Treatment of Schizophrenia, Cognition, Prodrome, First Episode, Relapse, Highlighting New Drugs and Dosing

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Issues We’ll Touch Upon

- Current understanding on schizophrenia and its unmet therapeutic needs
- What we know about the neurobiology of schizophrenia and what that means for treatment
- Review safety and efficacy of available antipsychotics
- Early intervention and the prodrome
- Relapse prevention: Role of LAIs
- Cognitive impairments and recovery
- Treatment resistance: Focus on clozapine
- Future trends in schizophrenia treatment
Schizophrenia is common

Schizophrenia is heterogeneous with many Dimensions

Orbitofrontal Cortex
- Disorganization

Prefrontal Cortex
- Cognitive Deficits

Negative Symptoms

Positive Symptoms

Motor Symptoms

Mood Symptoms

N. accumbens, reward circuits

Mesolimbic, hippocampus

Thalamus, basal ganglia

Medial prefrontal, amygdala


Cognitive Deficits are a core aspect

Effect sizes from 4 meta-analyses on cross-sectional IQ impairment in individuals with psychosis or at risk for psychosis compared to controls (Cohen's d).

Schizophrenia evolves in phases

- Jeffrey is a 26-year-old single unemployed man living with his parents. His early milestones were slightly delayed. He had been evaluated by a psychologist for a possible attention deficit disorder.
- His grades began to decline during high school and his grades were mostly Cs by his junior year. He had increasing anxiety and feelings that he had more important missions in life than just getting a college degree. He withdrew socially, and began to post garbled political messages on twitter.
- During his second year of college, Jeffrey began believing that he is destined to become the President of the United States and that FBI and the CIA were “vetting him” to be groomed to the highest office. He was briefly hospitalized.
- Over the past 4 years, intermittently relapses because of poor adherence as well as forgetfulness. He has few significant friendships and has no steady job.
<table>
<thead>
<tr>
<th>Schizophrenia</th>
<th>Neurobiology</th>
<th>Antipsychotics</th>
<th>Early intervention</th>
<th>Relapse prevention</th>
<th>Cognition &amp; recovery</th>
<th>Treatment resistance</th>
<th>Future</th>
</tr>
</thead>
</table>

### Unmet Needs in Schizophrenia

- Cognitive impairments
- Negative symptoms
- Treatment-resistant positive symptoms
- Side effects
- Treatment nonadherence

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Schizophrenia is thought to be related to exaggerated synaptic pruning during adolescence, perhaps related to genetic factors.

- Glantz and Lewis 2000
- Liu, Keshavan, Tronick and Seidman Schiz Bulletin 2015
The emerging model of the brain chemical “imbalance” in schizophrenia.

108 Gene Loci in schizophrenia  Schiz Working Group, Nature 2014

genes may have to do with the excess synapse loss

Increased Mesolimbic DA

PSYCHOSIS

Decreased Mesocortical DA function

GABA Inter-neurons

NMDA receptor hypofunction

Inefficient Glu activity
MANY IMPLICATED GENES CONVERGE ON NMDA RECEPTOR FUNCTION

Schizophrenia Neurobiology Antipsychotics Early intervention Relapse prevention Cognition & recovery Treatment resistance Future

Adapted from Farde et al Arch Gen Psychiatry 1992

All current antipsychotics work by blocking dopamine receptors

Adapted from Farde et al Arch Gen Psychiatry 1992
First-Generation or typical Antipsychotics (FGAs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH-POTENCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6-20 mg/day</td>
<td>High selectivity for D₂</td>
</tr>
<tr>
<td>Fluphenazine</td>
<td>6-20 mg/day</td>
<td>EPS</td>
</tr>
<tr>
<td><strong>MID-POTENCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8-64 mg/day</td>
<td>Medium selectivity for D₂</td>
</tr>
<tr>
<td>Loxapine</td>
<td>30-100 mg/day</td>
<td>Moderate-high EPS, mild sedation</td>
</tr>
<tr>
<td><strong>LOW-POTENCY</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100-1000 mg/day</td>
<td>Low selectivity for D₂; H₁, AChR, AR antagonism</td>
</tr>
</tbody>
</table>

AcH₁ = acetylcholine; AR = adrenergic; EPS = extrapyramidal symptoms; H₁ = histamine.

Second-Generation Antipsychotics (SGAs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clozapine</td>
<td>25-900 mg/day</td>
<td>Sedation, weight gain, agranulocytosis</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>5-20 mg/day</td>
<td>Sedation, weight gain, dyslipidemia</td>
</tr>
<tr>
<td>Risperidone</td>
<td>0.5-8 mg/day</td>
<td>Sedation, weight gain, hyperprolactinemia</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>3-6 mg/day</td>
<td>Sedation, weight gain, hyperprolactinemia</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>25-750 mg/day</td>
<td>Sedation, weight gain, postural hypotension</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10-20 mg/day</td>
<td>Sedation, weight gain, EPS</td>
</tr>
<tr>
<td>Iloperidone</td>
<td>12-24 mg/day</td>
<td>Sedation, moderate weight gain</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>40-160 mg/day, with food</td>
<td>Akathisia, QTc prolongation, minimal weight gain</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>40-160 mg/day, with food</td>
<td>Akathisia, EPS, minimal weight gain Procognitive?</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>400-800 mg/day</td>
<td>Sedation, hyperprolactinemia</td>
</tr>
</tbody>
</table>

Partial Agonist/Antagonist Antipsychotics

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>10-30 mg/day</td>
<td>Akathisia, activation, some weight gain, tremor</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Can reverse prolactin increases</td>
</tr>
<tr>
<td>Brexpiprazole</td>
<td>2-4 mg/day</td>
<td>Akathisia, insomnia, minimal weight gain;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Has antidepressant effects</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>3-6 mg/day</td>
<td>Akathisia, EPS, insomnia, tremor, minimal weight</td>
</tr>
<tr>
<td></td>
<td></td>
<td>gain; Good for Negative symptoms?</td>
</tr>
<tr>
<td>Lumateperone</td>
<td>42 mg single daily dose</td>
<td>Akathisia, EPS, insomnia, tremor, minimal weight gain; Good for Negative symptoms?</td>
</tr>
</tbody>
</table>


Treatment Selection with Antipsychotics

- All antipsychotics are effective against psychotic symptoms
- Clozapine more effective than other agents in otherwise treatment-refractory patients
- SGAs have lower risk of EPS and TD than FGAs
- Some SGAs (clozapine, olanzapine, Quetiapine have significant metabolic side effects
- Individual patients may respond preferentially to different medications

Comparison of Antipsychotic Efficacy Relative to Placebo

SGA=second-generation antipsychotic; FGA=first-generation antipsychotic; EPS=extrapyramidal symptoms; TD=tardive dyskinesia.
Antipsychotic side effects

<table>
<thead>
<tr>
<th></th>
<th>EPS/TD</th>
<th>Dyslipidemia</th>
<th>Weight gain/T2DM</th>
<th>Elevated prolactin</th>
<th>Anticholinergic effects</th>
<th>Orthostatic hypotension</th>
<th>QTC prolongation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>chlorpromazine</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>haloperidol</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td></td>
<td>-</td>
<td>++ (+++ if H)</td>
</tr>
<tr>
<td>fluphenazine</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td></td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>aripiprazole</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+/-</td>
</tr>
<tr>
<td>asenapine</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>brexpiprazole</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
</tr>
<tr>
<td>lurasidone</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+/-</td>
<td></td>
<td></td>
<td>+/-</td>
</tr>
<tr>
<td>olanzapine</td>
<td>+</td>
<td>+++</td>
<td>+++</td>
<td>+</td>
<td></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>paliperidone</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>paliperidone</td>
<td>+++</td>
<td>+</td>
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<td></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>paliperidone</td>
<td>+++</td>
<td>+</td>
<td>+++</td>
<td>-</td>
<td></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>ziprasidone</td>
<td>+</td>
<td>+/-</td>
<td>+/-</td>
<td>+</td>
<td></td>
<td>-</td>
<td>++</td>
</tr>
<tr>
<td>clozapine</td>
<td>+/-</td>
<td>+++</td>
<td>+++</td>
<td>+/-</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
</tr>
</tbody>
</table>
Limitations of Antipsychotic Therapies

- Incomplete efficacy
- Significant adverse effects
- Poor treatment adherence
  - Leads to recurrent relapses with adverse consequences
  - Higher mortality
  - Worse functional ability
  - Worse quality of life


Atypical antipsychotics may reduce conversion to psychosis, but potential benefits are limited by side effects

Cognitive behavior therapy and family focused treatment have modest benefits to prevent conversion to psychosis

Cognitive remediation improved cognition and functioning, but no data yet on preventing psychosis

Devoe et al 2019 Early Interventions in Psychiatry
Personalized medication management  Family psychoeducation; Resilience-focused individual therapy; Supported employment and education, Team based approach

Premorbid biology  Prodromal neuro-psychotics  Prodromal ant-intervention  Prodromal psychosis

Future Early intervention Improves outcome Especially in those with Brief duration of Untreated psychosis

All cause discontinuation Psych hospitalization / Relapse Remission Recovery School/ work

Positive symptoms Negative symptoms General symptoms Depressive symptoms Global functioning Quality of life

Comparison of Early Intervention Services vs Treatment as Usual for Early-Phase Psychosis: Meta-analysis Of 10 RCTs Correll C et al JAMA Psychiatry
Relapse is Common

Relapse can cause:

- Rehospitalization
- Slow and incomplete recovery
- Treatment-resistant illness
- Persistent symptoms
- Progressive cognitive decline and possibly brain changes
- Increasing difficulty to regain previous level of functioning
- Reduced quality of life

Antipsychotics Reduce Relapse Rates (five-fold)

Winton-Brown et al 2017
Methods to Improve Adherence

- Adherence training (eg, motivational interviewing, CBT)
- Reminder cues
- Simplify treatment regimens
- Patient/family psychoeducation
- Long-acting antipsychotic formulations


LAIs Have Less Relapses Than Oral Antipsychotics

![Graph showing proportion of relapses over time for oral and long-acting injectable antipsychotics.](image)

Schizophrenia

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (IM) &amp; Frequency</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haloperidol decanoate</td>
<td>50-300 mg Q4wks</td>
<td>Overlap with PO</td>
</tr>
<tr>
<td>Fluphenazine decanoate</td>
<td>12.5-100 mg Q2-3wks</td>
<td>Overlap with PO</td>
</tr>
<tr>
<td>Risperidone LA (Consta)</td>
<td>25-50 mg Q2wks</td>
<td>3 week overlap with PO</td>
</tr>
<tr>
<td>Risperidone (Perseris)</td>
<td>90-120 mg monthly</td>
<td>No overlap with PO</td>
</tr>
<tr>
<td>Paliperidone palmitate</td>
<td>39-234 mg Q4wks</td>
<td>No overlap with PO</td>
</tr>
<tr>
<td>(Invega Sustenna)</td>
<td>273-819 mg Q12wks</td>
<td>Q12wks can be used after 4 months on Q4wks</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>150 or 300 mg Q2wks</td>
<td>Monitor for 3 hours post injection</td>
</tr>
<tr>
<td></td>
<td>405 mg Q4wks</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole monohydrate</td>
<td>300, 400 mg Q4wks</td>
<td>2 week overlap with PO</td>
</tr>
<tr>
<td>(Maintena)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>441, 662, 882 mg Q4wks</td>
<td>3 week overlap with PO</td>
</tr>
<tr>
<td>(One day alternative with</td>
<td>882 mg Q6wks</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole inj+ single oral dose)</td>
<td>1064 mg Q8wks</td>
<td>(especially for oily LAI)</td>
</tr>
</tbody>
</table>
Current Recommendations: LAIs

- LAIs should not be restricted to patients with adherence problems, but instead should be more widely prescribed
- LAIs should systematically be offered to all patients through shared decision-making
- Any patient for whom long-term treatment is indicated should be considered a candidate for an LAI
- Even if patients initially refuse an LAI, it would be helpful to discuss it further to better understand the potential advantages
- A common reason for non-acceptance of LAI therapy may be that psychiatrists are ambivalent or unenthusiastic about this option even as they recommend it
- Recent evidence suggests that LAIs are effective for treating first-episode psychosis and for early initiation of treatment for schizophrenia

Stevens et al Early Intervention in Psychiatry, 10(5), 365–37

About a third of schizophrenia patients
Do not respond to conventional antipsychotics (typical or atypical)

Treatment resistance: Focus on clozapine

About a third of schizophrenia patients
Do not respond to clozapine

? ECT ?? Addition of D2 blocker
Before concluding that patient has Treatment resistance, verify:

- Correct diagnosis (of a psychotic disorder)?
- Continuing psychosocial stressors?
- Comorbid condition (such as depression or substance abuse)?
- Compliance (Is patient is taking the meds?)
- Concentration (Is level within therapeutic limits?)

**Resistant Schizophrenia**

Kane’s criteria (Arch Gen Psychiatry, 1988):

- ≥ 3 Antipsychotic Treatments, ≥ 2 Chemical classes, doses equi 1000 mg/d chlorpromazine, 6 weeks, without significant relief.
Managing treatment resistance

• The evidence is limited that adding a second antipsychotic to improve symptom response helps patients who are already taking one antipsychotic (Lin, 2020).
• Evidence is also limited for augmenting antipsychotics with mood stabilizers (Lin, 2020).
• Adding dopamine partial agonists such as aripiprazole may help treat negative symptoms but this might be achieved by a simple switch to a dopamine partial agonist.
• Consider early introduction of clozapine.
• Augmentation with ECT may be effective in clzapine resistant schizophrenia (Petrides et al, 2019).
• Consider augmentation with psychotherapy.


Schizophrenia | Neurobiology | Antipsychotics | Early intervention | Relapse prevention | Treatment resistance | Cognition & recovery | Future
---|---|---|---|---|---|---|---
Dopamine | Stimulants | Acetylcholine (nicotinergic) | Norepinephrine | Atomoxetine | Modafinil | Nicotinic agonists
Histamine | H3 antagonists | Acetylcholine (muscarinic) | | | | Ach-ase antagonists | Muscarinic agonists
GABA | GABA agonists | Cannabinoid receptors | Glutamate | Glutamate modulators | | CB1 antagonists

Several pharmacologic agents being tried now for cognitive deficits in schizophrenia, but have little benefit.
Cognitive remediation works... better than antipsychotics for community functioning

**Treatment Effects of Antipsychotics on Community Functioning for People with Schizophrenia**

Swartz et al 2007

**Treatment Effects of Cognitive Rehabilitation for People with Schizophrenia**

Hogarty et al 2004

Many glutamate compounds being investigated

**Keshavan et al 2015**

**Schizophrenia** | **Neurobiology** | **Antipsychotics** | **Early Intervention** | **Relapse Prevention** | **Treatment Resistance** | **Cognition & Recovery** | **Future**
---|---|---|---|---|---|---|---
Sodium benzoate | Glutamate | GABA | mGLU2/3 | PDE antagonists | Action potentials | Post-synaptic
Serine | Glycine | Lamotrigine | Presynaptic |
Glutamine | Bituprine, Glycine transporter inhibitor | NMDA receptors |
Serotonin

Pimavanserin, (Nuplazid)
5HT2a inverse agonist

- FDA approved for Parkinsonism,
- Pending in dementia Related psychosis
- Negative trial in depression
- Not effective for Pos sx schizophrenia but may help Neg SX


Acetylcholine

KarXT
Xanomeline (M1/M4 agonist)+
Tropium (peripheral anti-Cholinergic)

(Karuna)
Promising Phas II results for psychosis, neg sx

A7 nicotinic Encenicline,
Mixed results

Keefe R et al Neuropsychopharmacology 2015
Xanomeline–Tropium for Schizophrenia

**DOUBLE-BLIND, PHASE 2 TRIAL**

<table>
<thead>
<tr>
<th>Patients with schizophrenia</th>
<th>Xanomeline–tropium (twice daily)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>(N=90)</td>
<td>-17.4</td>
<td>-5.9</td>
</tr>
</tbody>
</table>

Change in PANSS total score at 5 wk (range 30–210; higher score = greater symptom severity)

Safety and adverse events
- Constipation, nausea, dry mouth, dyspepsia, and vomiting
- —

Xanomeline–tropium resulted in a greater decrease in the PANSS total score at 5 wk but was associated with cholinergic and anticholinergic adverse events.

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Cannabinoid agonists
- Cannabidiol

Prefrontal cortex
- GLU
- GABA
- CB1

Cannabinoids

Negative results
- Boggs et al 2018

Trace amine-associated receptor 1 (TAAR1) agonist and 5HT1a agonist (Sepracor) Koblan et al NEJM 2020

Change in PANSS scores from baseline

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Week 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>4.0</td>
</tr>
<tr>
<td>SEP-363806</td>
<td>125</td>
<td>125</td>
<td>122</td>
<td>117</td>
<td>113</td>
<td>100</td>
</tr>
</tbody>
</table>

No. of Patients

|       | 120 | 120 | 115 | 109 | 102 | 96   |

Inflammation

Anti-inflammatory agents
Minocycline, metformin

Anti-oxidants
N-acetyl cysteine

Oxidative stress

Glutamatergic dysfunction

Dopaminergic

GABA

GLU

Anti-inflammatory agents

Inflammation

Valbenazine for tardive dyskinesia

Dopamine function after exposure to antipsychotics

Valbenazine
Vesicle monoamine transporter inhibitor
40-80 mg po qd
No evidence of increased depression or suicidality (though tetrabenazine has a boxed warning)
Can prolong QT interval

Summary

- While the neurobiology of schizophrenia is increasingly better understood, many unmet therapeutic needs remain.
- All currently used antipsychotics impact dopaminergic function, are effective in psychosis, but are limited by metabolic and/or extrapyramidal side effects, and treatment resistance in many patients.
- Early intervention of psychotic disorders in coordinated specialty care programs can improve outcome and quality of life.
- Clozapine is an effective treatment for treatment-resistant schizophrenia, but is limited by substantive side effects.
- Nonadherence is a common problem; long-acting injectable antipsychotics have an important role in management of nonadherence.
- Psychosocial cognitive remediation is effective, but no clear pharmacological treatments of cognitive impairments yet available.
- Novel treatments being investigated include drugs targeting non-dopaminergic mechanisms (such as glutamate, serotonin, acetylcholine, TAAR1, cannabinoid).
Thank you!