



Schizophrenia

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Objectives



1. Discuss the epidemiology and pathophysiology of schizophrenia
2. Describe the social and financial burdens of schizophrenia
3. Review, compare and contrast treatment options (pharmacological and non-pharmacological)
4. Review health plan quality measures and monitoring parameters around antipsychotic use

What is Schizophrenia?

DSM-5 Definition:

A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be 1,2, or 3:

1. Delusions
2. Hallucinations
3. Disorganized Speech
4. Grossly Disorganized or catatonic Behavior
5. Negative Symptoms (Anhedonia, flattened affect)



- B. For a significant portion of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset
- C. *Duration*: Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A and may include periods of prodromal or residual symptoms.
- D. Other Mental disorders have been ruled out
- E. Substance abuse has been ruled out

Epidemiology

- Schizophrenia is a chronic and severe mental disorder that affects 20 million people worldwide
- It is estimated that <1% of the US population has schizophrenia
- Males=Females
- Male Onset: Late teens – Early 20's
- Female Onset: Early 20's- Early 30's



- Risk Factors:

- Genetic
- Environmental (prenatal maternal immune activation, perinatal hypoxia, toxins, nutrient deprivation, substance abuse, stress)



Pathophysiology

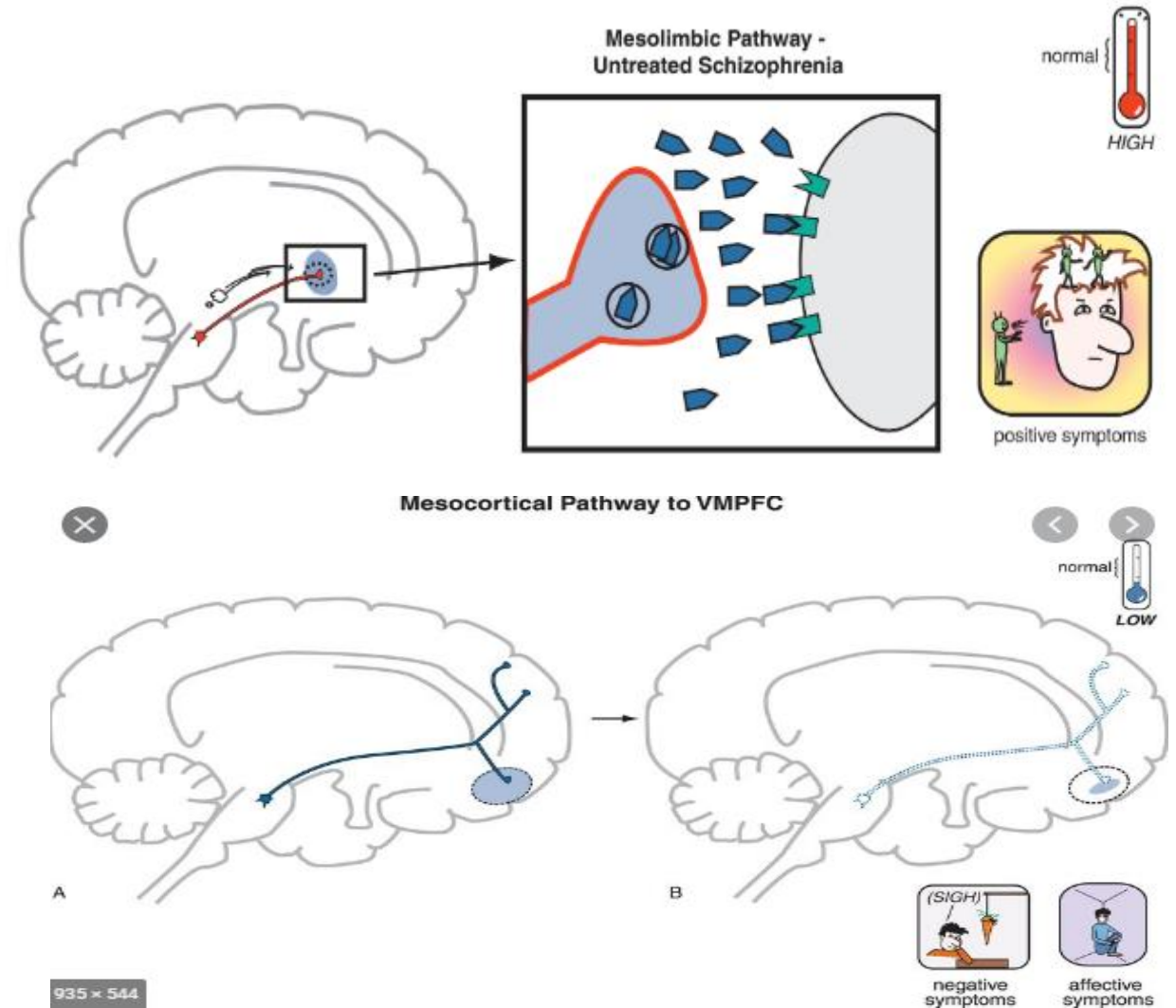
Dysregulation of the Dopamine System

Mesolimbic Pathway

-Hyperactivity of DA leads to positive symptoms

Mesocortical Pathway

-Diminished activity of DA leads to negative symptoms



Symptoms of Schizophrenia

Positive



- ☐ Hallucinations
- ☐ Delusions
- ☐ Disorganized Speech/Behavior
- ☐ Catatonic Behavior
- ☐ Agitation

Negative



- ☐ Alogia
- ☐ Affective Blunting/Flattening
- ☐ Asociality
- ☐ Anhedonia
- ☐ Avolition

Pathophysiology

Interplay of Glutamate and GABA

- Hypofunction of NMDA receptors located on GABAergic interneurons leads to diminished GABAergic activity.
- Diminished GABA can induce disinhibition of downstream glutamatergic activity in pyramidal cells.



Social/Financial Burden Of Schizophrenia

- **2-3x more** likely to die early than general population due to cardiovascular, metabolic, and infectious diseases.
- High stigma around schizophrenia leads to discrimination and eventually limited access to healthcare, education, and employment.
-  **World Health Organization (WHO)** initiated the **Mental Health Action Plan**.
 - **Goal:** promote mental well-being, prevent mental disorders, provide care, enhance recovery, promote human rights and reduce mortality, morbidity, and disability for persons with mental disorders.
- Estimated economic burden of \$155.7 billion. **Direct** healthcare costs accounting for **\$37.7 billion (24%)** and **indirect** costs estimated at **\$117.3 billion (76%)**.

Non-Pharmacological Treatment

Family Intervention

- Goal: Help individuals repair or strengthen their connections with family members and other members of their support system
- Benefits of family interventions are greatest when more than 10 treatment sessions are delivered over a period of at least 7 months.

Psychotherapy

- Goal: It commonly aims to help patients cope with symptoms, improve adaptive skills, and enhance self-esteem

Cognitive Remediation

- Goal: Address cognitive difficulties that can accompany schizophrenia, with the aim of enhancing function and quality of life
- Improvements were seen over 16 weeks of treatment

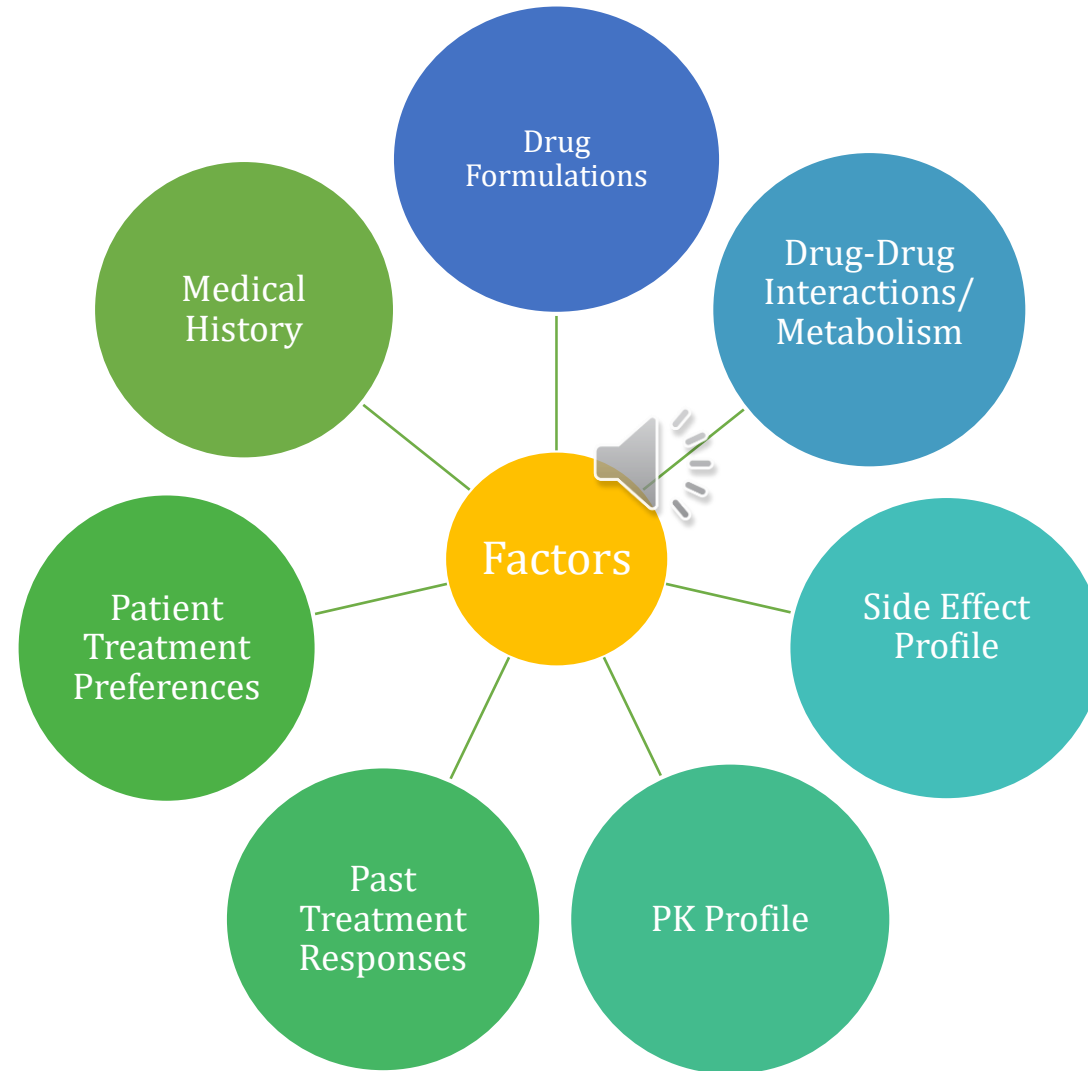
Social Skills Training

- Goal: Improve interpersonal and social skills

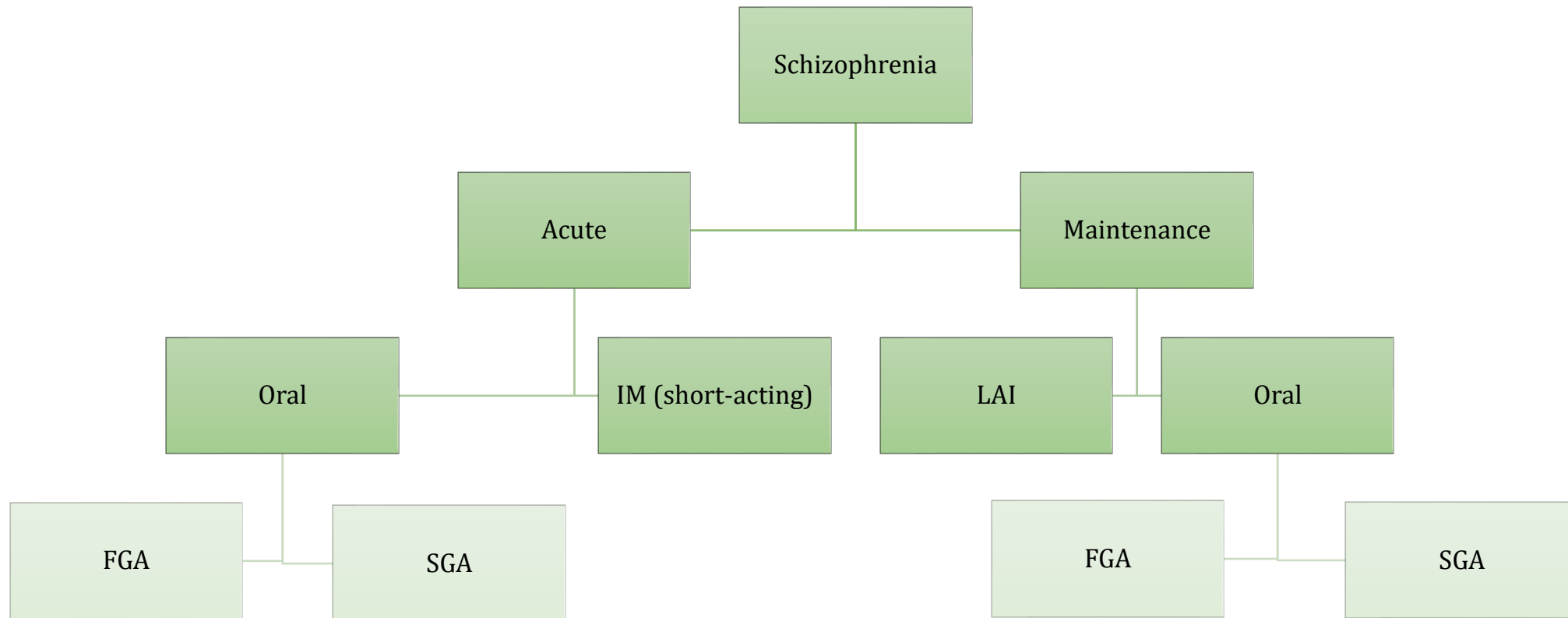
Self-Management Skills/Recovery Focused Intervention

- Goal: Reduce the risk of relapse, recognizing signs of relapse, developing a relapse prevention plan, and enhancing coping skills to address persistent symptoms, with the aim of improving quality of life and social and occupational functioning

Factors Influencing Choice of Antipsychotic



Treatment Road Map



First Generation Antipsychotics (FGA)

MOA

- Mainly block Dopamine-2 (D2) Receptors with minimal serotonin (5-HT₂) receptor blockade

Side Effects

- Sedation, dizziness
- Orthostatic hypotension
- Anticholinergic effects

Warnings

- EPS (akathisia, tardive dyskinesia, parkinsonism, dystonia)
- Hyperprolactinemia
- QT Prolongation
- Neuroleptic Malignant Syndrome (NMS)

BBW

- Increased risk of death in elderly patients with dementia-related psychosis

Treatment: FGA

Potency	Drug	Dosing
Low	Chlorpromazine	300-1,000 mg/day, divided
	Thioridazine	300-800 mg/day, divided
Mid	Loxapine (Loxitane®, Adasuve®)	30-100 mg/day, divided
	Perphenazine	8-64 mg/day, divided
High	Haloperidol (Haldol®)	Oral- 0.5-2 mg BID-TID, max-30mg/day IV- 5-10mg Injection (IM)- 10-20x PO dose Qmon
	Fluphenazine	Oral- 6-12 mg/day, divided Injection (IM)- Q2weeks
	Thiothixene	15-60 mg/day, divided
	Trifluoperazine	15-50 mg/day, divided

Second Generation Antipsychotics (SGA)

MOA

- Block Dopamine-2 (D2) and Serotonin (5-HT₂) receptors
- Depending on the agent, they bind alpha, muscarinic, and histamine receptors as well

Side Effects

- Weight gain, glucose abnormalities, hyperlipidemia
- Sedation
- Orthostatic hypotension
- Anticholinergic effects

Warnings

- Cerebrovascular events in elderly patients with dementia-related psychosis
- Metabolic changes
- QT prolongation
- Hyperprolactinemia

BBW

- Increased risk of death in elderly patients with dementia-related psychosis
- **Increased risk of suicidal thoughts and behavior in children, adolescents and young adults taking antidepressants (Abilify®, Latuda®, Seroquel®, Rexulti®)**

Second Generation Antipsychotics

TABLE 5. Antipsychotic receptor binding properties

	Trade name	D ₁	D ₂	D ₃	D ₄	D ₅	5-HT _{1A}	5-HT _{2A}	5-HT _{2C}	5-HT ₇	H ₁	Musc M ₁	α ₁	α ₂
Second-generation antipsychotics														
Aripiprazole	Abilify	+	////	+++	+	0	///	+++	++	++	++	0	++	+
Asenapine	Saphris, Secuado	+++	+++	++++	+++		+++	++++	++++	++++	+++	0	+++	+++
Brexipiprazole	Rexulti	+	///	+++	++++		////	++++	++	+++	++	0	+++	++++
Cariprazine	Vraylar		///	++++			///	++	+	+	++	0	+	
Clozapine	Clozaril, FazaClo, Versacloz	+	+	+	++	+	/	+++	++	++	+++	///	+++	+
Iloperidone	Fanapt	+	++	++	++	+	//	++++	++	++	+	0	+++	+++
Lurasidone	Latuda	+	+++	++	++		/	++++	+	++++	0	0	++	++
Olanzapine	Zyprexa	++	++	++	++	++	0	+++	++	+	+++	+++	++	+
Paliperidone	Invega	+	+++	+++	++	++	+	++++	++	+++	+++	0	+++	++
Quetiapine	Seroquel	0	+	+	0	0	/	+	0	+	+++	+	++	0
Risperidone	Risperdal	+	+++	+++	+++	+	+	++++	++	+++	++	0	+++	+++
Ziprasidone	Geodon	+	+++	+++	++	+	///	++++	++++	+++	++	0	+++	+

Treatment: SGA

Drug	Formulations				
	PO	ODT	Solution	Patch	Injection
Aripiprazole (Abilify®)	X	X	X		X
Brexpiprazole (Rexulti®)	X				
Clozapine (Clozaril®)	X	X	X		
Olanzapine (Zyprexa®)	X	X			X
Quetiapine (Seroquel®)	X				
Asenapine (Saphris®)		X		X	
Paliperidone (Invega®)	X				X
Risperidone (Risperdal®)	X	X	X		X
Ziprasidone (Geodon®)	X				X
Lurasidone (Latuda®)	X				
Iloperidone (Fanapt®)	X				
Cariprazine (Vraylar®)	X				
Lumateperone (Caplyta®)	X				

Aripiprazole (Abilify Maintena®, Aristada®)



Establish tolerability with oral aripiprazole. Continue oral therapy **x 2 weeks** after first injection

Administer 400mg IM (deltoid, gluteal) every 4 weeks

****Administer 300mg if unable to tolerate 400mg**

Administer IM: 441mg or 662mg Q4weeks, 882mg Q6weeks, or 1,064mg Q8weeks

1 Day Start: Administer 30mg aripiprazole PO + single 675mg injection of Aristada Initio + 1 dose of Aristada within 10 days

21 Day Overlap: Oral for 21 days with 1st dose of Aristada concurrently

Paliperidone (Invega Sustenna®, Invega Trinza®)



Establish tolerability to oral paliperidone or risperidone in treatment naïve patients.

Initiation: Administer 234mg IM on Day 1 followed by 156mg on Day 8.

Maintenance: Administer 39-234mg IM every month.



Patient must be treated with Invega Sustenna for 4 months
Administer IM Every 3 months

Olanzapine (Zyprexa Relprevv®)



ZYPREXA Relprevv
(olanzapine) For Extended Release
Injectable Suspension

Establish tolerability with oral olanzapine prior to initiating treatment

WARNING: Post-injection delirium/sedation syndrome. Patients must be observed for at least 3 hours in a registered facility.
****Only available through restricted distribution program called Zyprexa Relprevv Patient Care Program**

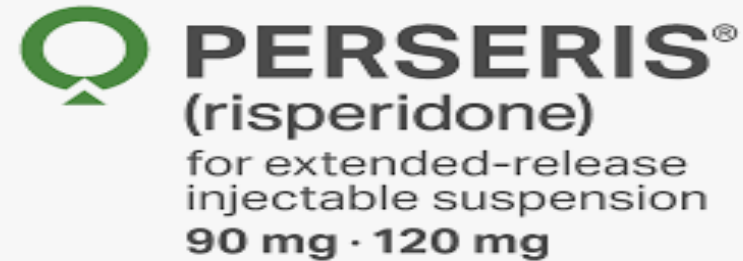
Target Oral Zyprexa Dose	Dosing During the first 8 weeks	Maintenance Dose after 8 weeks
10mg/day	210mg/2 weeks or 405mg/4 weeks	150mg/2 weeks or 300mg/ 4 weeks
15mg/day	300mg/2 weeks	210mg/2 weeks or 405mg/4 weeks
20mg/day	300mg/2 weeks	300mg/2 weeks

Risperidone (Risperdal Consta®, Perseris®)



Oral Risperdal should be given with the first injection and continued x **3 weeks** and then discontinued

Administer 25mg, 37.5mg, or 50 mg IM every 2 weeks

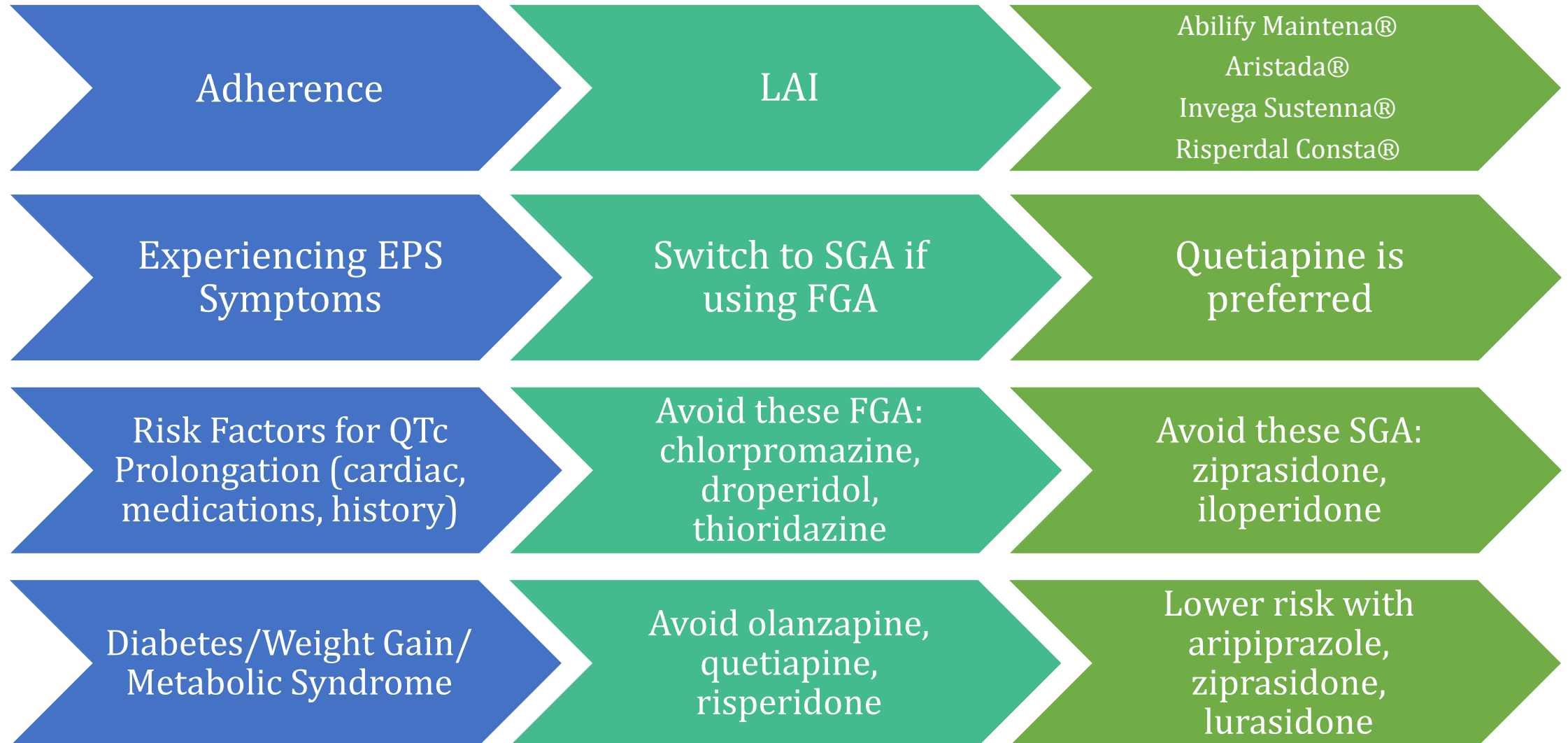


Establish tolerability with oral risperidone

No loading dose or oral supplementation is required

Administer via abdominal **SC injection** every 4 weeks

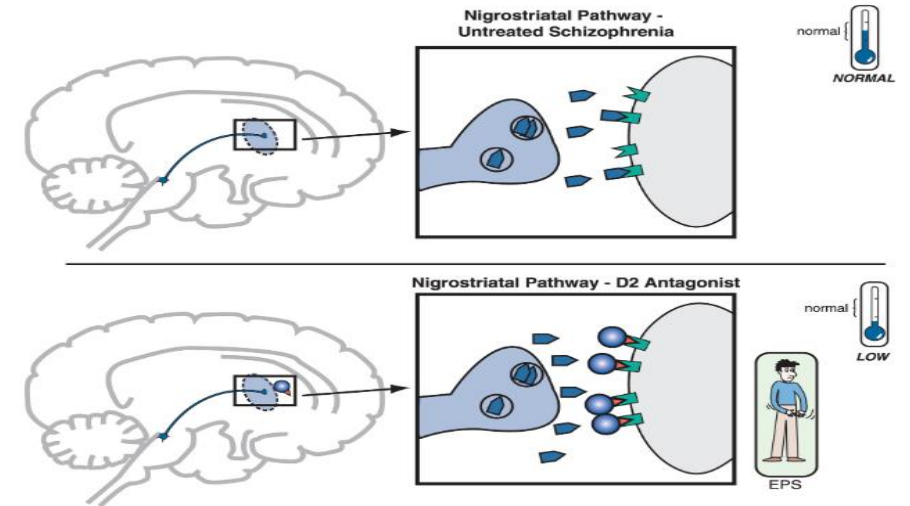
Navigating Treatment



EPS and Hyperprolactinemia

Nigrostriatal Pathway

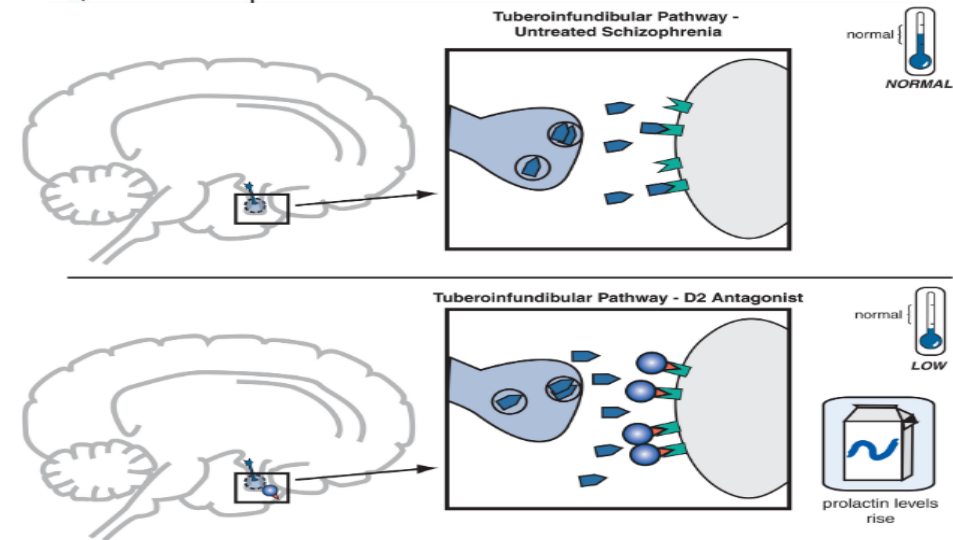
- Normal levels of DA.
- Antipsychotics block DA leading to **EPS symptoms**.



 = pure D2 antagonist

Tuberoinfundibular Pathway

- Normal levels of DA, DA inhibits Prolactin release
- Antipsychotics block DA leading to **↑ Prolactin**
- Increased incidence with **risperidone** and **paliperidone**



 = pure D2 antagonist

Managing Adverse Events



Adverse Event	Pharmacological Treatment
Acute Dystonia	Diphenhydramine (IM, PO), Benztropine (IM, PO), Trihexyphenidyl (PO)
Parkinsonism	Amantadine, Benztropine, Diphenhydramine, Trihexyphenidyl
Akathisia	Lorazepam, Clonazepam, Propranolol
Tardive Dyskinesia	Deutetrabenazine (Austedo®), Tetrabenazine (Xenazine®), Valbenazine (Ingrezza®)

AHRQ Key Findings: FGA vs SGA



Core Illness Symptoms:

There were significant differences in total PANSS between haloperidol and olanzapine and risperidone, both favoring the SGA over haloperidol

Quality of Life:

There was little evidence of a difference between FGA and SGA in quality of life using various measures based on a good-quality systematic review

Withdrawal:

Withdrawals due to adverse events were significantly higher with haloperidol use compared with aripiprazole, olanzapine, risperidone, and ziprasidone

AHRQ Key Findings: SGA vs SGA

Core Illness Symptoms:

Olanzapine and risperidone were both superior to the other SGAs in total PANSS score, except for paliperidone and clozapine

Mortality:



No difference were found between SGA's

Withdrawal:

Risperidone LAI had significantly lower risk of withdrawal due to adverse events than five other SGAs: clozapine, lurasidone, quetiapine ER, risperidone and ziprasidone

Treatment Resistant Schizophrenia: Clozapine

BBW: Risk of life-threatening neutropenia/
Agranulocytosis, Orthostatic
Hypotension/Bradycardia/Syncope, Myocarditis,
Cardiomyopathy, Seizures

REMS Program

Side Effects: Agranulocytosis, seizures,
constipation, sialorrhea, metabolic syndrome,
somnolence

Monitoring: Baseline ANC must be $\geq 1,500\text{mm}^3$. Check
ANC weekly x 6 months, then every 2 weeks x 6 months,
then monthly. STOP if ANC $<1,000\text{mm}^3$

ONLY RECOMMENDED AFTER 2
FAILED ANTIPSYCHOTICS (At least 1
SGA)

Monitoring Parameters

Parameter	Baseline	4-6 months	Annually	As Clinically Indicated
Pulse/ Blood Pressure	x			x
BW/Height	x	x		
CBC/ANC	x			x
Blood Chemistries	x			x
Pregnancy	x			
Diabetes	x	x	x	
Hyperlipidemia	x	x	x	
Metabolic Syndrome	x	x	x	
QTc Prolongation	x			x
Hyperprolactinemia	x			x
Antipsychotic-Induced Movement Disorders	x	x	x	x

HEDIS/Star and other Quality Metrics

First-Line Psychosocial Care for Children and Adolescents on Antipsychotics (APP)

- Children and adolescents 1–17 years of age who had a new prescription for an antipsychotic medication and had documentation of psychosocial care as first-line treatment

Metabolic Monitoring for Children and Adolescents on Antipsychotics (APM)

- Children and adolescents 1–17 years of age who had blood glucose and cholesterol testing

Adherence to Antipsychotic Medications for Individuals with Schizophrenia (SAA)

- Use of an antipsychotic medication for at least 80 percent of the treatment period

Diabetes Screening for People with Schizophrenia or Bipolar Disorder who are using Antipsychotic Medications (SSD)

- Adults on antipsychotic medications who have had diabetes screening

Psychotropic Medication Utilization Review (PMUR)

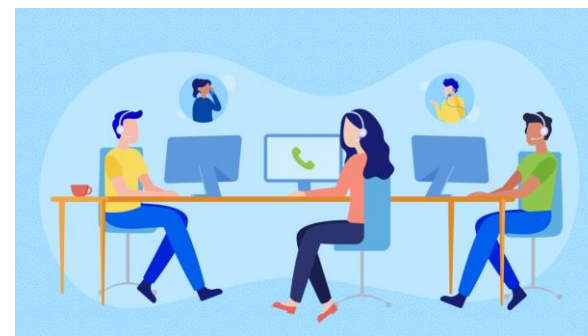
- Use of four or more psychotropic medications at the same time for sixty (60) or more consecutive days

Antipsychotic Use in Person's with Dementia (APD)

- 65 years or older with dementia who received prescription fills for antipsychotics without evidence of a psychotic disorder or related condition

Health Plan Activities

- Provider and Member Outreach
 - Fax/Letter
 - Clinical telephonic outreach – lab monitoring discussion
 - Case management



Conclusion



- Dopamine, serotonin, glutamate, and GABA are involved in the pathophysiology of schizophrenia
- Every patient should have their treatment plan tailored to them depending many factors
- Long-acting injectables should be considered for maintenance therapy and adherence
- Antipsychotics have many adverse effects, therefore, careful monitoring of patient symptoms is crucial

Abbreviations Key

D2: Dopamine-2 Receptors

5-HT: Serotonin

AHRQ: Agency for Healthcare Research and Quality

HEDIS: Healthcare Effectiveness Data and Information Set

NCQA: National Committee for Quality Assurance

FGA: First Generation Antipsychotic

SGA: Second Generation Antipsychotic

EPS: Extrapyramidal Symptoms

REMS: Risk Evaluation and Mitigation Strategies

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