Recent Advances in Schizophrenia Management

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Issues We’ll Touch Upon

- Burden of disease and unmet therapeutic needs in schizophrenia
- Current understanding on schizophrenia neurobiology and how it relates to treatment
- Review safety and efficacy of available antipsychotics
- Identifying and managing nonadherence
- Future trends in schizophrenia
Schizophrenia: Burden of Disease and Unmet Treatment Needs
Pharmacologic Treatment of Any Disease

- Know the disease that you are treating
  - Nature; treatment targets; treatment goals

- Know the treatments at your disposal
  - What they do; how they compare; costs

- Principles of treatment
  - Measurement-based; targeted; individualized

Prevalence of Schizophrenia

Relative Prevalence of Schizophrenia

<table>
<thead>
<tr>
<th>Condition</th>
<th>Relative Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schizophrenia</td>
<td>1x</td>
</tr>
<tr>
<td>Alzheimer's</td>
<td>2x</td>
</tr>
<tr>
<td>Multiple Sclerosis</td>
<td>5x</td>
</tr>
<tr>
<td>Insulin-dependent Diabetes</td>
<td>6x</td>
</tr>
<tr>
<td>Muscular Dystrophy</td>
<td>60x</td>
</tr>
</tbody>
</table>

Adapted from J.A. Lieberman


Direct Costs
$47 billion
- Health Care: 24%
- Non-Health Care: 6%

Indirect Costs
$117 billion
- Caregiving: 34%
- Premature Mortality: 2%
- Productivity Loss: 2%
- Unemployment: 38%
Schizophrenia: Heterogeneous Disease with Many Dimensions

Orbitofrontal Cortex
Disorganization

Prefrontal Cortex
Cognitive Deficits

Negative Symptoms
N. accumbens, reward circuits

Positive Symptoms
Mesolimbic, hippocampus

Different Underlying Pathophysiology and Treatment Response

Mood Symptoms
Medial prefrontal, amygdala

Motor Symptoms
Thalamus, basal ganglia
Psychosis Begins in Adolescence, but Cognitive Deficits Begin Earlier

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).

PRE=premorbid; PRO-C=prodrome converter; FE=first episode; CSZ=chronic schizophrenia.
Unmet Needs in Schizophrenia

- Cognitive impairments
- Negative symptoms
- Treatment-resistant positive symptoms
- Side effects
- Treatment nonadherence
Neurobiology of Schizophrenia: Current Understanding
The emerging model of the brain chemical “imbalance” in schizophrenia.
MANY IMPLICATED GENES CONVERGE ON NMDA RECEPTOR FUNCTION

Glutamate
Dysbindin
Neuregulin
DISC1

Serine
Glycine

DAOA

Dopamine
COMT
DRD2

GABA
RGS4
Neuregulin

Acetylcholine
CHRNA7

NMDAR

5HTT
RGS4

POST-SYNAPTIC

PRESYNAPTIC

GLIA

Keshavan et al prog Neurobiol 2015
An impaired balance between excitatory and inhibitory circuits may underlie at least part of the pathophysiology of schizophrenia. Keshavan et al Schiz Res 2013
Management of Schizophrenia: Current Pharmacotherapy
Clinical Nature of Schizophrenia: What We Know

Chronic, remitting and relapsing disease with incomplete remissions

- Multiple symptom dimensions
  - Different time course, neurobiology, & patterns of treatment response

- Distinct natural course of illness
  - Distinct stages with evolution of pathology
  - Begins premorbidly and progresses through prodrome to psychosis
  - Much of the decline occurs early in the illness
  - Functional impairment and social dysfunction peaks within 3 to 5 years of psychotic phase

Toward measurement-based care: Diagnosis-Specific Severity Assessment:

**Symptom Domains**

- Hallucinations
- Delusions
- Disorganized speech
- Abnormal psychomotor behavior (catatonia)
- Negative symptoms
- Impaired cognition
- Depression
- Mania

0 = Not Present
1 = Equivocal
2 = Present, but mild
3 = Present and moderate
4 = Present and severe

Relapse is Common in Schizophrenia

- About 82% of patients with schizophrenia or schizoaffective disorder experienced ≥1 relapse over 5 years

- Relapse can cause:
  - Rehospitalization
  - Slow and incomplete recovery
  - Treatment-resistant illness
  - Persistent symptoms
  - Progressive cognitive decline
  - Increasing difficulty to regain previous level of functioning
  - Reduced quality of life

Cumulative relapse rates in patients with schizophrenia, by year following recovery from the first episode

(104 patients at risk of relapse)

First-Generation Antipsychotics (FGAs)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose Range</th>
<th>Side Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HIGH-POWERNTY</strong></td>
<td></td>
<td>High selectivity for D&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>6-20 mg/day</td>
<td>EPS</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>Medium selectivity for D&lt;sub&gt;2&lt;/sub&gt;</td>
</tr>
<tr>
<td>Perphenazine</td>
<td>8-64 mg/day</td>
<td>Moderate-high EPS, mild sedation</td>
</tr>
<tr>
<td>Loxapine</td>
<td>30-100 mg/day</td>
<td>Moderate EPS, moderate sedation</td>
</tr>
<tr>
<td><strong>LOW-POTENCY</strong></td>
<td></td>
<td>Low selectivity for D&lt;sub&gt;2&lt;/sub&gt;; H&lt;sub&gt;1&lt;/sub&gt;, AChR, AR antagonism</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>100-1000 mg/day</td>
<td>Sedation, anticholinergic side effects, hypotension</td>
</tr>
</tbody>
</table>

AChR=acetylcholine; AR=adrenergic; EPS=extrapyramidal symptoms; H<sub>1</sub>=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</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>Brexpiprazole</td>
<td>2-4 mg/day</td>
<td>Akathisia, insomnia, minimal weight gain</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>3-6 mg/day</td>
<td>Akathisia, EPS, insomnia, tremor, minimal weight gain</td>
</tr>
</tbody>
</table>

Treatment Selection with Antipsychotics

- All antipsychotics are effective against psychotic symptoms
- Clozapine is more effective than other agents in otherwise treatment-refractory patients
- SGAs have lower risk of EPS and TD than FGAs
- Each medication has unique side effects
- Each medication has unique pharmacokinetics
- Individual patients may respond preferentially to different medications

SGA=second-generation antipsychotic; FGA=first-generation antipsychotic; EPS=extrapyramidal symptoms; TD=tardive dyskinesia.
Antipsychotic agents cause range of side-effects - can profoundly impact patient’s life

- **Activating – akathisia**
  - Emotional symptoms: depression, obsessive–compulsive, distress, paranoid ideation
  - Cognition: selective attention, perception, discrimination, coping responses
  - Risk of tardive dyskinesia
  - Cognitive dysfunction
  - Negative symptoms
  - Prolactin elevation can have profound effects on reproductive health and sexual function

- **Sedating**
  - Risk of unintentional injury
  - Reduced cognitive performance and functional capacity

- **Extrapyramidal symptoms**
  - Risk of tardive dyskinesia
  - Cognitive dysfunction
  - Negative symptoms

- **Sexual/endocrine**
  - Prolactin elevation can have profound effects on reproductive health and sexual function

- **Cardiovascular**
  - Suggested link to torsade de pointes, but risk is minimal
  - Difficulty establishing intimate relationships

- **Cardiometabolic**
  - weight gain; hypertension
  - Secrete eating
  - Lack of a sense of self-worth

**Side-Effects**

SGAs are Better than FGAs for Most

Greater Ease of Obtaining Antipsychotic Effect without EPS

- Fewer Negative Symptoms
- Fewer EPS
- Less TD
- Better Cognition
- Less Nonadherence
- Less Depression

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

The Best Treatment Today: Targeted, Measurement-Based, Individualized

- **Targeted**
  - Define targets for AND with patient

- **Ongoing, careful monitoring is critical!**
  - Reliable and repeated assessment of the efficacy of treatment using defined treatment targets
    - Use standard rating scales: DSM-5 Scale, CGI, PANSS
  - Careful assessment of adverse effects of treatment
    - Protocols for health monitoring
  - Ongoing collaboration with patient in decision-making

- **Standard protocols should be customized in response to individual vulnerabilities/needs and specific agent**

The Issue of Nonadherence: Identifying and Managing
Medications Don’t Work When Patients Don’t Take Them!

- Consequences of poor adherence
  - Increases likelihood of illness exacerbation
  - Impairs recovery
  - Associated with illness progression
  - Impairs functional recovery
  - Treatment costs are higher

Poor adherence leads to a 3-fold increase in risk of relapse and relapse prevention is CRITICAL.

Antipsychotics Reduce Relapse Rates (70%)

Log-rank test, \( P \)-value < 0.0001

Antipsychotics vs Placebo

- Antipsychotic
- Placebo

Estimated Percent of Patients Without a Relapse

Days since Randomization

0 20 40 60 80 100 120 140 160 180 200 220 240 260 280 300 320
Methods to Improve Adherence

- Adherence training (eg, motivational interviewing, CBT)
- Hand-holding
- Patient-specific behavioral tailoring
- Reminder cues
- Simplify treatment regimens
- Encourage disease acceptance
- Patient/family psychoeducation
- Long-acting antipsychotic formulations

LAIs Have Less Relapses Than Oral Antipsychotics

## Long-Acting Injectable Antipsychotics

<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 90-120 mg monthly</td>
<td>3 week overlap with PO</td>
</tr>
<tr>
<td>Risperidone (Perseris)</td>
<td>25-50 mg Q2wks 90-120 mg monthly</td>
<td>No overlap with PO</td>
</tr>
<tr>
<td>Paliperidone palmitate (Sustenna)</td>
<td>39-234 mg Q4wks 273-819 mg Q12wks</td>
<td>No overlap with PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Q12wks can be used after 4 months on Q4wks</td>
</tr>
<tr>
<td>Olanzapine pamoate</td>
<td>150 or 300 mg Q2wks 405 mg Q4wks</td>
<td>No overlap with PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Monitor for 3 hours post injection</td>
</tr>
<tr>
<td>Aripiprazole monohydrate (Maintena)</td>
<td>300, 400 mg Q4wks</td>
<td>2 week overlap with PO</td>
</tr>
<tr>
<td>Aripiprazole lauroxil</td>
<td>441, 662, 882 mg Q4wks 882 mg Q6wks 1064 mg Q8wks</td>
<td>3 week overlap with PO</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(One day alternative with Aripiprazole initio inj+ single oral dose)</td>
</tr>
</tbody>
</table>
LAI Antipsychotics: **Advantages**

- No need for daily administration
- Guaranteed administration and transparency of adherence
- If a relapse occurs, it is due to other reasons beyond nonadherence
- Lower relapse rates
- Minimal GI absorption problems, circumventing first-pass metabolism
- More consistent bioavailability
- More predictable correlation between dosage and plasma levels
- Reduced peak-trough plasma levels
- Improved patients’ and physicians’ satisfaction
- Regular contact between the patient and mental healthcare team
- Improved patient outcomes

LAI Antipsychotics: Disadvantages

- Slow dose titration
- Longer time to achieve steady state levels
- Less flexibility of dose adjustment
- Delayed disappearance of distressing and/or severe side effects
- Pain at the injection site can occur, and leakage into the subcutaneous tissue and/or the skin may cause irritation and lesions (especially for oily LAI)
- Perception of stigma

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.
Communication with Patient

- Many psychiatrists believe that their patients who take oral antipsychotics would, if offered, refuse a recommendation for LAI antipsychotic medications.
- Research suggests that the offer of LAI therapy itself is often characterized by hesitation and reluctance and that this may hinder the acceptance rate.
- Patients might have accepted the offer of LAI therapy if it had been presented differently.
- 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.

Novel Therapeutic Targets and Adjunctive Treatments
Schizophrenia: New Drugs Lead the Way

**Medicines in Development By Disease and Phase**

Some medicines are listed in more than one category.

- **All Medicines**: 119
- **Anxiety Disorders**: 15
- **Attention-Deficit Hyperactivity/Disorder**: 15
- **Autism Spectrum Disorders**: 6
- **Bipolar Disorders**: 5
- **Depression**: 29
- **Eating Disorders**: 2
- **Schizophrenia**: 36
- **Substance Use Disorders**: 20
- **Tic Disorders**: 3
- **Other Disorders**: 2

Available at www.schizophrenia.com.
MANY WAYS TO TARGET THE SYNAPSE

1. GABA allosteric modulators
2. NMDA agonists (glycine, D-serine)
3. 5HT2 antagonists
4. GlyT1 inhibitors
5. A-7 nicotinic receptor agonists
6. MGlue2/3 agonists
7. Dopamine D1 agonists
8. PDE 10 antagonists
9. CB1 antagonists
10. COMT agonists
11. Ampakines
12. Antioxidant (N-acetylcysteine)
13. Anti-inflammatory agents (celecoxib, minocycline)
A lot of focus is on glutamate.
Potential Therapeutic Targets

Prefrontal cortex

Serotonin (pimavanserin, Nuplazid)

5 HT1a

GLU

GABA

Raphe

5HT

5 HT2a,2c

VTA

DA

Prefrontal cortex

A7 nicotinic, M1 muscarinic

GLU

GABA

Raphe

ACh

VTA

DA

Other potential pharmacological targets: Acetylcholine

Encenicline, ongoing studies

Keefe R et al Neuropsychopharmacology 2015
Other potential pharmacological targets: Cannabinoid agonists
Cannabinoids
Cannabidiol: mixed results

Inflammation

Anti-inflammatory agents
Minocycline, metformin

Oxidative stress

Anti-oxidants
N-acetyl cysteine

Glutamatergic dysfunction

Prefrontal cortex

GLU
GABA

VTA
DA

Cognitive Remediation Can Reverse Gray Matter Deficits

Valbenazine (Ingrezza) is a new medicine for TD.

Antipsychotics & Tardive Dyskinesia

- Chronic blockade of D2 receptors leads them to up-regulate.
- tardive: slow or belated onset
- dyskinesia: presence of involuntary movements, tongue thrusts, lip smacking,
- eye blinking
- Potentially permanent!

- This may cause involuntary movements.
Stratified medicine (e.g. circuit based)

Precision medicine
Circuit based treatments? Neuromodulation Can Improve Symptoms via Network Manipulation

**Hypothesis:** If network disconnectivity causes negative symptoms, modulating connectivity by repetitive transcranial magnetic stimulation (rTMS) should modulate symptom severity.

**Result:** TMS induced increase in connectivity strongly and significantly correlates with improvement in negative symptoms \((r=-0.809, \ p=0.003)\). Active rTMS resulted in a greater change in Cerebellar-DLPFC connectivity than sham rTMS, \((p = .017)\).

Precision medicine approaches?


- Kelly et al. Randomized controlled trial of a gluten-free diet in patients with schizophrenia positive for antigliadin antibodies (AGA IgG): Deanna Kelly et al. J Psychiatry Neurosci. 2019

- Ketogenic diet prevents impaired prepulse inhibition of startle in an acute NMDA receptor hypofunction model of schizophrenia. (Palmer et al. Schiz Res 2019)
Prevention is Possible at Several Stages

**Primary Prevention**
- Early detection of risk
- Parental support
- Family-centered care

**Secondary Prevention**
- CBT, family-centered care
- Cognitive remediation
- Anti-inflammatory treatments
- Antioxidants
- Omega-3 fatty acids
- GABA modulators

**Tertiary Prevention**
- Relapse prevention
- Optimal pharmacotherapy
- Early detection of treatment resistance
- Addressing comorbid mood, medical and substance use disorders
- Cognitive rehabilitation, exercise
- Supportive employment
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.
- 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.
- Best treatment practice today involves a targeted, individualized and measurement-based approach.
- Novel treatments being investigated include drugs targeting non-dopaminergic mechanisms (such as glutamate, serotonin), neuromodulation and psychosocial approaches such as cognitive remediation.
- Circuit-based and precision medicine based interventions are on the way.
Thank You!