TO DOPAMINE AND BEYOND:
NOVEL MECHANISMS OF ANTIPSYCHOTICS
Learning Objectives

• Recognize the potential advantages of antipsychotic agents that work outside of dopamine D2 receptors

• Evaluate data on novel antipsychotic agents with mechanisms of action outside of dopamine D2 receptors
Challenges of Treating Schizophrenia

- Chronic, severe, and debilitating brain disorder resulting in positive and negative affective impairments, and cognitive dysfunction

- Most challenging components of treatment effectiveness: adherence, efficacy, and adverse side effects
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

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Target</th>
<th>Strategy</th>
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<tbody>
<tr>
<td>Dopamine</td>
<td>Dopamine stabilizers</td>
<td>Improve medication adherence</td>
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<tr>
<td>Glutamate</td>
<td>NMDAR, AMPA receptor, or metabotropic receptors</td>
<td>Improve negative symptoms and cognitive impairments</td>
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<tr>
<td>Serotonin</td>
<td>5HT1A agonists, 5-HT2C antagonists and agonists, 5-HT3 antagonists, 5-HT6 antagonists, and 5HT7 antagonists, 5HT reuptake inhibitors</td>
<td>Reduce the extrapyramidal effects; Improve negative symptoms and cognitive impairments; 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 modulators</td>
<td>Nicotinic agonists for cognitive symptoms; Muscarinic agonists for positive symptoms</td>
</tr>
<tr>
<td>GABA</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>Inflammation</td>
<td>Cytokines</td>
<td>Possibly the early period of the psychosis</td>
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NMDAR: N-methyl-D-aspartate receptors; AMPA: alpha-amino-3-hydroxy-5-methyl-4-isooazolepropionic acid; 5-HT: 5-hydroxytryptamine; GABA: gamma-aminobutyric acid

Novel Pharmaceutical Advancements in Efficacy

• Lumateperone (ITI-007)

• Lu AF35700 (granted fast track designation)
Lumateperone (ITI-007)

- Improves sleep quality
- Reduces anxiety and hostility
- Enhances antipsychotic and antidepressant activity

Dopamine Phosphoprotein D2 Modulator (DPPM)
- Antipsychotic efficacy for positive symptoms
- Reduced agitation

Serotonin Reuptake Inhibitor
- Antidepressant 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.

Graph showing occupancy of ITI-007 parent plasma concentration.
# 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

• In three controlled clinical trials, lumateperone (60 mg) improved symptoms of schizophrenia on the PANSS

• In the two studies that included risperidone as an active control, lumateperone was statistically better on adverse effects related to prolactin, glucose, lipids, and weight

• 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 for 2 weeks
  • Statistically significant improvements from SOC were observed in body weight, cardiometabolic and endocrine parameters, which worsened when switched back to SOC

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

• A phase III clinical trial recruited participants (approximately 1000 patients) with treatment-resistant schizophrenia
  • Two doses of Lu AF35700 (10 mg and 20 mg) are being evaluated
  • The primary endpoint is the change from baseline to week 10 in the PANSS total score

• Press release from 10/25/2018: “Lu AF35700 was as effective as olanzapine for treatment-resistant patients, but did not demonstrate superiority”

• Lu AF3570 was well tolerated and safe at 10mg and 20mg doses

Fellher et al. Pipeline Plus 2017;42(2):130-134.
Novel Advancements in Treating Side Effects

• Olanzapine/samidorphan
What’s So Great About Samidorphan?

- 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>Ki (nM)</th>
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<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

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**: 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: Recent Phase III Efficacy Results

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

Olanzapine/Samidorphan: Recent Phase III 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
Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis

Treatment of Negative Symptoms: Serotonergic Strategies

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

• MIN-101 (5HT2A and sigma receptor binding)
  • In development; positive

Novel Pharmaceutical Treatments for Cognitive Impairment in Schizophrenia

- BI 409306
- HTL9936 (M1 agonist)
BI 409306

• Cognitive dysfunction is associated with NMDA receptor dysfunction
  • NMDA activation increases levels of the 2nd messenger cyclic guanosine monophosphate (cGMP) and subsequent activation of protein kinases involved in long-term potentiation and synaptic plasticity

• BI 409306 is a potent, selective phosphodiesterase 9 inhibitor (PDE9A)
  • PDE9A hydrolyses cGMP and is highly expressed in the neocortex and hippocampus
  • Inhibition of PDE9A improves intracellular cGMP levels and thereby improves glutamatergic neurotransmission and synaptic plasticity → in theory this may improve cognition

BI 409306 for Cognitive Impairment in Schizophrenia

• In a recent double-blind, 12-week monotherapy trial, 580 patients received 10, 25, 50, or 100 mg per day

  • Performance on a variety of neuropsychological batteries (CANTAB, MCCB, and SCoRs) was evaluated

• Not effective at improving cognition

• While BI 409306 did not improve cognitive impairment related to schizophrenia, there was a signal that it may improve positive symptoms compared to placebo (but perhaps not as sufficiently as monotherapy)

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.

M1 Muscarinic Agonists for the Treatment of Cognitive Impairment in Schizophrenia

• Xanomeline (LY 593093), a selective M1 agonist, was developed in 2002 and produced strong improvements in both positive and negative symptoms of patients with SZ
  • Effects were superior to atypical antipsychotics and statistically significant after only 1 week of treatment

• Unfortunately, dose-limiting GI side effects were observed--removed from consideration for long-term clinical use monotherapy

• Currently being explored in a combination with trospium to mitigate the peripheral adverse effects (Karuna Pharmaceuticals)

Targeting M1 Muscarinic Receptors for Cognitive Symptoms Observed in Schizophrenia

• A clinical study utilizing the M1-selective allosteric agonist GSK1034702 improved cognition in a nicotine abstinence model of episodic memory impairment in healthy smokers

  • Proof of concept that selective M1 agonists might be viable options for cognitive dysfunction in schizophrenia

• Development of GSK1034702 has not proceeded beyond phase I, with no clinical trials since 2010

M1 Muscarinic Receptor Agonist: HTL9936

• HTL9936 was designed to be an M1 receptor agonist
  • Confirmed clinically through the absence of activity typically attributed to the stimulation of M2 and M3 receptors

• Phase I data in healthy volunteers demonstrated EEG changes consistent with cognitive-enhancing effects

• Being proposed for cognitive dysfunction in schizophrenia and for dementia of the Alzheimer Type
Why Aren’t Negative Symptoms Sufficiently Improved With Dopamine 2 Antagonists?

Why Aren’t Negative Symptoms Sufficiently Improved With Dopamine 2 Antagonists? (Cont.)

Mesolimbic reward circuits

Mesocortical reward circuits

Overview of the Dopamine Synapse

In the striatum

- VMAT2
- D2/3 autoreceptor
- DAT
- D1 D2 D3 D4 D5

In the prefrontal cortex

- VMAT2
- DA
- D1 D1 D1 D1 D1

Volume Neurotransmission

DA neuron

D1 receptors

Synaptic neurotransmission at 1 and diffusion to 2 and 3

Postsynaptic Dopamine Receptors Either Promote Or Inhibit Second Messenger Systems

D1-like receptors
- G coupled
- Leads to **stimulation** of AC and cAMP pathways

D2-like receptors
- G coupled
- Leads to **inhibition** of AC and cAMP pathways

Functional Output of Cortical Dopamine

Cognitive performance

Activity optimal

Dopamine receptor activity too low

Dopamine receptor activity too high

Dopamine levels (PFC)

Blocking D1

Blocking D3

Dopamine Receptor Affinities

Regulation of Dopamine Levels at the Synapse

Receptor affinities dictate neuronal response to tonic and phasic firing

- Tonic firing:
  - Slow, irregular
  - Sets background DA level

- Phasic firing:
  - Rapid, synchronous burst
  - Spike in extracellular DA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Binding affinity for D1</th>
<th>Binding affinity for D2 (Ki)</th>
</tr>
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<tbody>
<tr>
<td>Asenapine</td>
<td>2.9nM</td>
<td>80nM</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>1173nM</td>
<td>41nM</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>129nM</td>
<td>1090nM</td>
</tr>
<tr>
<td>Clozapine</td>
<td>240nM</td>
<td>1096nM</td>
</tr>
<tr>
<td>Clozapine</td>
<td>240nM</td>
<td>1096nM</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>262nM</td>
<td>262nM</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>56.6nM</td>
<td>1096nM</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>41nM</td>
<td>1173nM</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1096nM</td>
<td>1173nM</td>
</tr>
<tr>
<td>Risperidone</td>
<td>327nM</td>
<td>1173nM</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80nM</td>
<td>1173nM</td>
</tr>
</tbody>
</table>

The graph shows the relative binding affinities of various drugs for D1 and D2 receptors, with the y-axis representing the magnitude of affinity. The x-axis represents the drugs, with the most potent affinity at the top and the least potent at the bottom.
Conclusion

• All antipsychotics have equal or lower affinity for D1 receptors than they have for D2 receptors
1 order of magnitude higher affinity than for D2

2 orders of magnitude higher affinity than for D2

3 orders of magnitude higher affinity than for D2

1 order of magnitude lower affinity than for D2

2 orders of magnitude lower affinity than for D2

3 orders of magnitude lower affinity than for D2

Blonanserin binding affinity for D3 (0.49nM)

Brexpiprazole binding affinity for D3 (1.1nM)

Lurasidone binding affinity for D3 (15.7nM)

Cariprazine binding affinity for D3 (0.09nM)

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)

Olanzapine binding affinity for D3 (38.1nM)

Clozapine binding affinity for D3 (310nM)

Quetiapine binding affinity for D3 (394nM)
Conclusions

- Most antipsychotics have about the same affinity for D3 receptors as they have for D2 receptors
- Cariprazine has somewhat higher affinity for D3 receptors than for D2 receptors
- Lurasidone, brexpiprazole, and iloperidone have lower affinity for D3 receptors than for D2 receptors
So what?

• 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 (0.49nM)
Blonanserin binding affinity for D2 (0.14nM)
Brexpiprazole binding affinity for D2 (0.3nM)
Cariprazine binding affinity for D2 (0.49nM)
Lurasidone binding affinity for D2 (0.66nM)

Paliperidone binding affinity for D2 (1.4nM)  
Asenapine binding affinity for D2 (1.7nM)  
Aripiprazole binding affinity for D2 (2.3nM)  
Risperidone binding affinity for D2 (3.7nM)  
Ziprasidone binding affinity for D2 (4.75nM)  
Iloperidone binding affinity for D2 (8.3nM)  

Olanzapine binding affinity for D2 (30.8nM)
Clozapine binding affinity for D2 (147nM)
Quetiapine binding affinity for D2 (437nM)

DA Binding affinity for D2 (Ki = 540nM)

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
Conclusions

• Every antipsychotic has the same or higher affinity for D2 receptors as dopamine has for D2 receptors

• Not surprising, or they wouldn’t be antipsychotics

• However…
Dopamine can displace antipsychotics from D2

PET scan in patients with schizophrenia before and after amphetamine stimulation

Dopamine overflow was stimulated by amphetamine injection (0.2 mg/kg) in schizophrenia patients

Antagonist/Partial Agonist Effects at D2 Dopamine Receptors

Dysregulation of D2-mediated signaling in the motor striatum can result in EPS. This mitigates the effects of overactive mesolimbic dopamine, reducing positive symptoms.

D2 antagonists block and inhibit activity of postsynaptic D2 receptors.

Dysregulation of D2-mediated signaling in the motor striatum can result in EPS.

Cariprazine binding affinity for D1 (1000nM)
Blonanserin binding affinity for D1 (1090nM)
Brexpiprazole binding affinity for D1 (164nM)
Asenapine binding affinity for D1 (2.9nM)
Paliperidone binding affinity for D1 (41nM)
Olanzapine binding affinity for D1 (56.6nM)
Ziprasidone binding affinity for D1 (80nM)
Iloperidone binding affinity for D1 (129nM)
Clozapine binding affinity for D1 (240nM)
Lurasidone binding affinity for D1 (262nM)
Risperidone binding affinity for D1 (327nM)
Aripiprazole binding affinity for D1 (1173nM)
Cariprazine binding affinity for D1 (1000nM)

DA Binding affinity for D1 (Ki = 1766nm)

- 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
Conclusions

• Some antipsychotics have so much higher affinity for D1 receptors than dopamine has for D1 receptors that it results in net D1 blockade

  • asenapine > paliperidone, olanzapine, ziprasidone
Antagonist Effects at D1 Dopamine Receptors

D1 antagonists block and inhibit the activity of postsynaptic D1 receptors. This further reduces DA activity in the cortex and could theoretically worsen cognitive function.

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)

Clozapine binding affinity for D3 (310nM)
Quetiapine binding affinity for D3 (394nM)
Olanzapine binding affinity for D3 (38.1nM)
Lurasidone binding affinity for D3 (15.7nM)
Iloperidone binding affinity for D3 (10.5nM)
Ziprasidone binding affinity for D3 (7.3nM)

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
Conclusions

• Almost all antipsychotics have about the same affinity for D3 receptors as dopamine, resulting in little net D3 blockade in the presence of dopamine and at antipsychotic doses

• However, two antipsychotics have even higher affinity for D3 receptors than dopamine does, and do result in net blockade of D3 receptors
  • cariprazine > blonanserin
Who Cares If You Block D3 receptors?

• Increased dopamine delivery to prefrontal cortex and possibly limbic striatum

• Disinhibition of D3 autoreceptors especially in the VTA/SN

• Enhancement of mood, cognition, negative symptoms, apathy, anhedonia?
Antagonist/Partial Agonist Effects at D3 Dopamine Receptors

Prefrontal cortex

Nucleus accumbens

Ventral tegmental area

Increased DA release in the PFC re-regulates aberrant cortical activity and could theoretically improve negative symptoms and cognitive impairment.

This results in an increase in DA release in the PFC.

D3 antagonists/partial agonists block and inhibit the activity of somatodendritic D3 receptors.

Summary:
Antipsychotic Binding at Dopamine Receptors

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

D3 (Cariprazine) vs. D2 (Risperidone) for Negative Symptoms


Week 0 5 10 15 20 25 30

Least squares mean change from baseline in PANSS-FSNS

*p=0.0079
**p=0.0011
***p=0.0016
****p=0.0022

p=0.0092 for the overall treatment effect of cariprazine versus risperidone

cariprazine (n=230)
 risperidone (n=231)
D3 (Cariprazine) vs. D2 (Risperidone) for Negative Symptoms (Cont.)


Least squares mean change from baseline in PSP total score

Week 0 5 10 15 20 25 30

0 4 8 12 16

*p=0.0053.

**p=0.0046.

***p=0.0004

† p<0.0001

‡ p<0.0001

PSP: Personal and social performance

Cariprazine (n=230) vs. Risperidone (n=231)
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)
• MIN-101 (5HT2A and sigma receptor binding)
  • In development; positive

244 symptomatically stable schizophrenia patients were withdrawn from antipsychotics and randomly assigned to placebo or MIN-101.

Placebo group

MIN-101 32 mg/day group

MIN-101 64 mg/day group

* *p≤0.05. **p≤0.01

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 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)
- HMG CoA reductase inhibitors
  - Small positive trial of adjunct simvastatin

Veerman SRT et al. Drugs 2017;77:1423-59;
Treatment of Negative Symptoms: Psychosocial Strategies

• Exercise
  • Meta-analyses show moderate effect of aerobic exercise and yoga
• Cognitive remediation
  • Meta-analysis: small improvement compared to TAU
• Music therapy
  • Meta-analysis: large significant effect compared to TAU
• Cognitive behavioral therapy
  • Recent meta-analysis of 30 studies did not find beneficial effect

Clinical Translation:
Treatment Mechanisms Beyond Dopamine

- Neurobiological data: rationale for why current antipsychotics don't seem to improve cognition

- Prospect of novel mechanisms
  - Glutamatergic
  - GABA-ergic
  - Cholinergic
  - 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**

- **Postsynaptic metabotropic receptors**
- **NMDA receptors**
- **AMPA receptors**

**Glia cell**

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

**Direct acting glycine site agonists**
- d-cycloserine
- d-serine
- glycine

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

**mGlu receptor modulators**
- LY354740
- LY2140023
Summary

• D3 antagonism is a potential mechanism for reducing negative symptoms

• Other pharmacologic mechanisms are being investigated but so far nothing shows robust efficacy

• Clinicians both overestimate adherence and underestimate the impact of partial adherence

• Adherence can be optimized with careful monitoring, addressing intolerability, and considering LAIs