Improving Long-Term Outcomes in SCHIZOPHRENIA:

Translating Evidence to Practice

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Faculty Disclosure

- **Dr. Melnick**: Speaker—Alkermes, Lundbeck, Merck, Neurocrine, Otsuka, Sunovion, Takeda.
- **Dr. Tandon** has no relevant financial disclosures.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Recognize patient- and physician-level barriers to effective long-term schizophrenia management
- Examine the latest clinical evidence regarding long-acting injectable antipsychotics, including their pharmacologic profiles and impact on medication adherence
- Translate clinical evidence to informed and individualized treatment selection, monitoring, and management in schizophrenia
- Develop schizophrenia management strategies that address patient nonadherence and support the coordination of care transitions

Long-Term Management of Schizophrenia: *Principles, Opportunities, and Challenges*

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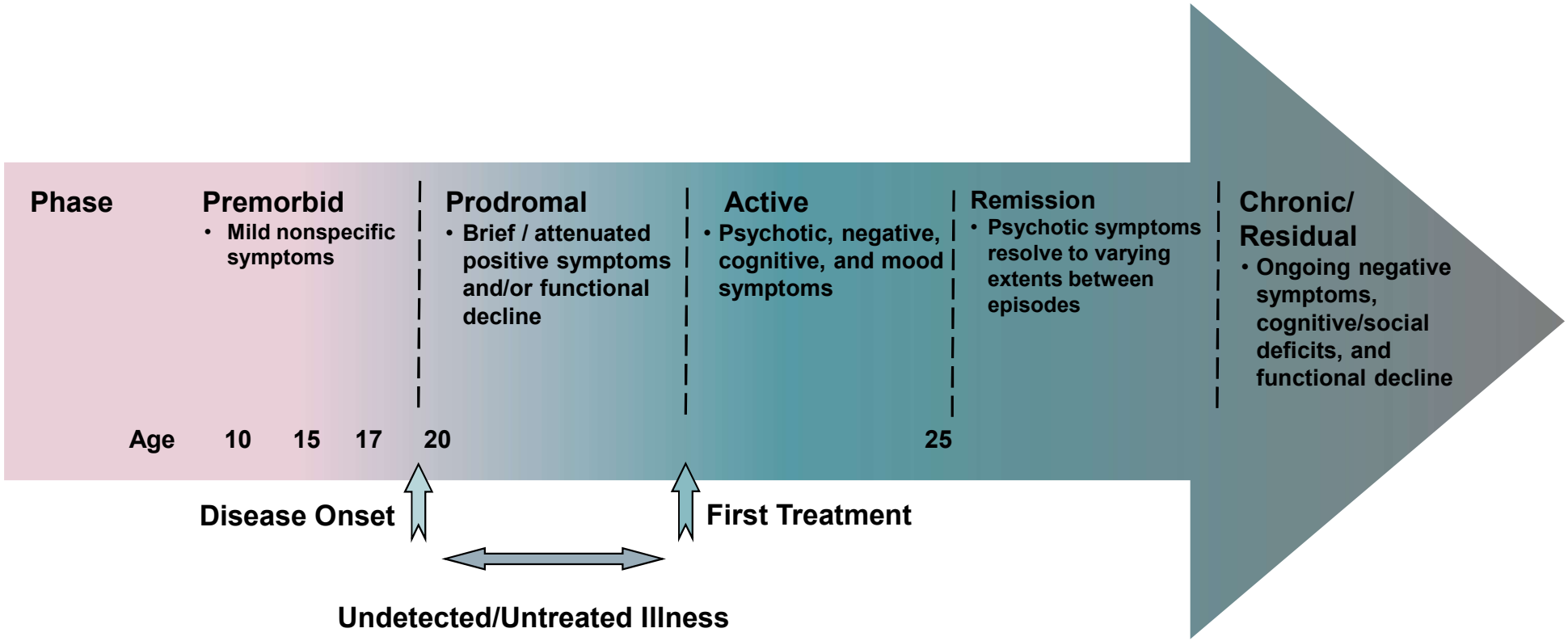
Pharmacologic Treatment of Any Disease

- **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

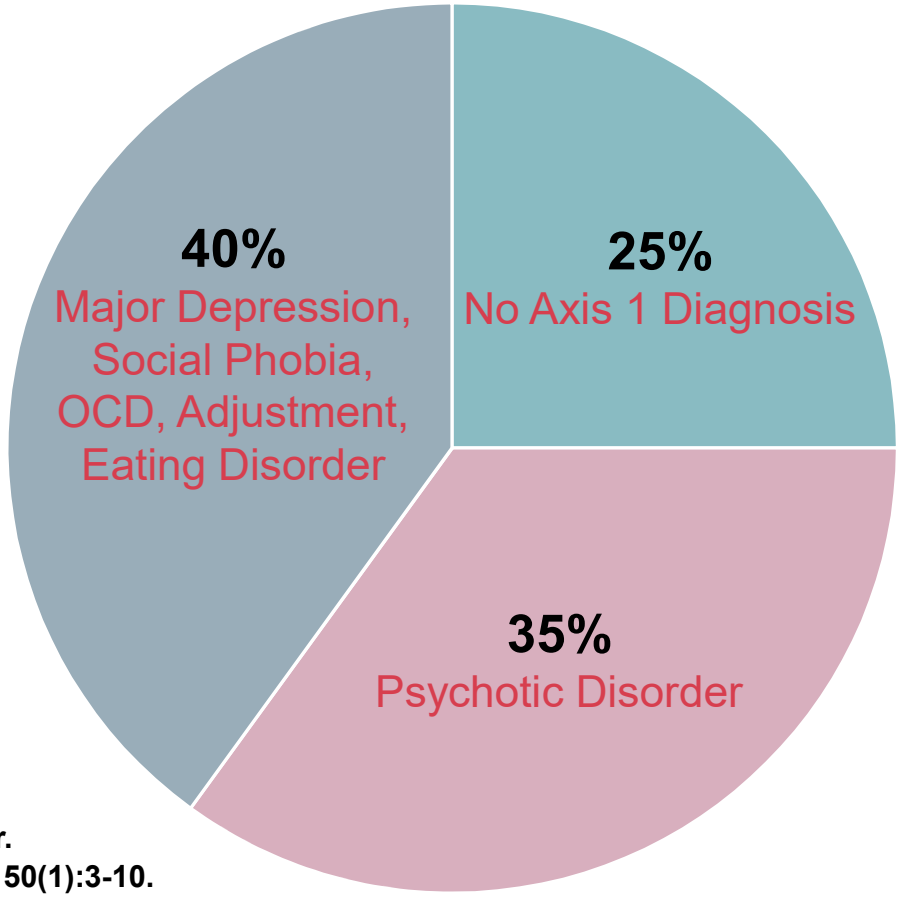
Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23.

Natural History of Schizophrenia



Hales RE, et al (Eds). *The American Psychiatric Publishing Textbook of Psychiatry.* Fifth Edition. Arlington, VA: American Psychiatric Publishing; 2008. Lieberman JA, et al. *Biol Psychiatry*. 2001;50(11):884-897. Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23.

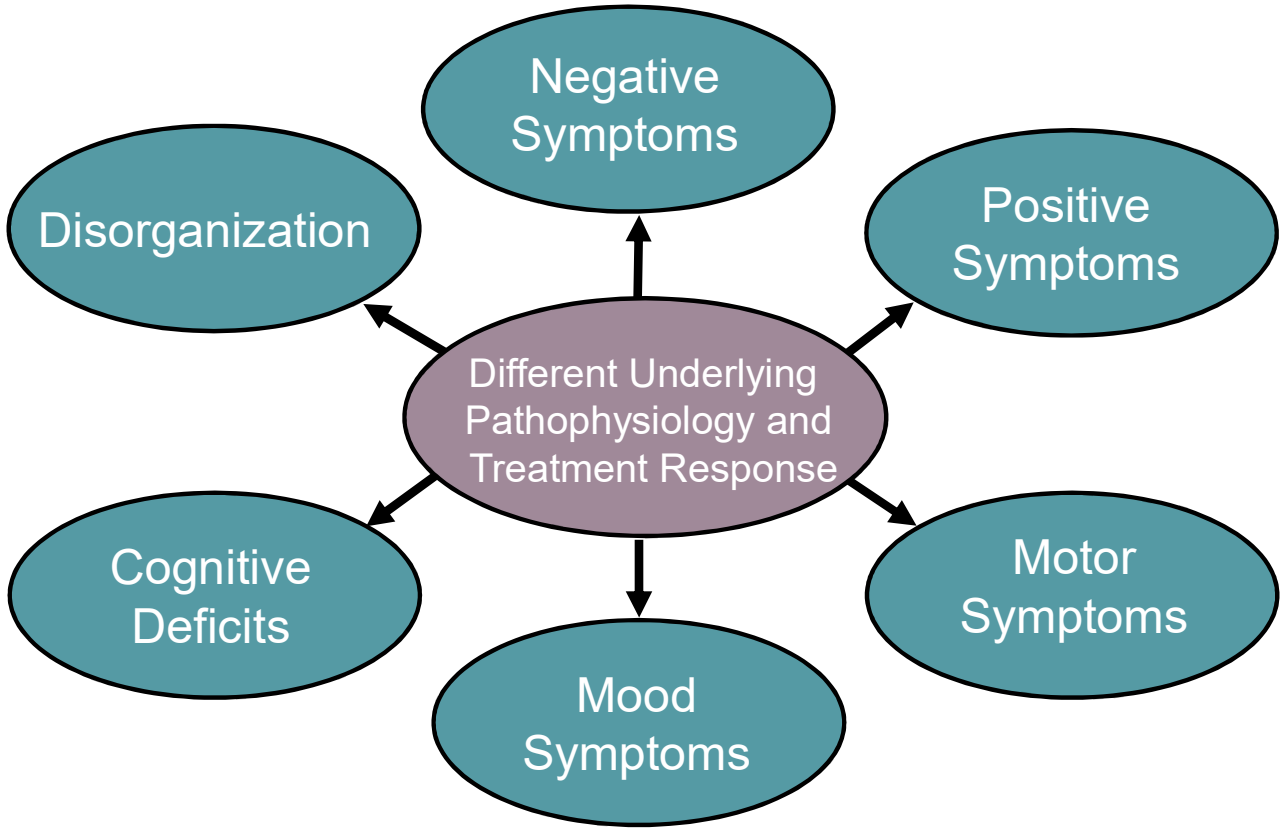
Diagnosis at 1 Year Follow-Up for Patients with Attenuated Psychosis Syndrome



OCD = obsessive-compulsive disorder.

Tandon R, et al. *Schizophr Res*. 2013;150(1):3-10.

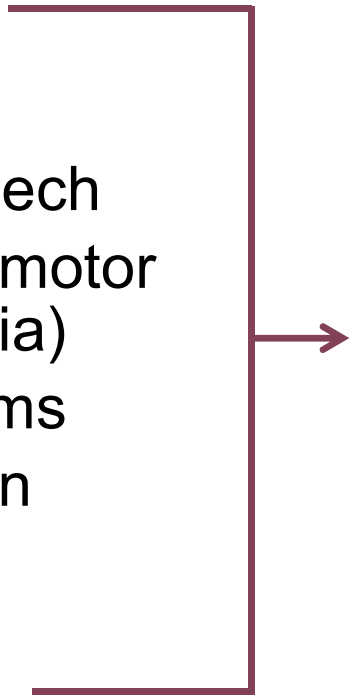
Dimensions of Schizophrenia



Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23.

Diagnosis-Specific Severity Assessment: *Symptom Domains*

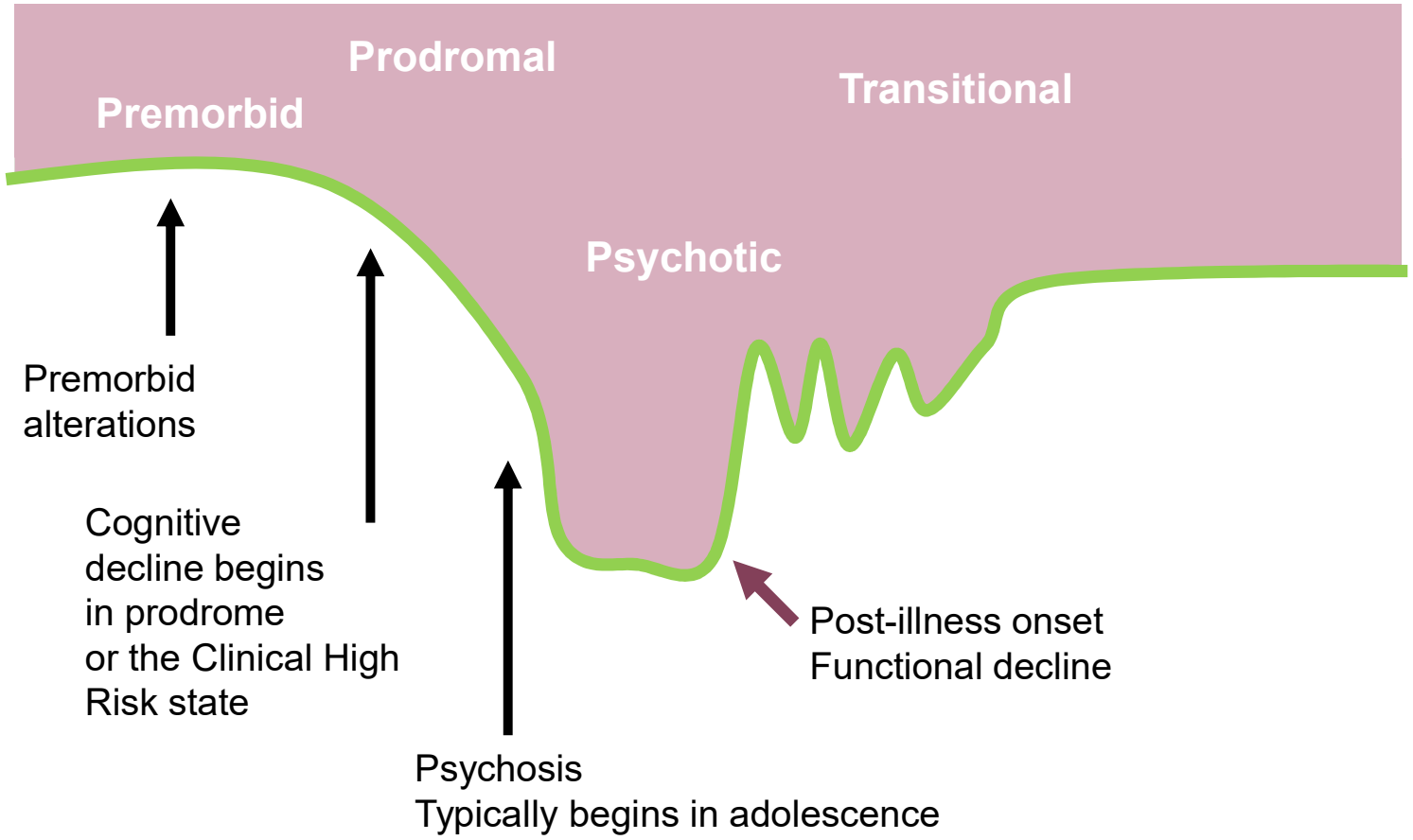
- Hallucinations
- Delusions
- Disorganized Speech
- Abnormal Psychomotor Behavior (catatonia)
- Negative Symptoms
- Impaired Cognition
- Depression
- Mania



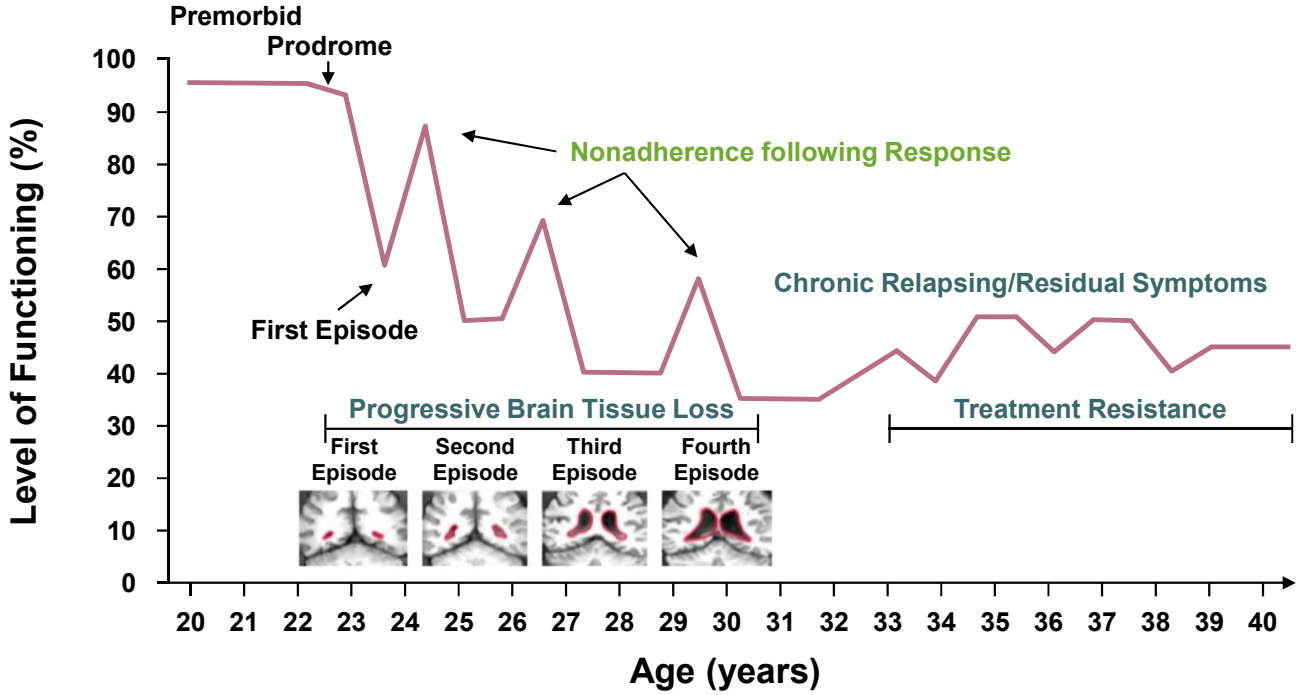
0 = Not Present
1 = Equivocal
2 = Present, but mild
3 = Present and moderate
4 = Present and severe

Tandon R, et al. *Schizophr Res*. 2013;150(1):3-10.

Phases of Schizophrenic Illness



The Deteriorating Course, Tissue Loss, and Treatment Resistance with Repetitive Relapses following the First Episode in Schizophrenia



Nasrallah HA, et al. *Contemporary Diagnosis and Management of the Patient with Schizophrenia*. Second Edition. Newton, PA: Handbooks in Health Care; 2011.

Importance of Relapse Prevention in Schizophrenia

- Each relapse associated with (**short-term**)
  - Increased distress and dysfunction
  - Vocational and social disruption
  - Increased risk of suicide and violence
  - Increased costs of care

- With each relapse (**LONG-TERM**)
  - Subsequent recovery is less complete
  - Remission takes longer to achieve
  - Illness becomes more resistant to treatment
  - Regaining prior function level more difficult

Tandon R, et al. *Schizophr Res*. 2010;122(1-3):1-23. Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23.

Clinical Nature of Schizophrenia: *What We Know*

- **Multiple Symptom Dimensions**
  - Different time course, neurobiology
  - Different expression across patients and time
- **Distinct Natural Course of Illness**
  - Distinct stages with evolution of pathology
- **Significant Functional Impairment and Social Dysfunction**
  - Most of the decline occurs very early in the illness
  - Begins premorbidly, progresses through prodrome, and peaks within 3 to 5 years of psychotic phase

Tandon R, et al. *Schizophr Res*. 2010;122(1-3):1-23.

Goals of Pharmacotherapy

Optimizing Individual Outcome

- **Short-Term**
  - Symptom reduction
  - Patient safety

- **Long-Term**
  - Relapse prevention
  - Treatment of comorbid syndromes
  - Minimization of adverse effects

Tandon R, et al. *Schizophr Res*. 2010;122(1-3):1-23.

Basic Principles in the Long-Term Pharmacologic Treatment of Schizophrenia

- **Optimizing Individual Outcome**
  - Targeted Treatment
  - Measurement-Based Care
  - Individualized Treatment

Tandon R, et al. *Schizophr Res*. 2010;122(1-3):1-23.

Pharmacologic Treatment of Any Disease

- **Know the Disease that you are treating**
  - Nature; treatment targets; treatment goals
- **Know the Treatments at your disposal**
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- **Principles of Treatment**
  - Measurement-based; targeted; individualized

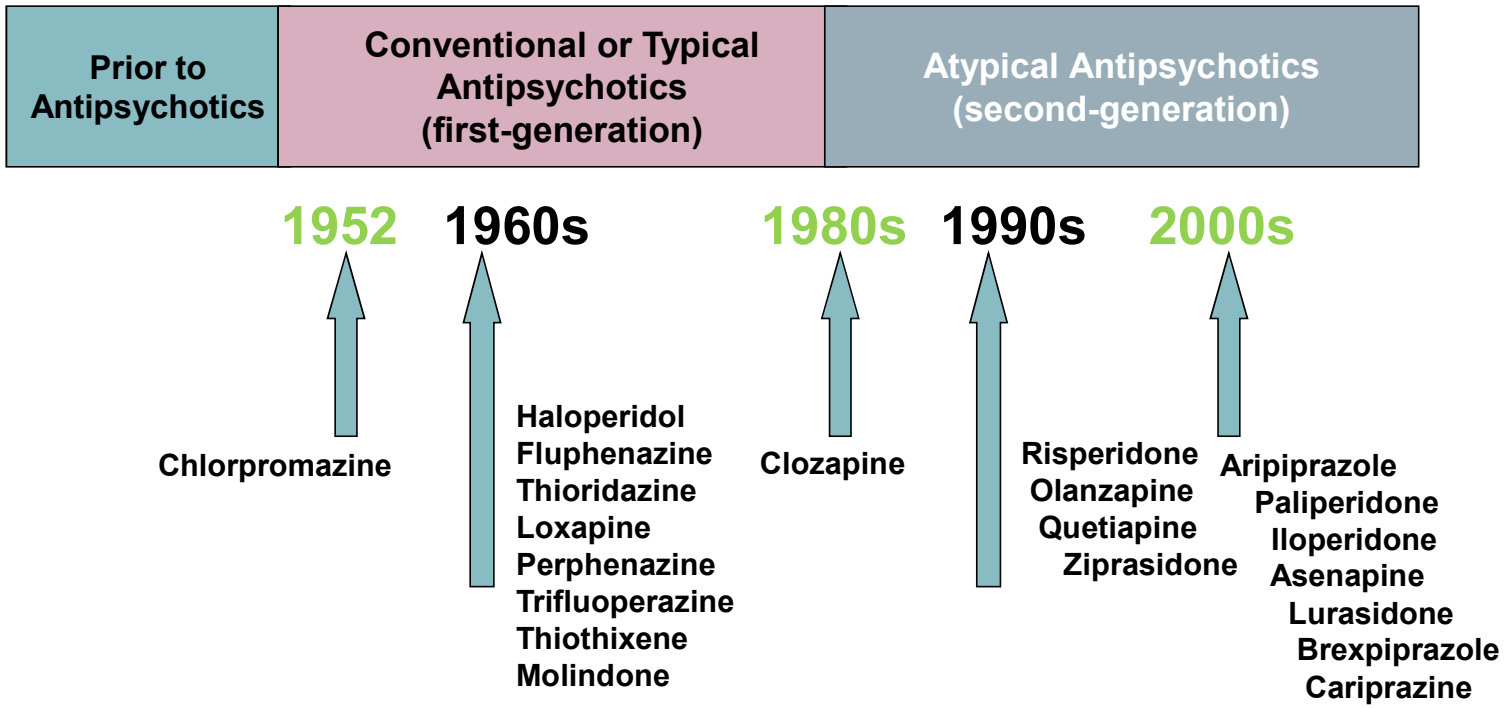
Tandon R, et al. *Schizophr Res*. 2009;110(1-3):1-23.

Pharmacologic Treatment of Schizophrenia

- **Antipsychotics are the mainstay**
  - Variably effective on different treatment targets
  - Treatment of acute exacerbation
  - Prevention of psychotic relapse

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

Options for Antipsychotic Therapies



Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

Treatment Selection with Antipsychotics

- All antipsychotics are broadly equally effective against psychotic symptoms (*with ONE exception)*
- Clozapine is more effective than other antipsychotic agents in improving psychotic symptoms 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

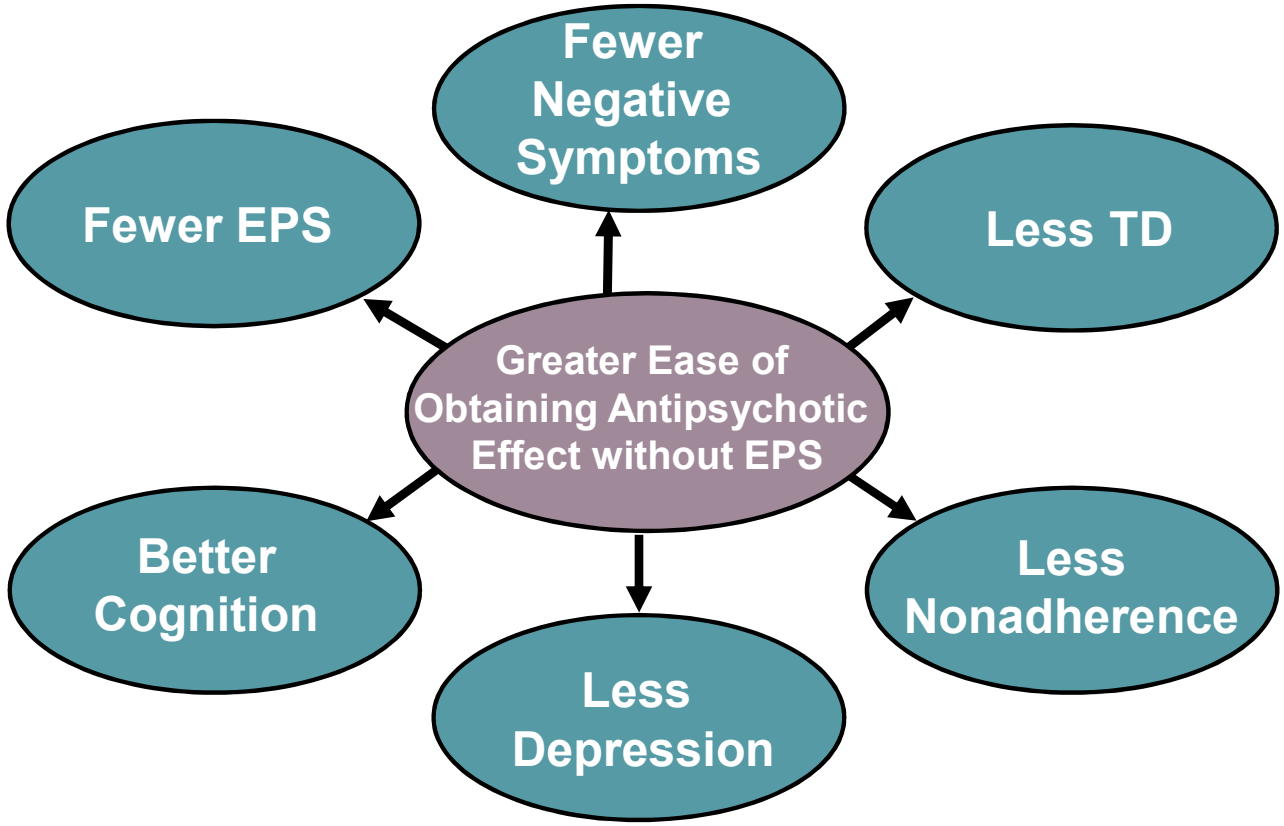
SGA = second-generation antipsychotic; FGA = first-generation antipsychotic; EPS = extrapyramidal symptoms; TD = tardive dyskinesia.
Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

Limitations in Antipsychotic Treatment of Schizophrenia

- **Incomplete efficacy**
  - Not effective for negative symptoms
  - Not effective for cognitive symptoms
  - Not completely effective for positive symptoms and relapse prevention
  - Unsatisfactory functional and social outcomes
- **Significant adverse effects**
- **Poor treatment adherence**

Keshavan MS, et al. *Prog Neurobiol*. 2017;152:3-20.

Why SGAs are Better than FGAs for Many Individuals



Tandon R, et al. *Schizophr Res*. 2010;122(1-3):1-23.

Limitations in Antipsychotic Treatment of Schizophrenia

- **Incomplete efficacy**
- **Significant adverse effects**
  - EPS and TD
  - Weight gain, dyslipidemia, diabetes
  - Sedation, hypotension, hyperprolactinemia
  - Anticholinergic side effects
- **Poor treatment adherence**

Keshavan MS, et al. *Prog Neurobiol*. 2017;152:3-20.

Minimizing Side Effects of Antipsychotic Treatment

All side effects involve interactions between
(i) Individual patient vulnerability,
(ii) Specific agent profile, and
(iii) How the agent is utilized

- EPS
- Metabolic side effects
- Other side effects

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

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

CGI = Clinical Global Impression; PANSS = Positive and Negative Syndrome Scale.

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

Limitations in Antipsychotic Treatment of Schizophrenia

- **Incomplete efficacy**
- **Significant adverse effects**

- **Poor treatment adherence**
  - Leads to recurrent relapses with adverse consequences
  - Higher mortality
  - Worse functional ability
  - Worse quality of life

Keshavan MS, et al. *Prog Neurobiol*. 2017;152:3-20.

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 THREE-FOLD INCREASE IN RISK OF RELAPSE and RELAPSE PREVENTION IS CRITICAL.

Tandon R, et al. *Schizophr Res*. 2010;122(1-3):1-23.

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 formulations

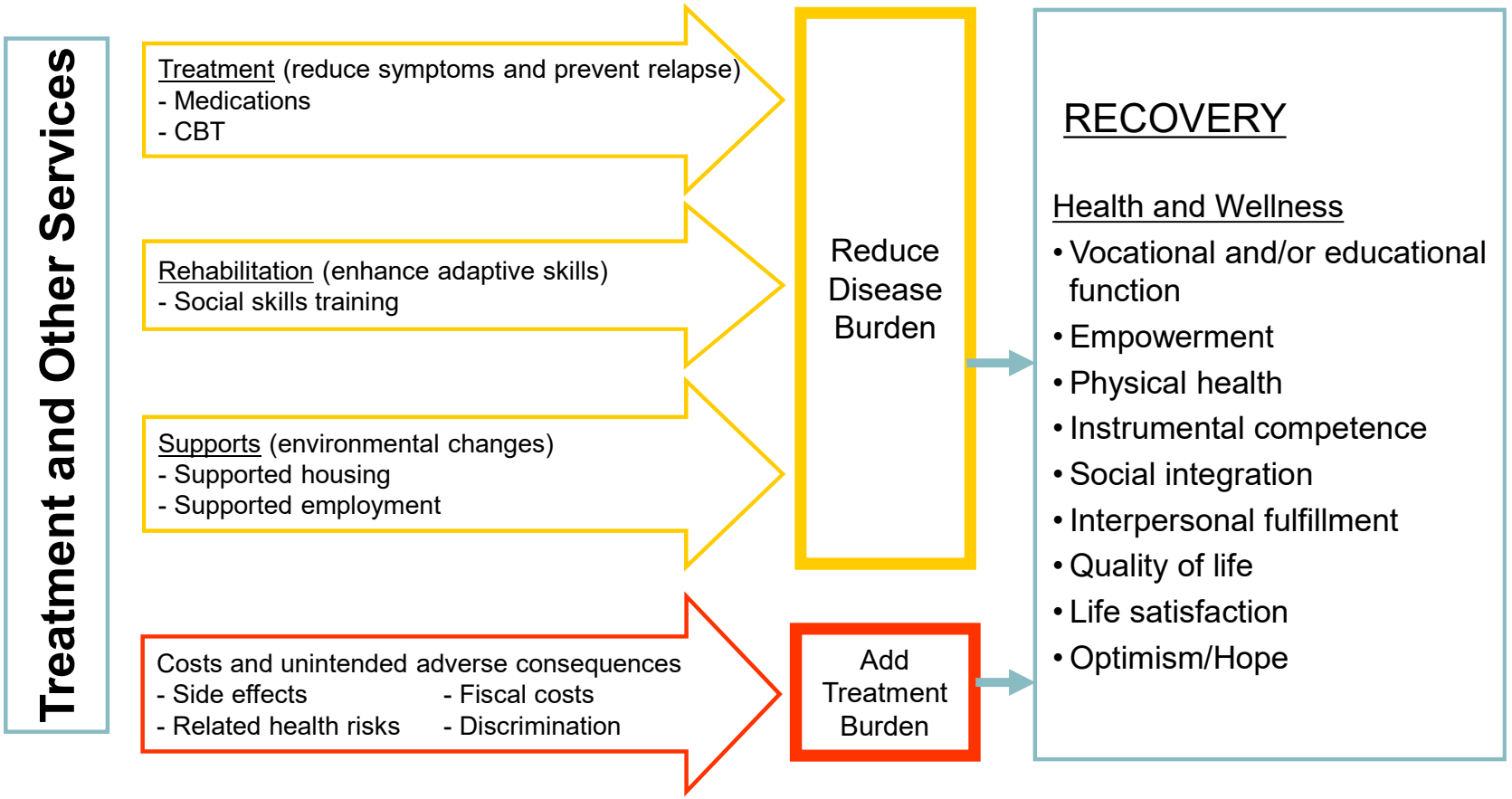
CBT = cognitive-behavioral therapy.

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.


Your husband is suffering from a very severe stress disorder. If you don't do the following he will surely die. Each morning fix him a healthy breakfast. Be pleasant at all times. For lunch make him a nutritious meal. For dinner prepare an especially nice meal No chores. No nagging. Oh yes, and make love several times a week. Do this for the next year and he'll regain his health completely!

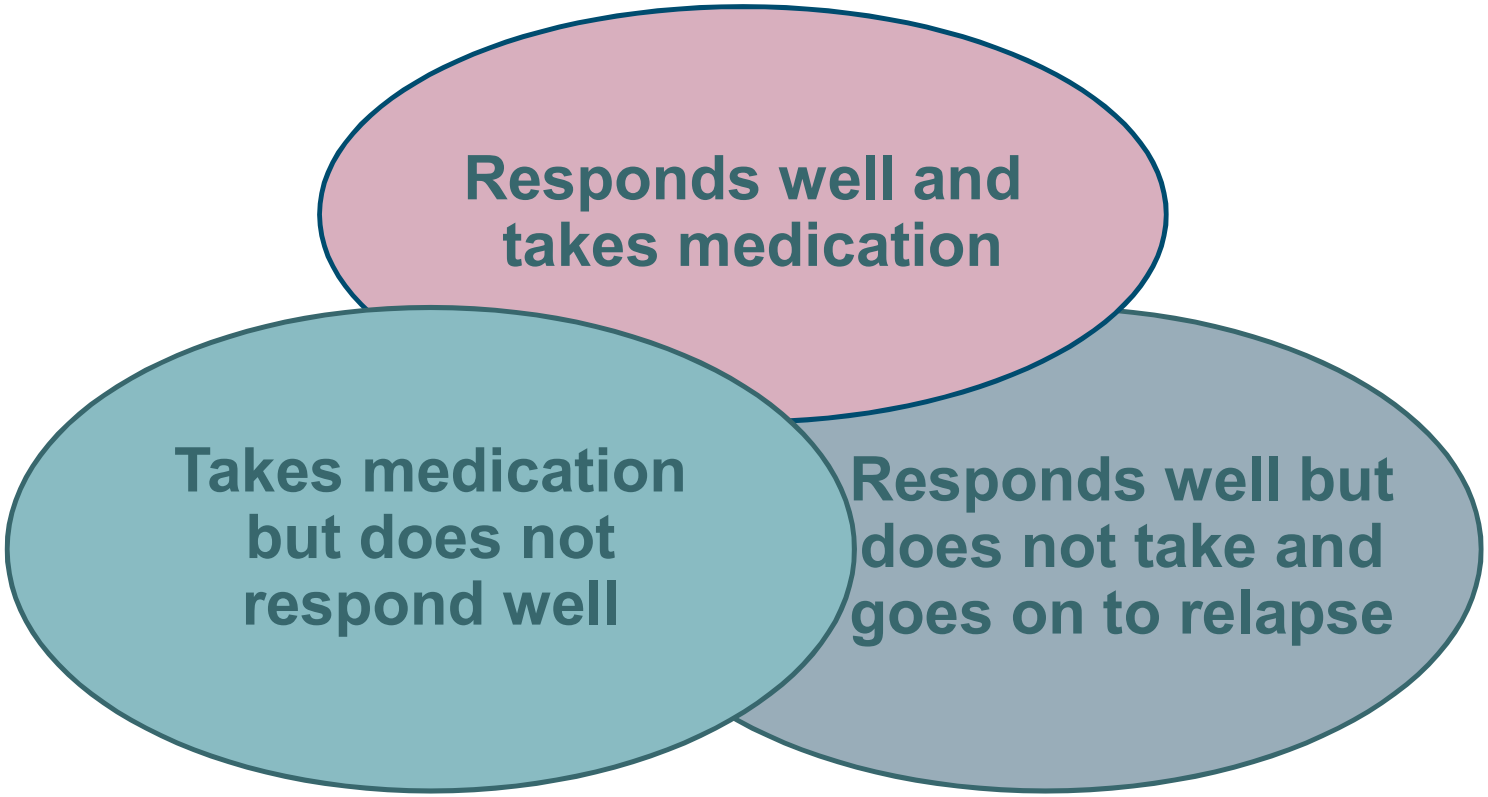

What did the doctor say ?
You're going to die!

Optimizing Individual Treatment Outcomes



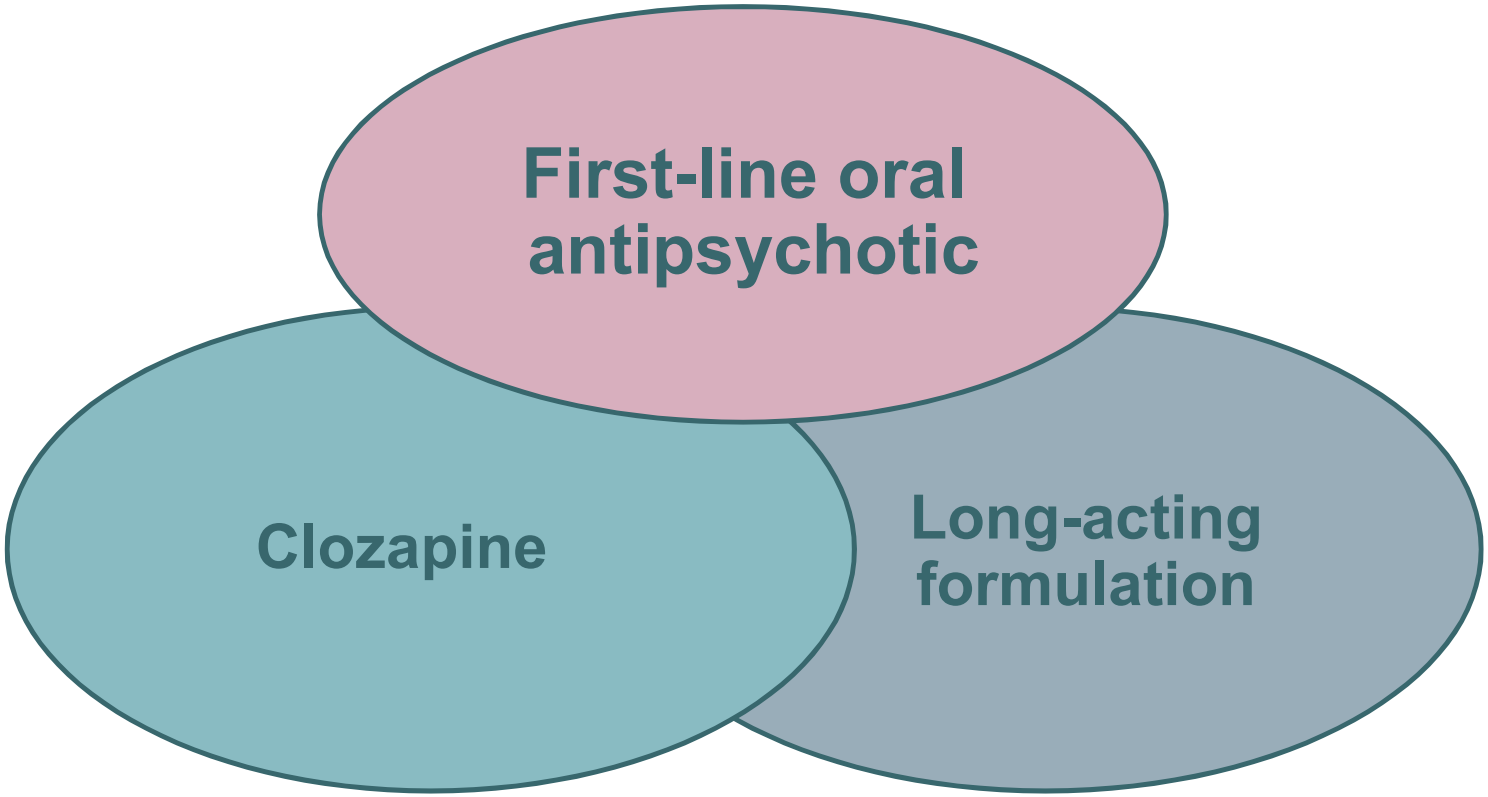
Tandon R, et al. *J Psychiatr Pract*. 2006;12(6):348-363.

Idealized Patient Profiles



Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

Matching Profile to Medication



Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

Guidelines for Pharmacologic Treatment of Patients with Schizophrenia

LEVEL 0. **COMPREHENSIVE ASSESSMENT**

LEVEL 1. **Monotherapy with an antipsychotic (SGA or FGA) –** preferably SGA other than clozapine

↓

LEVEL 2. **If Level 1 ineffective or not tolerated**: FGA or different SGA

↓

LEVEL 3. **If Levels 1 and 2 ineffective or not tolerated**:

- Clozapine or long-acting antipsychotic agent

↓

LEVEL 4. **If Levels 1–3 ineffective or not tolerated:**

- Clozapine if not tried earlier
- SGA or FGA + ECT
- Clozapine augmentation with SGA or FGA, if clozapine monotherapy not successful
- SGA or FGA augmentation with anticonvulsant
- Other antipsychotic combinations (if partial response with 1 agent)

ECT = electroconvulsive therapy.

Bruijnzeel D, et al. *Asian J Psychiatr*. 2014;11:3-7.

The Challenges in the Treatment of Schizophrenia, Circa 2018

- **Treatments Only Partially Effective**
  - Fairly effective for psychotic symptoms
  - High rates of treatment nonadherence
  - Not very effective for negative and cognitive symptoms
  - Significant adverse effects: metabolic, neurological …
  - Increasing mortality gap: 15 to 25 years!
  - Varying degrees of functional recovery
  - Very high rates of homelessness, unemployment

- **Treatment Nonadherence**
  - Increased morbidity and mortality
  - Worse functional outcomes

Keshavan MS, et al. *Prog Neurobiol*. 2017;152:3-20. Tiihonen J, et al. *JAMA Psychiatry*. 2017;74(7):686-693.

Efficacy, Safety, Tolerability, and Indications *of Available Long-Acting Injectable Antipsychotics*

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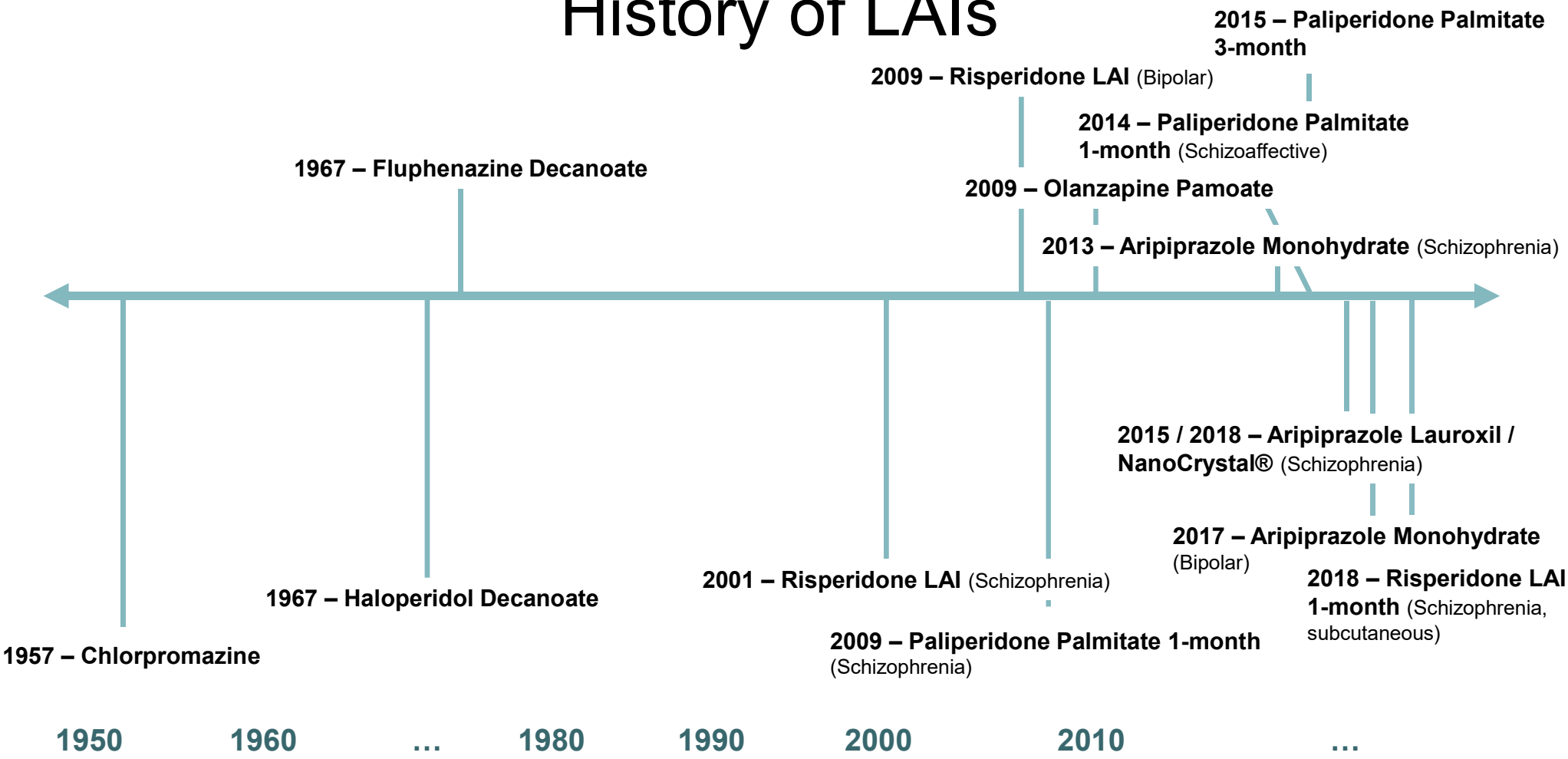
History of LAIs



Types of LAIs: FGAs

- Fluphenazine decanoate
  - Sesame oil-based
  - Given every 2–4 weeks
  - High EPS
  - Higher risk of brain atrophy

- Haloperidol decanoate
  - Sesame oil-based
  - Given every 4 weeks
  - High EPS
  - Higher risk of brain atrophy

LAI = long-acting injectable.

Nasrallah HA. Haloperidol clearly is neurotoxic. Should it be banned? *Current Psychiatry*. 2013;12(7):7-8.

Types of LAIs: SGA – Risperidone LAI (intramuscular)

- FDA approved for bipolar disorder and schizophrenia
- Water-based biodegradable microspheres (requires refrigeration)
- 3 weeks to release
- 21 days of any oral antipsychotic supplementation
- Injection given every 2 weeks and there is a 3-week delay
- Deltoid or gluteal
- Processed by CYP 2D6
- Most common adverse reactions (≥ 5%) in clinical trials in patients with schizophrenia: headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Types of LAIs: SGA – Risperidone LAI (subcutaneous)

- FDA approved for schizophrenia
- Risperidone is both dissolved and suspended in a polymeric solution; after subcutaneous injection, it solidifies upon contact with bodily fluids, and becomes a biodegradable subcutaneous implant
- Neither a loading dose nor any supplemental oral risperidone is recommended
- Given every 4 weeks
- For abdominal subcutaneous injection only
- Processed by CYP 3A4 and 2D6
- Most common adverse reactions in clinical trials (≥ 5% and greater than twice placebo): increased weight, sedation/somnolence, and musculoskeletal pain

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Types of LAIs: SGA – Paliperidone Palmitate

Paliperidone Palmitate 1-month

- FDA approved for schizophrenia and schizoaffective
- No oral supplementation, 234 mg on treatment day 1 and 156 mg one week later, both administered in the deltoid muscle
- Following the second initiation dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle
- Missed dose +/- 1-week window
- Median apparent half-life: between 25 and 49 days
- Limited CYP 450 metabolism
- Most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo): injection site reactions, somnolence/sedation, dizziness, akathisia, and extrapyramidal disorder

Paliperidone Palmitate 3-month

- FDA approved for schizophrenia
- Initiate only after the patient has been adequately treated with paliperidone palmitate 1-month for at least 4 months
- Administered once every 3 months
- Missed dose +/- 1-week window
- Median apparent half-life: dose range of 273 to 819 mg – from 84 and 95 days following deltoid injections, and 118 and 139 days following gluteal injections
- Limited CYP 450 metabolism
- Most common adverse reactions (incidence ≥ 5% and occurring at least twice as often as placebo): injection site reaction, weight increased, headache, upper respiratory tract infection, akathisia, and parkinsonism

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Types of LAIs: SGA – Olanzapine Pamoate

- FDA approved for schizophrenia
- Establish tolerability with oral olanzapine prior to initiating treatment
- Given every 2–4 weeks
- Post-injection delirium/sedation syndrome (PDSS)
- Risk Evaluation and Mitigation Strategies (REMS)
  - Requires a 3-hour observational period
  - Pharmacy/clinic/patient/physician need to register
  - Require to report within a week post-injection to report PDSS
- Processed by CYP 1A2 (caution with cigarette smoking)
- Most common adverse reactions (≥ 5% and greater than placebo): headache, sedation, weight gain, cough, diarrhea, back pain, nausea, somnolence, dry mouth, nasopharyngitis, increased appetite, and vomiting

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Types of LAIs: SGA – Aripiprazole Monohydrate

- FDA approved for bipolar disorder and schizophrenia
- Water-based monohydrate aripiprazole
- Long half-life of 45 days; 2-week oral supplementation (of any antipsychotic)
- Given every 4 weeks
- Missed dose - 6 day / + 2–3 weeks window
- Deltoid or gluteal
- Low metabolic side effects
- Processed by CYP 2D6 and CYP 3A4
- Most common adverse reactions (≥ 5% and greater than placebo): increased weight, akathisia, injection site pain, and sedation

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Types of LAIs: SGA – Aripiprazole Lauroxil

- FDA approved for schizophrenia
- Water-based prodrug of aripiprazole
- 3-week oral supplementation of aripiprazole; or 30 mg aripiprazole oral dose with 675 mg of NanoCrystal® formulation
- Low metabolic side effects
- Missed dose - 2 weeks / + 6–8 weeks window
- Given every 4–8 weeks
- Most common adverse reaction (≥ 5% and greater than placebo): akathisia

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/.

Late Stage of Clinical Development

- BB-0817 – Phase 3
  - 6-month risperidone polyurethane implant
- Paliperidone palmitate 6-month – Phase 3
- Risperidone *in situ* microparticles – Phase 3
  - Risperidone once-monthly intramuscular formulation; does not require oral supplementation
  - Biodegradation of this risperidone formulation occurs slowly, providing a sustained and controlled release of medication for up to 1 month
- TV-46000 – Phase 3
  - Risperidone extended-release injectable suspension for subcutaneous use as maintenance treatment in adult patients with schizophrenia

NDA = new drug application.

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. ClinicalTrials.gov Identifier: NCT03503318. ClinicalTrials.gov Identifier: NCT03345342.

Clinical Update:

Recent Data on the Expanding Role of Long-Acting Injectable Antipsychotics

First-Episode Schizophrenia

- LAIs have been recommended in involuntary hospital stays, with the goal of increasing treatment adherence among patients with FES, and of avoiding future deterioration
- Current guidelines, regarding FES, have a conservative position, but recent evidence suggests that these perhaps need to be updated
- Given the importance of continuous treatment in the early phases of schizophrenia, LAIs may also be a viable treatment option
- Using LAIs earlier, in the context of a shared decision-making approach, could reduce the negative image and stigmatization attached to LAIs

FEP = first episode schizophrenia.

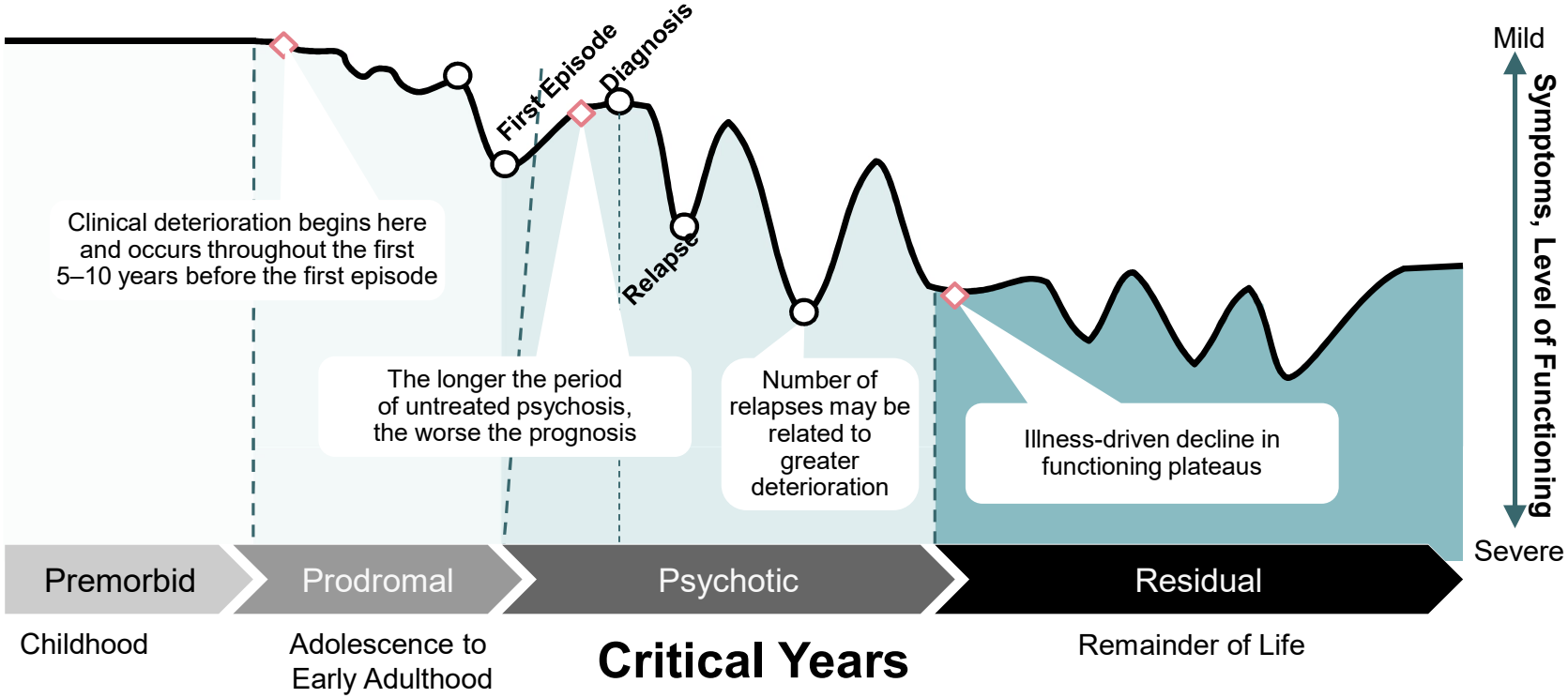
Brissos S, et al. *Ther Adv Psychopharmacol*. 2014;4(5):198-219. Stip E, et al. *Can J Psychiatry*. 2011;56(6):367-376. Vaughan K, et al. *Aust N Z J Psychiatry*. 2000;34(5):801-808. Muirhead D, et al. *Aust N Z J Psychiatry*. 2006;40(6-7):596-605. Parellada E, et al. *Schizophr Res Treatment*. 2012;2012:318535. Kim S, et al. *Patient Prefer Adherence*. 2012;6:533-545. Emsley R, et al. *Early Interv Psychiatry*. 2013;7(3):247-254. Kirschner M, et al. *Ther Adv Psychopharmacol*. 2013;3(2):89-99.

First-Episode Schizophrenia (cont'd)

- Treatment of FES is particularly important to improve long-term outcomes, as most clinical and psychosocial deterioration, cognitive decline, and progressive structural changes in brain volume occur within the first 5 years from the disease onset
- Many individuals in the early stages do not accept the illness itself or its severity, and there can even be a false sense of treatment being unnecessary or an unwanted imposition
- Relapse rates in FES during the first year after diagnosis are over 70%
- The cohort study by Tiihonen et al of 2588 patients with FES found that fewer than 50% of patients in the Finnish health care system continued treatment for the first 2 months after their initial hospitalization
- In this study, route of administration affected relapse; LAIs had a 64% lower relapse rate than the equivalent oral medication

Brissos S, et al. *Ther Adv Psychopharmacol*. 2014;4(5):198-219. Agarwal N, et al. *Radiology*. 2010;255(1):23-41. Brugger S, et al. *Biol Psychiatry*. 2011;69(5):495-503. Nickl-Jockschat T, et al. *Eur Arch Psychiatry Clin Neurosci*. 2011;261 Suppl 2:S166-S171. Rocca P, et al. Risperidone Long-Acting Injection in the Treatment of First Episode Schizophrenia. *Current Psychopharmacology*. 2013;2(1):29-36. Kim SW, et al. *Int Clin Psychopharmaco*l. 2013;28(2):80-86. Kane JM, et al. *Br J Psychiatry Suppl*. 2009;52:S63-S67. Emsley R, et al. *J Clin Psychiatry*. 2012;73(4):e541-e547. Tiihonen J, et al. *Am J Psychiatry*. 2011;168(6):603-609.

Functional Decline over Time



Lieberman JA, et al. *Biol Psychiatry*. 2001;50(11):884-897.

First-Episode Schizophrenia (cont'd)

- The use of LAIs in FEPs may be more effective than oral medication in controlling symptoms and relapse
- It is generally accepted that LAIs have a more favorable side effect profile in comparison with their oral counterparts due to lower variation in peak and trough levels

Brissos S, et al. *Ther Adv Psychopharmacol*. 2014;4(5):198-219. Taylor M, et al. *Aust N Z J Psychiatry*. 2013;47(7):624-630. Taylor D. *Br J Psychiatry Suppl*. 2009;52:S13-S19.

LAI Antipsychotics

- When I was doing My Residency Training I was told to save LAIs for the sick of the sick, the most nonadherent, and the “train wrecks”
- Were they right?
  - **YES**, but they were talking about the wrong patient
- Who are the patients who have the poorest amount of insight?
  - Early in the disease state
- Who are the patients who are the most nonadherent?
  - Early in the disease state
- Who are more likely to accept injectable medications?
  - Early in the disease state
- Who are the patients who have the healthiest brains and have the best chance for success with low medication doses?
  - Early in the disease state

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 gastrointestinal 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 health care team
- Improved patient outcomes

Brissos S, et al. *Ther Adv Psychopharmacol*. 2014;4(5):198-219.

LAI Antipsychotics: *Disadvantages*

- Slow dose titration
- Longer time to achieve steady state levels
- Less flexibility of dose adjustment for good responders
- 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)
- Risperidone LAI needs refrigeration, which may be cumbersome in some latitudes
- Perception of stigma

Brissos S, et al. *Ther Adv Psychopharmacol*. 2014;4(5):198-219.

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

Altamura AC, et al. *Int Clin Psychopharmacol*. 2012;27(6):336-349. Llorca PM, et al. *BMC Psychiatry*. 2013;13:340. Kane JM, et al. *Br J Psychiatry Suppl*. 2009;52:S63-S67.

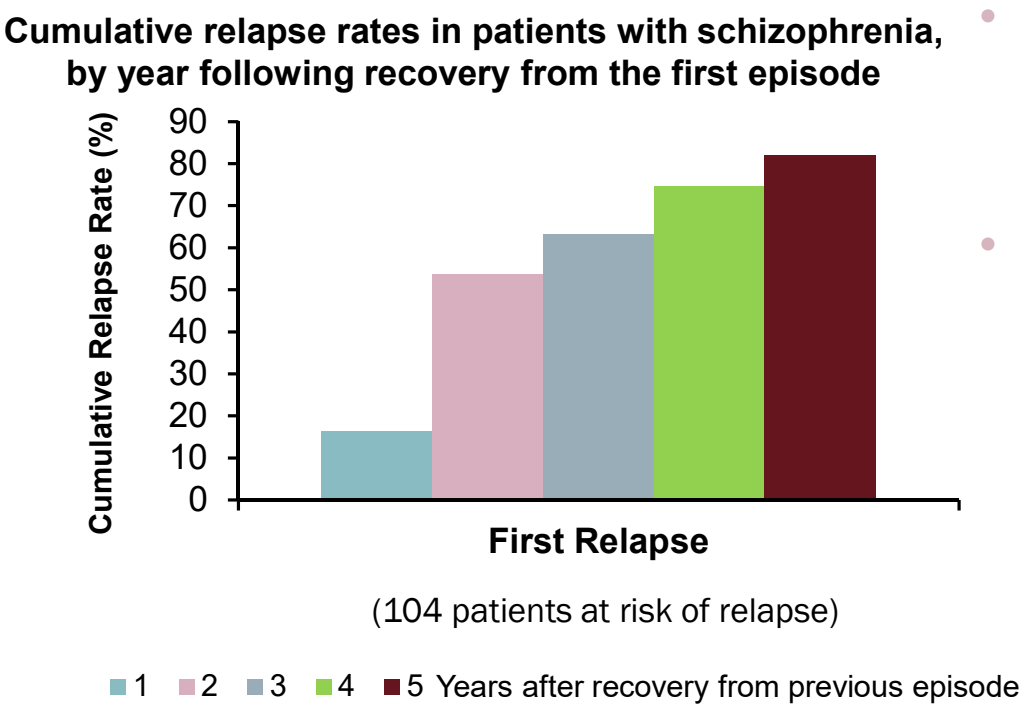
LAIs

"Treating with LAI [antipsychotic drugs] as early as possible, from the first episode if possible, can reduce relapse, number and duration of re-hospitalization and cognitive symptoms and can improve the quality of life and prognosis."

Viala A, et al. *Schizophr Res Treatment*. 2012;2012:368687.

Impact of Long-Acting Injectable Antipsychotics on Adherence

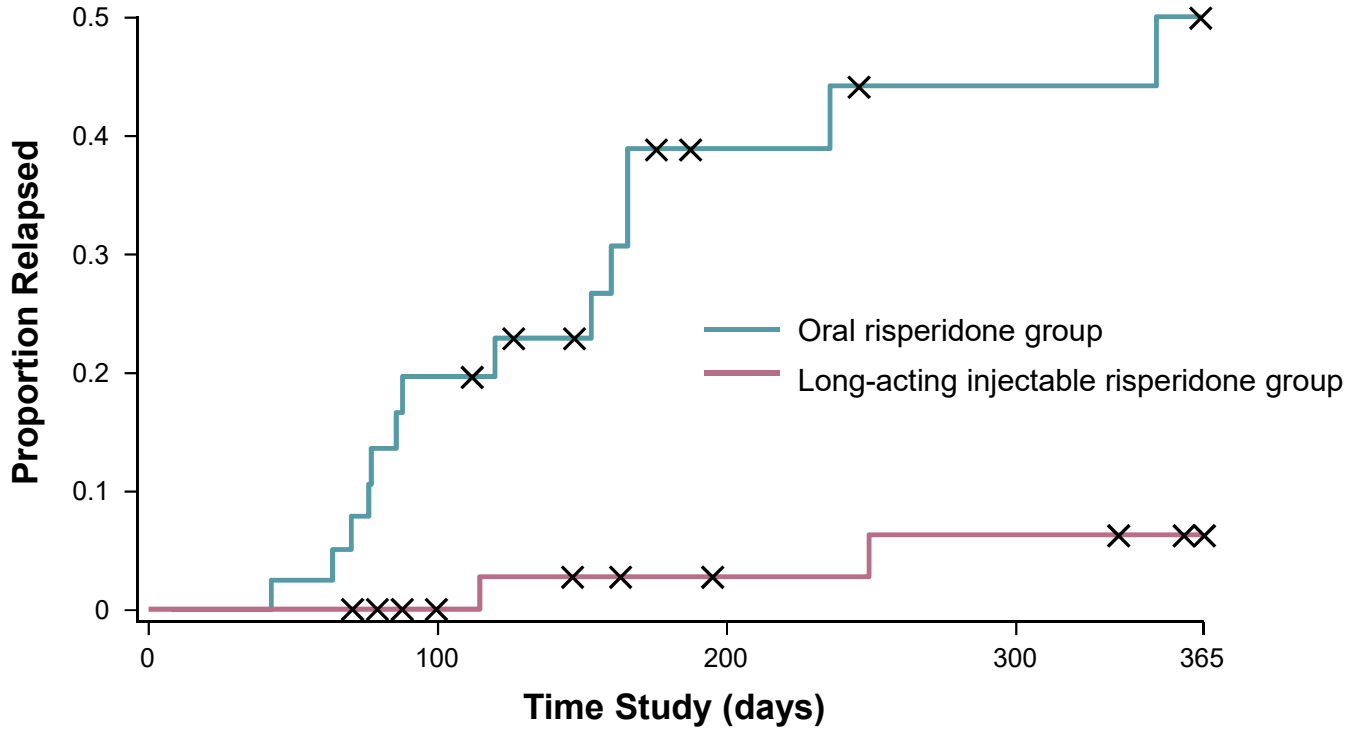
Relapse is Common



- 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

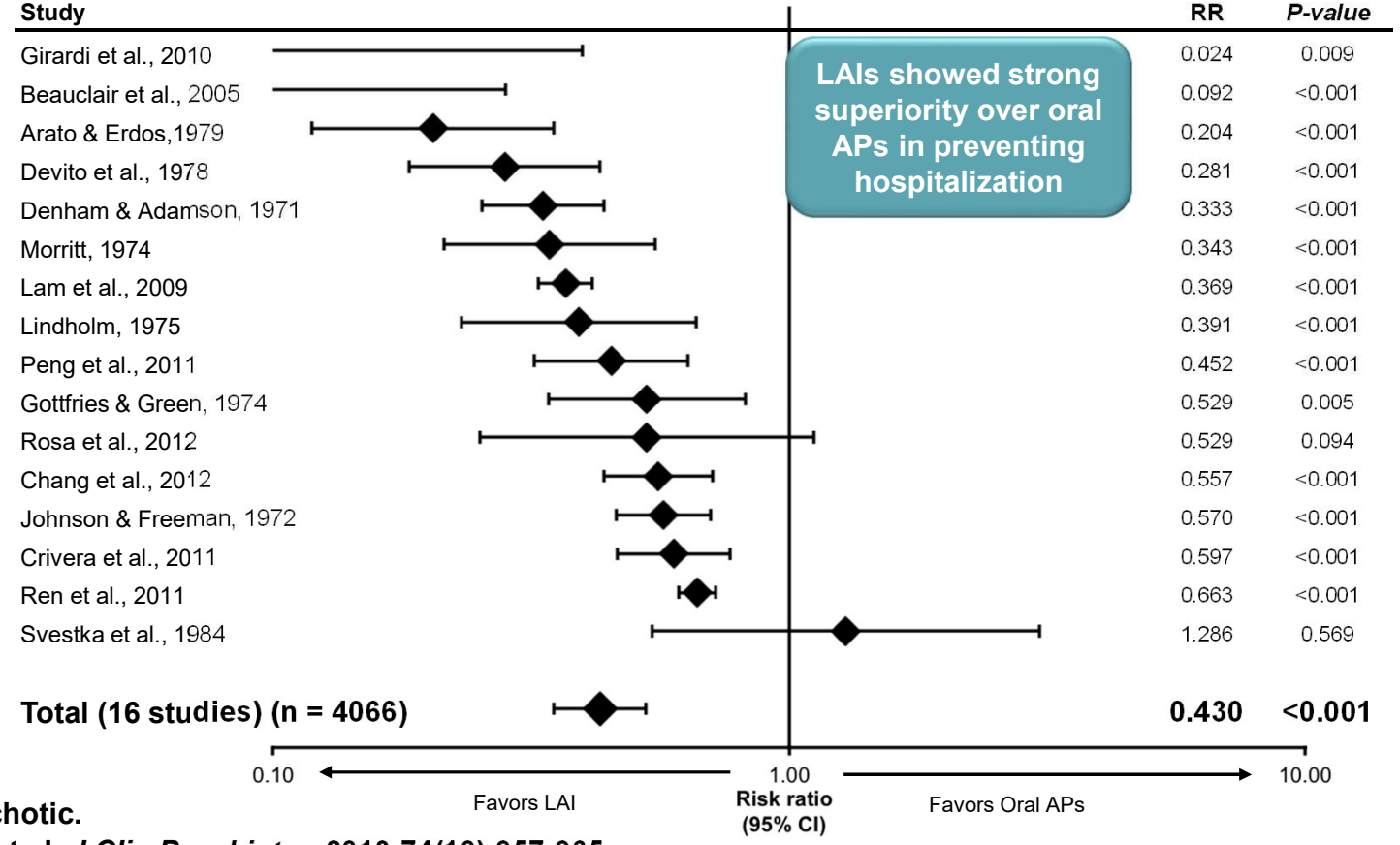
Robinson D, et al. *Arch Gen Psychiatry*. 1999;56(3):241-247. Csernansky JG, et al. *CNS Drugs*. 2002;16(7):473-484. Kane JM. *J Clin Psychiatry*. 2007;68 Suppl 14:27-30. Lewis DA, et al. *Neuron*. 2000;28(2):325-344. Levander S, et al. *Acta Psychiatr Scand Suppl*. 2001;104(408):65-74. Briggs A, et al. *Health Qual Life Outcomes*. 2008;6:105.

LAIs Have Less Relapses Than Oral Antipsychotics



Time to first psychotic exacerbation and/or relapse as a function of form of medication administration in 83 patients.
Subotnik KL, et al. *JAMA Psychiatry*. 2015;72(8):822-829.

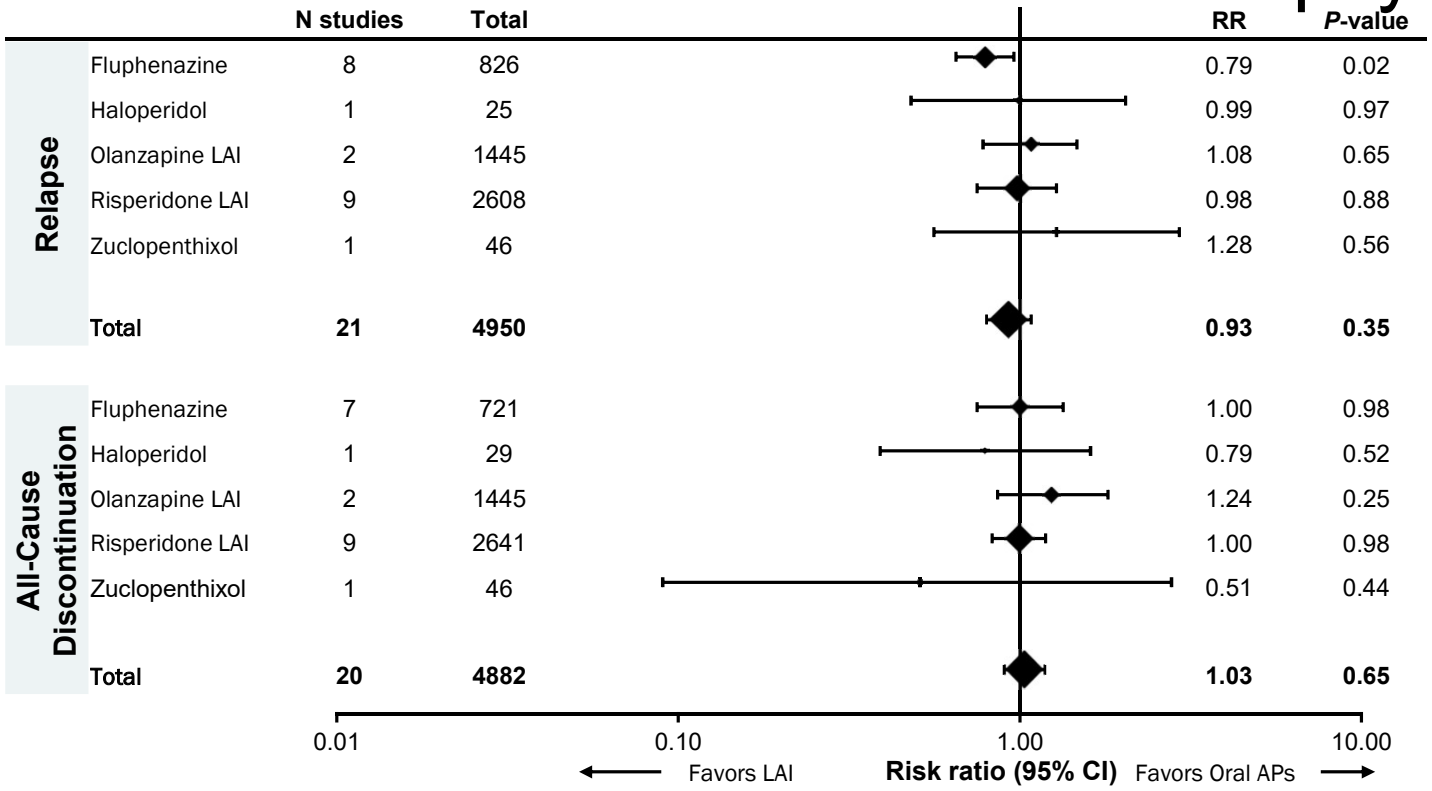
In Mirror Image Studies, LAIs Reduce Risk of Hospitalization Compared with Oral Antipsychotics



AP = antipsychotic.

Kishimoto T, et al. *J Clin Psychiatry*. 2013;74(10):957-965.

No Differences in Study-Defined Relapse/All-Cause Discontinuation between LAIs and Oral Antipsychotics



No difference in adherence between pooled LAIs and oral APs (measured in 10 studies)

21 studies, n=5176.

Kishimoto T, et al. *Schizophr Bull*. 2014;40(1):192-213.

Strategies for Initiating and Maintaining Long-Acting Injectable Antipsychotics Treatment

Fundamental Challenge

- The active agent in both the oral and long-acting formulations of an antipsychotic is the same—the actual antipsychotic molecule
- If a patient takes the oral formulation exactly as prescribed their outcome should be similar to that of a patient taking a long-acting formulation
- But we know that half or less of patients take oral formulations as prescribed
- Adherence plays a big role in keeping patients stable

Do LAIs Improve Adherence?

Do LAIs Improve Adherence?

- **They do not!!!**
- Definition of adherence
  - If I give you a pill today will you take the pill tomorrow
  - If I give you an LAI today will you return in a month
- LAIs give you the assurance of adherence
  - If I give you an injection today then I know you are being adherent
  - If you did not come for your injection today then I know you are nonadherent
- Patients suffering from schizophrenia have a primary thought disorder and often have a tough time making good decisions every day, yet we ask them to take a pill every day and wonder why they are nonadherent

Suggestions for Better Communication about LAIs

- 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

Weiden PJ, et al. *J Clin Psychiatry*. 2015;76(6):684-690.

Clinical Case Examples

Case Presentation #1: *Jack*

- Jack is a 33-year-old male with a long history of paranoid schizophrenia. He was first admitted to the ward in 2007 for this condition
- He has decompensated and has been readmitted 15 × in < 5 years. In this period, Jack has tried to commit suicide 3 × with overdose of aspirin and/or lorazepam
- Other psychiatric conditions include intermittent depression and psychogenic polydipsia
- Jack is receiving treatment with haloperidol decanoate in combination with quetiapine. He did not respond successfully to monotherapy trials with haloperidol, olanzapine, quetiapine, risperidone, and aripiprazole
- Other current psychotropic medications include benztropine, fluoxetine, nefazodone, sertraline, divalproex, and lorazepam

Case Presentation #1: *Jack* (cont'd)

- Should you continue this patient's current drug therapy regimen? Why or why not?
- What are the critical aspects of this case that drive decision-making about his therapy?
- Would you change this patient's current therapy? If not, why? If so, what drugs would you change and how would you discontinue treatment?
- What new or additional drugs would you recommend? Be specific regarding the dose and frequency of any new or additional therapies.
- How would you monitor the patient? What additional tests will be needed?

Case Presentation #2: *Ms. Jones*

History

- First met her at the state hospital while I was a resident
- 21-year-old female
- No previous psychosis, but had “acted strange” in the past
- High school graduate and was in college
- No previous drug use and rarely drinks more and a few drinks a months

Case Presentation #2: *Ms. Jones* (cont'd)

Initial Presentation

- She was brought to jail after she killed her boyfriend
- She was previously on olanzapine to control some "strange thoughts" that she was having when she was 20 years old
- She would feel that the TV was giving her messages, and the olanzapine kept those thoughts under control
- She was quite stable on the current medications when her boyfriend told her that she was gaining too much weight on her medication and that she didn't need it any more
- Without telling her doctor she decided to stop her medications

Case Presentation #2: *Ms. Jones* (cont'd)

- After a few weeks she did not recognize that she was beginning to hear voices again. She was getting messages from the TV
- One of the messages would tell her that the end of the world was coming and that she was chosen to battle the devil
- One afternoon she finally got the signal to do battle, while watching the local news
- According to the message the devil took the shape of the boyfriend and it was her job to kill the devil
- She grabbed her guitar and hit him over the head with it, when she realized that he was just unconscious, she grabbed a kitchen knife and removed his organs placing them around the living room in a ritualistic manner
- She then proceeded to call the police from the gas station across the street asking to speak to the mayor because she wanted a parade because she killed the devil. When the police came and saw what had happened, they quickly arrested her

Case Presentation #2: *Ms. Jones* (cont'd)

Inpatient Course

- She spent 3 years in the forensic state hospital
- Received oral medication
- When she would get transitioned to a less restrictive environment she was often caught cheeking her medications
- When asked why, she replied that she was cured of her illness

Outpatient Course

- She was finally transitioned to my forensic community control program where we started her on an LAI

Case Presentation #2: *Ms. Jones* (cont'd)

Outpatient Course (cont'd)

- We began the conversation about LAIs by asking her about her goals
- She told me that she wanted to get a job and go back to school to become a secretary
- We talked about outcomes and that the best results come from consistent and predictable blood levels
- I explained to her that the medications are only as powerful as the lowest trough and have as many side effect as its highest peak and that LAIs have peaks and troughs closest to the average
- It would also cut down the times she would need medications from 365 pills/year to 13 injections/year
- She accepted the injectable and has been stable ever since

Case Presentation #2: *Ms. Jones* (cont'd)

- She has been on the LAI since coming into our program
- She completed vocational school and is now working as a secretary for a local company
- She has good conversations with her family and no longer feels paranoid about her environment and no longer gets those messages from the TV
- LAIs gave her a better quality of life, she is no longer psychotic and no longer a danger to self or others. She has successfully integrated into society
- LAIs gave her freedom, from not taking medications on a daily basis and being trusted by the court to live independently

Components of the Discharge Plan

- Living arrangements
  - Housing, food, clothing, transportation (bus passes)
- Social support
  - Involve friends and family in the transition of care
- Financial needs, legal requirements
  - Financial aid, contact numbers for social services
  - Possible legal issues
- Daily activities
  - Employment, cooking, cleaning, budgeting
- Medication plan
  - Prescription information, medication options, contact information at community mental health centers
- Community treatment plan
  - Appointments with case manager, contact numbers, patient's attitude toward adherence, follow-up psychiatric and vocational rehabilitation services, assessment for other nonpsychiatric medical services

Olfson M, et al. *New Dir Ment Health Serv*. 1997;(73):75-85.

Q&A