<td><strong>Neurological and endocrine adverse effects</strong></td>
<td>Side effects include weight gain, extrapyramidal symptoms (EPS), increased prolactin levels</td>
<td>Produces little to no weight gain, does not negatively affect metabolic parameters, does not increase prolactin levels, and reduces akathisia</td>
</tr>
<tr>
<td><strong>Metabolic adverse effects</strong></td>
<td>QTc prolongation and other cardiometabolic side effects</td>
<td>Does not produce alterations in cardiovascular function QTc prolongation; does not increase heart rate</td>
</tr>
<tr>
<td><strong>Suicidal ideation</strong></td>
<td>Suicidal ideation reported</td>
<td>No evidence of suicidal ideation/behavior</td>
</tr>
</tbody>
</table>
## Lumateperone: Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Study Title/Type</th>
<th>Sample Size</th>
<th>Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>005, Randomized Controlled Trial (RCT)</td>
<td>n=335</td>
<td>60mg ITI-007, 120mg ITI-007, 4mg risperidone, or placebo for 4 weeks</td>
<td>60 mg dose: significant improvement over placebo at Day 28 on PANSS total score; ITI-007 significantly better than risperidone</td>
</tr>
<tr>
<td>301, RCT</td>
<td>n=450</td>
<td>60mg ITI-007, 40mg ITI-007, or placebo for 4 weeks</td>
<td>60 mg dose: significant improvement over placebo at Day 28 on PANSS total score</td>
</tr>
<tr>
<td>302</td>
<td>n= 696</td>
<td>60mg ITI-007, 20mg ITI-007, 4mg risperidone, or placebo for 6 weeks</td>
<td>60 mg dose: significant improvement over placebo at Day 28 on PANSS total score; ITI-007 significantly better than risperidone</td>
</tr>
</tbody>
</table>

In a 6-week open-label study, patients were switched from standard of care (SOC) antipsychotics to daily lumateperone, and then switched back to SOC. Statistically significant improvements from SOC were observed in body weight, cardiometabolic and endocrine parameters, which worsened when switched back to SOC.

In patients with moderate to severe depression symptoms at baseline (CDSS≥6; N=55), lumateperone treatment was associated with marked improvement in CDSS scores. Specifically, mean CDSS scores decreased by approximately 60% from 7.4 (baseline) to 3.1 (Day 300).
Patients Can’t Achieve Functional Outcomes Without Relief of Negative Symptoms

- Difficulty forming a therapeutic alliance
- Impaired occupational functioning
  - Impaired social functioning
  - Impairment in relationships
- Reduced quality of life

Phase II Study: Lu AF11167 for Negative Symptoms in Stable Patients with Schizophrenia

- Lu AF11167 inhibits the activity of the PDE10-enzyme, which alters dopamine signaling. Ideally, negative symptoms will improve while positive symptoms remain controlled.
- In Jan 2019, a Phase II study was launched (3 arm, randomized) for a total of 240 patients from various European countries.
- Primary objective: evaluate the efficacy of two doses of Lu AF11167 versus placebo as monotherapy on negative symptoms in stable outpatients.
- Secondary objective: evaluate the efficacy of Lu AF11167 on patients’ functioning, safety, and tolerability.
Cognitive Impairment in Schizophrenia

Healthy Normative Sample, N=300

Schizophrenia Patients, N=323

Mean T Score

Composite Processing Speed

Attention

Working Memory

Verbal Learning

Visual Learning

Reasoning

Social Cognition

I Think I Can: Efficacy With Cognitive Improvement

• Novel pharmaceuticals under development have demonstrated effective improvements on cognitive measures and in neuroimaging

• New approaches to previously established non-pharmacological methods (e.g., CRT) and novel treatments (HF-rTMS) may improve cognitive dysfunction
M1/M4 Muscarinic Agonists for Treatment of Cognitive Impairment in Schizophrenia

• M2/M3 receptors are the major peripheral subtypes hypothesized to underlie dose-limiting clinical side effects (e.g., GI)

• M1 and M4 muscarinic cholinergic receptors are highly expressed in the cortex, hippocampus, and striatum and have been implicated in cognitive impairment

• First generation agonists have modest selectivity for M1/M4 receptor subtypes over M2/M3
  • More recent medicinal chemistry optimization of orthosteric agonists, allosteric agonists, and positive allosteric modulators (PAMs) has resulted in highly selective M1 and M4 agonists that may result in improved cognition

Felder et al. Neuropharmacology 2018; S0028-3908(18)30028-5.
# M1 Muscarinic Agonists for Cognitive Impairment in Schizophrenia: Xanomeline (LY 593093)

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of Patients</th>
<th>Protocol</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot study on xanomeline monotherapy (RCT)</td>
<td>n=20</td>
<td>Randomly assigned to placebo or titrated to 225mg xanomeline over 6 days and remained at that dose for the remainder of the 4 weeks</td>
<td>Significant improvements on total BPRS scores and total PANSS scores. Showed improvements in verbal learning and short-term memory function</td>
</tr>
<tr>
<td>Phase I Study on xanomeline/trospium (KarXT)</td>
<td>n=69</td>
<td>Randomly assigned to 225mg xanomeline + placebo or 225mg xanomeline + 40mg trospium</td>
<td>KarXT co-formulation demonstrated improved tolerability, and side effects were mild to moderate</td>
</tr>
<tr>
<td>Phase II Study on xanomeline/trospium (KarXT)</td>
<td>n=160</td>
<td>Randomly assigned to receive 120mg/20mg xanomeline/trospium with an option to increase dose to 125mg/30mg xanomeline/trospium following</td>
<td>Ongoing. Primary objective: change from baseline PANSS scores. Additional objectives: improvement in cognitive/negative</td>
</tr>
</tbody>
</table>

Novel Advancements in Minimizing Risk
Olanzapine/Samidorphan

• Samidorphan (SAM)
  • Opioid antagonist at the μ-opioid receptor, with significant activity at kappa opioid receptors
  • Investigated for addiction treatment (e.g., alcohol, cocaine)
    • By blocking opioid receptors involved in the brain reward pathway, reinforcement is reduced
    • Shows similar efficacy to naltrexone but with reduced side effects
  • Research in animals suggests that naltrexone reduces food cravings but has no effect on weight gain
  • Co-administration of olanzapine and SAM, but not naltrexone-mitigated olanzapine-induced weight gain, suggesting that the added K-opioid receptor properties may be clinically relevant

<table>
<thead>
<tr>
<th>Receptor</th>
<th>K_i (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>μ</td>
<td>0.052</td>
</tr>
<tr>
<td>k</td>
<td>0.28</td>
</tr>
<tr>
<td>δ</td>
<td>2.6</td>
</tr>
</tbody>
</table>

Olanzapine/Samidorphan Study Program

- **ALKS 3831**: flexible dose of olanzapine and a fixed dose of 10 mg SAM
  - The combination has been studied in phase I trials (healthy volunteers) and phase II trials (patients with stable schizophrenia)
  - In the phase II study, co-administration of SAM mitigated OLZ-associated weight gain, and OLZ/SAM combination had similar antipsychotic efficacy to OLZ
- **Phase III (ENLIGHTEN I)**: 4-week randomized, double-blind active (OLZ monotherapy) and PBO-controlled study of ALKS 3831 in acute exacerbation of schizophrenia
  - 2-week inpatient treatment (OLZ titration permitted) followed by 2-week inpatient/outpatient treatment (fixed OLZ dose)
- **Outcomes**: PANSS and Clinical Global Impression-Scale (CGI-S)

Olanzapine/Samidorphan: Phase III (ENLIGHTEN I) Efficacy Results

Mean OLZ dose: 18.4 mg/day for both active treatment arms

Olanzapine/Samidorphan: Phase III (ENLIGHTEN II) Weight Gain Results

**Figure 2.** Percent Change from Baseline in Body Weight Over 12 Weeks (Full Study Population)

- OLZ
- ALKS 3831 (10 mg SAM)

*p ≤ 0.05
**p ≤ 0.01

Non-pharmacological Treatments for Positive Symptoms in Schizophrenia
TMS for Auditory Hallucinations in Psychosis

• Promising results have been reported for both high frequency (HF) and neuronavigated repetitive transcranial magnetic stimulation (rTMS).

• Recent study examined the efficacy of HF (20 Hz) rTMS applied precisely over the left temporal region using neuronavigation.
  
  • 59 patients with schizophrenia or schizoaffective disorders were treated with rTMS or sham over 4 weeks.

• The proportion of patients demonstrating ≥ 30% decrease in the Auditory Hallucinations Rating Scale (AHRS) differed significantly between conditions (p=0.016) at day 14.

Dollfus et al. Schizophr Bull 2018;44(3):505-514.
Non-pharmacological Treatments for Negative and Cognitive Symptoms in Schizophrenia
Cognitive Remediation Therapy (CRT) in Schizophrenia

• CRT targets cognitive and functional difficulties. The goal is to improve attention, memory, language, executive functions

• CRT is associated with neurobiological and cognitive improvement, and affects several regions and circuits, including prefrontal, parietal, and limbic areas
  
  • Changes to prefrontal areas are the most reported finding

• Two approaches: Training or Strategy
  
  Training: exercises that are regularly repeated and allow for specific training in the deficient aspect of cognitive function; restoring the deficient function

  Strategy: works with preserved functions to develop strategies for processing information

• Both methods show improvements in behavior and increased cerebral activity

• Several meta-analyses suggest CRT effectiveness in schizophrenia patients, especially from early intervention

CRT and Cerebral Activity

- Recent meta-analysis included eight studies comparing cerebral activity in MRIs when the training method was used vs. the strategy method.
- Several studies reported correlations between increases in cerebral activity and improvements in cognitive function (e.g., attention, working memory, verbal memory, and cognitive control).
- Training method is capable of activating more of the targeted brain areas than the strategy method; increases in cerebral activity were observed primarily in prefrontal / temporal regions.
- Strategy method appears to encourage more extensive activation of the cerebral networks; increased cerebral activity was concentrated in frontal regions, parietal, and occipital areas.

TMS for Cognition in Schizophrenia

• A recent pilot study explored the effects of bilateral high frequency repetitive transcranial magnetic stimulation (HF-rTMS) on cognitive function in patients with early-phase psychosis

• Over 2 weeks, 21 subjects underwent ten sessions of HF, bilateral, sequential rTMS over the dorsolateral prefrontal cortex (DLPFC) or sham treatment

• Those who received rTMS displayed improvement on a standardized cognitive test battery, both immediately following the course of study treatment and at follow-up 2 weeks later

• MRI results indicated that left frontal cortical thickness at baseline was correlated with treatment response

Summary

- Pharmacological management of schizophrenia can be challenging, especially because of the need for increased efficacy, reduced side effects, and relief from negative and cognitive symptoms.

- All approved medications bind D2. There are several in development that focus on mechanisms that extend beyond the dopamine/D2 hypothesis of schizophrenia.

- Exciting developments have also been made in behavioral and other non-pharmacological approaches to treat cognitive impairment in schizophrenia.