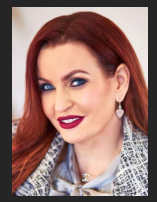
REAL PSYCHIATRY

An Educational Experience Designed for and by
APPs on the Frontline of Modern Practice

ATYPICAL

MODERN PHARMACOKINETIC/DYNAMIC CONSIDERATIONS WITH ANTIPSYCHOTICS

— JANUARY 13, 2024 —



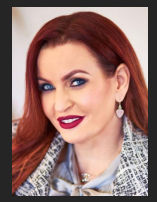
Program Overview

- Atypical antipsychotics is a **global term** that does not capture the diversity of clinical indications and therapeutic impact of this class of agents.

- Due to the **large selection of treatment options** for both **oral and long-acting injectable atypical antipsychotics (LAIs)**, clinicians are challenged with selecting an ideal agent and route of administration optimal for any given patient.

OBJECTIVE: Help clinicians navigate the pharmacological underpinnings of available antipsychotics that guide their optimal and individualized use.

- This session utilizes expert-led discussion examining differences in the **time of onset, half-life, available formulations, and dosing frequency** for both oral and LAIs to help provide guidance on clinical decision making for antipsychotic management



Presenting Faculty

Tina Matthews-Hayes, DNP, PMHNP-BC, FNP-BC

Psychiatric Nurse Practitioner

Seaside Behavioral Health

Virginia Beach, VA

Christina Fuchs, DNP, PMHNP-BC

Psychiatric Nurse Practitioner

Alay Psychiatry

Pewaukee, WI

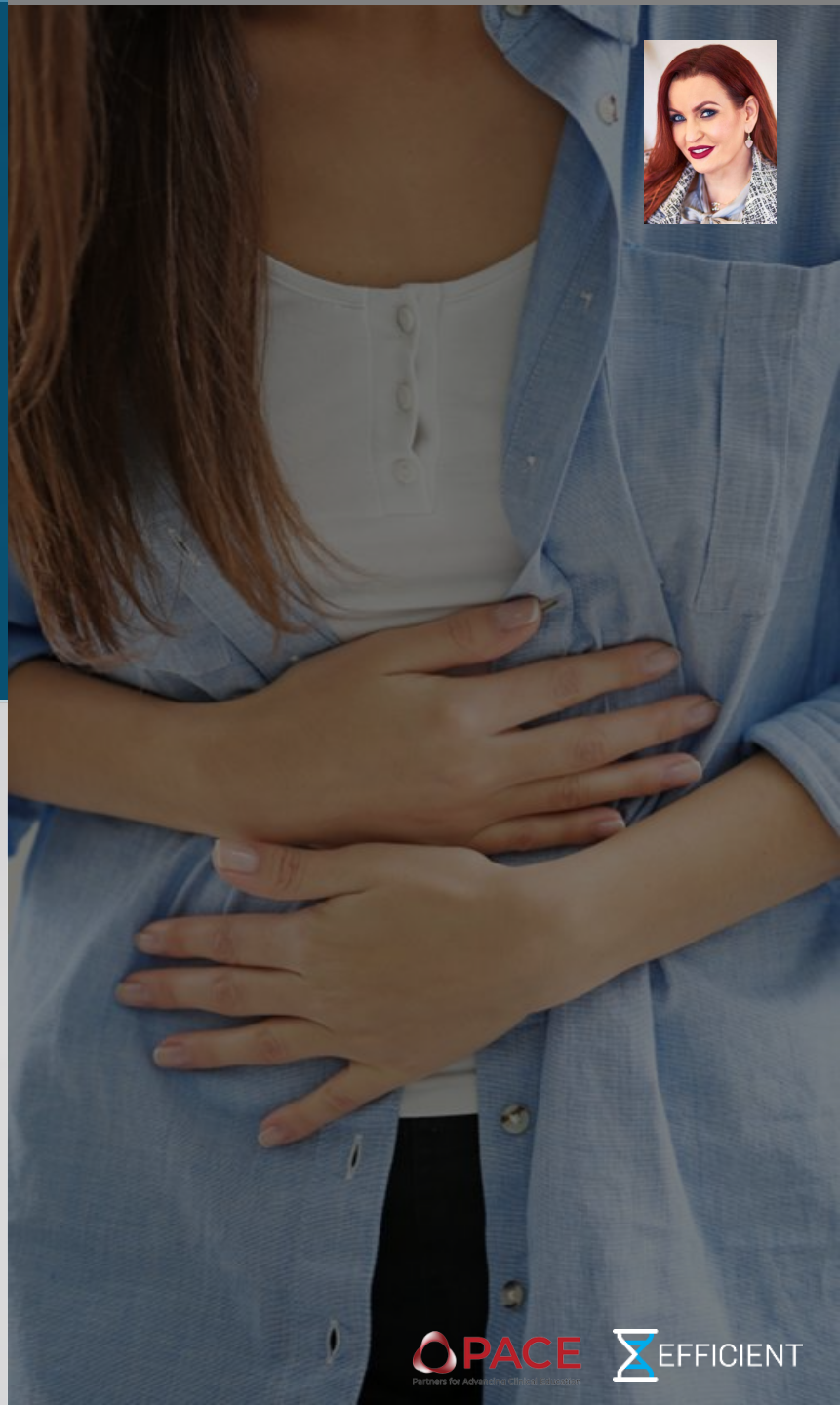
Shawn P. Gallagher, PhD, PMHNP-BC, PMHCNS-BC, FNP-BC

Psychiatric Nurse Practitioner

Tucson, AZ

MODULE
— 1 —

UNIQUE ATTRIBUTES OF ORAL STRATEGIES



CASE 1*

INTRODUCTION

John, a 28-year-old male, presents with 2 weeks of **auditory hallucinations** and **avoidance of social interactions**. He has no prior history of mania, psychosis, or depressive episodes.

No known past medical history. No current medication. Denies history of alcohol or substance use.

Family History

Paternal uncle with schizophrenia

Upon Exam

John is noted to have a **blunted affect**.

WHAT IS THE NEXT BEST STEP IN TREATMENT?

*Fictional case.

ATYPICAL ANTIPSYCHOTICS
NOMENCLATURE

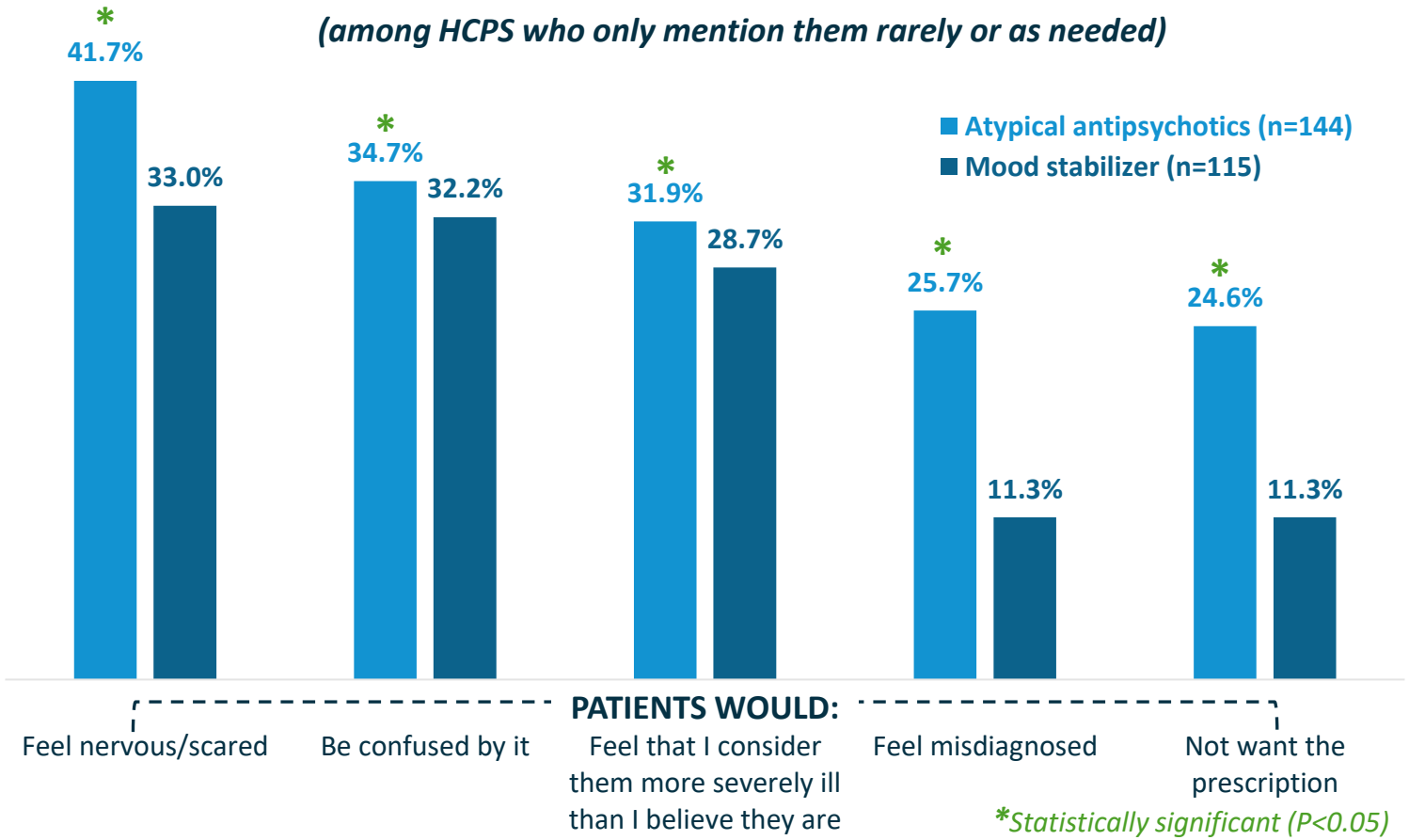
"Atypical antipsychotics" is an **outdated term**[1]

- Not so "atypical" anymore: have ***variable and widely utilized mechanisms*** of action[1,2]
- Not just for psychosis: ***many also approved for other conditions*** *(e.g., mood disorders, irritability associated with autism, agitation due to AD)*

The term itself may have a negative impact.

- Carries ***stronger negative feelings*** compared with mood stabilizers[1]

HCP REASONS FOR NOT MENTIONING CLASS NAMES
(among HCPS who only mention them rarely or as needed)



Adapted from Mattingly G et al. *Prim Care Companion CNS Disord*. 2023;25(1):22m03331

1. Mattingly G et al. Do we need a new nomenclature for atypical antipsychotics? A survey of health care professionals and patients. *Prim Care Companion CNS Disord*. 2023;25(1):22m03331. **2.** Volavka J et al. Oral antipsychotics for the treatment of schizophrenia: heterogeneity in efficacy and tolerability should drive decision-making. *Expert Opin Pharmacother*. 2009;10(12):1917-1928.

HCP: healthcare practitioners

PACE Partners for Advancing Clinical Education EFFICIENT

BROADER SCOPE OF CLINICAL EFFICACY

TYPICAL VS ATYPICAL ANTIPSYCHOTICS

- Typical antipsychotics generally have fewer clinical indications[1,2]
- Atypical antipsychotics generally have a ***broader scope of FDA- approved indications***[1-4]
- Selection of antipsychotic depends on many ***patient-specific factors***:
  - Symptoms and severity
  - Medical history
  - Prior response to therapies
  - Side effect profile

ONLY ATYPICAL[1-4]

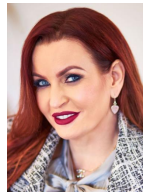
- Negative symptoms of schizophrenia (limited impact)
- Cognitive symptoms of schizophrenia (limited impact)
- Bipolar depression, mania, and maintenance
- Major depressive disorder (adjunctive use)
- Irritability in autism spectrum disorder
- Agitation associated with Alzheimer's disease

BOTH TYPICAL AND ATYPICAL[1,2]

- Positive symptoms of schizophrenia
- Acute psychosis
- Acute/severe agitation

1. Meltzer HY et al. Contrasting typical and atypical antipsychotic drugs. *Focus (Am Psychiatr Publ)*. 2021;19(1):3-13. **2.** Chokhawala K et al. Antipsychotic medications. In: *StatPearls*. NCBI Bookshelf. StatPearls Publishing; February 26, 2023. Accessed January 10, 2024. https://pubmed.ncbi.nlm.nih.gov/30137788/ **3.** Ansara ED. Management of treatment-resistant generalized anxiety disorder. *Ment Health Clin*. 2020;10(6):326-334. **4.** Kayser RR. Pharmacotherapy for treatment-resistant obsessive-compulsive disorder. *J Clin Psychiatry*. 2020;81(5):19ac13182.

ATYPICAL ANTIPSYCHOTICS
NEUROTRANSMITTERS



TYPICAL[1,2]

First-generation antipsychotics (FGA)

Primarily D2 antagonism

- Dopamine
  - D2 — *Antagonism*
  - Non-D2
- Serotonin
- Norepinephrine
- Histamine
- Acetylcholine
- Glutamate ✕
- Glycine ✕

ATYPICAL[1,2]

Second- (SGA)/third-generation (TGA) antipsychotics

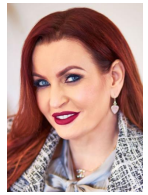
Weaker D2 effects

Greater effects on serotonin and other neurotransmitters

- Dopamine
  - D2 — *Partial agonism vs antagonism*
  - Non-D2
- Serotonin
- Norepinephrine
- Histamine
- Acetylcholine
- Glutamate
- Glycine

Increased/broader activity compared with typical antipsychotics (varies by agent)

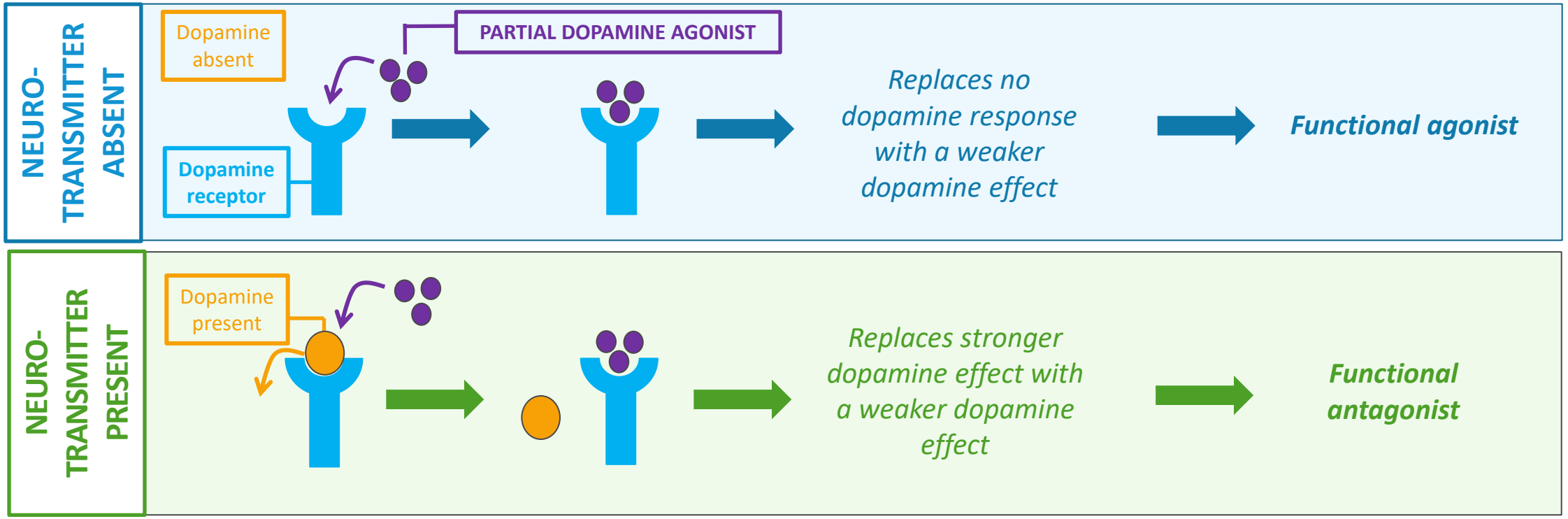
1. Meltzer HY et al. Contrasting typical and atypical antipsychotic drugs. *Focus (Am Psychiatr Publ)*. 2021;19(1):3-13. **2.** Siafis S et al. Antipsychotic drugs: from receptor-binding profiles to metabolic side effects. *Curr Neuropharmacol*. 2018;16(8):1210-1223.



PARTIAL AGONISM

- Unlike typical antipsychotics, some atypicals have partial agonism for dopamine and serotonin receptors[1,2]
- Partial agonist activity depends on the environment they are in:

EFFECTS OF PARTIAL AGONISM



* Dopamine is used as an example in this illustration, but the same principle applies to serotonin and any other neurotransmitter

1. Meltzer HY et al. Contrasting typical and atypical antipsychotic drugs. *Focus (Am Psychiatr Publ)*. 2021;19(1):3-13. **2.** Citrome L. The ABC's of dopamine receptor partial agonists - aripiprazole, brexpiprazole and cariprazine: the 15-min challenge to sort these agents out. *Int J Clin Pract*. 2015;69(11):1211-1220.

DOPAMINE

MORE THAN ONE RECEPTOR

- Typical antipsychotics primarily exert their effect via ***D_2 antagonism.***[1-3]
- Atypical antipsychotics can have variable effects (***agonism vs partial agonism vs antagonism***) on multiple dopamine receptors.[1-3]

→ Primary mechanism mediating drug-induced movement disorders (DIMDs)

→ Help to decrease DIMDs

DOPAMINE RECEPTOR FUNCTIONS / LOCALIZATION

Prefrontal cortex: cognitive symptoms	D_1	Distributed throughout the striatum
	D_2	
Associated with emotion / reward	D_3	Main targets of antipsychotics
Prefrontal cortex: cognitive symptoms	D_4	
Not well elucidated	D_5	

1. Mauri MC et al. Clinical pharmacokinetics of atypical antipsychotics: an update. *Clin Pharmacokinet*. 2018;57(12):1493-1528. **2.** Martel JC et al. Dopamine receptor subtypes, physiology and pharmacology: new ligands and concepts in schizophrenia. *Front Pharmacol*. 2020;11:1003. **3.** Mishra A et al. Physiological and functional basis of dopamine receptors and their role in neurogenesis: possible implication for Parkinson's disease. *J Exp Neurosci*. 2018;12:1179069518779829.

AUDIENCE POLL

How does the serotonin activity / selectivity of atypical antipsychotics impact clinical outcomes?

a) Decreased risk of drug-induced movement disorders (DIMDs)
b) Reduced risk of weight gain
c) Antidepressant effects
d) All the above
e) A & C
f) B & C
g) I do not know/I am unsure.

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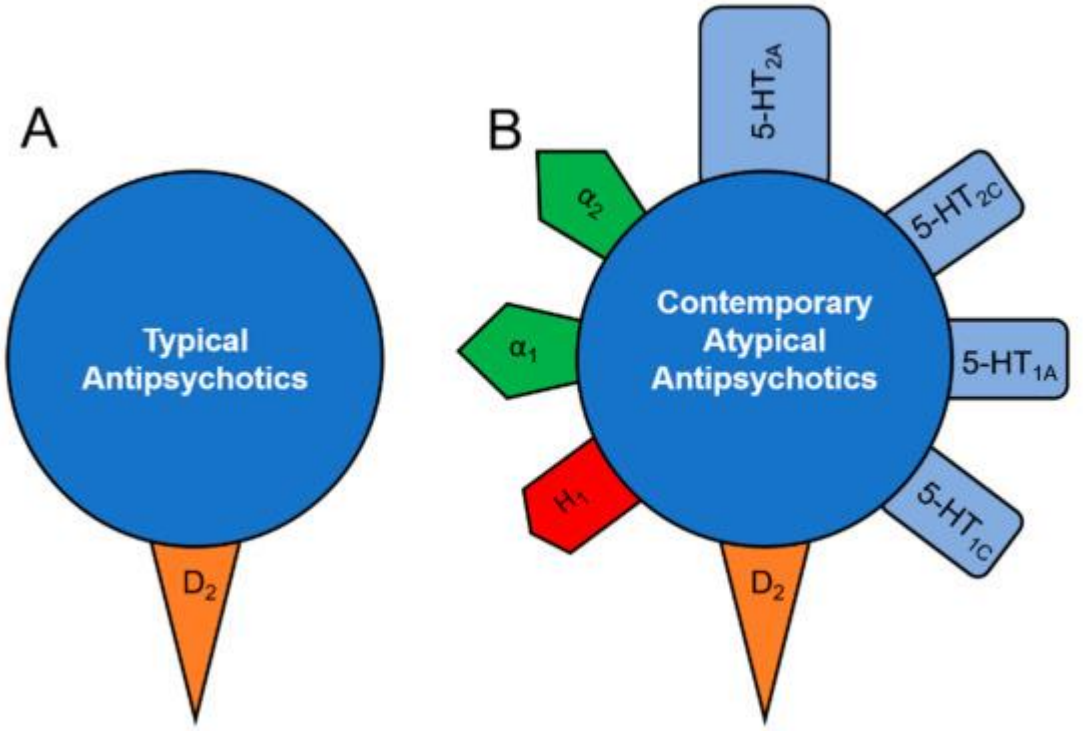
g) I do not know/I am unsure.

ATYPICAL ANTIPSYCHOTICS
CLINICAL IMPLICATIONS

FUNCTION / CLINCAL IMPACT BY RECEPTOR SUBTYPE

NEURO-TRANSMITTER	RECEPTOR	CLINICAL IMPACT
SEROTONIN[1,2]	5-HT	• Antidepressant effect[1] • Decreased drug-induced movement disorders (DIMDs)[2] • Improved cognition[2]
NOREPINEPHRINE[1]	α (alpha)	• Antidepressant effect[1]
HISTAMINE[1]	H	• Sleep, cognition, memory, mood regulation[1]



From Grinchii et al. *Int J Mol Sci*. 2020;21(24):9532

1. Grinchii D et al. Mechanism of action of atypical antipsychotic drugs in mood disorders. *Int J Mol Sci*. 2020;21(24):9532. **2.** Ślifirski G et al. 5-HT receptors and the development of new antidepressants. *Int J Mol Sci*. 2021;22(16):9015.

ATYPICAL ANTIPSYCHOTICS

SIDE EFFECT PROFILES

THE GOOD

Second-generation antipsychotics are ***less likely to cause DIMDs.***[1]

Stay tuned for "Extrapyramidal Symptoms: When are They Tardive Dyskinesia?" for more details.

DIMDs: drug-induced movement disorders

THE BAD

High rates of metabolic dysregulation[2]:

- Weight gain
- Decreased insulin sensitivity
- Cholesterol / triglyceride dysregulation

Likely due to antipsychotic impact on…[3]

- Serotonin (5-HT_{2A} / 5-HT_{2C})
- Dopamine (D_2/D_3)
- Histamine (H_1)
- Acetylcholine (M_3)
- Norepinephrine (α_2)

1. Ali T et al. Antipsychotic-induced extrapyramidal side effects: a systematic review and meta-analysis of observational studies. *PLoS One*. 2021;16(9):e0257129. **2.** Pillinger T et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7(1):64-77. **3.** Fonseca M et al. Metabolic effects of atypical antipsychotics: molecular targets. *J Neuroendocrinol*. 2023;35(12):e13347.

ANTIPSYCHOTICS: METABOLIC PROFILE

STUDY DESIGN

- Network meta-analysis (100 RCTS)

FINDINGS

- **Clozapine/olanzapine:** associated with the greatest degree of metabolic dysfunction

CONCLUSION

- Newer antipsychotics (e.g., lurasidone, cariprazine) have ***more favorable metabolic profiles***

	Weight	Body–mass index	Glucose	LDL cholesterol	Total cholesterol	HDL cholesterol	Triglycerides
Haloperidol	0·10	0·08	0·59		0·59		0·63
Ziprasidone	0·10		0·42	0·12	0·25	0·24	0·33
Aripiprazole	0·26	0·11	0·55	0·48	0·50	0·26	0·33
Lurasidone	0·32	0·37	0·09	0·27	0·27	0·45	0·26
Cariprazine	0·37		0·70	0·07	0·16	0·47	0·28
Fluphenazine	0·38						
Amisulpride	0·41		0·14		0·64	0·83	0·42
Brexipiprazole	0·45		0·40	0·66	0·52	0·18	0·23
Flupenthixol	0·44						
Asenapine	0·56		0·22				
Risperidone and Paliperidone	0·58	0·56	0·46	0·54	0·55	0·51	0·39
Quetiapine	0·65	0·68	0·47	0·91	0·82	0·59	0·71
Iloperidone	0·70		0·73		0·19		0·63
Sertindole	0·81	0·72	0·36		0·26		0·29
Zotepine	0·88		0·94				0·94
Clozapine	0·90	0·85	0·97		0·97		0·97
Olanzapine	0·92	0·93	0·67	0·96	0·91	0·76	0·83

P-score: 0 — 0·50 — 1·0

From Pillinger T et al. *Lancet Psychiatry*. 2020;7(1):64-77.

1. Pillinger T et al. Comparative effects of 18 antipsychotics on metabolic function in patients with schizophrenia, predictors of metabolic dysregulation, and association with psychopathology: a systematic review and network meta-analysis. *Lancet Psychiatry*. 2020;7(1):64-77.

RCT: randomized controlled trial

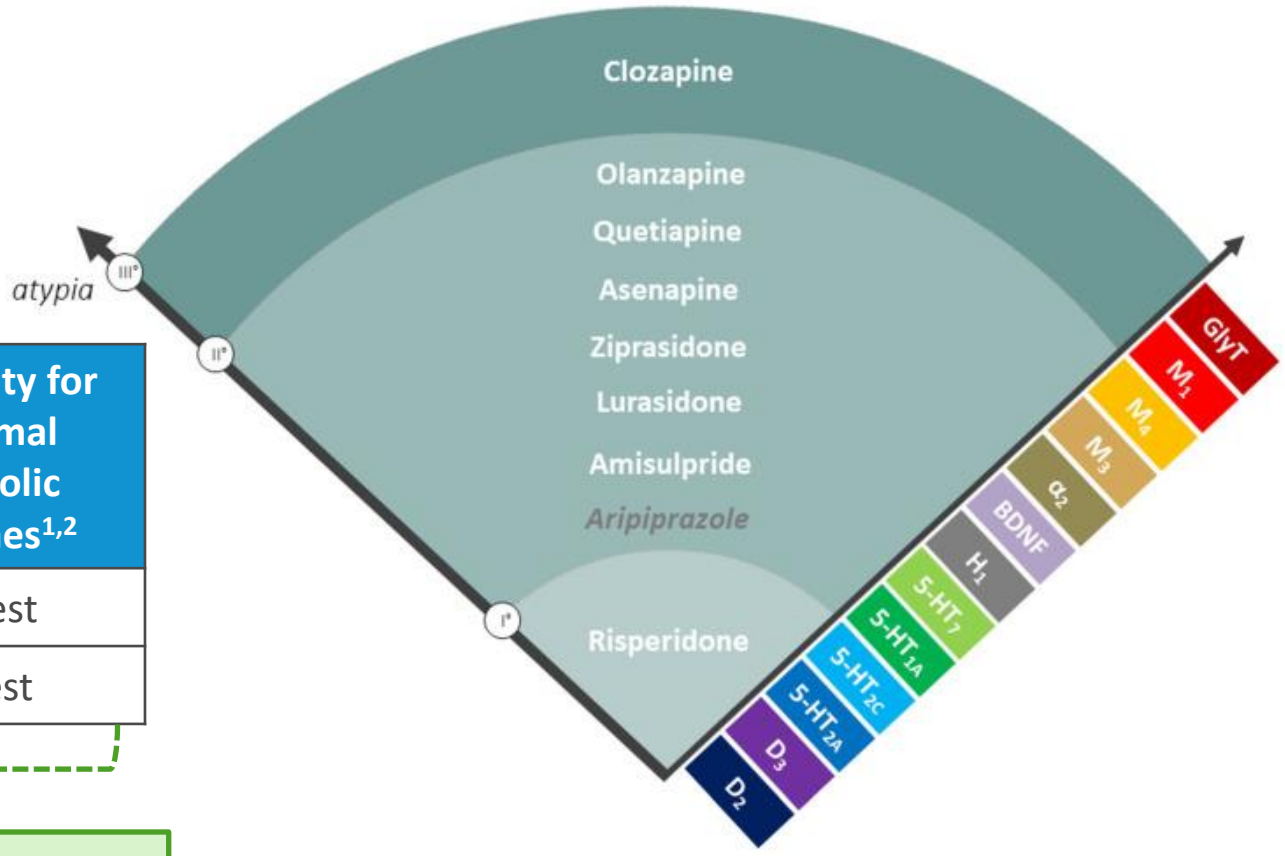
ANTIPSYCHOTICS
ATYPICAL SPECTRUM

NEW PARADIGM FOR ATYPICAL ANTIPSYCHOTICS

- Classification based on ***degree of atypia***[1,2]:
  - Can help categorize side effect profile

Atypical antipsychotic	Degree of atypia[1,2]	Propensity for DIMDs[3]	Propensity for abnormal metabolic outcomes[1,2]
Clozapine	Most atypical	Lowest	Highest
Risperidone	Least atypical	Highest	Lowest

Is this classification clinically useful? Can newer agents be integrated into this paradigm?



From Carli et al. *Pharmaceuticals (Basel)*. 2021;14(3):238.

DIMDs: drug-induced movement disorders

1. Carli M et al. Atypical antipsychotics and metabolic syndrome: from molecular mechanisms to clinical differences. *Pharmaceuticals (Basel)*. 2021;14(3):238. **2.** Fonseca M et al. Metabolic effects of atypical antipsychotics: molecular targets. *J Neuroendocrinol*. 2023;35(12):e13347. **3.** Divac N et al. Second-generation antipsychotics and extrapyramidal adverse effects. *Biomed Res Int*. 2014;2014:656370.

TREATMENT SELECTION
CLINICAL FACTORS

Limited data to suggest any single atypical antipsychotic has superior clinical efficacy for all patients

Important to prioritize patient-specific factors

CLINICAL SETTING →	Inpatient vs outpatient
SYMPTOM SEVERITY →	Hospital admission (faster onset of action)
CLINICAL INDICATION →	Schizophrenia vs. bipolar depression vs. MDD augmentation vs agitation
PATIENT ADHERENCE →	Adherent (oral/short-acting) vs nonadherent (injectable/long-acting)
COMORBIDITIES →	History of metabolic disturbances (less atypical) vs movement disorders (more atypical)

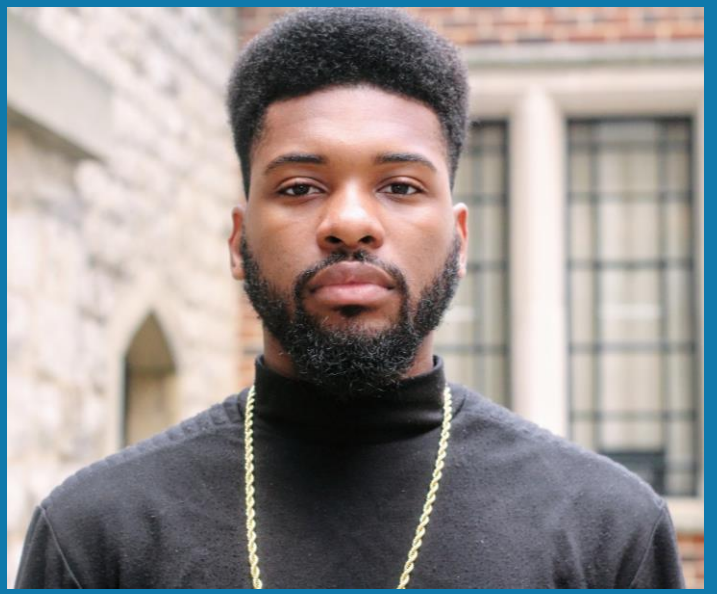
1. Huhn M et al. Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. *Lancet*. 2019;394(10202):939-951.

CASE 1*

PATIENT-SPECIFIC FACTORS

RECAP:

John is a 28-year-old male with a family history of schizophrenia who presents with 2 weeks of **auditory hallucinations** and **avoidance of social interactions**.



CLINICAL SETTING	→	Outpatient
SYMPTOM SEVERITY	→	Does not require admission
CLINICAL INDICATION	→	Schizophrenia
PATIENT ADHERENCE	→	Reports willingness to take oral meds

Is this patient a good candidate for oral antipsychotics?

*Fictional case.

CASE 1*

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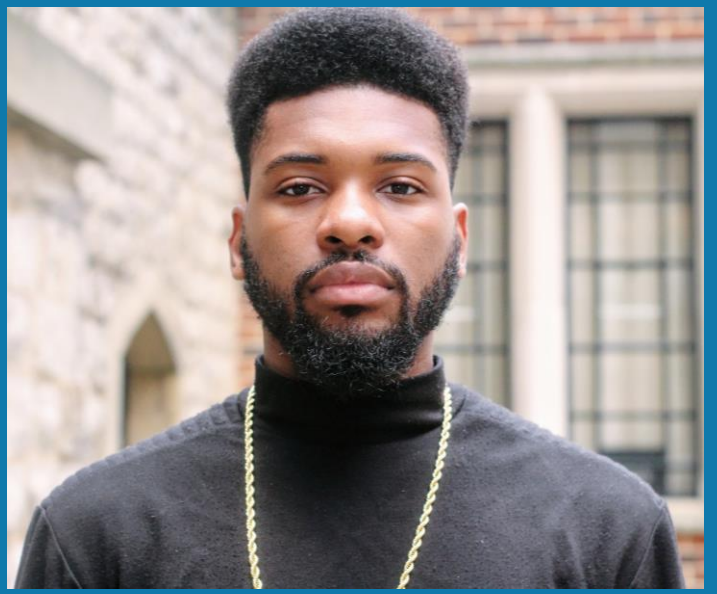
RECAP:

John is a 28-year-old male with a family history of schizophrenia who presents with 2 weeks of **auditory hallucinations** and **avoidance of social interactions**.



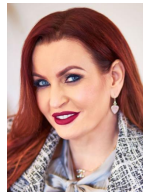
CLINICAL SETTING	→	Outpatient
SYMPTOM SEVERITY	→	Does not require admission
CLINICAL INDICATION	→	Schizophrenia
PATIENT ADHERENCE	→	Reports willingness to take oral meds

YES!…But which one?

*Fictional case.

SELECTING AN ORAL AGENT

EXPERT OPINION



Would this patient be interested in/a good candidate for an oral antipsychotic?

yes

IDEAL AGENT:

- Fast-acting
- Long-acting
- Minimal side effect profile

MOST COMMONLY USED AGENTS:

- First-line generics

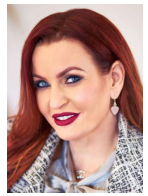
NEW/PREFERRED AGENTS IN MY PRACTICE:

- Lumateperone
- Cariprazine
- Lurasidone

no

Consider long-acting injectable (LAI) agents

Variable mechanisms of action, pharmacokinetic profiles, dosing protocols, and indications



BRANDED AGENT: LUMATEPERONE

MECHANISM OF ACTION

- *Primarily targets **serotonin** and **dopamine**[1-3]*

CLINICAL IMPLICATION

SEROTONIN[1-3]

- 5-HT_{2A} antagonist* → High affinity → Possible increased dopamine → Helps reduce DIMDs
- SERT antagonist → Moderate affinity → Increased synaptic serotonin → Antidepressant effects

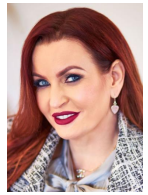
DOPAMINE[1-3]

- D_2 Pre: partial agonist Post: antagonist → High affinity → Blocks dopamine release/binding → Efficacy at lower levels of D_2 occupancy *Helps reduce DIMDs*
- D_1 partial agonist → Moderate affinity → Enhanced NMDA (glutamate) activity → May help cognition/mood

***~60 times more potent** for 5-HT_{2A} than D_2 [3]*

DIMDs: drug-induced movement disorders

1. Snyder GL et al. A review of the pharmacology and clinical profile of lumateperone for the treatment of schizophrenia. *Adv Pharmacol*. 2021;90:253-276.
2. Edinoff A et al. Lumateperone for the treatment of schizophrenia. *Psychopharmacol Bull*. 2020;50(4):32-59. 3. Greenwood J et al. Lumateperone: a novel antipsychotic for schizophrenia. *Ann Pharmacother*. 2021;55(1):98-104.



LUMATEPERONE

PHARMACOKINETICS / DOSING / INDICATIONS

PHARMACOKINETICS[1]

- **Half-life**: 13-21 hours
- **T_{max}**: 3-4 hours
- **Time to steady state:** 5 days

Fast-acting

DOSING[1]

- Once-daily dosing
- Only 42 mg (unless hepatic impairment or drug-drug interactions)

No dose adjustments / titrations

INDICATIONS[2]

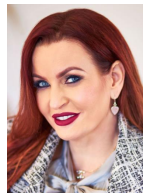
- Schizophrenia
- Bipolar depression

"Not just an antipsychotic"

BOTTOM LINE:

Fast-acting agent *without needing to titrate to an effective dose*

1. Greenwood J et al. Lumateperone: a novel antipsychotic for schizophrenia. *Ann Pharmacother*. 2021;55(1):98-104. **2.** Caplyta (lumateperone). Prescribing Information. Intra-Cellular Therapies; 2023.



LUMATEPERONE

CLINICAL EFFICACY / SAFETY

CLINICAL EFFICACY

Schizophrenia —*stick around*→ ***"The Real Schizophrenia: Using Modern Strategies to Address the Full Spectrum of the Patient and Caregiver Experience"***

Bipolar depression —*stick around*→ ***"Turning the Tide in Bipolar Depression"***

SAFETY[1,2]

- Minimal drug-induced movement disorders (DIMDs)
- Minimal adverse metabolic outcomes
- Somnolence is a common side effect →

***EXPERT EXPERIENCE*: Is somnolence persistent, or does it improve with treatment duration?**

BOTTOM LINE:

Different side effect profile *than some other atypical antipsychotics*

1. Greenwood J et al. Lumateperone: a novel antipsychotic for schizophrenia. *Ann Pharmacother*. 2021;55(1):98-104. **2.** Calabrese JR et al. Efficacy and safety of lumateperone for major depressive episodes associated with bipolar I or bipolar II disorder: a phase 3 randomized placebo-controlled trial. *Am J Psychiatry*. 2021;178(12):1098-1106.

BRANDED AGENT: CARIPRAZINE

MECHANISM OF ACTION[1,2]

Unique mechanism: *selective D_3 partial agonist*

HIGH POTENCY

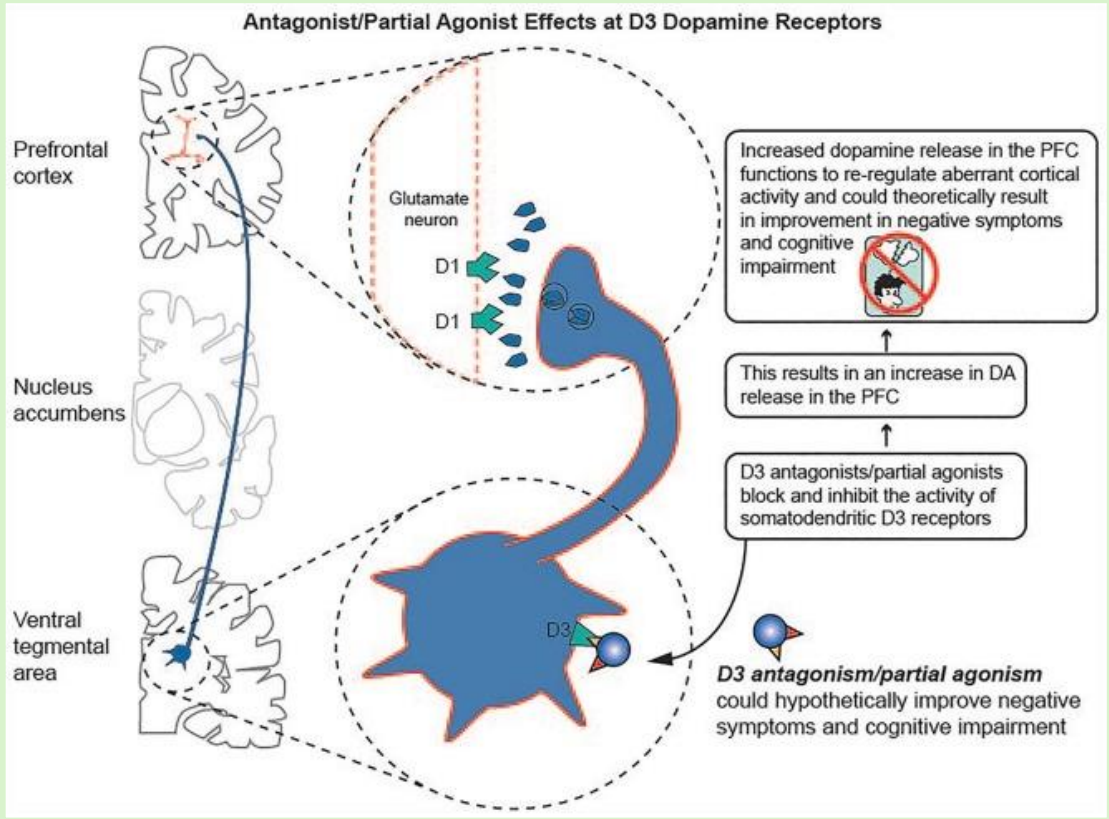
- D_3 partial agonist
  - ***10-fold greater affinity*** than D_2
  - **May improve negative symptoms, cognition, and mood**
- 5-HT_{2B} antagonist

MEDIUM POTENCY

- D_2 partial agonist
- 5-HT_{1A} partial agonist

LOW POTENCY

- 5-HT_{2A}
- H_1



From Stahl SM et al. *Ther Adv Psychopharmacol*. 2020;10:2045125320905752

1. Stahl SM et al. Cariprazine as a treatment across the bipolar I spectrum from depression to mania: mechanism of action and review of clinical data. *Ther Adv Psychopharmacol*. 2020;10:2045125320905752. **2.** Laszlovszky I et al. Cariprazine, a broad-spectrum antipsychotic for the treatment of schizophrenia: pharmacology, efficacy, and safety. *Adv Ther*. 2021;38(7):3652-3673.

CARIPRAZINE
PHARMACOKINETICS / DOSING / INDICATIONS

PHARMACOKINETICS[1-3]

- **Half-life cariprazine:** 2-4 days
- **Half-life DDCAR (active metabolite):** 1-3 weeks
- T_{max}: 3-6 hours

Fast-acting
+
Long-acting

DDCAR: didesmethyl-cariprazine

DOSING BY INDICATIONS[3]

Once-daily dosing (w/ or w/o food)
Starting dose: 1.5 mg *(may require titration)*

INDICATION	RECOMMENDED DOSES
Schizophrenia	1.5 – 6 mg daily
Bipolar depression	1.5 mg (but can go up to 3 mg) daily
Bipolar mania	3 – 6 mg daily
Adjunctive therapy for MDD	1.5 mg (but can go up to 3 mg) daily

BOTTOM LINE:

*Consider if concerned about **missing doses** (long half-life)*

1. Stahl SM et al. Cariprazine as a treatment across the bipolar I spectrum from depression to mania: mechanism of action and review of clinical data. *Ther Adv Psychopharmacol*. 2020;10:2045125320905752. **2.** Laszlovszky I et al. Cariprazine, a broad-spectrum antipsychotic for the treatment of schizophrenia: pharmacology, efficacy, and safety. *Adv Ther*. 2021;38(7):3652-3673. **3.** Vraylar (cariprazine). Prescribing information. AbbVie; 2023.

CARIPRAZINE

CLINICAL EFFICACY / SAFETY

CLINICAL EFFICACY

Schizophrenia —*stick around*→ ***"The Real Schizophrenia: Using Modern Strategies to Address the Full Spectrum of the Patient and Caregiver Experience"***

Bipolar depression —*stick around*→ ***"Turning the Tide in Bipolar Depression"***

MDD —*stick around*→ ***"The Changing Face of Major Depressive Disorder Treatment: New Paradigms and Emerging Strategies"***

SAFETY[1,2]

- Akathisia is relatively common
- Minimal metabolic complications

BOTTOM LINE:

Different side effect profile *than some other atypical antipsychotics*

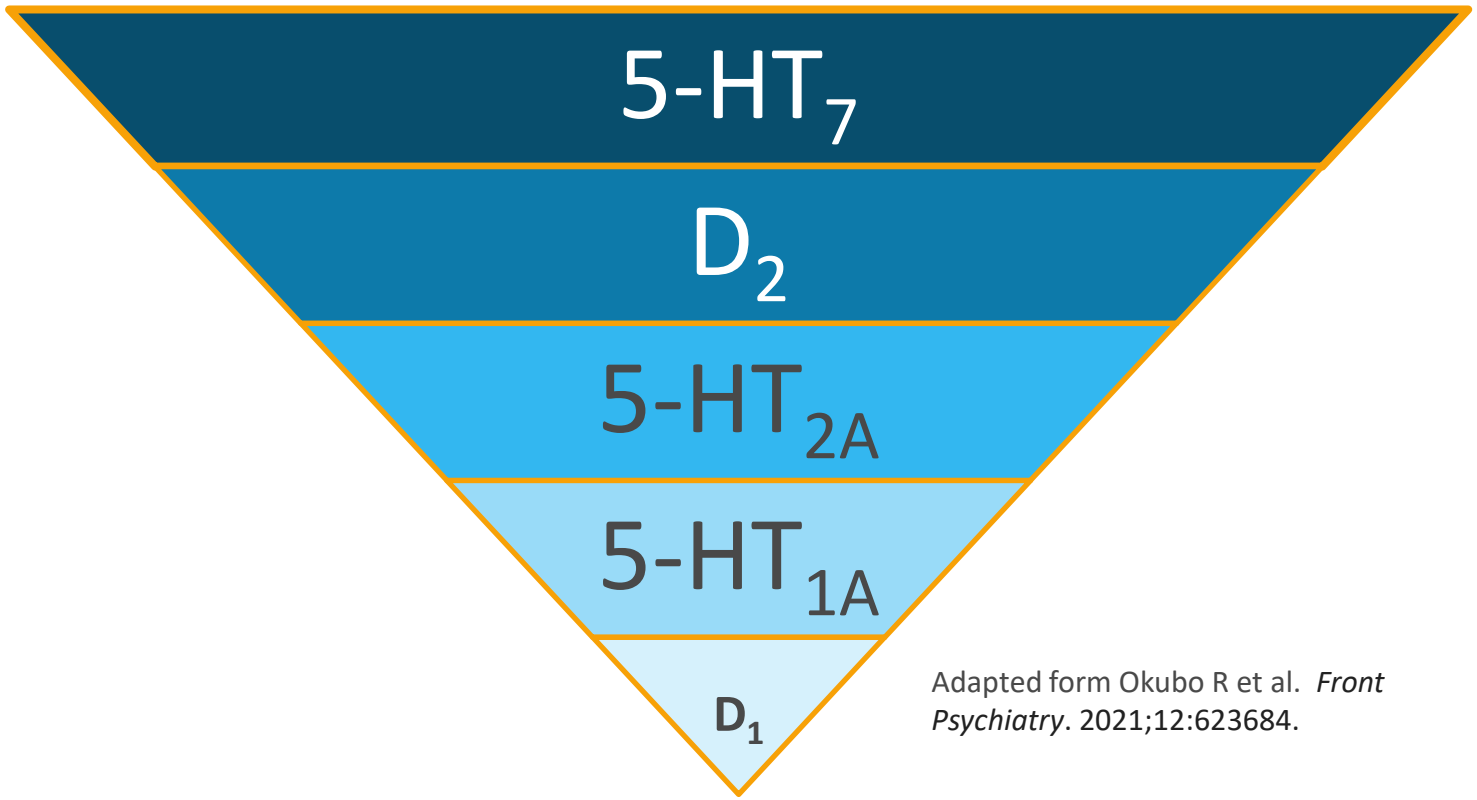
1. Tarzian M et al. Cariprazine for treating schizophrenia, mania, bipolar depression, and unipolar depression: a review of its efficacy. *Cureus*. 2023;15(5):e39309.

BRANDED AND GENERIC AGENT: LURASIDONE
MECHANISM OF ACTION

Unique mechanism: *highest affinity for 5-HT$_7$ receptor*

- **5-HT$_7$ antagonism[1,2]**
  - Highest affinity relative to other atypical antipsychotics
  - ***Helps to treat psychosis and improve cognition***
- **5-HT$_{1A}$ partial agonism[1,2]**
  - Similar mechanism / affinity as aripiprazole
- Minimal histaminergic and muscarinic activity[1,2]

RELATIVE RECEPTOR BINDING AFFINITY



Adapted form Okubo R et al. *Front Psychiatry*. 2021;12:623684.

1. Okubo R et al. Current limitations and candidate potential of 5-HT7 receptor antagonism in psychiatric pharmacotherapy. *Front Psychiatry*. 2021;12:623684.
2. Javed A et al. Practical guidance on the use of lurasidone for the treatment of adults with schizophrenia. *Neurol Ther*. 2019;8(2):215-230.

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LURASIDONE

PHARMACOKINETICS / DOSING / INDICATIONS

PHARMACOKINETICS[1]

- **Half-life**: 20-40 hours
- T_{max}: 1-3 hours
- **Time to steady state:** 7 days
- **Food considerations:** Take with food

Fast-acting
+
long-acting

DOSING BY INDICATIONS[2]

INDICATION	STARTING DOSE RECOMMENDATION	RECOMMENDED DOSAGE
Schizophrenia	40 mg	40 – 160 mg (adults and adolescents)
Bipolar depression	20 mg	20 – 120 mg (adults) 20 – 120 mg (peds)

BOTTOM LINE:

Once daily with food

1. Javed A et al. Practical guidance on the use of lurasidone for the treatment of adults with schizophrenia. *Neurol Ther*. 2019;8(2):215-230.
2. Latuda (lurasidone hydrochloride). Prescribing information. Sunovion Pharmaceuticals Inc.; 2023.

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LURASIDONE

CLINICAL EFFICACY / SAFETY

CLINICAL EFFICACY

BIPOLAR DEPRESSION[1]

Network meta-analysis comparing MADRS scores

- **Superior to aripiprazole, ziprasidone, and placebo**
- **Nonsuperior/noninferior to olanzapine and quetiapine**

SCHIZOPHRENIA[2]

Pooled analysis of 3 RCTs vs placebo

- **Reduction in PANSS total score**
- **Reduction in PANSS positive subscale**
- **Reduction in PANSS negative subscale**

SAFETY[1,2]

- Less weight gain than with some other atypical antipsychotics (e.g., olanzapine, quetiapine)
- DIMDs more common than with some other agents (e.g., olanzapine, quetiapine)
- Sedation – one of the most common side effects (if taken at nighttime may help with sleep)

BOTTOM LINE:

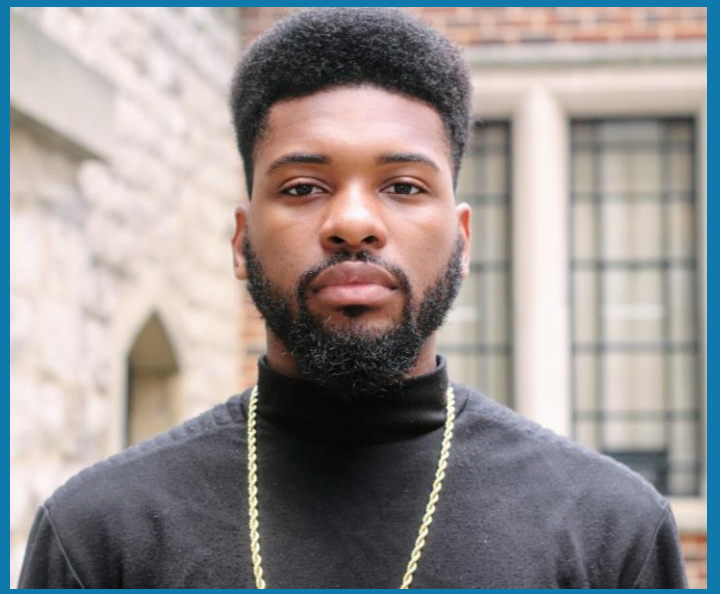
*When comparing the efficacy of lurasidone to other generic atypical antipsychotics, it is a **trade-off in side effect profiles***

1. Ostacher M et al. Lurasidone compared to other atypical antipsychotic monotherapies for bipolar depression: a systematic review and network meta-analysis. *World J Biol Psychiatry*. 2018;19(8):586-601. **2.** Calisti F et al. Efficacy and safety of lurasidone in schizophrenia: pooled analysis of European results from double-blind, placebo-controlled 6-week studies. *Int Clin Psychopharmacol*. 2022;37(5):215-222.

DIMDs: drug-induced movement disorders; **MADRS:** Montgomery–Åsberg Depression Rating Scale; **PANSS:** Positive and Negative Syndrome Scale; **RCT:** randomized controlled trial

CASE 1*
TREATMENT

RECAP:
John is a 28-year-old male with a family history of schizophrenia who presents with 2 weeks of **auditory hallucinations** and **avoidance of social interactions.** Based on his disease severity and preferences, he is a candidate for oral medication.



Which agent would you prescribe this patient?

*Fictional case.

AUDIENCE POLL

Which antipsychotic are you most likely to recommend this patient try?

a) Cariprazine
b) Lurasidone
c) Lumateperone
d) Olanzapine
e) Quetiapine
f) Ziprasidone
g) Other
h) I do not know/I am unsure.

LAB MONITORING

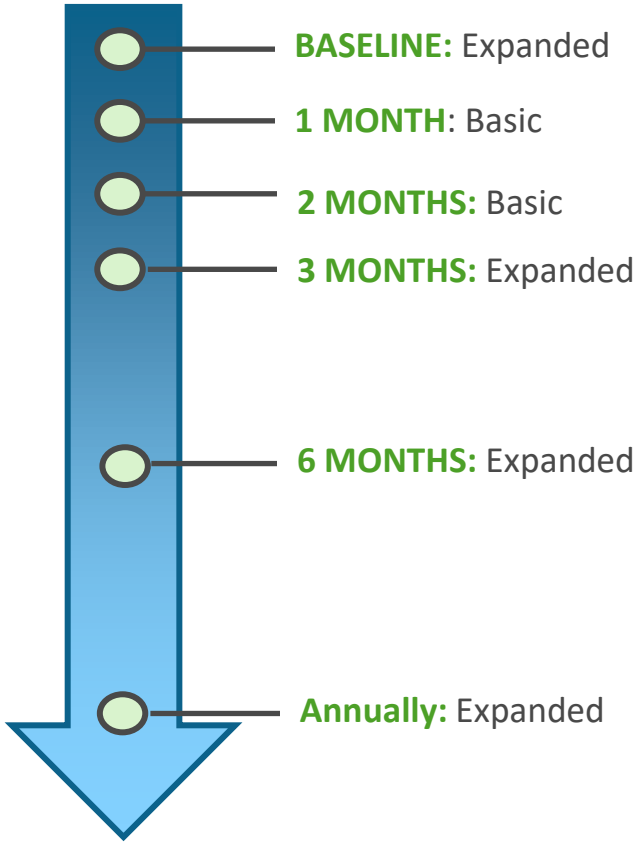
GENERAL RECOMMENDATIONS[1,2*]

BASIC MONITORING:

- Weight/BMI

EXPANDED MONITORING:

- Weight/BMI, CBC, fasting glucose or HgbA1c, fasting lipid panel (FLP), blood pressure (BP)



IMPORTANT NOTE[1]

- ❑ Certain antipsychotics may require baseline and serial EKGs
- ❑ Closely monitor for agranulocytosis for clozapine

**Please review the prescribing information guidelines and recommendations for each agent that you prescribe.*

QUESTION

How does your clinical practice compare to the monitoring recommendations listed?

1. Azfr Ali RS et al. Guidelines versus practice in screening and monitoring of cardiometabolic risks in patients taking antipsychotic medications: where do we stand?. *Gen Psychiatr*. 2021;34(4):e100561. **2.** DeJongh BM. Clinical pearls for the monitoring and treatment of antipsychotic induced metabolic syndrome. *Ment Health Clin*. 2021;11(6):311-319.

CBC: complete blood count; **HgbA1c:** hemoglobin A1c

MODULE
— 2 —

THE ROLE OF LONG-ACTING INJECTABLES

CASE 2*

INTRODUCTION

Beth is an 18-year-old female with a history of ***bipolar I disorder.*** She presents to the office with her mother due to ***severe physical aggression***. She is noted to have 4 charges pending in the court system for assault. During your interview, you learn the patient ***refuses to keep taking oral medications***. She previously had done well on risperidone but has been non-compliant with her medication for the past several weeks. Due to her behavior, Beth has been ***unable to attend school*** for the past week.

On exam, Beth has ***pressured speech*** and displays an ***irritable mood***.

WHAT IS THE NEXT BEST STEP IN TREATMENT?

*Fictionalized representation based on a real medical case.

PACE EFFICIENT

CASE 2*

PATIENT FACTORS

CLINICAL SETTING →	Outpatient
SYMPTOM SEVERITY →	Severe: Unable to attend school Physical assault
CLINICAL INDICATION →	Bipolar mania Irritability
PATIENT ADHERENCE →	Refuses oral meds History of medication non-adherence

Good candidate for long-acting injectable antipsychotics…

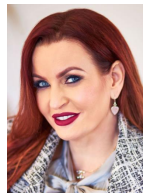
*Fictionalized representation based on a real medical case.

PACE EFFICIENT

AUDIENCE POLL

Which long-acting injectable antipsychotic (any formulation) are you most likely to recommend this patient try first?

a) Aripiprazole
b) Fluphenazine
c) Haloperidol
d) Olanzapine
e) Paliperidone
f) Risperidone
g) Other
h) I do not know/I am unsure.



LONG-ACTING INJECTABLES
ADVANTAGES

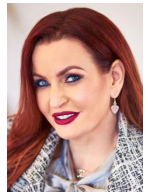
- **#1:** Help to ***reduce medication nonadherence***[1]
  - Ideal for patients with a history of poor or uncertain adherence
  - Extended release over time ***(longer half-life)***
- **#2:** May help to ***reduce hospitalization rates*** compared with oral agents for schizophrenia[2]
- **#3:** May be ***combined with oral agents***[1]

There are few atypical antipsychotics available as LAIs but many different formulations.

How do we select a specific agent/formulation?

1. Riboldi I et al. Practical guidance for the use of long-acting injectable antipsychotics in the treatment of schizophrenia. *Psychol Res Behav Manag*. 2022;15:3915-3929. **2.** Kishimoto T et al. Effectiveness of long-acting injectable vs oral antipsychotics in patients with schizophrenia: a meta-analysis of prospective and retrospective cohort studies. *Schizophr Bull*. 2018;44(3):603-619.

LAI: long-acting injectable



LONG-ACTING INJECTABLES

AVAILABLE AGENTS

ANTIPSYCHOTICS

Atypical

- ❑ Aripiprazole
- ❑ Olanzapine
- ❑ Paliperidone
- ❑ Risperidone

Typical

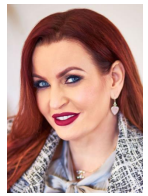
- ❑ Haloperidol
- ❑ Fluphenazine

BOTTOM LINE:

Limited head-to-head trials to suggest any given LAI is superior
Atypical LAIs, however, have more robust evidence than typical LAIs

1. Riboldi I et al. Practical guidance for the use of long-acting injectable antipsychotics in the treatment of schizophrenia. *Psychol Res Behav Manag*. 2022;15:3915-3929.

LAI: long-acting injectable



LONG-ACTING INJECTABLES: ATYPICAL

RELATIVE BINDING AFFINITIES

- **Aripiprazole** ------> D_2 partial agonist, 5-HT_{2A} partial agonist
- **Olanzapine**
- **Risperidone**
- **Paliperidone**

D_2 antagonists

RELATIVE RECEPTOR BINDING AFFINITIES[1*]

AGENTS	D_1	D_2	D_3	D_4	5-HT_{1A}	5-HT_{2A}	5-HT_{2B}	5-HT_7	H_1	M_3
ARIPIPRAZOLE		+++		+	+++	++	++++	++	++	
OLANZAPINE	++					+++	++		+++	++
RISPERIDONE	+	+++			+	++++		+++		
PALIPERIDONE						+++			++	

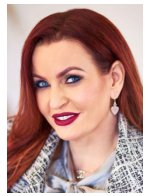
SIDE EFFECTS[2-4]

Metabolic	DIMDs	Sedation
Low	Low	Low
High	Low	Moderate
Medium	High	Moderate
Medium	High**	Low

*This is not an exhaustive list of receptor binding affinities but highlights key differences among the agents listed for select neurotransmitters.
**Debatable based on product label

1. Siafis S et al. Antipsychotic drugs: from receptor-binding profiles to metabolic side effects. *Curr Neuropharmacol*. 2018;16(8):1210-1223. 2. Stroup TS et al. Management of common adverse effects of antipsychotic medications. *World Psychiatry*. 2018;17(3):341-356. 3. Carli M et al. Atypical antipsychotics and metabolic syndrome: from molecular mechanisms to clinical differences. *Pharmaceuticals (Basel)*. 2021;14(3):238. 4. Eugene AR et al. Head-to-head comparison of sedation and somnolence among 37 antipsychotics in schizophrenia, bipolar disorder, major depression, autism spectrum disorders, delirium, and repurposed in COVID-19, infectious diseases, and oncology from the FAERS, 2004-2020. *Front Pharmacol*. 2021;12:621691.

DIMDs: drug-induced movement disorders



LONG-ACTING INJECTABLES
ARIPIPRAZOLE

Aripiprazole monohydrate

- **ABILIFY MAINTENA**[1,2] — *FDA approval: 2013*
- **ABILIFY ASIMTUFII**[3] — *FDA approval: 2023*

Aripiprazole lauroxil

- **ARISTADA**[4] — *FDA approval: 2015*

	ABILIFY MAINTENA[1,2]	ABILIFY ASIMTUFII[3]	ARISTADA[4]
FREQUENCY	q4w	q8w	q4w | q6w | q8w
T_{MAX} (DAYS)	4-7	30 – 47	41
HALF-LIFE (DAYS)	Variable: 1 – 49	???	54 – 57
BRIDGING ORAL ARIPIPRAZOLE	2 weeks		3 weeks *(One 30-mg dose with ARISTADA INITIO[5])*

How do you choose between the various aripiprazole LAI formulations?

1. Correll CU et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. *CNS Drugs*. 2021;35(1):39-59. **2.** ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension, for intramuscular use. Prescribing Information. Otsuka Pharmaceutical Co.; 2020. **3.** ASIMTUFII (aripiprazole) extended-release injectable suspension, for intramuscular use. Prescribing information. Otsuka Pharmaceutical Co.; 2023. **4.** ARISTADA (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing information. Alkermes, Inc.; 2020. **5.** ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing information. Alkermes, Inc.; 2023.

LAI: long-acting injectable; **q:** every; **w:** week

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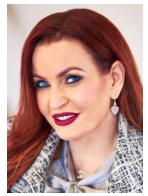

LONG-ACTING INJECTABLES
ARIPIPRAZOLE

Aripiprazole monohydrate

- **ABILIFY MAINTENA**[1,2] — *FDA approval: 2013*
- **ABILIFY ASIMTUFII**[3] — *FDA approval: 2023*

Aripiprazole lauroxil

- **ARISTADA**[4] — *FDA approval: 2015*

	ABILIFY MAINTENA[1,2]	ABILIFY ASIMTUFII[3]	ARISTADA[4]
FREQUENCY	q4w	q8w	q4w | q6w | q8w
T_{MAX} (DAYS)	4-7	30 – 47	41
HALF-LIFE (DAYS)	Variable: 1 – 49	???	54 – 57
BRIDGING ORAL ARIPIPRAZOLE	2 weeks		3 weeks *(One 30-mg dose with ARISTADA INITIO[5])*

LAI: long-acting injectable;
q: every; **w:** week

Less bridging therapy compared with ARISTADA (unless ARISTADA INITIO is used)

Can avoid oral bridging with ARISTADA INITIO but need to inject rapidly to avoid clogs!

1. Correll CU et al. Pharmacokinetic characteristics of long-acting injectable antipsychotics for schizophrenia: an overview. *CNS Drugs*. 2021;35(1):39-59. 2. ABILIFY MAINTENA (aripiprazole) extended-release injectable suspension, for intramuscular use. Prescribing Information. Otsuka Pharmaceutical Co.; 2020. 3. ASIMTUFII (aripiprazole) extended-release injectable suspension, for intramuscular use. Prescribing information. Otsuka Pharmaceutical Co.; 2023. 4. ARISTADA (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing information. Alkermes, Inc.; 2020. 5. ARISTADA INITIO (aripiprazole lauroxil) extended-release injectable suspension, for intramuscular use. Prescribing information. Alkermes, Inc.; 2023.

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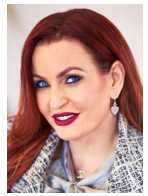

RISPERIDONE
LONG-ACTING INJECTABLES

SUBCUTANEOUS

- **PERSERIS[1]** — *FDA approval: 2018*
- **UZEDY[2]** — *FDA approval: 2023*

INTRAMUSCULAR (microspheres)

- **RISPERDAL CONSTA[3]** — *FDA approval: 2003*
- **RYKINDO[4]** — *FDA approval: 2023*

FREQUENCY	q4w	q4w | q8w	q2w	
T_{MAX} (DAYS)	10-14 (bimodal)	8-14	~30	14-17
HALF-LIFE (DAYS)	9-11	14-22	3-6	
BRIDGING ORAL RISPERIDONE	Establish tolerability first		First 21 days of therapy	First 7 days of therapy

How do you choose between the various risperidone LAI formulations?

1. PERSERIS (risperidone) extended-release injectable suspension, for subcutaneous use. Prescribing information. Indivior Inc.; 2018. **2.** UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use. Prescribing information. Teva Neuroscience, Inc.; 2023. **3.** RISPERDAL CONSTA (risperidone) long-acting injection. Prescribing information. Janssen Pharmaceuticals; 2021. **4.** RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use. Prescribing information. Luye Pharmaceuticals; 2023.

LAI: long-acting injectable; **q:** every; **w:** week

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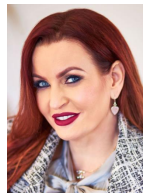


RISPERIDONE
LONG-ACTING INJECTABLES

SUBCUTANEOUS

- **PERSERIS**[1] — *FDA approval: 2018*
- **UZEDY**[2] — *FDA approval: 2023*

INTRAMUSCULAR (microspheres)

- **RISPERDAL CONSTA**[3] — *FDA approval: 2003*
- **RYKINDO**[4] — *FDA approval: 2023*

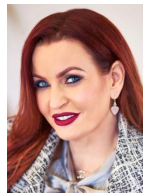
	PERSERIS[1]	UZEDY[2]	RISPERDAL CONSTA[3]	RYKINDO[4]
FREQUENCY	q4w	q4w | q8w	q2w	
T_{MAX} (DAYS)	10-14 (bimodal)	8-14	~30	14-17
HALF-LIFE (DAYS)	9-11	14-22	3-6	
BRIDGING ORAL RISPERIDONE	Establish tolerability first		First 21 days of therapy	First 7 days of therapy

LAI: long-acting injectable;
q: every; **w:** week

- **Reaches therapeutic plasma levels within 6 to 24 hours**
- **Smaller injection volume and needle gauge**
- **Pre-filled syringe that can be stored at room temp for 90 days**

Less oral supplementation. Currently only approved for gluteal injection

1. PERSERIS (risperidone) extended-release injectable suspension, for subcutaneous use. Prescribing information. Indivior Inc.; 2018. 2. UZEDY (risperidone) extended-release injectable suspension, for subcutaneous use. Prescribing information. Teva Neuroscience, Inc.; 2023. 3. RISPERDAL CONSTA (risperidone) long-acting injection. Prescribing information. Janssen Pharmaceuticals; 2021. 4. RYKINDO (risperidone) for extended-release injectable suspension, for intramuscular use. Prescribing information. Luye Pharmaceuticals; 2023.



PALIPERIDONE / OLANZAPINE

LONG-ACTING INJECTABLES

Paliperidone

- **INVEGA SUSTENNA[1]** — *FDA approval: 2009*
- **INVEGA TRINZA[2]** — *FDA approval: 2015*
- **INVEGA HAFYERA[3]** — *FDA approval: 2021*

Olanzapine

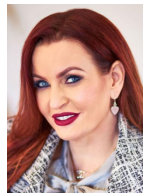
- **ZYPREXA RELPREVV[4]** — *FDA approval: 2009*

	INVEGA SUSTENNA[1]	INVEGA TRINZA[2]	INVEGA HAFYERA[3]	ZYPREXA RELPREVV[4]
FREQUENCY	q4w	q12w	q26w	q2w | q4w
T_{MAX} (DAYS)	13	30 – 33	29 – 32	~7 days
HALF-LIFE (DAYS)	25-49 days	Deltoid: 84-95 Gluteal: 118-139	148 – 159	30
BRIDGING THERAPY	Loading dose (second injection 1 week later), establish tolerability with oral	Minimum 4 months of INVEGA SUSTENNA	3 months of INVEGA TRINZA or 4 months of INVEGA SUSTENNA	Loading dose, establish tolerability with oral

How do you choose between LAI formulations for paliperidone? For olanzapine?

1. INVEGA SUSTENNA (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Prescribing information. Janssen Pharmaceuticals; 2018. **2.** INVEGA TRINZA (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Prescribing information. Janssen Pharmaceuticals; 2018. **3.** INVEGA HAFYERA (paliperidone palmitate) extended-release injectable suspension, for gluteal intramuscular use. Prescribing information. Janssen Pharmaceuticals; 2021. **4.** ZYPREXA RELPREVV (olanzapine) for extended release injectable suspension. Prescribing information. Lily Medical; 2009.

LAI: long-acting injectable; **q:** every; **w:** week



PALIPERIDONE / OLANZAPINE
LONG-ACTING INJECTABLES

Paliperidone

- **INVEGA SUSTENNA[1]** — *FDA approval: 2009*
- **INVEGA TRINZA[2]** — *FDA approval: 2015*
- **INVEGA HAFYERA[3]** — *FDA approval: 2021*

Olanzapine

- **ZYPREXA RELPREVV[4]** — *FDA approval: 2009*

	INVEGA SUSTENNA[1]	INVEGA TRINZA[2]	INVEGA HAFYERA[3]	ZYPREXA RELPREVV[4]
FREQUENCY	q4w	q12w	q26w	q2w | q4w
T_{MAX} (DAYS)	13	30 – 33	29 – 32	~7 days
HALF-LIFE (DAYS)	25-49 days	Deltoid: 84-95 Gluteal: 118-139	148 – 159	30
BRIDGING THERAPY	Loading dose (second injection 1 week later), establish tolerability with oral	Minimum 4 months of INVEGA SUSTENNA	3 months of INVEGA TRINZA or 4 months of INVEGA SUSTENNA	Loading dose, establish tolerability with oral

LAI: long-acting injectable;
q: every; **w:** week

Least frequent dosing

Greater risk of ***metabolic effects***
3-hour observation for postinjection delirium/sedation

1. INVEGA SUSTENNA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Prescribing Information. Janssen Pharmaceuticals. 2018. **2.** INVEGA TRINZA® (paliperidone palmitate) extended-release injectable suspension, for intramuscular use. Prescribing Information. Janssen Pharmacueticals. 2018. **3.** INVEGA HAFYERA™ (paliperidone palmitate) extended-release injectable suspension, for gluteal intramuscular use. Prescribing Information. Janssen Pharmaceuticals. 2021. **4.** ZYPREXA RELPREVV (olanzapine) For Extended Release Injectable Suspension Prescribing Information. Lily Medical. 2009.

CASE 2*
TREATMENT

RECAP:

Beth is a 16-year-old female with a history of ***BD-I.*** She presents due to ***increased aggression*** leading to multiple cases of assault. She previously had been taking risperidone but, due to nonadherence, has not been taking her medication.

TREATMENT CONSIDERATIONS:

- Already ***established oral tolerability of risperidone***
- Looking to avoid significant oral antipsychotic overlap

TREATMENT SELECTION:

- ❑ On day 1: Administer loading dose of INVEGA SUSTENNA 234 mg
- ❑ On day 8: Administer INVEGA SUSTENNA 117 mg

*Fictionalized representation based on a real medical case.

MODULE — 3 —

CREATING A CROSS-TITRATION PLAN: THE ART OF SWITCHING AND STOPPING ANTIPSYCHOTIC MEDICATIONS

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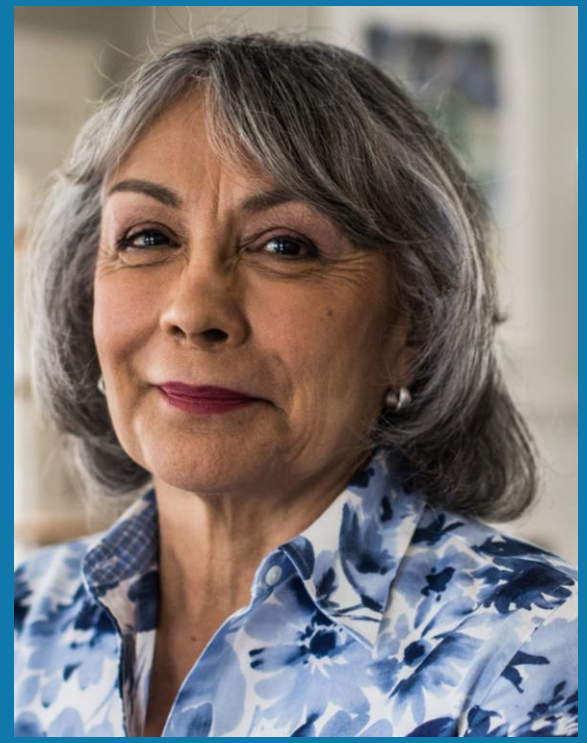
CASE 3*
INTRODUCTION

Sarah is a 62-year-old female with a history of ***bipolar I disorder*** who presents with ***rapid cycling moods*** alternating from suicidal ideation to agitation. She is currently taking the following medications:

- ❑ Quetiapine 200 mg
- ❑ Lithium 300 mg TID
- ❑ Trazodone 300 mg
- ❑ Sertraline 200 mg
- ❑ Clonazepam 2 mg PRN



How do we approach an antipsychotic switch in this patient?

*Fictionalized representation based on a real medical case.

PACE EFFICIENT

CHANGING ANTIPSYCHOTIC REGIMEN
TREATMENT STRATEGIES

OPTION #1: DIRECT SWITCH[1,2]

First antipsychotic stopped, next started the following day

- Requires ***careful treatment setting***
- Risk of ***drug-drug interactions***
- Risk of ***discontinuation syndromes***

NOT OPTIMAL (primarily considered for inpatient settings). However, patient may do it on their own

Limited clinical use

Not appropriate for this patient

1. Liao X et al. A review of switching strategies for patients with schizophrenia comorbid with metabolic syndrome or metabolic abnormalities. *Neuropsychiatr Dis Treat*. 2021;17:453-469. **2.** Keks N et al. Stopping and switching antipsychotic drugs. *Aust Prescr*. 2019;42(5):152-157.

CHANGING ANTIPSYCHOTIC REGIMEN
TREATMENT STRATEGIES

OPTION #2: CROSS-TITRATION[1,2]

Reduce first antipsychotic WHILE introducing second agent

Most common practice

OPTION #3: SEQUENTIAL TITRATION[1,2]

Increase second antipsychotic FIRST, then gradually reduce first

Minimizes risk of relapse

Based on patient severity, favor cross-titration to achieve therapeutic effect with new agent

1. Liao X et al. A review of switching strategies for patients with schizophrenia comorbid with metabolic syndrome or metabolic abnormalities. *Neuropsychiatr Dis Treat*. 2021;17:453-469. **2.** Keks N et al. Stopping and switching antipsychotic drugs. *Aust Prescr*. 2019;42(5):152-157.

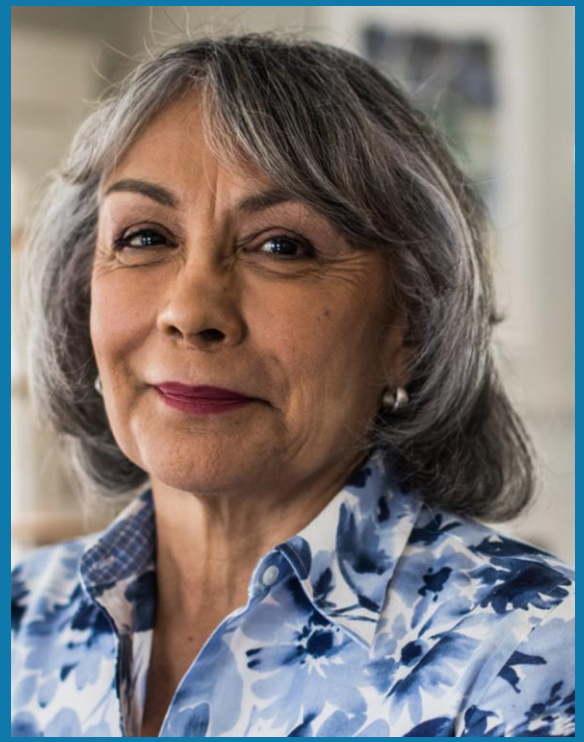
CASE 3*
TREATMENT

RECAP:

Sarah is a 62-year-old female with a history of ***bipolar I disorder*** who presents with ***rapid cycling moods,*** alternating from suicidal ideation to agitation. She is currently taking the following medications:

MEDICATION	PLAN
Quetiapine 200 mg	**WEAN**
Cariprazine	**CROSS-TITRATE w/ quetiapine**
Sertraline 200 mg	**CONSIDER WEANING as tolerated in the future**
Clonazepam 2 mg PRN	
Lithium 300 mg TID	
Trazodone 300 mg	

What labs would you consider obtaining?



*Fictionalized representation based on a real medical case.


Q&A