OPTIMIZING FUNCTIONAL OUTCOMES IN SCHIZOPHRENIA: MANAGING NEGATIVE SYMPTOMS, COGNITIVE IMPAIRMENT, AND ADVERSE EFFECTS
Learning Objectives

- Implement evidence-based strategies to address the negative symptoms of schizophrenia
- Examine evidence-based strategies to address the cognitive symptoms of schizophrenia
- Apply pre-emptive and monitoring strategies to mitigate the impact of adverse effects
- Evaluate the status of plasma monitoring and long-acting injectables (LAIs) with treatment adherence
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

Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis

Why aren't negative symptoms sufficiently improved with dopamine 2 antagonists?

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

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

Functional Output of Cortical Dopamine and Cognition

- Cognitive performance

- Activity optimal

- Dopamine receptor activity too low

- Dopamine receptor activity too high

- Cognitive symptoms

Dopamine levels (PFC)

- Blocking D1

- Blocking D3

Dopamine Receptor Affinities

K (nM) for dopamine

Dopamine receptor

D1
D2
D3
D4
D5

Regulation of Dopamine Levels at the Synapse

D1  D2  D3  D4  D5

VMAT2

D2 auto-receptor

D3 auto-receptor

Receptor affinities dictate neuronal response to tonic and phasic firing.

- VMAT2
  - Slow, irregular
  - Sets background DA level

- Rapid, synchronous burst
- Spike in extracellular DA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Binding affinity for D3 (Ki)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cariprazine</td>
<td>0.09nM</td>
</tr>
<tr>
<td>Bionanserin</td>
<td>0.49nM</td>
</tr>
<tr>
<td>Asenapine</td>
<td>1.8nM</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>2.6nM</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>4.6nM</td>
</tr>
<tr>
<td>Risperidone</td>
<td>7.3nM</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>7.3nM</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>38.1nM</td>
</tr>
<tr>
<td>Clozapine</td>
<td>310nM</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>394nM</td>
</tr>
</tbody>
</table>
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)  
Brexipiprazole 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)  
Aripiprazole binding affinity for D2 (1.7nM)  
Asenapine binding affinity for D2 (1.7nM)  
Olanzapine binding affinity for D2 (3.0nM)  
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)
Conclusions

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

• Not surprising, because if they didn’t they wouldn’t be antipsychotics

• However…
Dopamine can displace antipsychotics from D2.

Dopamine overflow was stimulated by amphetamine injection (0.2 mg/kg) in schizophrenia patients. PET scan in patients with schizophrenia before and after amphetamine stimulation showed elevated dopamine levels.

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 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)
Iloperidone binding affinity for D3 (10.5nM)
Lurasidone binding affinity for D3 (15.7nM)
Olanzapine binding affinity for D3 (38.1nM)

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

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

d2
d1 d2 d3

d2

d1 d2 d3

Predominately D2

Plus D1

Plus D3

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


Least squares mean change from baseline in PANSS-FLSNS

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

p=0.0092 for the overall treatment effect of cariprazine versus risperidone
D3 (Cariprazine) vs. D2 (Risperidone) for Negative Symptoms (cont.)


Least squares mean change from baseline in PSP total score

PSP: Personal and social performance

* p=0.0053.
** p=0.0046.
*** p=0.0004
† p<0.0001
‡ p<0.0001
Treatment of Negative Symptoms: Other Strategies

- **Exercise** - Meta-analyses show moderate effect of aerobic exercise and yoga
- **Music therapy** - Meta-analysis show large significant effect compared to treatment as usual (TAU)
- **Cognitive behavioral therapy** - Recent meta-analysis of 30 studies did not find beneficial effect
- **Cognitive remediation therapy** (CRT)
- **High frequency repetitive transcranial magnetic stimulation** (HF-rTMS)

CRT Effectiveness

• Current evidence suggests that CRT is associated with both neurobiological and cognitive improvement in patients with schizophrenia

• Studies indicate that CRT affects several brain regions and circuits, including prefrontal, parietal, and limbic areas, both in terms of activity and structure

• Changes to prefrontal areas are the most reported finding, fitting to previous evidence of dysfunction in this region

Neuroimaging and CRT

- CRT group exhibited significantly greater improvements than the TAU group in verbal fluency ($p=0.012$)
- CRT group demonstrated significantly greater improvements than the TAU group in global cognitive scores ($p=0.049$)
- CRT group also exhibited significantly greater hippocampal volume than in the TAU group ($p < 0.001$)
- Changes in verbal fluency scores and right hippocampal volumes were positively correlated
- Results suggest that CRT induces cognitive improvement through hippocampal plasticity

Transcranial Magnetic Stimulation for Treatment of Schizophrenia

- Recent pilot study: 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
- Participants completed a cognitive assessment and MRI prior to and after completion of the study
- Those who received rTMS displayed improvement on a standardized cognitive battery test both immediately following the course of study treatment and at follow-up two weeks later
- MRI results indicated that left frontal cortical thickness at baseline was correlated with treatment response
- Study treatment was safe and well tolerated
- rTMS may be an effective treatment of cognitive dysfunction in the early phase of psychosis

Transcranial Magnetic Stimulation for Treatment of Cognitive Impairment in Schizophrenia

Cognitive assessment at baseline

MRI at baseline

2 weeks; ten sessions HF, bilateral sequential rTMS over DLPFC or sham

Cognitive assessment at end of study

MRI at end of study

Pilot study: 21 participants

Results:
• rTMS improved scores on standardized cognitive battery test both immediately after study treatment and at follow-up two weeks after
• MRI results indicated that left frontal cortical thickness at baseline was correlated with treatment response

MANAGING ADVERSE EFFECTS
Monitoring Challenging Adverse Effects

- Antipsychotic (AP)-related weight gain
- Extrapyramidal Symptoms (EPS)
- Akathisia
Weight Gain & Antipsychotics

- Most antipsychotics
  - Younger and AP naive patients are more sensitive
- Tip: don’t just look at mean change in weight; also look at proportion of patients in each group who gained or lost ≥ 7% of baseline body weight
- Tip: must compare to placebo
- Mechanisms: H1 or 5HT2C blockade
Weight Gain Management: Let’s Prescribe Metformin More Often

• Metformin reduces weight, BMI, fasting glucose, fasting insulin, triglycerides, and total cholesterol
• Of treatments for antipsychotic-induced weight gain/metabolic abnormalities, metformin was the most effective
• Average weight loss: 6.5 lbs
• Hypoglycemia is rare with metformin, and the risk of lactic acidosis is extremely low until eGFR is < 30 mL/min
  • Reevaluate metformin if eGFR < 45 mL/min, and stop if < 30 mL/min

Zheng et al., 2015 (PMID: 26280837). Maayan et al., 2010 (PMID: 20336059); Kirpichnikov et al., 2002 (PMID: 12093242); Lipska KJ Diabetes Care 2011; 34: 1431-37 (PMID 21617112).
Metformin: for Whom

- Metformin works whether or not there is increased blood sugar or hemoglobin A1C

- Who is most likely to respond?
  1. Younger patients
  2. Recently started on the antipsychotic
  3. Before weight gain (to prevent it)
  4. Early on if weight gain occurs

Standard titration: 500 mg qam the first week. Increase by 500 mg/wk if tolerated to 1000 mg BID. Use extended release formulation if GI adverse effects.

Jarskog et al., 2013 (PMID: 23846733); Hasnain and Viewing, 2013 (PMID: 23659558).
Combination of Metformin and Lifestyle Intervention

• Recent meta-analysis of six RCTs: metformin, placebo, or metformin and lifestyle combination (MLC)
• MLC group had significant reduction in weight and body mass index
• Less frequent weight gain of ≥ 7% in the MLC group over placebo
• No other group differences in total adverse drug reactions, total psychopathology, and all-cause discontinuation
• Combining metformin and lifestyle intervention significantly reduces AP-related weight gain

Zheng et al. Pharmacopsychiatry 2018;Epub ahead of print.
Weight Gain Management: Topiramate

• Eight RCTs for weight gain on second-generation antipsychotics
• Mean decrease in weight: 6.2 lbs
• Which (again) means—many of the patients lost more than that

Mahmood et al., 2013 (PMID: 23277264).
Weight Gain Management: Topiramate Considerations

BUT:

• Cognitive dulling
• Risk of renal stones
• Drug interactions

Ellinger et al., 2010 (PMID: 20233913).
What are extrapyramidal signs (EPS) and extrapyramidal side effects (EPSE)?

• Movement disorders that occur with antipsychotics

• Thought to involve structures outside of the pyramidal tract

• Occur in acute and late (tardive) forms

• Reason for the older term "neuroleptic" to describe antipsychotics
Extrapyramidal Side Effects

• Acute extrapyramidal side effects
  • Dystonia
    • Disturbance in muscle tone leading to prolonged contractions of muscle groups
    • Occurs within 24–48 hours of antipsychotic initiation
    • Only acute EPS that is less common in the elderly
  • Parkinsonism
    • Classic triad of bradykinesia, rigidity, and tremor
    • Occurs within days of starting treatment or dose increase in 1/4 to 1/3 of patients
    • Can occur in up to 75% of older patients
Pathophysiology and Treatment

• Pathophysiology
  • Due to D2 blockade in the dorsal striatum

• Treatment
  • Reduction in dose
  • Anticholinergics and other antiparkinsonians (e.g., amantadine) until plasma antipsychotic levels have been reduced below the threshold for motor adverse effects
  • Chronic anticholinergic treatment should be avoided due to adverse cognitive effects and increased ileus risk
Akathisia: Subjective Symptoms

• Often extraordinarily difficult for the patient to describe, to some extent, because there are few subjective states to which it can be compared.

• Patients often use terms such as "anxiety" or "itching," although these do not really capture the essence of the condition.

• Since many clinicians have never experienced it, there is often a lack of common ground in communicating the problem.
Hypothesized Mechanism of Akathisia: the Role of the Nucleus Accumbens

<table>
<thead>
<tr>
<th>Agent</th>
<th>Incident Rates of Akathisia for Schizophrenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>10-13% monotherapy; 19-25% with lithium, divalproex, or antidepressants</td>
</tr>
<tr>
<td>Asenapine</td>
<td>4-11%</td>
</tr>
<tr>
<td>Brexipiprazole</td>
<td>4-7% (dosed 1-4 mg/day)</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>9-14%</td>
</tr>
<tr>
<td>Clozapine</td>
<td>3%</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>1-2%</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>6-22%</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>3%</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>6-9%</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>1-4%</td>
</tr>
<tr>
<td>Risperidone</td>
<td>5-9%</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>8-10%</td>
</tr>
</tbody>
</table>

BP: bipolar depression. MDD: major depressive disorder. SZ: schizophrenia.
Treatment Strategies for Akathisia

• Dosage reduction

• Change to lower-risk agents if feasible
  • Withdrawal akathisia can occur; allow at least 6 weeks before judging effectiveness of dose reduction/medication switch

• Adjunctive medications

Adjunctive Treatment Strategies for Akathisia

• Centrally-acting beta blockers
  • Propranolol: nonselective, lipophilic. Dose: 30-90 mg/day: start at 10 mg BID, increase by 10 mg BID increments as tolerated
  • Betaxolol: beta$_1$, selective, lipophilic 10-20 mg/day

• Mirtazapine: 5HT2A antagonist property helps mitigate akathisia
  • 15 mg/day is the most common mirtazapine dose studied; unclear if higher doses are more effective. Avoid if h/o mania

• Clonazepam
  • Anticholinergics (e.g., benztropine): appear less effective than other agents, and carry the anticholinergic burden. Generally avoided

Rathbone and Soares-Weiser, 2006 (PMID: 17054182);
Laoutidis and Luckhaus, 2014 (PMID: 24286228); Poyurovsky et al., 2006 (PMID: 16497273).
Reverberations From Side Effects

How patient and clinician responses may differ

- Side effect appears
- Subjective distress
- Objective severity
- Adherence impact
- Safety and risk

Influencing patient response

Influencing clinician response

Considering the Side Effect Profile When Choosing a Treatment

• Important because side effects may:
  • Contribute to treatment nonadherence
  • Limit return to maximal levels of social functioning
  • Potentially contribute to long-term morbidity

• Atypical antipsychotics are better tolerated than typical antipsychotics (mainly due to decreased EPS)

• Differences in drug-specific adverse effect profiles, including metabolic effects, may impact treatment adherence and long-term outcomes

NONADHERENCE AND PLASMA LEVELS
Rates of Relapse
With Continued vs. Discontinued Treatment

178 asymptomatic patients treated for ≥1 year with AP and randomized
to quetiapine 400 mg/day (n=89) or placebo (n=89).\(^1\)

50% of patients become nonadherent within 1 year of hospital discharge\(^2\)

quetiapine vs. placebo: \(p<0.001\)

We Are Not Good at Estimating Adherence: Clinician Assessment vs. Plasma Levels

Among 105 patients admitted to a US psychiatric hospital previously on antipsychotics:

- Therapeutic plasma levels: 34%
- Sub-therapeutic plasma levels: 66%

Staff correctly identified:
- 67%
- 52%

Antipsychotic: risperidone, olanzapine, quetiapine, paliperidone, aripiprazole

Many treatment-resistant patients have subtherapeutic plasma levels.

**Study 1:** Antipsychotic plasma levels were measured in 36 outpatients identified as having treatment-resistant schizophrenia by their treating clinicians in the UK. 44% of patients showed subtherapeutic levels, 43% of which were undetectable. 56% of patients had levels in the therapeutic range.

**Study 2:** Antipsychotic plasma levels were measured in 99 outpatients identified as having treatment-resistant schizophrenia by their treating clinicians in the UK. 35% of patients showed subtherapeutic levels, 34% of which were undetectable. 65% of patients had levels in the therapeutic range.

Which antipsychotics are recommended for plasma level monitoring?

<table>
<thead>
<tr>
<th>Usual Doses to Achieve 60–80% D2 Receptor Occupancy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Usual dose range (mg/d)</strong></td>
</tr>
<tr>
<td>Aripiprazole</td>
</tr>
<tr>
<td>Clozapine</td>
</tr>
<tr>
<td>Fluphenazine</td>
</tr>
<tr>
<td>Haloperidol</td>
</tr>
<tr>
<td>Olanzapine</td>
</tr>
<tr>
<td>Paliperidone</td>
</tr>
<tr>
<td>Perphenazine</td>
</tr>
<tr>
<td>Risperidone</td>
</tr>
<tr>
<td>Ziprasidone</td>
</tr>
</tbody>
</table>

*In schizophrenia

Dosing/Plasma Levels for Newer Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Usual dose range (mg/d)*</th>
<th>Rec plasma levels (ng/mL)¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asenapine</td>
<td>10–20</td>
<td>2–5</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>2–4</td>
<td>?</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>1.5–6</td>
<td>?</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>12–24</td>
<td>5–10</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40–160</td>
<td>&gt;70²</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>400–800</td>
<td>Not reliable or used</td>
</tr>
</tbody>
</table>

*In schizophrenia

Obtaining Plasma Levels

• 12-hour trough
• For patients on twice/day dosing, make sure they hold the morning dose until the AM trough is obtained
• Levels may fluctuate up to 30% in adherent patients
• Greater fluctuations likely reflect nonadherence or kinetic issues
Technology-Based Services

- Text reminders
  - Two studies found that 3–4 texts/day (about adherence, socialization, and hallucinations) significantly improved adherence in patients living independently for up to 6 months
- Phone calls
  - Weekly calls led to significantly higher adherence
- Electronic pill counters
  - Adherence rate of 67% at 6 weeks
- Tracking devices?

Summary

• D3 antagonism is a potential mechanism for reducing negative symptoms
• Other pharmacological mechanisms are being investigated, but so far nothing shows robust efficacy
• Established psychosocial methods may effectively treat cognitive symptoms of schizophrenia
• Nonpharmacological methods are on the horizon (e.g., TMS) for treating cognitive symptoms of schizophrenia
• There are many medications available to effectively manage adverse effects associated with antipsychotics
• Adherence can be optimized with careful monitoring