Advances in the Treatment of **SCHIZOPHRENIA**: Integrating New and Emerging Options into Therapy to Meet Unmet Needs

This live CE broadcast is being conducted in conjunction with the Virtual CPNP 2020 Meeting.

PTce

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Current Landscape for the Treatment of Schizophrenia

Lindsey Miller, PharmD, BCPP

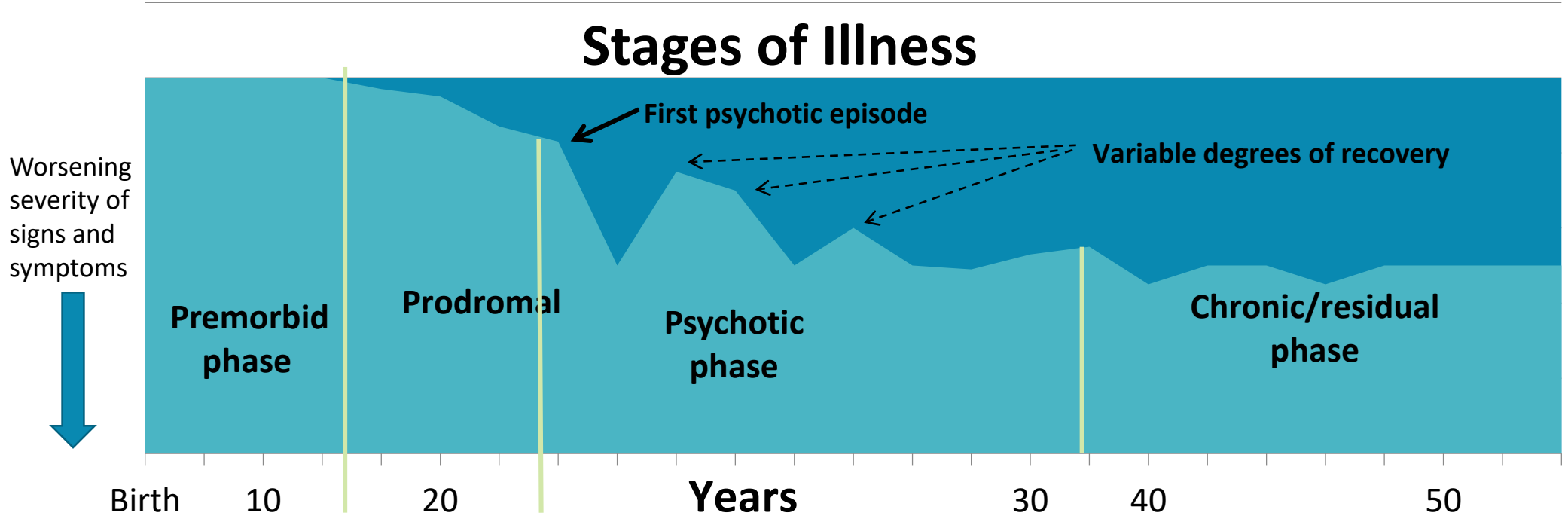
Educational Objectives

At the completion of this activity, participants will be able to:

- Explain goals associated with acute phase and maintenance phase schizophrenia treatment and the need for updated treatment guidelines
- Illustrate treatment challenges, risk of relapse, and the subsequent impact on patient outcomes
- Study new and emerging therapies, and their unique abilities to meet unmet needs
- Identify how to safely and effectively incorporate new therapies into patient-specific treatment plans

Natural Progression of Schizophrenia

Schizophrenia is a chronic thought disorder characterized by disturbances in perceptions, emotional response, and social interactions.



Adapted from: Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23; Lieberman JA, First MB. *N Engl J Med*. 2018;379:270-280; National Institute of Mental Health. Accessed April 9, 2020. nimh.nih.gov/health/topics/schizophrenia/index.shtml

Schizophrenia Overview

The World Health Organization estimates that 20 million people are affected by schizophrenia worldwide

The incidence of schizophrenia is approximately 0.6%-1.9% in the United States

Worldwide, schizophrenia is among the leading causes of disability

- Nearly 5% of people with schizophrenia die by suicide

National Institute of Mental Health. Accessed April 9, 2020. nimh.nih.gov/health/statistics/schizophrenia.shtml; World Health Organization. Accessed April 9, 2020. who.int/news-room/fact-sheets/detail/schizophrenia; van Os J, Kapur S. *Lancet*. 2009;374(9690):635-645; Patel KR, et al. *P T.* 2014; 39(9):638-645; Global Health Metrics. *Lancet*. 2017;390(10100):1211-1259; Palmer BA, et al. *Arch Gen Psychiatry*. 2005;62(3):247-253.

DSM-5 Criteria for Schizophrenia

- **2 or more symptoms*** present for a period of **1 month** or more:

Hallucinations | **Delusions** | **Disorganized speech** | **Disorganized behavior** | **Negative symptoms**

*1 symptom must include hallucinations, delusions, or disorganized speech.

- Must cause a *significant* disturbance in one's life
- Total duration of symptoms lasts at least **6 months**
- Other disorders (eg, schizoaffective disorder, substance use) should be ruled out

Adapted from: American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders. Fifth edition*. 2013.

Statistics

Adherence	Approximately 50%-75% of people with schizophrenia are nonadherent to medication treatment.
	Nearly 75% of patients discontinue medication due to adverse effects.
	Partial adherence may occur in as high as 70% of patients with schizophrenia.

Masand PS, et al. *Prim Care Companion J Clin Psychiatry*. 2009;11(4):147-154; Brissos S, et al. *Ther Adv Psychopharmacol.* 2014;4(5):198-219; Emsley R, et al. *BMC Psychiatry.* 2013;13:50; Lieberman JA, et al. *N Engl J Med*. 2005;353(12):1209-1223; Rummel-Kluge C, et al. *Aust N Z J Psychiatry*. 2008;42(5):382-388.

Statistics

General	13%-27% of patients with schizophrenia experience persistent negative symptoms.
	Patients with multiple negative symptoms have nearly a 60% higher risk of readmission at 1 year post hospitalization.
	Due to the impact of negative symptoms in schizophrenia, new treatment therapies are being developed to help target these symptoms.

Hovington CL, et al. *BMC Psychiatry*. 2012;12:224; Patel R, et al. *BMJ Open*. 2015;5(9):e007619.

Current Treatment

Treatment Goals

- Reduce acute symptoms
- Prevent relapse
- Optimize functioning
- Minimize adverse effects of treatment
- Improve quality of life

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines; Gottdiener WH, Haslam N. *J Am Acad Psychoanal Dyn Psychiatry*. 2003;31(1):191-208.

Treatment Approach

- American Psychiatric Association (APA) recommends that patients with schizophrenia have a documented, comprehensive, and *person-centered* treatment plan that includes evidence-based nonpharmacologic and pharmacologic treatments
- Treatment plan should include
  - Patient involvement
  - Social support
  - Engaging family members
  - Addressing barriers to treatment
  - Assess risk for harm to self and others
  - Collaboration with other providers

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

General Pharmacologic Approach to Treatment

1. Second-generation antipsychotic
2. Switch to a second-generation antipsychotic or first-generation antipsychotic
3. Clozapine
4. Combination treatment and adjunctive therapies

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines; Gottdiener WH, Haslam N. *J Am Acad Psychoanal Dyn Psychiatry*. 2003;31(1):191-208.

Medications for the Treatment of Schizophrenia

First-generation Antipsychotics

Chlorpromazine[ab]

Thioridazine

Loxapine[c]

Perphenazine

Trifluoperazine

Pimozide

Thiothixene

Fluphenazine[bd]

Haloperidol[abd]

Second-generation Antipsychotics

Aripiprazole[de]

Asenapine[fg]

Brexpiprazole

Cariprazine

Clozapine[eh]

Iloperidone

Lurasidone

Olanzapine[bde]

Paliperidone[di]

Quetiapine [i]

Risperidone[de]

Ziprasidone[b]

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

a intravenous formulation available
b intramuscular- immediate release available
c inhalation formulation available
d intramuscular- long-acting formulation available
e oral disintegrating formulation available
f sublingual formulation available
g transdermal formulation available
h oral solution formulation available
i extended-release oral formulation available

Treatment Selection Considerations

- Patient preference
- Previous response and tolerability
- Adverse effect profile
- Medical conditions
- Pharmacokinetic considerations
- Drug-drug interactions
- Receptor-binding profiles
- Formulations

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines; Gottdiener WH, Haslam N. *J Am Acad Psychoanal Dyn Psychiatry*. 2003;31(1):191-208.

Role of Long-acting Injectable (LAI) Antipsychotics

What do the guidelines say about LAI antipsychotics?

- Potential to reduce hospitalizations, mortality, and discontinuation due to inefficacy
- Should be considered if the patient prefers this formulation
- Should be considered if the patient has known poor adherence

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Role of LAI Antipsychotics

- Effect on relapse
  - Meta-analysis included 10 studies with 1700 participants
  - Reduce relapse: depot injection (21.6%) versus oral (33.3%) (RR, 0.70; number needed to treat [NNT], 10)
  - Limited data on adherence and rehospitalization rates
- Effect on reduced hospitalizations and cost
  - **Purpose:** Assess change in hospitalization and cost of care from 6 months pre- to 6 months post-initiation of any depot antipsychotic among patients with schizophrenia

Parameter	Pre-LAI	Post-LAI	P-value
Psychiatric hospitalization	49.7%	22.4%	<0.001
Hospitalization duration (days)	7.3	4.7	0.05
Total health care cost	$11,111	$7884	<0.05
Cost of psychiatric hospitalization	$5384	$2538	<0.05

Leucht C, et al. *Schizophr Res*. 2011;127(1-3):83-92; Peng X, et al. *ClinicoEconomics Outcomes Res*. 2011;3:9-14.

Role of LAI Antipsychotics

- Effect on adherence
  - Non-superiority has been demonstrated in randomized controlled trials
  - However, “mirror images” studies show increased adherence (≈41% to ≈67% in oral and long-acting injections, respectively)
- Other advantages of LAI antipsychotics
  - Nonadherence is easier to recognize
  - No first-pass metabolism
  - More consistent delivery of antipsychotic/stable plasma levels
  - Levels take longer to decline if doses are missed; opportunity to re-engage the patient
  - Reduced risk of accidental harm

Kane JM, Correll CU. *J Clin Psychiatry*. 2019;80(5):IN18031AH1C; Bosanac P, Castle DJ. *BJPsych Advances*. 2015;21:98-105.

LAI Antipsychotic Administration Overview

Name	Available dose	Injection site	Oral overlap	Frequency	Comments
Haloperidol decanoate	50 mg/mL 100 mg/mL	Gluteal or deltoid (Z track method)	Taper and stop after 2nd/3rd injection	4 weeks	Do not administer more than 3 mL per injection site. Monitor for sesame oil allergy.
Fluphenazine decanoate	25 mg/mL	Gluteal or deltoid (Z track method)	Reduce to 50% with 1st injection; stop after second	2-4 weeks	Monitor for sesame oil allergy.
Aripiprazole	300 mg, 400 mg	Gluteal or deltoid	14 days	4 weeks	Do not massage muscle after injection.
Aripiprazole lauroxil initial	675 mg	Gluteal or deltoid	Not applicable	One-time dose	Initial dose. Administer with 30 mg oral tablet.
Aripiprazole lauroxil	441 mg, 662 mg, 882 mg, 1064 mg	Gluteal/deltoid (441 mg), gluteal for all others	None if given with 675 mg injection; 21 days if given without.	4-8 weeks*	Administer in alternative site, then one time 675 mg aripiprazole lauroxil injection.

*Frequency depends on a combination of the strength of the injection and stable oral dose.

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Role of LAI Antipsychotics

Name	Available dose	Injection site	Oral overlap	Frequency	Comments
Olanzapine pamoate	210 mg, 300 mg, 405 mg	Gluteal	Not required	2-4 weeks*	REMS program; 3-hour observation required
Paliperidone palmitate (1-month)	39 mg, 78 mg, 117 mg, 156 mg, 234 mg	Deltoid (first 2 injections); gluteal or deltoid thereafter	Not required	4 weeks	Loading dose of 234 mg on day 1 followed by 156 mg on day 8, achieve steady state rapidly. Requires vigorous shaking.
Paliperidone palmitate (3-month)	273 mg, 410 mg, 546 mg, 819 mg	Gluteal or deltoid	Not applicable	12 weeks	Shake for 15 seconds within 5 minutes of administration.
Risperidone intramuscular (IM)	12.5 mg, 25 mg, 37.5 mg, 50 mg	Gluteal or deltoid	21 days	2 weeks	Requires refrigeration; warm to room temperature 30 minutes prior to injection.
Risperidone subcutaneous (SC)	90 mg, 120 mg	Abdominal SC injection	Not needed	4 weeks	Do not massage injection site. Requires refrigeration; warm to room temperature 15 minutes before injection.

*Frequency depends on a combination of the strength of the injection and stable oral dose.

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Role of LAI Antipsychotics

LAI utilization	Increased patient possession rates • Increased adherence
	Decreased rehospitalizations • 20%-30% lower than oral formulations
	Positive patient perception for increased access to provider with LAI treatment

Kane JM, Correll CU. *J Clin Psychiatry*. 2019;80(5):IN18031AH1C.

Treatment Challenges

Treatment Response

- Up to approximately two-thirds of patients respond to antipsychotic treatment for schizophrenia
- What about the other 33%?
- Treatment-resistant schizophrenia
  - Generally defined as failing 2 or more antipsychotics
  - 10%-30% of patients will have minimal response to antipsychotic treatment

Potkin SG, et al. *NPJ Schizophr*. 2020;6(1):1; Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines; Patel KR, et al. *P T.* 2014;39(9):638-645.

Reasons for Relapse

- Pharmacotherapy reduces the risk of relapse in patients
  - 18%-32% relapse rate in patients receiving maintenance pharmacotherapy treatment
  - 60%-80% relapse rate in patients *not* receiving pharmacotherapy treatment
- Predictors of relapse:

Childhood/early adolescent Premorbid Adjustment Scale score

Duration of symptoms

Baseline disorganization

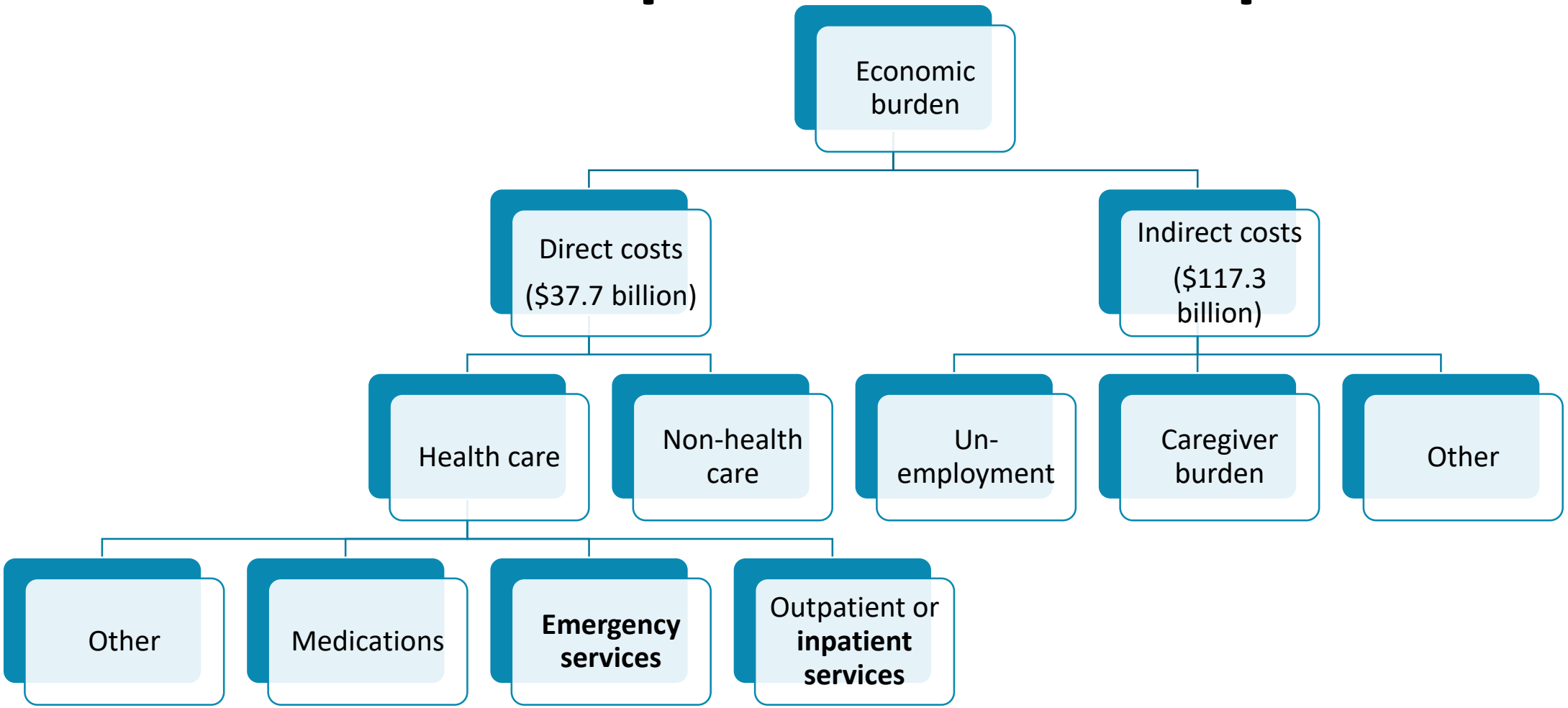
Extrapyramidal adverse effects

Residual symptoms

Presence of neuropsychologic symptoms

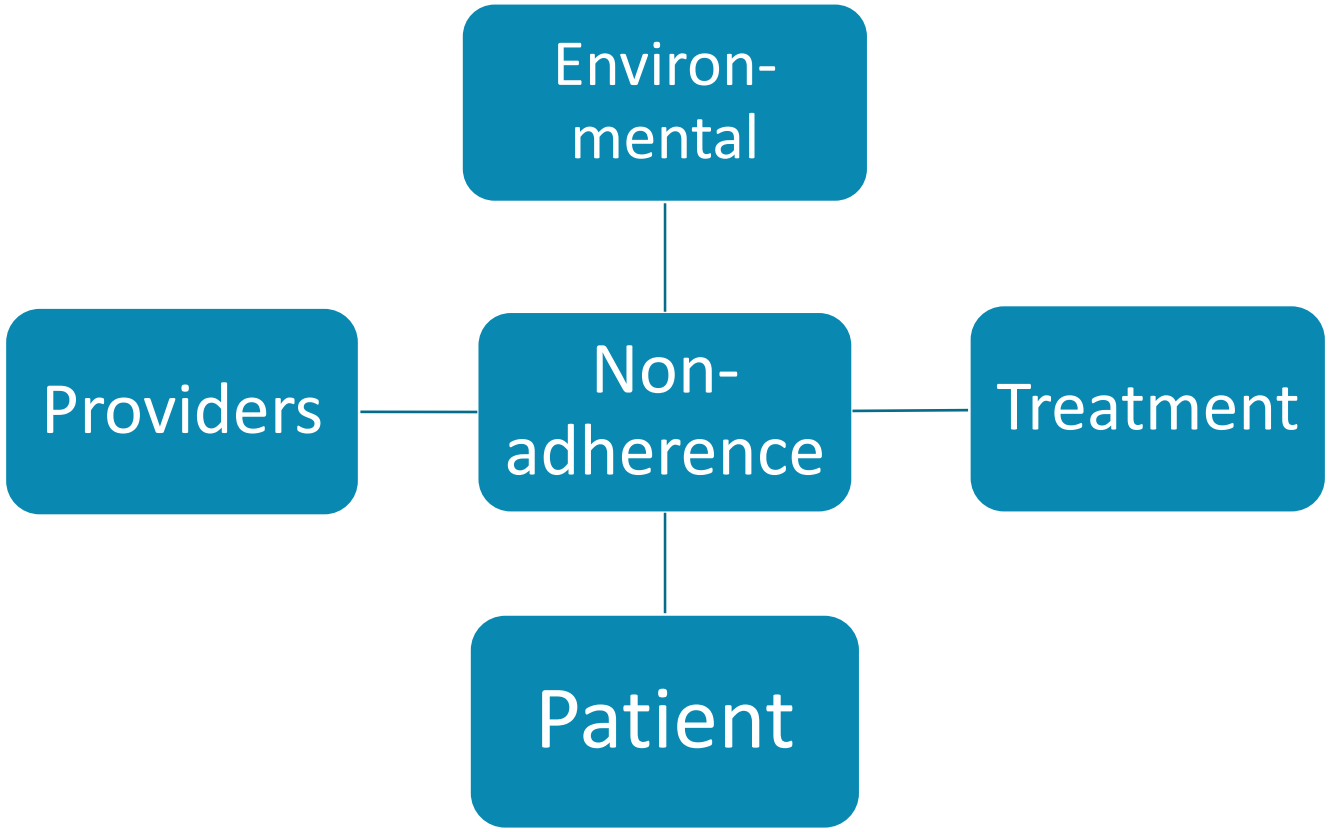
Patel KR, et al. *P T.* 2014;39(9):638-645; Robinson D, et al. *Arch Gen Psychiatry.* 1999;56(3):241-247; Lieberman JA, et al. *N Engl J Med*. 2005;353(12):1209-1223.

Economic Implications of Relapse



Cloutier M, et al. *J Clin Psychiatry*. 2016;77(6):764-771.

Nonadherence: Contributing Factors



Haddad PM, et al. *Patient Relat Outcome Meas*. 2014;5:43-62; Acosta FJ, et al. *World J Psychiatr*. 2012;2(5):74-82.

Nonadherence: Contributing Factors

Patient and Environmental

- Newly started treatment
- Younger/older age
- Substance use
- Lack of social support
- Stigma
- Poor insight

Treatment and Provider

- Lack of patient–provider rapport
- Treatment failure
- Residual symptoms
- Adverse effects (or fear of)
- Complex regimens

Haddad PM, et al. *Patient Relat Outcome Meas*. 2014;5:43-62; Acosta FJ, et al. *World J Psychiatr*. 2012;2(5):74-82; Eticha T, et al. *PLoS One*. 2015;10(3):e0120560.

Nonadherence: Contributing Factors

Positive Factors

Attribute	AOR
Positive attitudes	1.40
Fewer adverse effects	0.97
Awareness of illness	1.44
Ability to relabel symptoms	1.57

Negative Factors

Attribute	AOR
Khat chewers	0.24
Illiteracy	0.13
Older age	0.03

AOR, adjusted odds ratio.

Eticha T, et al. *PLoS One*. 2015;10(3):e0120560.

Negative Outcomes Associated With Nonadherence

- Rehospitalization/relapse: Increased risk of rehospitalization at 2 years (OR, 1.55)
- Use of emergency services: Increased usage at 2 years (OR, 1.49)
- Arrests: Twice as likely to be arrested
- Victimization: Nearly twice as likely to be victimized
- Substance use: Higher rate of substance use
- Self-harm, suicide: 4-fold increase in risk of suicide

Haddad PM, et al. *Patient Relat Outcome Meas*. 2014;5:43-62; Higashi K, et al. *Ther Adv Psychopharmacol.* 2013;3(4):200-218; Herings RM, Erkens JA. *Pharmacoepidemiol Drug Saf*. 2003;12(5):423-424.

Readmission Risks Associated With Nonadherence

Gap days in treatment	Readmission odds ratio
1-10	1.98
11-30	2.81
30+	3.96

Haddad PM, et al. *Patient Relat Outcome Meas*. 2014;5:43-62.

Health Care Provider Impact on Adherence

- Provider communication
  - Nonadherence is 1.47 times more likely to occur when the provider is a poor communicator
  - Patients are 2.16 times more likely to adhere when their provider communicates well
- Relationships with pharmacists increase adherence to LAI medications
  - 4.5-fold more likely to adhere to LAI antipsychotics when received in alternative injection locations (eg, pharmacies)

Haskard Zolnierek KB, DiMatteo MR. *Med Care.* 2009;47(8):826-834; Skelton JB, et al. *J Am Pharm Assoc*. 2017;57(4):e1-e12.

Adverse Effects

Adverse Effects

- Sedation
- Orthostatic hypotension
- Anticholinergic effects
- QTc prolongation
- Acute extrapyramidal symptoms (EPS)
- Tardive dyskinesia
- Neuroleptic malignant syndrome
- Metabolic effects
- Hyper-prolactinemia

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Adverse Effects

- Nearly 80% of patients report having at least 1 *somewhat bothersome* adverse effect while taking antipsychotic medications
  - Contributes to more than 50% of these patients being nonadherent to their treatment regimen
- Metabolic syndrome
  - Estimated that 42% of patients on second-generation antipsychotics will develop metabolic syndrome
- EPS
  - Nearly 62% of patients on first-generation antipsychotics will develop EPS

DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20; Roerig JL, et al. *CNS Drugs.* 2011;25(12):1035-1059; D'Souza RS, Hooten WM. Extrapyramidal symptoms (EPS). Updated November 29, 2019. In: *StatPearls*. StatPearls Publishing; January 2020. Accessed April 9, 2020. ncbi.nlm.nih.gov/books/NBK534115

Metabolic Monitoring

Metabolic Monitoring Parameters from American Diabetes Association/American Psychiatric Association Consensus Guidelines						
	Baseline	Week 4	Week 8	Week 12	Quarterly	Annually
Medical history*	X					X
Weight (BMI)	X	X	X	X	X	
Waist circumference	X					X
Blood pressure	X			X		X
Fasting glucose/A1C	X			X		X
Fasting lipids	X			X		**

*Personal and family history of obesity, diabetes, hypertension, and cardiovascular disease.
**Recommended every 5 years.

American Diabetes Association, American Psychiatric Association, American Association of Clinical Endocrinologists, North American Association for the Study of Obesity. *Diabetes Care*. 2004;27(2):596-601.

EPS Monitoring

Antipsychotic-induced movement disorders

Assessment with a structured tool (eg, AIMS, DISCUS)	Assess for EPS at every clinic visit	Assess every 6 months if at high risk for tardive dyskinesia (12 months for other patients)

AIMS, Abnormal Involuntary Movement Scale; DISCUS, Dyskinesia Identification System Condensed User Scale.

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Adverse Effects

- Adverse effects and adherence
  - **Purpose:** Assess how adverse effects correlate with adherence in a real-world setting
    - Analyzed data from a nationwide survey of adults with self-reported diagnosis and currently taking antipsychotic medications (N = 876)

Relationship between adverse effects and complete medication adherence		
Adverse effect	**Odds ratio**	***P*-value**
Agitation/EPS	0.57	0.0007
Sedation/cognition	0.70	0.0331
Prolactin/endocrine	0.69	0.0342
Metabolic	0.64	0.0079

DiBonaventura M, et al. *BMC Psychiatry*. 2012;12:20.

Adverse Effects

A closer look: first-generation antipsychotics

Adverse Effects

	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Hyper-prolactinemia	Anticholinergic
Chlorpromazine	++	++	++	+++	+	+++
Fluphenazine	+++	+++	+++	+++	+++	+
Haloperidol	+++	+++	+++	+++	+++	+
Loxapine	++	++	++	++	++	++
Perphenazine	++	++	++	++	++	++
Pimozide	+++	+++	++	+++	+++	+
Thioridazine	+	+	+	+	++	+++
Thiothixene	+++	+++	+++	+++	+++	+
Trifluoperazine	++	++	++	++	++	++

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Adverse Effects

	Sedation	Seizures	Orthostasis	QTc prolongation	Weight gain	Hyperlipidemia	Glucose abnormalities
Chlorpromazine	+++	++	+++	+++	++	+	++
Fluphenazine	+	+	+	++	++	+	+
Haloperidol	+	+	+	++	++	+	+
Loxapine	++	+	++	++	+	+	+
Perphenazine	++	+	++	++	++	+	+
Pimozide	+	+++	+	+++	+	+	+
Thioridazine	+++	++	+++	+++	++	+	+
Thiothixene	+	+++	+	++	+	+	+
Trifluoperazine	+	+	+	++	++	+	+

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Adverse Effects

A closer look: second-generation antipsychotics

Adverse Effects

	Akathisia	Parkinsonism	Dystonia	Tardive dyskinesia	Hyper-prolactinemia	Anticholinergic
Aripiprazole	++	+	+	+	+	+
Asenapine	++	+	++	++	++	+
Brexpiprazole	++	+	+	+	+	+
Cariprazine	++	+	+	+	+	++
Clozapine	+	+	+	+	+	+++
Iloperidone	+	+	+	+	++	+
Lurasidone	++	++	++	++	+	+
Olanzapine	++	++	+	+	++	++
Paliperidone	++	++	++	++	+++	+
Quetiapine	+	+	+	+	+	++
Risperidone	++	++	++	++	+++	+
Ziprasidone	++	+	+	+	++	+

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Adverse Effects

	Sedation	Seizures	Orthostasis	QTc prolongation	Weight gain	Hyperlipidemia	Glucose abnormalities
Aripiprazole	+	+	+	+	+	+	+
Asenapine	++	+	++	++	++	++	++
Brexpiprazole	++	+	+	++	+	++	+
Cariprazine	++	+	+	++	++	+	+
Clozapine	+++	+++	+++	++	+++	+++	+++
Iloperidone	++	+	+++	+++	++	+	++
Lurasidone	++	+	+	+	+	++	++
Olanzapine	+++	++	++	++	+++	+++	+++
Paliperidone	+	+	++	++	++	++	+
Quetiapine	+++	++	++	++	++	+++	++
Risperidone	++	+	++	++	++	+	++
Ziprasidone	++	+	++	+++	+	+	+

Keepers GA, et al. *The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia* [draft]. American Psychiatric Association; 2019. Accessed February 14, 2020. psychiatry.org/psychiatrists/practice/clinical-practice-guidelines

Emerging Therapies

Megan Maroney, PharmD, BCPP

Overview

Novel Treatments

- Lumateperone
- Olanzapine/samidorphan
- Pimavanserin
- Roluperidone

Novel Formulations

- Asenapine transdermal
- Risperidone ISM
- Paliperidone 6-month LAI

Novel Treatments

Lumateperone

- FDA approved in December 2019
- Novel mechanism of action
  - Selective 5-HT_{2A} receptor antagonist
  - Presynaptic D_2 partial agonist
  - Postsynaptic D_2 antagonist – increases phosphorylation of glycogen synthase kinase 3 (GSK3)
  - Serotonin reuptake inhibitor
  - May increase NMDA activity via D_1 activity
    - Phosphorylation of GluN2B subunit of NMDA receptor
- Dosing: 42-mg capsule once daily with food
  - Avoid with **CYP3A4 inducers**, moderate-strong **CYP3A4 inhibitors**, **UGT inhibitors**
  - Avoid with moderate-severe hepatic impairment
- Efficacy for schizophrenia established in two phase 3 studies

Caplyta. Prescribing information. Intra-Cellular Therapies; 2019; Snyder GL, et al. *Psychopharmacology (Berl).* 2015;232(3):605-621; Kantrowitz JT. *JAMA Psychiatry*. Published online January 8, 2020; Correll CU, et al. *JAMA Psychiatry*. 2020;77(4):349-358; Intra-Cellular Therapies. Published September 28, 2016. Accessed February 27, 2020. ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-top-line-results-second-phase; Novel Drug Approvals for 2019. FDA. Updated January 14, 2020. Accessed April 10, 2020. www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019

Lumateperone Phase 3 Studies: ITI-007-301

- Study purpose: Determine the efficacy of lumateperone 28 mg and 42 mg for the treatment of an acute exacerbation of schizophrenia
- Study design:
  - Multicenter, double-blind, fixed-dose, randomized, placebo-controlled trial
  - 450 adult patients with schizophrenia randomized to once-daily treatment for 4 weeks
    - Lumateperone 28 mg (L40) (n = 150)
    - Lumateperone 42 mg (L60) (n = 150)
    - Placebo (n = 150)
- Primary outcome: Change from baseline PANSS total score to week 4
- Secondary outcome: Change from baseline CGI-S score to week 4

Correll CU, et al. *JAMA Psychiatry*. 2020;77(4):349-358.

CGI-S, Clinical Global Impression-Severity;
PANSS, Positive and Negative Syndrome Scale.

Lumateperone Phase 3 Studies: ITI-007-301

- Primary outcome: Change from baseline PANSS total score to week 4

Lumateperone 28 mg L40 group (LS mean ± SD)	Lumateperone 42 mg L60 group (LS mean ± SD)	Placebo group (LS mean ± SD)	*P*-value
-12.9 ± 1.3	-14.5 ± 1.3	-10.3 ± 1.3	L40 vs placebo: 0.16
			L60 vs placebo: 0.02

- Secondary outcome: Change from baseline CGI-S score to week 4

Lumateperone 28 mg L40 group (LS mean ± SD)	Lumateperone 42 mg L60 group (LS mean ± SD)	Placebo group (LS mean ± SD)	*P*-value
-0.8 ± 0.08	-0.8 ± 0.07	-0.5 ± 0.08	L40 vs placebo: 0.03
			L60 vs placebo: 0.003

Correll CU, et al. *JAMA Psychiatry*. 2020;77(4):349-358.

Lumateperone Phase 3 Studies: ITI-007-302

- Study design:
  - Multicenter, double-blind, fixed-dose, randomized, placebo- and active-controlled 6-week trial
  - 696 patients randomized 1:1:1:1 to once daily treatment
    - Lumateperone tosylate 20 mg
    - Lumateperone tosylate 60 mg
    - Risperidone 4 mg (active control)
    - Placebo
- Primary outcome: Change from baseline PANSS score to week 6
  - Neither dose of lumateperone had statistically significant change vs placebo
  - Risperidone had a statistically significant change compared with placebo
  - High placebo effect compared with ITI-007-301: -15.1 vs -10.3

Intra-Cellular Therapies. Published September 28, 2016. Accessed February 27, 2020. ir.intracellulartherapies.com/news-releases/news-release-details/intra-cellular-therapies-announces-top-line-results-second-phase

Lumateperone: Adverse Effects

Pooled Short-term Studies vs Placebo

- Most common ADEs:
  - Somnolence/sedation: 24% vs 10%
  - Dry mouth: 6% vs 2%
- EPS: 6.7% vs 6.3%
- Changes in weight, glucose, and lipids were similar to placebo

Open-label 1-year Data

- Mean weight change: -3.2 kg
- Shifts from normal to high:
  - Glucose: 8%
  - Insulin: 12%
  - A1C: 4.7%
  - Total cholesterol: 8%
  - Triglycerides: 5%
  - LDL-C: 4%

ADE, adverse drug effect.

Caplyta. Prescribing information. Intra-Cellular Therapies; 2019.

Olanzapine/Samidorphan

- Currently under review by FDA
  - PDUFA date November 15, 2020
- Combination tablet of fixed-dose samidorphan 10 mg (μ-opioid receptor antagonist) and olanzapine 10 or 20 mg daily
  - Samidorphan: May reduce olanzapine-related adverse metabolic profile and weight gain
- Two phase 3 studies
  - ENLIGHTEN-1: efficacy for acute exacerbation of schizophrenia
  - ENLIGHTEN-2: efficacy in preventing significant weight gain with olanzapine

PDUFA, Prescription Drug User Fee Act.

Sun L, et al. *Clin Ther*. 2018;40(11):1845-1854; Potkin SG, et al. *J Clin Psychiatry.* 2020;81(2):19m12769; National Institutes of Health. ClinicalTrials.gov identifier: NCT02694328. Updated February 10, 2020. Accessed February 27, 2020; Maroney M. *Am J Manag Care*. 2020;26:S801-S807.

Olanzapine/Samidorphan: ENLIGHTEN-1

- Study design:
  - 4-week, double-blind, randomized, placebo-controlled trial
  - 403 adult patients with schizophrenia randomized to once daily
    - Olanzapine/samidorphan (n = 134)
    - Olanzapine (n = 133)
    - Placebo (n = 134)

- Interventions:

Olanzapine/samidorphan (O-S)	Olanzapine 10 mg/samidorphan 10 mg Olanzapine 20 mg/samidorphan 10 mg
Olanzapine monotherapy (O)	Olanzapine 10 mg Olanzapine 20 mg

Potkin SG, et al. *J Clin Psychiatry*. 2020;81(2):19m12769.

Olanzapine/Samidorphan: ENLIGHTEN-1

- Primary objective: Change from baseline PANSS total score to week 4

O-S Group (mean ± SD)	Olanzapine (mean ± SD)	Placebo (mean ± SD)	*P*-value
-23.9 ± 1.28	-22.8 ± 1.29	-17.5 ± 1.32	O-S vs placebo: <0.001
			O vs placebo: 0.004

- Secondary objective: Change from baseline CGI-S score to week 4

O-S Group (mean ± SD)	Olanzapine (mean ± SD)	Placebo (mean ± SD)	*P*-value
-1.21 ± 0.082	-1.27 ± 0.083	-0.84 ± 0.085	O-S vs placebo: 0.002
			O vs placebo: <0.001

Potkin SG, et al. *J Clin Psychiatry*. 2020;81(2):19m12769.

Olanzapine/Samidorphan: ENLIGHTEN-1

- Safety end points:
  - Mean change in weight from baseline to week 4
    - Olanzapine/samidorphan: 3.02 kg
    - Olanzapine: 2.38 kg
    - Placebo: 0.24 kg
  - Most common ADEs:

	O-S group (n [%])	Olanzapine (n [%])	Placebo (n [%])
Weight gain	25 (18.7%)	19 (14.3%)	4 (3.0%)
Somnolence	12 (9.0%)	13 (9.8%)	3 (2.2%)
Dry mouth	10 (7.5%)	7 (5.3%)	1 (0.7%)
Headache	8 (6.0%)	7 (5.3%)	4 (3.0%)

Potkin SG, et al. *J Clin Psychiatry*. 2020;81(2):19m12769.

Olanzapine/Samidorphan: ENLIGHTEN-2

- Study design:
  - 24-week, double-blind, randomized, parallel-group, multicenter outpatient trial
  - 561 adult patients with schizophrenia randomized to once daily
    - Olanzapine/samidorphan (n = 274)
    - Olanzapine (n = 276)

- Interventions:

Olanzapine/samidorphan (O-S)	Olanzapine 10 mg/samidorphan 10 mg Olanzapine 20 mg/samidorphan 10 mg
Olanzapine monotherapy (O)	Olanzapine 10 mg Olanzapine 20 mg

National Institutes of Health. ClinicalTrials.gov identifier: NCT02694328. Updated February 10, 2020. Accessed February 27, 2020; Alkermes. Published November 29, 2018. Accessed April 2, 2020. investor.alkermes.com/news-releases/news-release-details/alkermes-announces-positive-topline-results-enlighten-2-phase-3

Olanzapine/Samidorphan: ENLIGHTEN-2

- Primary end points:
  - Percent change in baseline body weight to week 24

O-S group (%)	Olanzapine group (%)	*P*-value	NNT
4.21	6.59	0.003	42

  - Percentage of patients with >10% weight gain at week 24

O-S group (%)	Olanzapine group (%)	*P*-value	NNT
17.8%	29.8%	0.003	8

National Institutes of Health. ClinicalTrials.gov identifier: NCT02694328. Updated February 10, 2020. Accessed February 27, 2020; Alkermes. Published November 29, 2018. Accessed April 2, 2020. investor.alkermes.com/news-releases/news-release-details/alkermes-announces-positive-topline-results-enlighten-2-phase-3

Olanzapine/Samidorphan: ENLIGHTEN-2

- Secondary end point: Percentage of patients with ≥7% weight gain at week 24
  - Olanzapine: 42.7%
  - O-S: 27.5% (*P* = 0.001, NNT = 7)
- Safety end points:

	O-S group (n [%])	Olanzapine group (n [%])
Weight gain	68 (24.82%)	100 (36.23%)
Increased appetite	30 (10.95%)	34 (12.32%)
Somnolence	58 (21.17%)	50 (18.12%)
Dry mouth	35 (12.77%)	22 (7.97%)

National Institutes of Health. ClinicalTrials.gov Identifier: NCT02694328. Updated February 10, 2020. Accessed February 27, 2020; Alkermes. Published November 29, 2018. Accessed April 2, 2020. investor.alkermes.com/news-releases/news-release-details/alkermes-announces-positive-topline-results-enlighten-2-phase-3

Pimavanserin: Residual Positive Symptoms

- Currently FDA approved for Parkinson disease psychosis
- Mechanism of action: 5-HT_{2A} inverse agonist/antagonist
- Phase 3 ENHANCE trial
  - Study design:
    - 6-week, randomized, double-blind, placebo-controlled, multicenter outpatient study
    - 396 patients with moderate-severe psychotic symptoms, persistent inadequate response to current antipsychotic
    - Randomized 1:1 to flexible-dose pimavanserin or placebo + current antipsychotic
  - Primary end point: change in PANSS did not reach statistical significance (*P* = 0.0940)
  - Secondary end point: change in PANSS negative sub-score was significant (*P* = 0.0474)

Nuplazid. Prescribing information. ACADIA Pharmaceuticals; 2019; ACADIA Pharmaceuticals. Published July 22, 2019. Accessed March 1, 2020. ir.acadia-pharm.com/news-releases/news-release-details/acadia-pharmaceuticals-announces-top-line-results-phase-3?field_nir_news_date_value[min]=

Pimavanserin: Negative Symptoms

- Currently in phase 2 development for adjunctive use for negative symptoms
- ADVANCE study
  - Study design:
    - 26-week, randomized, double-blind, placebo-controlled, flexible-dose study
    - 403 patients with predominantly negative symptoms
    - Randomized to once-daily pimavanserin (n = 201) or placebo (n = 202) + ongoing antipsychotic
  - Primary end point: change on Negative Symptom Assessment-16 (NSA-16) score
    - Pimavanserin: -10.4
    - Placebo: -8.5 (*P* = 0.043)
  - Secondary end point: Personal and Social Performance Scale (PSP) – **not significant**
- Fixed-dose study with pimavanserin 34 mg daily planned for first half of 2020

ACADIA Pharmaceuticals. Published November 25, 2019. Accessed March 1, 2020. ir.acadia-pharm.com/news-releases/news-release-details/acadia-pharmaceuticals-announces-positive-top-line-results?field_nir_news_date_value[min]=

Roluperidone

- Novel mechanism antipsychotic
  - Selective σ-2 and 5-HT_{2A} receptor antagonist
  - Low affinity for muscarinic, dopaminergic, cholinergic, and histaminergic receptors
- Active phase 3 study
  - Multicenter, double-blind, randomized, placebo-controlled, parallel-group study
  - 501 adult patients with schizophrenia
  - Intervention:

Roluperidone group 1	Roluperidone 64 mg once daily for 12 weeks
Roluperidone group 2	Roluperidone 32 mg once daily for 12 weeks
Placebo group	Placebo once daily for 12 weeks

  - Primary outcome: Change from baseline Marder **negative symptoms** factor score

Davidson M, et al. *Am J Psychiatry*. 2017;174(12):1195-1202; Keefe RS, et al. *J Clin Psychiatry*. 2018;79(3); National Institutes of Health. ClinicalTrials.gov identifier: NCT03397134. Updated February 7, 2020. Accessed February 28, 2020.

Novel Formulations

Asenapine Transdermal

- FDA approved in October 2019
- Dosing
  - Starting dose: 3.8 mg/24 hours (≈5 mg SL BID)
  - May increase to 5.7 mg/24 hours or 7.6 mg/24 hours after 1 week
  - Apply to hip, abdomen, upper arm, back
- Drug interactions
  - Consider dose reduction with CYP1A2 inhibitors
  - Reduce dose of paroxetine by half
  - Monitor blood pressure and adjust antihypertensive medications
- Contraindicated with severe hepatic impairment, hypersensitivity

Secuado. Prescribing information. Noven Therapeutics; 2019.

Asenapine Transdermal Phase 3 Trial

- Study design:
  - Randomized, double-blind, placebo-controlled, fixed-dose 6-week study
  - 607 adults with schizophrenia exacerbation, randomized to
    - Asenapine 3.8 mg/24 hours
    - Asenapine 7.6 mg/24 hours
    - Placebo
- Primary outcome: change in PANSS from baseline to week 6

Asenapine 3.8 mg (mean ± SE)	Asenapine 7.6 mg (mean ± SE)	Placebo group (mean ± SE)	Placebo-subtracted difference (95% CI)
-22.1 ± 1.2	-20.4 ± 1.2	-15.5 ± 1.2	-6.6 (-9.81, -3.40)
			-4.8 (-8.06, -1.64)

Secuado. Prescribing information. Noven Therapeutics; 2019.

Asenapine Transdermal Adverse Effects

- Most commonly observed vs placebo

	Asenapine 3.8 mg	Asenapine 7.6 mg	Placebo
EPS	8%	13%	2%
Application-site reaction	15%	14%	4%
Weight gain	4%	6%	2%
≥7% change in weight	18.3%	14.3%	3.9%

- Application-site reactions: erythema, pruritus; 1 case of hyperpigmentation

Secuado. Prescribing information. Noven Therapeutics; 2019.

Advantages and Disadvantages of Transdermal Drug Delivery

Advantages	Disadvantages
Visual adherence check possible	Appropriate application required
Steady drug delivery	Lag time to peak concentration
Reduced risk of overdose	Adhesion/absorption variability (eg, heat, oily skin)
Decreased absorption-related food and drug interactions	Self-interruption of treatment possible
Decreased gastrointestinal adverse effects	Application-site reactions
Potentially less frequent administration	Embarrassment if patch seen by others

Citrome L, et al. *J Clin Psychiatry.* 2019;80(4):18nr12554.

Risperidone ISM

- Reconstituted fluid precipitates in situ after IM injection, forming biodegradable solid polymeric matrix system (implant)
- Phase 3 PRISMA-3 study
  - Study design:
    - Randomized, double-blind, placebo-controlled, multicenter 12-week study
    - 438 adults with schizophrenia exacerbation, randomized 1:1:1 to every-4-week injection of
      - Risperidone ISM 75 mg
      - Risperidone ISM 100 mg
      - Placebo
  - Primary outcome: Change in PANSS from baseline to week 12
    - Both doses significant vs placebo (P <0.0001)
  - Secondary outcomes: Change in CGI-S, CGI-I, overall response rate, PANSS response rate

Carabias LA, et al. *Int Clin Psychopharmacol.* 2018;33:79-87; National Institutes of Health. ClinicalTrials.gov identifier: NCT03160521. Updated December 20, 2019. Accessed March 1, 2020; Laboratorios Farmacéuticos. Published March 19, 2019. Accessed March 1, 2020. edisongroup.com/publication/doria-phase-iii-trial-hits-primary-endpoint/23705

Paliperidone 6-month LAI

- Medications with a longer duration of action may help to improve adherence in patients with schizophrenia
- Active phase 3 study
  - Multicenter, double-blind, randomized, active-controlled, parallel-group study
  - 841 adult patients with schizophrenia
  - 3 phases:

Screening phase	Patients achieve stability on 1- or 3-month paliperidone
Maintenance phase	Patients maintain response to current dose
Double-blind phase	Patients randomized to receive 3- or 6-month paliperidone

  - Primary outcome: Time to relapse

Pilon D, et al. *J Med Econ*. 2018;21(2):135-143; National Institutes of Health. ClinicalTrials.gov identifier: NCT03345342. Updated April 6, 2020. Accessed April 22, 2020.

Additional Medications in Development

- Evenamide – residual positive symptoms, treatment-resistant patients
  - Mechanism of action: glutamate modulator, voltage-gated sodium channel blocker
  - Phase 3 trials expected to begin soon
- SEP-363856
  - Mechanism of action: trace amine-associated receptor 1 (TAAR1) agonist, 5-HT_{1A} agonist
  - Received breakthrough designation from FDA in May 2019
  - Currently in phase 3

Newron Pharmaceuticals. Published January 9, 2020. Accessed March 9, 2020. businesswire.com/news/home/20200109005366/en/Newron-Announces-Initiation-New-Clinical-Trial-Evenamide; Maroney M. *Am J Manag Care*. 2020;26:S801-S807; Sunovion Pharmaceuticals. Published September 27, 2019. Accessed March 10, 2020. news.sunovion.com/press-releases/press-releases-details/2019/Sunovion-and-PsychoGenics-Initiate-DIAMOND-Phase-3-Clinical-Studies-for-SEP-363856-in-the-Treatment-of-Adults-and-Adolescents-with-Schizophrenia/default.aspx

Case Example 1

- JC is a 20-year-old man with a history of schizophrenia x 3 years. He is in his second semester of college, although his first semester was difficult. JC was able to pass his classes; however, he did take an extended leave of absence due to a 3-week-long hospitalization.
- JC has been seen in the outpatient setting by Dr Smith since his diagnosis. During this time, JC has been on aripiprazole 20 mg daily (treatment failure), asenapine 20 mg daily (treatment failure), olanzapine 20 mg daily (weight gain), and is currently on quetiapine 350 mg nightly. JC says that his medication seems to help, but he is often too tired for his 8 AM biology class, thus he sometimes skips his evening dose.
- JC does have insight into his illness. He would like to finish college and become an engineer. In order to do this, JC recognizes the need for medication. However, he does express a low threshold for tolerating adverse effects.

Case Questions

- What additional information would you want to inquire about regarding the patient's history?
- What emerging treatment option might be appropriate for JC?
- What monitoring should be done?
- What patient education should be done?

Case Example 2

- JB is a 28-year-old man who was diagnosed with schizophrenia 5 years ago. He was admitted to the hospital today due to increasing symptoms of paranoia and agitation. His mother is concerned that he has not been taking care of his personal hygiene and has become more socially withdrawn as well. She indicates that she observes him taking his medication daily, but that his current medication, lurasidone 160 mg daily, does not seem to be working.
- JB's past medication history includes olanzapine, aripiprazole, and ziprasidone.

Case Questions

- What additional information would you want to inquire about regarding the patient's history?
- What emerging treatment option might be appropriate for JB?
- What monitoring should be done?
- What patient education should be done?

Conclusion

- Emerging treatments for schizophrenia aim to fill current gaps in therapy by targeting negative symptoms and residual positive symptoms, promoting adherence, and reducing adverse effect burden
- Psychiatric pharmacists are in a unique position to gather information to make informed treatment decisions, monitor treatment response, and educate patients regarding antipsychotic medications

Additional Resources

Current trials for emerging treatments	clinicaltrials.gov
Schizophrenia treatment guidelines	cpnp.org/guideline/external/schizophrenia
SAMHSA presentation on strategies to promote medication adherence	integration.samhsa.gov/about-us/Med_Adherence_Final.pdf
Patient resources	• nami.org/Learn-More/Mental-Health-Conditions/Schizophrenia • psychiatry.org/patients-families/schizophrenia