KEEPING UP WITH THE CLINICAL ADVANCES: SCHIZOPHRENIA
Learning Objectives

• Evaluate the potential clinical implications of evolving data on the neuropathology of schizophrenia
• Evaluate the mechanisms and latest clinical data on new and emerging antipsychotics
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
What’s on the horizon for treating schizophrenia?

- Evaluate the mechanisms and latest clinical data on new and emerging long-acting injectable and oral antipsychotics, and medications for cognitive dysfunction
- Evaluate the data on nonpharmacological strategies for cognitive dysfunction in schizophrenia
- Discuss the use of opioid receptor modulation to mitigate antipsychotic-associated weight gain
Schizophrenia: Consequences of Non-Adherence

- Increased mortality rates
- Risk of psychotic relapse
- Risk of suicide
- Potential for hospital readmission
- Declined quality of life
- Social and occupational difficulty

What’s on the Horizon: Novel Long-Acting Injectables (LAIs)

• Aripiprazole lauroxil nanocrystal dispersion (newly approved)
• Risperidone (RBP-7000) (newly approved)
Aripiprazole Lauroxil Nanocrystal Dispersion

• A 1-day regimen involving a single **675 mg injection** of the NanoCrystal® dispersion formula of AL (ALNCD) + **a single 30 mg dose of oral aripiprazole** achieves aripiprazole concentrations comparable to the 21-day oral coverage regimen (15 mg/day oral aripiprazole)
  - Patients also receive their regular dose of aripiprazole lauroxil at the same time. Due to the long onset of action, this does not contribute significantly during the first weeks of treatment
• Most common adverse effects were injection-site pain, headache, increased weight, insomnia, dyspepsia, and anxiety for both regimens
• On July 2, 2018, the FDA approved the combination of ALNCD 675 mg IM and one dose of 30 mg oral aripiprazole as a substitute for 21 days of oral aripiprazole
Aripiprazole Lauroxil Nanocrystal Dispersion

- Nanocrystal delivery system is just a smaller molecule
- Allows for the medication to dissolve faster, allowing patients to arrive at appropriate blood levels within 1-2 days, instead of 3 weeks

Pharmacokinetics: ALNCD

- AL 441 mg/1-day initiation (N = 39)
- AL 882 mg/1-day initiation (N = 41)
- AL 441 mg/21-day initiation (N = 40)
- AL 882 mg/21-day initiation (N = 41)

Concentration (ng/mL) vs. Sampling time (days)

Pharmacokinetics: ALNCD
Total Drug Exposure (AUC) Over First 28 Days

ALNCD: (Aristada Initio)

• FDA approved on July 2nd, 2018
• For patients who have never taken aripiprazole, establish tolerability with oral aripiprazole first
• Can be used for initiation of any Aristada dose
• First Aristada dose should be administered on the same day as Aristada Initio or up to 10 days later

<table>
<thead>
<tr>
<th>Aristada Dose Options</th>
<th>Time</th>
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<tbody>
<tr>
<td>441 mg, 662 mg, or 882 mg</td>
<td>Monthly</td>
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<tr>
<td>882 mg</td>
<td>Every 6 weeks</td>
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<tr>
<td>1064 mg</td>
<td>Every 2 months</td>
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Novel LAIs: Risperidone (RBP-7000)

- FDA approved Perseris™ on July 27\textsuperscript{th} 2018
- Subcutaneously (SC) administered depot formulation of risperidone using the ATRIGEL\textsuperscript{©} delivery system
- After SC injection, the delivery system solidifies upon contact with bodily fluids, and the resulting biodegradable implant delivers risperidone for an extended period of time, depending on the dose strength the injection volume 0.6 - 0.8 ml
- Designed to achieve rapid therapeutic concentrations without the need for supplemental oral dosing

ATRIGEL® Delivery System

Administration

Atrigel

Applied as liquid

Hardening

Atrigel

Hardened Atrigel

solidifies in body

Controlled Drug Release

Drug molecules

systemic drug release

PK: 90 mg and 120 mg Doses of RBP-7000

120 mg = 4 mg oral risp
90 mg = 3 mg oral risp

Pharmacokinetics: RBP-7000 D2 Occupancy

- In December 2017, the FDA accepted the New Drug Application
- The NDA submission included the results from the pivotal Phase III study on the efficacy and safety of RBP-7000 and an open-label, long-term safety study

Establish tolerability with oral risperidone
Perseris may be initiated at 90 mg or 120 mg
Supplementation with oral risperidone not recommended
Failure to fully mix the medication could result in incorrect dosage
Administer monthly by subcutaneous injection in the abdomen
Do not administer more than one dose (90 mg or 120 mg) per month
NOT approved for use in patients with dementia-related psychosis
Efficacy: Beyond D2 Hypothesis

- Schizophrenia has been primarily associated with dopamine dysfunction
  - All effective treatments directly target the dopamine D2 pathway

- 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 the dopamine hypothesis, including glutamate, serotonin, acetylcholine, GABA, and inflammatory cytokines
<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>
</tr>
<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 GABA-C 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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Novel Pharmaceutical Advancements in Efficacy

- Lumateperone (ITI-007)
- Lu AF35700 (Granted FastTrack Designation)
Lumateperone (ITI-007)

- 5-HT2A Receptor Antagonist - Improves sleep quality - Reduces anxiety and hostility - Enhances antipsychotic and antidepressant activity

Dopamine Phosphoprotein D2 Modulator (DPPM) - D2 Pre-synaptic partial agonist and post-synaptic antagonist - Antipsychotic efficacy for positive symptoms - Reduced agitation

Serotonin Reuptake Inhibitor - Antidepressant activity

Glutamatergic Phosphoprotein modulator - D1/GluN2B Modulation - Antipsychotic efficacy for negative and positive symptoms - Improved cognition and affect

PHARMACOLOGY PREDICTS ROBUST EFFICACY ACROSS A BROAD RANGE OF SYMPTOM DOMAINS AND PREDICTS HIGHLY FAVORABLE SAFETY/TOLERABILITY PROFILE

Lumateperone: Mechanism of Action

### Lumateperone (ITI-007) Efficacy and Tolerability

<table>
<thead>
<tr>
<th>Properties</th>
<th>Risperidone</th>
<th>ITI-007</th>
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<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>
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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.
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. at Pipeline Plus 2017;42(2):130-134.
TMS for Psychosis

- Promising results have been reported for both high frequency (HF) and neuronavigated repetitive transcranial magnetic stimulation (rTMS).

- Recent study examined the efficacy of HF (20 Hz) rTMS applied precisely over the left temporal region using neuronavigation.
  - 59 patients with schizophrenia or schizoaffective disorders were treated with rTMS or sham over 4 weeks.
  - rTMS target was determined by morphological MRI at the crossing between the projection of the ascending branch of the left lateral sulcus and the superior temporal sulcus (STS).

- The proportion of patients demonstrating ≥ 30% decrease in the Auditory Hallucinations Rating Scale (AHRS) differed significantly between conditions (p=0.016) at day 14.

Dollfus et al. Schizophr Bull 2018;44(3):505-514.
Cognitive Impairment in Schizophrenia

• Majority of schizophrenia patients demonstrate cognitive impairment relative to healthy controls
  • A small percentage does not, but might still be below expectations

• Almost all monozygotic twins perform worse than the unaffected co-twin

• 98% of schizophrenia patients have cognitive functioning lower than expected based on mother's education

• Meta-analyses have described cognitive dysfunction as a complex interaction of selective hypo- and hyperactivity in both cortical and subcortical areas, including frontal, parietal, and limbic structures
  • These neural activity patterns are associated with dysfunctions of distributed networks related to attention, cognitive control, and working memory

Cognitive Impairment in Schizophrenia

Healthy Normative Sample, N=300
Schizophrenia Patients, N=323

Mean T Score

Cognitive Impairment Begins Premorbidly and Persists Throughout the Course

- Premorbid risk
  - Genetic vulnerability
  - Mild cognitive impairment
  - Disability

- Prodrome
  - Change in thoughts
  - Social isolation
  - Reduced school performance

- Acute
  - Hallucinations
  - Delusions
  - Disorganized thoughts
  - Cognitive deficits
  - Social deficits
  - Loss of insight
  - Loss of function

- Chronic
  - Loss of function
  - Medical complications
  - Unemployment
  - Homelessness

- Positive symptoms
- Negative symptoms
- Cognitive deficits

I Think I Can: Efficacy With Cognitive Improvement

• Novel pharmaceuticals under development have demonstrated effective improvements on cognitive measures and in neuroimaging

• New approaches to previously established non-pharmacological methods (e.g., CRT) and novel treatments (HF-rTMS) may improve cognitive dysfunction
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 2\textsuperscript{nd} 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 $\Rightarrow$ 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

Felder et al Neuropharmacology 2018; S0028-3908(18)30028-5.
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.

(Sosei R&D day presentation, June 2015)
Non-pharmacological Treatments for Cognitive Impairment in Schizophrenia

- Cognitive remediation therapy (CRT)
- High-frequency repetitive transcranial magnetic stimulation (HF-rTMS)
Cognitive Remediation Therapy (CRT) in Schizophrenia

• CRT targets cognitive and functional difficulties. The goal is to improve attention, memory, language, executive functions.

• CRT is associated with neurobiological and cognitive improvement, and affects several regions and circuits, including prefrontal, parietal, and limbic areas
  • Changes to prefrontal areas are the most reported finding

• Two approaches: **Training or Strategy**
  
  **Training**: exercises which are regularly repeated and allow for specific training in the deficient aspect of cognitive function; restoring the deficient function
  
  **Strategy**: works with preserved functions to develop strategies for processing information

• Both methods show improvements in behavior and increased cerebral activity

• Several meta-analyses suggest CRT effectiveness in schizophrenia patients, especially from early intervention

Neuroimaging and CRT

- Recent study used **structural neuroimaging** to assess neuroanatomical effects of CRT, along with the association between changes in cortical volume and neurocognitive performance

- RCT of 16 patients in the CRT group, compared to 15 patients in the treatment-as-usual (TAU) group

- CRT participants engaged in twice-weekly computer-assisted CRT sessions and weekly group meetings for 12 weeks

- T1-weighted MRI was performed prior to, and after, the intervention period

- **Outcomes:** Cortical gray matter volume changes, and correlations between cortical volume changes, and CRT-derived neurocognitive improvements

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

Verbal Fluency and R Hippocampal Volume

- CRT showed marked improvement in verbal fluency compared to TAU
- Change in verbal fluency positively correlated with increased R hippocampal volume

CRT and Cerebral Activity

• Recent meta-analysis included eight studies comparing cerebral activity in MRIs when the training method was used vs. the strategy method

• Several studies reported correlations between increases in cerebral activity and improvements in cognitive function (e.g., attention, working memory, verbal memory, and cognitive control)

• Training method is capable of activating more of the targeted brain areas than the strategy method; increases in cerebral activity were observed primarily in prefrontal / temporal regions

• Strategy method appears to encourage more extensive activation of the cerebral networks; increased cerebral activity was concentrated in frontal regions, parietal, and occipital areas
Comparison of Training vs. Strategy Methods

Right hemisphere: representations of zones showing significantly high levels of activation after CRT (red=strategy, blue=training)

Left hemisphere: representations of zones showing significantly high levels of activation after CRT (red=strategy, blue=training)

Transcranial Magnetic Stimulation for Treatment of Schizophrenia

• A recent pilot study explored the effects of 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 treatment

• Those who received rTMS displayed improvement on a standardized cognitive test battery 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

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


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<tr>
<th>Receptor</th>
<th>Ki (nM)</th>
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<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>
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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

Figure 3. Change from baseline in PANSS total score by week (MMRM)

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)

* p ≤ 0.05
** p ≤ 0.01

Summary

• The most challenging issues in schizophrenia pharmacological management are the need for increased efficacy, reduced side effects, and novel approaches to cognitive dysfunction.

• There is one newly approved LAI for treatment initiation and a promising LAI utilizing a novel subcutaneous injection that provides early and sustained plasma levels. These additional options may help increase LAI use and improved clinical outcomes for poorly adherent schizophrenia patients.

• There are exciting improvements in behavioral approaches and use of neuromodulation (hf-TMS) to treat cognitive impairment in schizophrenia.

• There are drugs in development that reduce weight gain through impact on reward pathways without affecting antipsychotic efficacy or tolerability.
The NanoCrystal® dispersion formula of AL (ALNCD), when combined with a single 30 mg oral dose, enables rapid achievement of therapeutic levels and replaces the need for ____ oral coverage when commencing aripiprazole lauroxil.

A. 3 day
B. 1 week
C. 2 weeks
D. 3 weeks
A recent phase II study evaluated different samidorphan (SAM) doses in combination with olanzapine (OLZ) and found that 10 mg of SAM was optimal for mitigation of OLZ-induced ____________ .

A. Gastrointestinal problems
B. Extrapyramidal symptoms
C. Weight gain
D. Headaches
According to research, which approach to cognitive remediation therapy is effective in treating cognitive impairment?

A. Strategy
B. Training
C. They are both effective in treating cognitive impairment