OUT OF THE PIPELINE: NOVEL TARGETS AND TREATMENTS FOR SCHIZOPHRENIA
Learning Objectives

• Describe the mechanisms of action of emerging and investigational treatments for schizophrenia

• Evaluate the latest clinical data for new and emerging antipsychotic treatments
MECHANISMS OF PSYCHOSIS AND ITS TREATMENT
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.

Match Each Symptom to Hypothetically Malfunctioning Brain Circuits
Therapeutic Mechanisms of Drugs for Psychosis

- **5HT2A/D2 antagonist**
- **5HT2A antagonist**
- **D2 antagonist**
- **D2/5HT1A partial agonist**
Antipsychotic Binding at Dopamine Receptors

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

D2 predominately
D2 plus D1
D2 plus D3

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

Efficacy: Beyond The 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

• Trace amines
  – Agonists may enhance presynaptic D2 autoreceptors while simultaneously reducing some of the unwanted downstream functions of overly active postsynaptic D2 receptors

# Novel Treatment Targets for Schizophrenia

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Target</th>
<th>Strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dopamine</strong></td>
<td>Dopamine stabilizers</td>
<td>Improve medication adherence</td>
</tr>
<tr>
<td><strong>Glutamate</strong></td>
<td>NMDA, AMPA, or metabotropic receptors</td>
<td>Improve negative symptoms and cognitive impairments</td>
</tr>
<tr>
<td><strong>Serotonin</strong></td>
<td>5HT1A agonists, 5HT2C antagonists and agonists, 5HT3 antagonists, 5HT6 and 5HT7 antagonists, and 5HT reuptake inhibitors</td>
<td>Reduce extrapyramidal symptoms; Improve negative symptoms, mood and cognitive impairments; Potential treatment for different phases of the illness</td>
</tr>
<tr>
<td><strong>Acetylcholine</strong></td>
<td>α-7 nicotinic, M1 muscarinic, and M4 muscarinic agonists and positive allosteric modulators</td>
<td>Nicotinic agonists for cognitive symptoms; M1 muscarinic agonists for cognitive symptoms; M4 muscarinic agonists for positive symptoms</td>
</tr>
<tr>
<td><strong>GABA</strong></td>
<td>Selective GABA-A agonists, GABA-B antagonists, and allosteric modulators at GABA-A receptor subtypes</td>
<td>Augmentation of psychosis treatment</td>
</tr>
<tr>
<td><strong>Inflammation</strong></td>
<td>Cytokines</td>
<td>Possibly the early period of psychosis</td>
</tr>
<tr>
<td><strong>Phosphodiesterase (PDE) inhibitors</strong></td>
<td>PDE10A inhibitor</td>
<td>Activates cAMP/PKA signaling, leading to potentiation of D1 receptor signaling, and inhibition of D2 receptor signaling</td>
</tr>
</tbody>
</table>

NMDA: N-methyl-D-aspartate; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isooazolepropionic acid; 5HT: 5-hydroxytryptamine (serotonin); GABA: gamma-aminobutyric acid; cAMP: cyclic adenosine monophosphate; PKA: protein kinase A.

BEYOND DOPAMINE
Beyond Dopamine: Lumateperone

FDA-Approved
December 23, 2019
# D2 Occupancy of Lumateperone and Other Antipsychotics


<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Mean D2 Receptor Occupancy in Caudate and Putamen&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumateperone</td>
<td>60 mg/day</td>
<td>~40%</td>
</tr>
<tr>
<td>Clozapine</td>
<td>75-90 mg/day</td>
<td>48-61%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>150-750 mg/day</td>
<td>30-62%</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40-160 mg/day</td>
<td>56 to &gt;59%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4 mg/day</td>
<td>72-81%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5-60 mg/day</td>
<td>61-80%</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40-80 mg</td>
<td>&gt;65%</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>1.5-3 mg/day</td>
<td>69 to &gt;99%</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>10-30 mg</td>
<td>88-90%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Measured by displacement of [¹¹C]-raclopride
## Lumateperone Efficacy and Tolerability

<table>
<thead>
<tr>
<th>Properties</th>
<th>Risperidone</th>
<th>Lumateperone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Receptor binding</td>
<td>12-fold difference in affinities for 5HT2A and D2 receptors</td>
<td>60-fold difference in affinities for 5HT2A and D2 receptors</td>
</tr>
<tr>
<td>Negative symptom efficacy</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>Neurological and endocrine adverse effects</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>Metabolic adverse effects</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>Suicidal ideation</td>
<td>Suicidal ideation reported</td>
<td>No evidence of suicidal ideation/behavior</td>
</tr>
</tbody>
</table>

Vanover K et al. Schizophr Bull 2018;44(Suppl 1):S44 [Poster Presentation].
# Lumateperone: Placebo-Controlled Clinical Trials

<table>
<thead>
<tr>
<th>Randomized Controlled Trial</th>
<th>Sample Size</th>
<th>Design</th>
<th>Primary Endpoint Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>005</td>
<td>N=335</td>
<td>60 mg ITI-007, 120 mg ITI-007, 4 mg risperidone, 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>301</td>
<td>N=450</td>
<td>60 mg ITI-007, 40 mg ITI-007, or placebo for 4 weeks</td>
<td>40 and 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>60 mg ITI-007, 20 mg ITI-007, 4 mg risperidone, or placebo for 6 weeks</td>
<td>Neither dose of ITI-007 separated from placebo at Day 28 on PANSS total score (^a)</td>
</tr>
</tbody>
</table>

\(^a\) High placebo response in Study 302. ITI-007: lumateperone; PANSS: Positive and Negative Syndrome Scale.

Lumateperone has a favorable safety profile; the most common adverse effects (≥5%) are somnolence, sedation, fatigue, and constipation

Trace Amine Associated Receptor Type 1 (TAAR1)

TAAR1 is widely expressed throughout the brain, including in monoamine brainstem centers (dorsal raphe nucleus, ventral tegmental area) and in monoamine projection areas.
Agonism of TAAR1

• When TAAR1 receptors are bound by an agonist, they translocate to the synaptic membrane and couple with D2 receptors

• Amplification of the Gi pathway leads to inhibition of the synthesis and release of dopamine, which would be beneficial in cases of psychosis

SEP-363856: An Agonist at TAAR1 Receptors

- Agonist at TAAR1 receptors; it also has 5HT1D, 5HT1A, and 5HT7 receptor binding properties

Efficacy and Tolerability of SEP-363856

Phase-II, randomized, double-blind, placebo-controlled 4-week, flexible-dose study comparing effects of SEP-363856 (50 or 75 mg/day; n=120) to placebo (n=125) in patients with schizophrenia

**PANSS Total Score**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 4</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEP-363856</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effect size at Week 4: 0.45**

**PANSS Negative Subscale Score**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 4</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>SEP-363856</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

**Effect size at Week 4: 0.37**

Good safety/tolerability profile; SEP-363856 was not associated with extrapyramidal symptoms, akathisia, or hyperprolactinemia

Adapted from Koblan KS et al. APA 2019;P7-066 [Poster Presentation].
M1/M4 Muscarinic Agonists for the Treatment of Schizophrenia

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

- Patients with schizophrenia have lower levels of muscarinic M1 receptors, muscarinic M4 receptors, or both receptors in the cortex, hippocampus, and striatum

- Xanomeline is a muscarinic M1/M4 agonist that improved Brief Psychiatric Rating Scale (BPRS) and Positive and Negative Syndrome (PANSS) scores in patients with schizophrenia

  - Gastrointestinal side effects limited further clinical development

Xanomeline/Trospium (KarXT)

- Trospium is a muscarinic receptor antagonist that has minimal, if any, penetration of the blood brain barrier, blocking unwanted peripheral cholinergic side effects of xanomeline

<table>
<thead>
<tr>
<th>Randomized Controlled Trial</th>
<th>Number of Patients</th>
<th>Design</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase I study on xanomeline/trospium (KarXT)</td>
<td>n=69</td>
<td>225 mg xanomeline + placebo or 225 mg xanomeline + 40 mg trospium</td>
<td>KarXT co-formulation demonstrated improved tolerability; side effects were mild to moderate</td>
</tr>
<tr>
<td>Phase II study on xanomeline/trospium (KarXT)</td>
<td>n=160</td>
<td>120 mg/20 mg xanomeline/trospium with an option to increase dose to 125 mg/30 mg xanomeline/trospium following week 1</td>
<td>Significant and clinically meaningful 11.6 point mean reduction in total PANSS score compared to placebo (p&lt;0.0001); demonstrated good overall tolerability</td>
</tr>
</tbody>
</table>

PANSS: Positive and Negative Syndrome Scale.

Efficacy and Safety of KarXT

Results from 5-week, randomized, double-blind, placebo-controlled phase II study of hospitalized patients with schizophrenia who experienced acute psychotic exacerbation (N=182):

Primary Outcome: PANSS Total Score

<table>
<thead>
<tr>
<th>Adverse Events (AEs) ≥ 5%</th>
<th>Placebo (n=90)</th>
<th>KarXT (n=89)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation</td>
<td>3 (3.3%)</td>
<td>15 (16.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>4 (4.4%)</td>
<td>15 (16.9%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1 (1.1%)</td>
<td>8 (9.0%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (4.4%)</td>
<td>8 (9.0%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (4.4%)</td>
<td>8 (9.0%)</td>
</tr>
<tr>
<td>Headache</td>
<td>5 (5.6%)</td>
<td>6 (6.7%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4 (4.4%)</td>
<td>5 (5.6%)</td>
</tr>
</tbody>
</table>

The majority of the most common cholinergic/anticholinergic AEs associated with KarXT treatment decreased over the course of the study.

Adapted from Brannan S et al. ASCP 2020 [Poster Presentation].
BEYOND DOPAMINE: AMELIORATING SIDE EFFECTS
Olanzapine/Samidorphan

- Samidorphan (SAM) is an opioid antagonist at the μ-opioid receptor, with significant activity at k-opioid receptors
  - By blocking opioid receptors involved in the brain reward pathway, reinforcement is reduced
  - Shows similar efficacy to naltrexone but with reduced side effects
  - Investigated for addiction treatment (e.g., alcohol, cocaine)
  - 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>Ki (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>

Proposed Mechanism: Brain Reward Pathway

Krogmann A et al. CNS Spectr 2019;24(S1):38-69;
Image adapted from Kenny PJ. Neuron 2011;69(4):664-79.
Olanzapine (OLZ)/Samidorphan (SAM) 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 II)**: 4-week randomized, double-blind active (OLZ monotherapy) and placebo-controlled study of ALKS 3831 in acute exacerbation of schizophrenia
  - Significant improvement versus placebo in PANSS total scores
  - Superior to placebo in reducing olanzapine-induced weight gain

Silverman BL et al. Schizophr Res 2017;195:245-51;
Olanzapine/Samidorphan: Phase III (ENLIGHTEN II) Weight Gain Results

DiPetrillo L et al. APA 2018 [Poster Presentation].
BEYOND DOPAMINE: TREATING NEGATIVE SYMPTOMS
Patients Cannot 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

- Reduced speech
- Limited eye contact
- Reduced interest
- Reduced emotional responsiveness
- Reduced social drive
- Poor grooming

Why Aren’t Negative Symptoms Sufficiently Improved With Dopamine 2 Antagonists?

Why Aren’t Negative Symptoms Sufficiently Improved With Dopamine 2 Antagonists?

Beyond Dopamine: Pimavanserin

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

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

34 mg/day pimavanserin for 4–8 weeks

- 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

Results from randomized, double-blind study examining efficacy of pimavanserin (10-34 mg) adjunctive to main antipsychotic versus placebo treatment for 26 weeks in patients with predominant negative symptoms of schizophrenia (N=403).

Results from randomized, double-blind study examining efficacy of pimavanserin (10-34 mg) adjunctive to main antipsychotic versus placebo treatment for 6 weeks in patients with schizophrenia who have not achieved adequate response to their current antipsychotic treatment.

PANSS negative symptoms scale subscore was significantly reduced with pimavanserin versus placebo treatment (secondary endpoint; p=0.0474)

ClinicalTrials.gov identifier NCT02970292
Roluperidone (MIN-101) is a 5HT2A antagonist with additional sigma 2 antagonism.

Symptomatically stable schizophrenia patients (N=244) were withdrawn from antipsychotics and randomly assigned to placebo or MIN-101 in a phase 2b trial.


Roluperidone failed to meet endpoints in a Phase III clinical trial for the treatment of negative symptoms of schizophrenia.
OTHER STRATEGIES FOR TREATING NEGATIVE SYMPTOMS
Treatment of Negative Symptoms: Other Dopaminergic Strategies

- Low dose/dose reduction of D2 antagonists
- Add-on with D2 partial agonist
  - Significant effect in meta-analysis of aripiprazole
- Dopamine agonists
  - Small significant effect in meta-analysis of modafinil/armodafinil

Treatment of Negative Symptoms: Serotonergic Strategies

- Add-on with serotonergic antidepressants
  - Meta-analyses show small beneficial effects (NNT=10–15 and NNT=9)

Treatment of Negative Symptoms: Glutamatergic Strategies

- Topiramate
  - Multiple meta-analyses show efficacy
- Lamotrigine, memantine, amantadine, NMDA agonists
  - Inconsistent or disappointing results
- Metabotropic glutamate receptor (mGluR) 2/3 agonists
  - Disappointing results
- mGluR positive allosteric modulators
  - Efficacious in animal studies; currently Phase II

Treatment of Negative Symptoms: Other Strategies

- **Anti-inflammatory agents**
  - Disappointing results for nonsteroidal anti-inflammatory drugs (NSAIDs)
  - Meta-analysis showed efficacy for minocycline

- **Anti-oxidant**
  - Mixed results for N-acetylcysteine (NAC)
  - Meta-analysis shows moderate efficacy for Ginkgo biloba

- **Hormone treatment**
  - Preliminary evidence for raloxifene (selective estrogen receptor modulator)

- **β-Hydroxy β-methylglutaryl-CoA (HMG-CoA) reductase inhibitors**
  - Small positive trial of adjunct simvastatin

<table>
<thead>
<tr>
<th>Treatment of Negative Symptoms: Psychosocial Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exercise</strong></td>
</tr>
<tr>
<td>- Meta-analyses show moderate effect of aerobic exercise and yoga</td>
</tr>
<tr>
<td><strong>Cognitive remediation</strong></td>
</tr>
<tr>
<td>- Meta-analysis: small improvement compared to treatment-as-usual (TAU)</td>
</tr>
<tr>
<td><strong>Music therapy</strong></td>
</tr>
<tr>
<td>- Meta-analysis: large significant effect compared to TAU</td>
</tr>
<tr>
<td><strong>Cognitive behavioral therapy</strong></td>
</tr>
<tr>
<td>- Recent meta-analysis of 30 studies did not find beneficial effect</td>
</tr>
</tbody>
</table>

BEYOND DOPAMINE: TREATING COGNITIVE SYMPTOMS
Functional Output of Cortical Dopamine and Cognition

Dopamine levels (prefrontal cortex)

- Blocking D1
- Blocking D3

Dopamine receptor activity too low
Dopamine receptor activity too high

Activity optimal

Cognitive Performance

Clinical Translation: Treatment Mechanisms Beyond Dopamine

- Neurobiological data: rationale for why current antipsychotics do not seem to improve cognition

- Prospect of novel mechanisms
  - Glutamatergic
  - Cholinergic
  - GABA-ergic
  - Anti-inflammatory
Glutamate and Schizophrenia

• NMDA hypofunction hypothesis of schizophrenia
• Neurodevelopmentally abnormal glutamate synapses
• Hypofunctional NMDA receptors
• Overstimulation of downstream glutamate receptors
Novel Treatment Mechanisms: Glutamate

**Glutamate neuron**
- Direct acting glycine site agonists
  - d-cycloserine
  - d-serine
  - glycine
- Presynaptic metabotropic receptor (mGluR2/3)

**Glial cell**
- Glycine transporter inhibitors
  - sarcosine
  - bitopertin (RG1678)

**AMPA modulators**
- CX-516
- piracetam
- cyclothiazide
- LY404187

**mGlu receptor modulators**
- LY354740
- LY2140023

**AMPA receptor**
**NMDA receptors**

**Glycine transporter**
### Efficacy of Cognitive Enhancers in Schizophrenia

<table>
<thead>
<tr>
<th>Cognitive Enhancer</th>
<th>Positive Effect on Cognition</th>
<th>Effect size $^a$</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glutamatergic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>0.19</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td>Working memory</td>
<td>0.13</td>
<td>0.040</td>
<td></td>
</tr>
<tr>
<td>- Glycine site</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>- AMPA receptor agonists</td>
<td>Working memory</td>
<td>0.28</td>
<td>0.30</td>
</tr>
<tr>
<td>- Memantine/amantadine</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td><strong>Cholinergic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>- Alpha 4 nicotinic agonists</td>
<td>Problem solving</td>
<td>-0.175</td>
<td>0.027</td>
</tr>
<tr>
<td>- Alpha 7 nicotinic agonists</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>- Cholinesterase inhibitors</td>
<td>Working memory</td>
<td>0.26</td>
<td>0.031</td>
</tr>
<tr>
<td><strong>OVERALL $^b$</strong></td>
<td>Overall</td>
<td>0.10</td>
<td>0.023</td>
</tr>
</tbody>
</table>

$^a$ Hedges’ g; $^b$ Includes glutamatergic, cholinergic, serotoninergic, dopaminergic, GABAergic, noradrenergic, and miscellaneous (sildenafil, armodafinil, and modafinil) agents; ns=not significant.

Meta-analysis of 93 randomized controlled trials (N=5,630) measuring effects of pharmacological agents on cognition in patients with schizophrenia, schizophreniform, schizoaffective, delusional, or psychotic disorder not otherwise specified

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.
When TAAR1 receptors are bound by an agonist, they translocate to the synaptic membrane and couple with:

A. 5HT1D receptors  
B. 5HT1A receptors 
C. 5HT7 receptors  
D. D1 receptors  
E. D2 receptors
Roluperidone is a…

A. 5HT1A agonist
B. 5HT2A antagonist
C. D2 antagonist