REAL PSYCHIATRY

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

THE REAL SCHIZOPHRENIA

USING MODERN STRATEGIES TO ADDRESS THE FULL SPECTRUM OF THE PATIENT AND CAREGIVER EXPERIENCE

— JANUARY 13, 2024 —

Program Overview

CHALLENGES

- **Schizophrenia (SZ)** has a tremendous disease burden on both the individual and healthcare system. With no pathognomonic presentation, the multiple phenotypes of SZ make it difficult to identify and treat the full spectrum of disease.
- Many current antipsychotics primarily exert their effect through D_2 postsynaptic antagonism leading to **unfavorable side effect profiles and poor adherence**.
- **Most available agents also primarily impact positive symptoms** such as hallucinations, leaving disabling negative and neurocognitive impairments ineffectively treated.

OPPORTUNITIES

- **OBJECTIVE:** To guide clinicians through identification of the full clinical spectrum of SZ and provide the most up-to-date information for new and emerging treatment strategies.
  - This activity will utilize expert-led case-based discussion to highlight challenges in the management of negative and neurocognitive impairments in SZ and the potential role of new therapies in targeting these symptoms.

Presenting Faculty

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

Psychiatric Nurse Practitioner

Seaside Behavioral Health

Virginia Beach, VA

Amber Hoberg, MSN, PMHNP-BC, APRN

Psychiatric Nurse Practitioner

Morning Star Family Medicine

Floresville, TX

Bobbi Jo Durst, MSN, PMHNP-BC, APNP

Psychiatric Nurse Practitioner

Alay Health Team

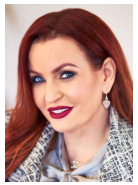
Pewaukee, WI

MODULE
— 1 —

THE HIDDEN SIDE OF SCHIZOPHRENIA: THE ROLE OF COGNITIVE AND NEGATIVE SYMPTOMS

PACE Providers for Advancing Clinical Education

EFFICIENT



SCHIZOPHRENIA
MORBIDITY / MORTALITY

*Schizophrenia (SZ) has a **high morbidity and mortality**[1]*

MORBIDITY

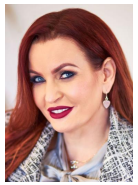
- Physical comorbidities
- Antipsychotic side effects
- Limited therapeutic efficacy for certain disease manifestations
- Poor quality of life

MORTALITY

- **Life expectancy is ~15 years less** than the general population[2]
- **>9.5-fold increased risk of suicide**
- ~2-5 times the risk of other serious health conditions (endocrine, cardiovascular, cerebrovascular)[3]

1. Keepers GA et al. The American Psychiatric Association Practice Guideline for the Treatment of Patients With Schizophrenia. *Am J Psychiatry*. 2020;177(9):868-872. **2.** Smeland OB et al. The polygenic architecture of schizophrenia - rethinking pathogenesis and nosology. *Nat Rev Neurol*. 2020;16(7):366-379. **3.** Correll CU et al. Mortality in people with schizophrenia: a systematic review and meta-analysis of relative risk and aggravating or attenuating factors. *World Psychiatry*. 2022;21(2):248-271

SCHIZOPHRENIA
HEALTHCARE / SOCIETAL BURDEN



*Total estimated economic burden **doubled** between 2013 and 2019*

2019 estimated economic burden: $343.2 billion

DIRECT HEALTH CARE COSTS
$62.3 billion

- **Inpatient** $30.2 billion
- **Outpatient** $12.9 billion
- **Pharmacy** $12.1 billion
- **Emergency department** $5.6 billion

DIRECT NON-HEALTH CARE COSTS
$35.0 billion

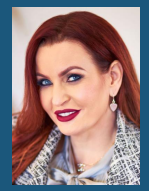
- **Law enforcement** $26.1 billion
- **SSI and SSDI** $6.5 billion
- **Homeless shelters** $2.1 billion

INDIRECT COSTS
$251.9 billion

- **Caregiving** $112.3 billion
- **Premature mortality** $77.9 billion
- **Unemployment** $54.2 billion
- **Productivity loss** $7.4 billion

SSI: Supplemental Security income; **SSDI:** Social Security Disability income

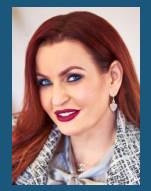
1. Kadakia A et al. The Economic Burden of Schizophrenia in the United States. *J Clin Psychiatry*. 2022;83(6):22m14458.



AUDIENCE POLL

Which of the following is **TRUE** regarding the presentation of patients with schizophrenia?

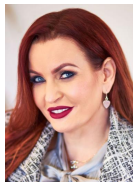
a) May present initially with depressive symptoms
b) Absence of a prodromal phase
c) Positive symptoms are more challenging to treat than negative symptoms.
d) Cognitive impairment is a late clinical manifestation of SZ.
e) I do not know/I am unsure.



AUDIENCE POLL

Which of the following is **TRUE** regarding the presentation of patients with schizophrenia?

a) May present initially with depressive symptoms
b) Absence of a prodromal phase
c) Positive symptoms are more challenging to treat than negative symptoms.
d) Cognitive impairment is a late clinical manifestation of SZ.
e) I do not know/I am unsure.

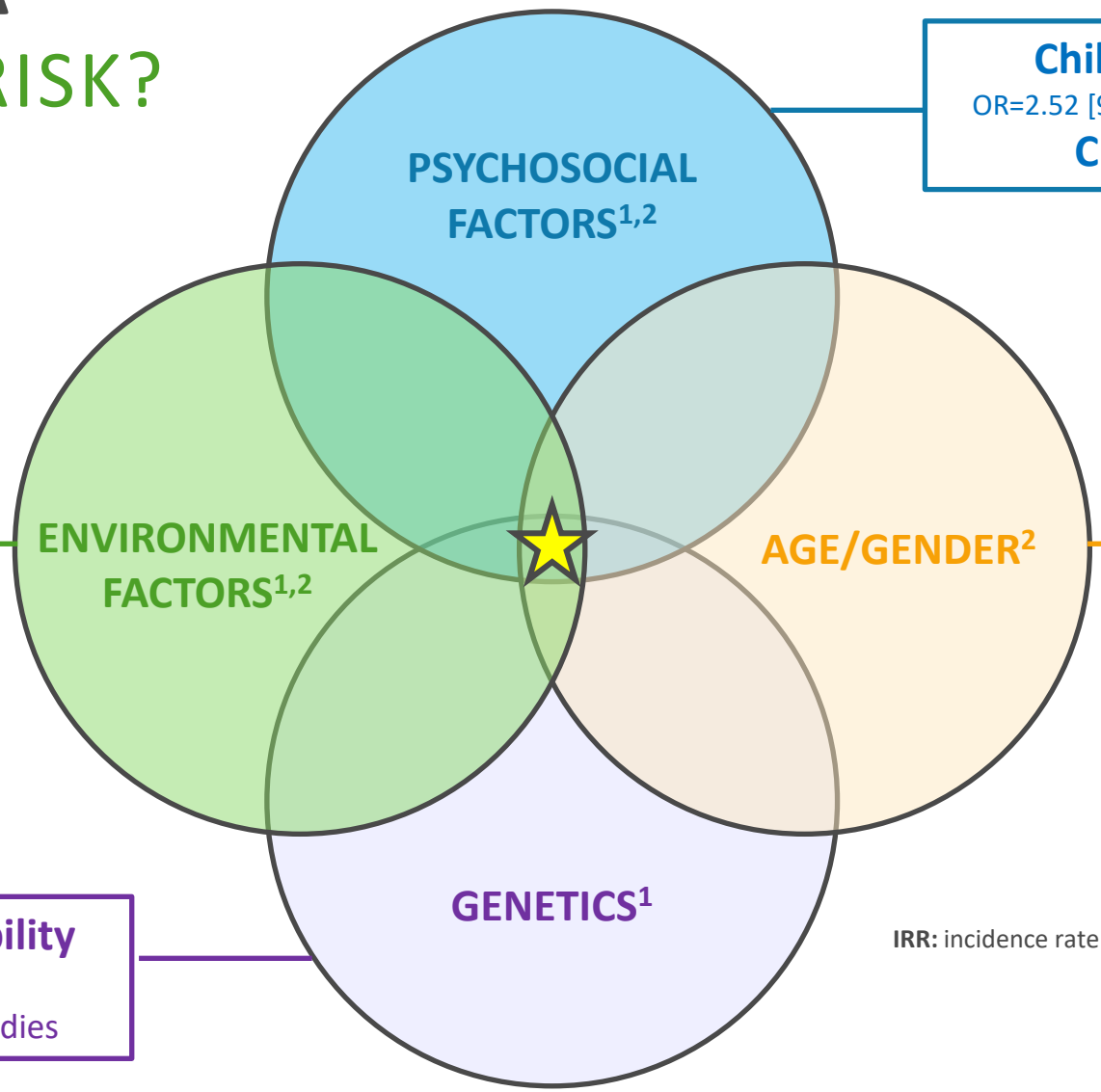


SCHIZOPHRENIA

WHO IS MOST AT RISK?

Childhood trauma
OR=2.52 [95% CI, 1.27-5.02]; *P*=0.009
Chronic stress

Obstetric complications
OR=1.84 [95% CI, 1.25-2.70]; *P*=0.002
Urban living
OR=2.19 [95% CI, 1.55-3.09]; *P*<0.001
Immigration (1st generation)
IRR=2.10 [95% CI, 1.72-2.56]; *P*<0.001
Heavy cannabis use
OR=5.17 [95% CI, 3.64-7.36]; *P*<0.001
Tobacco use
RR=2.19 [95% CI,1.36-3.53]; *P*=0.001



- **Younger age**
  (age 20-29 years)
- **Male**

Upwards of 80% **heritability**
- Twin-twin studies
- Genome-wide association studies

IRR: incidence rate ratio; **OR:** odds ratio; **RR:** relative risk

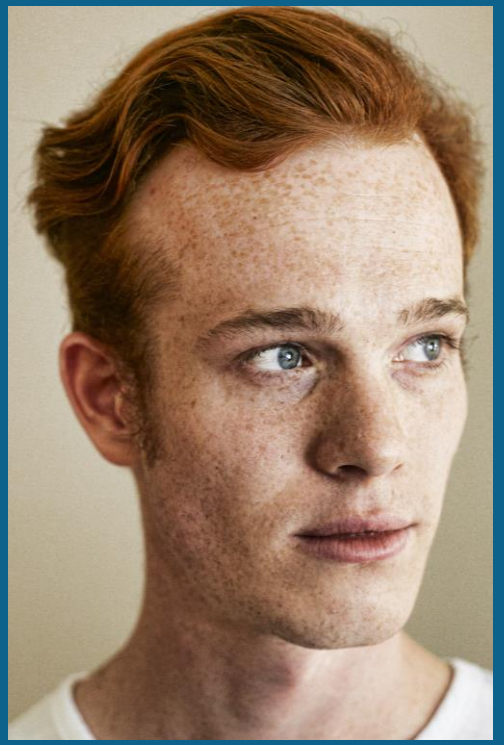
1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. **2.** Radua J et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry*. 2018;17(1):49-66.

CASE 1*

INTRODUCTION

Alex is a 23-year-old male presenting with auditory hallucinations. He was previously a high-achieving student majoring in computer science for the first 3 years. His grades, however, gradually declined during his final year. Both parents note that Alex did not have friends in college. When asked about his grades, Alex states that he frequently forgot homework assignments and had difficulty staying on task.

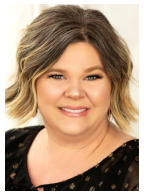
Upon exam, Alex is noted to have a flat affect with limited facial expressions.



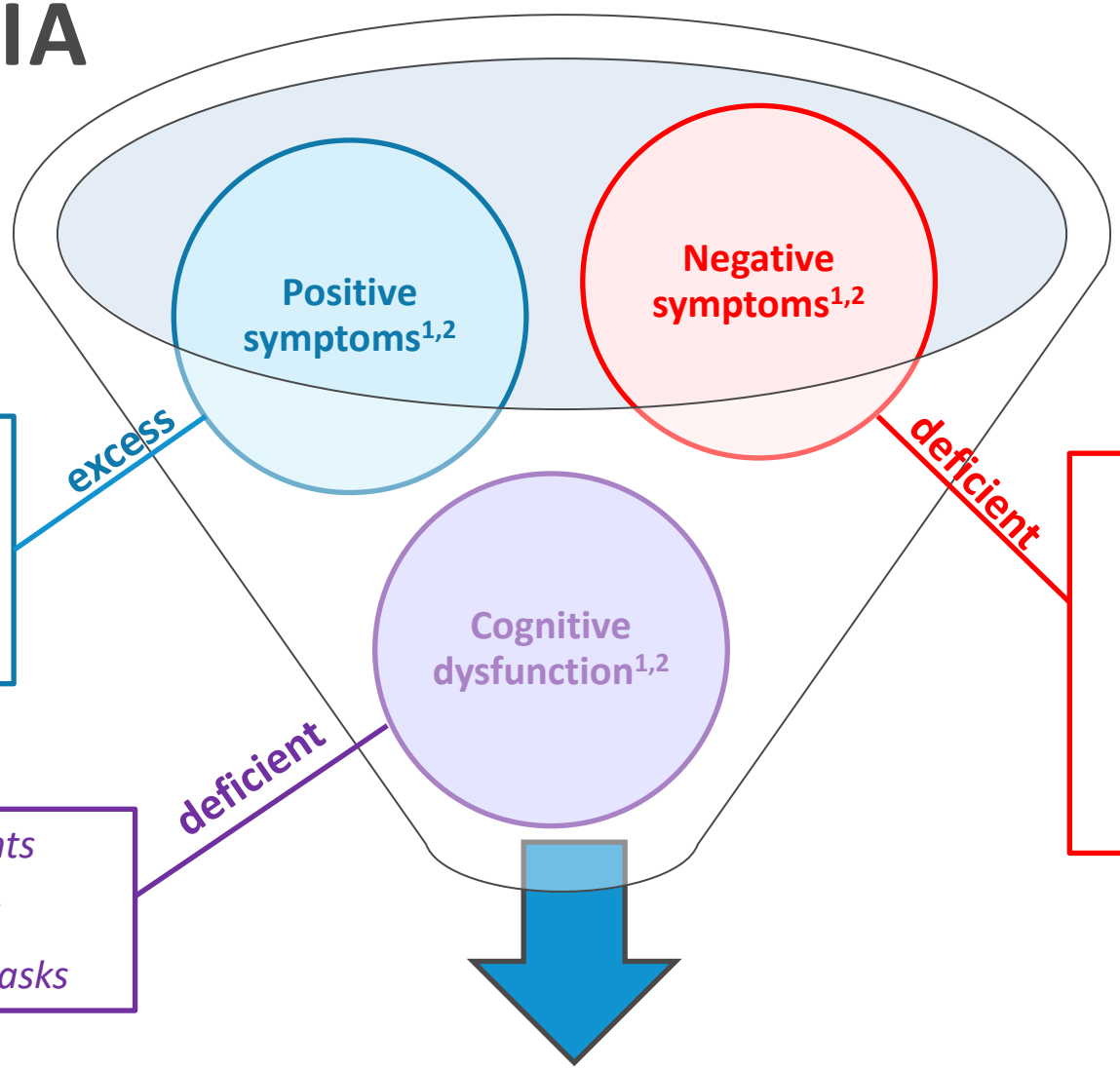
HOW CAN WE CATEGORIZE THIS PATIENT'S SYMPTOMATOLOGY?

*Fictional case.

PACE EFFICIENT



SCHIZOPHRENIA
CLINICAL SPECTRUM



No single pathognomonic presentation of schizophrenia

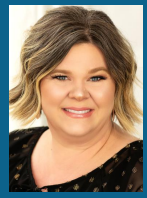
1. Luvsannyam E et al. Neurobiology of Schizophrenia: A Comprehensive Review. *Cureus*. 2022;14(4):e23959. 2. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210.

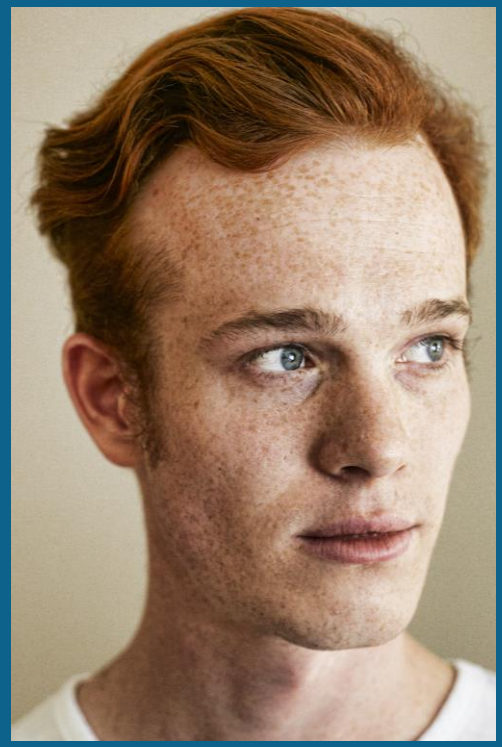
CASE 1*

CLINICAL SPECTRUM

Alex is a 23-year-old male presenting with **auditory hallucinations**. He was previously a high-achieving student majoring in computer science for the first 3 years. His grades, however, gradually declined during his final year. Both parents note that Alex **did not have friends in college**. When asked about his grades, Alex states that he frequently **forgot homework assignments** and had **difficulty staying on task**.

On exam, Alex is noted to have a **flat affect** with **limited facial expressions**.



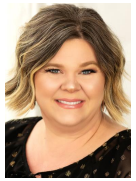


POSITIVE SYMPTOMS

NEGATIVE SYMPTOMS

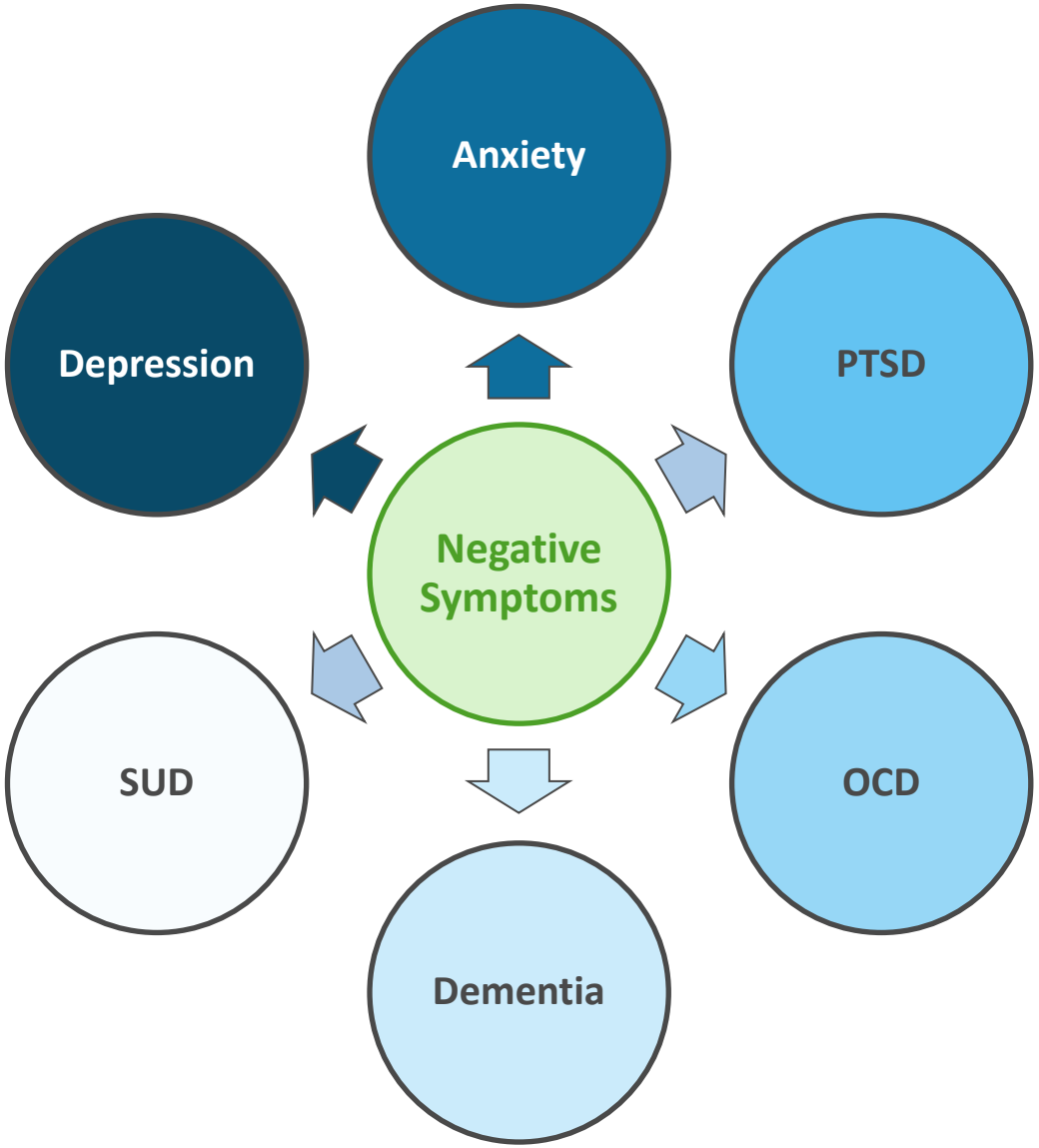
COGNITIVE SYMPTOMS

*Fictional case.



NEGATIVE SYMPTOMS

- **High prevalence**: Up to 60% of patients have prominent or predominant negative symptoms
- **Higher burden of disease (disability)** compared with positive symptoms
  - Linked to worse functional outcomes
- **Difficult to recognize** due to
  - Lack of patient insight
  - Overlapping symptoms with other psychiatric conditions



Adapted from Correll CU et al. *Neuropsychiatr Dis Treat*. 2020;16:519-534

1. Correll CU et al. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatr Dis Treat*. 2020;16:519-534.

OCD: obsessive-compulsive disorder; **PTSD:** posttraumatic stress disorder; **SUD:** substance use disorder

NEGATIVE SYMPTOMS
RECOGNITION

NEGATIVE SYMPTOM	CLINICAL CLUES
BLUNTED AFFECT	Decreased facial/vocal expressions Poor eye contact Minimal body gestures
ALOGIA	Short/monosyllabic answers Uses few words/avoids conversations
ANHEDONIA	Few hobbies Lack of interest in sexual activity Difficulty anticipating future pleasure
ASOCIALITY	Few friends/minimal social interaction Lack of interest in relationships
AVOLITION	Poor grooming/hygiene Less involvement with work/school Emotional withdrawal

1. Correll CU et al. Negative Symptoms in Schizophrenia: A Review and Clinical Guide for Recognition, Assessment, and Treatment. *Neuropsychiatr Dis Treat*. 2020;16:519-534.

COGNITIVE DYSFUNCTION

Cognitive dysfunction occurs in up to 80% of people with schizophrenia[1]

- **Contributes to poor outcomes**[2]
  - Unemployment
  - Inability to live independently
- **Difficult to recognize**[2] due to
  - Lack of patient insight
  - Clinical overlap with other psychiatric conditions (e.g., bipolar disorder)
  - Weak correlation between subjective reports and objective cognitive measures

How do you elicit symptoms of impaired cognition from your patient?

Do you formally assess for cognitive impairment in your patients?

1. Carbon M et al. Thinking and acting beyond the positive: the role of the cognitive and negative symptoms in schizophrenia. *CNS Spectr*. 2014;19 Suppl 1:38-53. **2.** McCutcheon RA et al. Cognitive impairment in schizophrenia: aetiology, pathophysiology, and treatment. *Mol Psychiatry*. 2023;28(5):1902-1918.

CASE 1*

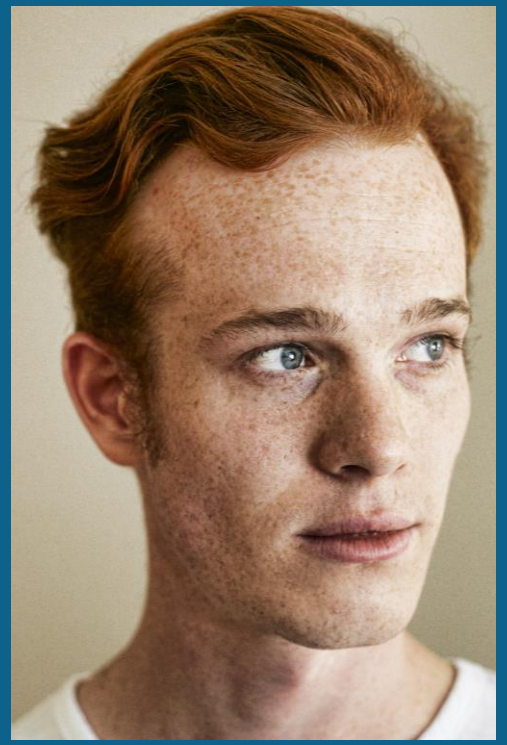
CLINICAL SPECTRUM

ADDITIONAL HISTORY:

Alex reports that his **auditory hallucinations** have been ongoing for the **last 3 months**. Upon further questioning, Alex reveals that he **stopped talking to all his friends 2 years ago**. He cannot recall when his **memory issues** began but notes that it has been for **at least 2 years**.

When speaking to Alex's parents privately, they report that Alex had **"paranoid" periods** in high school where he thought his computer was being monitored. They note that Alex has distanced himself from the family. He is currently living at home due to concerns that he cannot live independently.

What elements in a patient's history help raise early clinical suspicion for SZ?



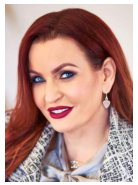
POSITIVE SYMPTOMS

NEGATIVE SYMPTOMS

COGNITIVE SYMPTOMS

*Fictional case.

PACE EFFICIENT



SCHIZOPHRENIA
DIAGNOSIS

- **DSM-5 Diagnostic Criteria** encapsulate many clinical manifestations
  - Elements of other psychiatric disease may present alongside schizophrenia (depression, mania, psychosis)
  - ***Timeline of predominant symptomatology*** is critical to help differentiate SZ from schizoaffective and bipolar disorder

DSM-5 Diagnostic Criteria		
Criteria A	**Criteria B**	**Criteria C**
CLINICAL PRESENTATION	**FUNCTIONAL IMPAIRMENT**	**DURATION**
≥2 following: Delusions Hallucinations Disorganized speech Grossly disorganized or catatonic behavior Negative symptoms	Work Interpersonal relationships Self-care	Continuous symptoms for ≥6 months

1. American Psychiatric Association. Diagnostic and statistical manual of mental disorders. (DSM-5). 5th ed. *American Psychiatric Publishing*. 2022

CASE 1*
CLINICAL SPECTRUM

RECAP:

Positive symptoms
(hallucinations, paranoia) → **Several years**

Negative symptoms
(social withdrawal, blunted affect) → **2 years**

Cognitive symptoms
(memory/attention) → **2 years**

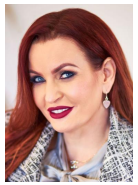
Functional impairment
(social) → **1 year**

Alex is diagnosed with SZ

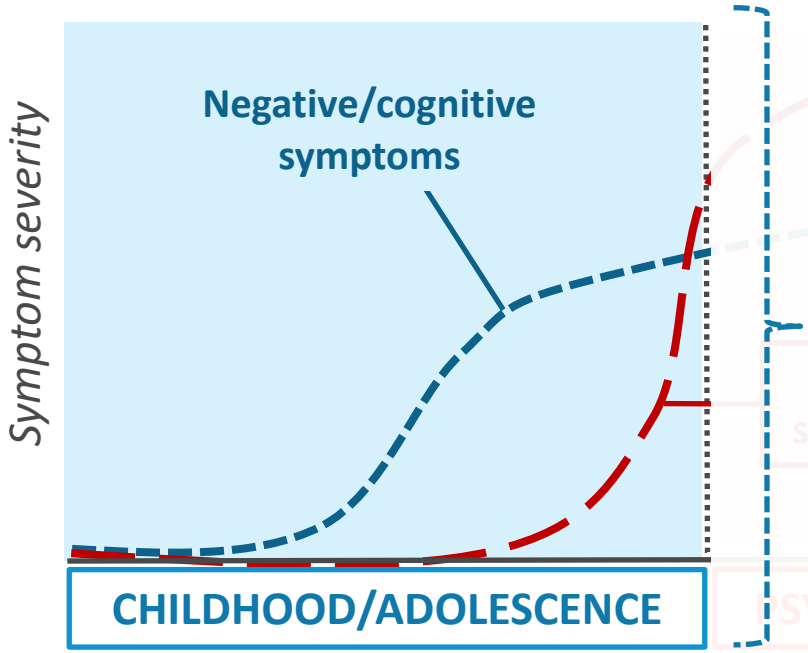
DOES ALEX'S CLINICAL PRESENTATION FOLLOW THE TYPICAL CLINICAL COURSE OF SZ?

*Fictional case.

PACE EFFICIENT



SCHIZOPHRENIA
CLINICAL COURSE

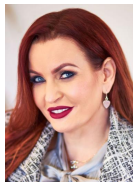


PSYCHOSIS PRODROME[1,2]

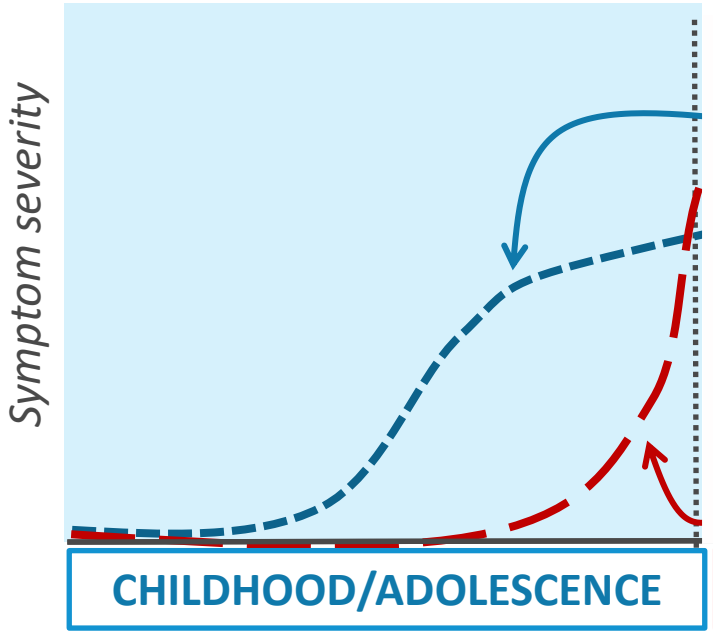
- Prodrome may last for months or years
- Subtle/gradual changes in behavior, personality, and functioning
- **Negative / cognitive symptoms** are more common than positive symptoms early on

Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. **2.** Faden J et al. Schizophrenia: One Name, Many Different Manifestations. *Med Clin North Am*. 2023;107(1):61-72.



SCHIZOPHRENIA
CLINICAL COURSE



NEGATIVE/COGNITIVE SYMPTOMS

Alex demonstrated several years of social withdrawal and cognitive impairment ***significantly impacting his social functioning.***

POSITIVE SYMPTOMS

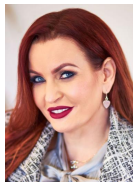
Alex demonstrated intermittent periods of paranoid thinking that ***did not interfere with his daily functioning.***

*Fictional case.

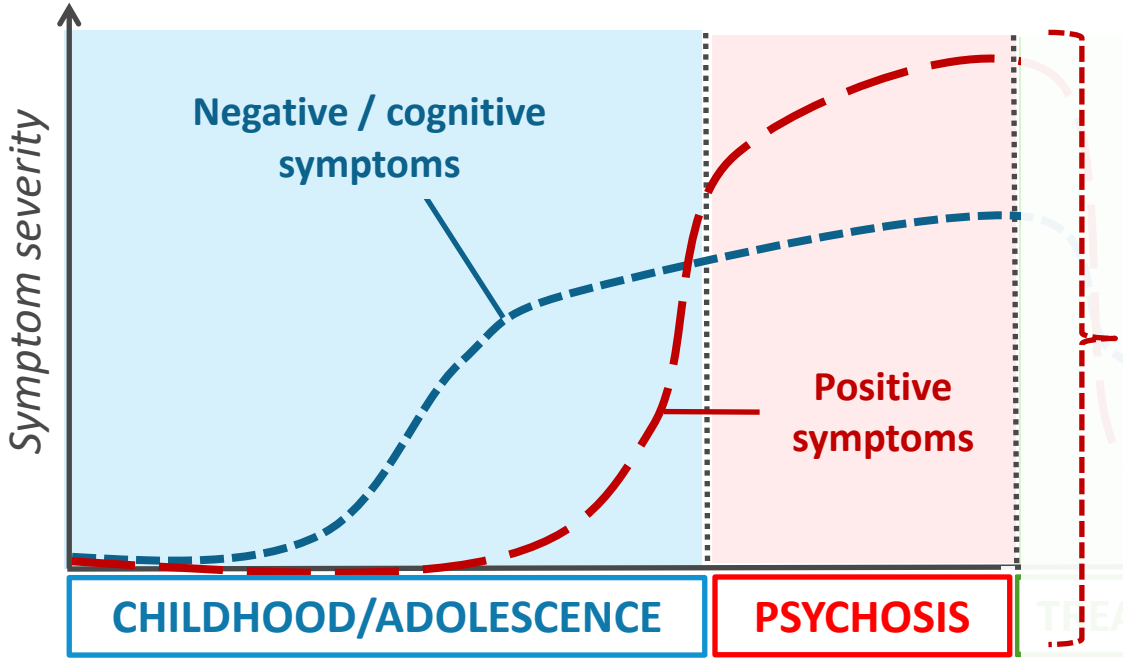
Adapted form McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210.

PACE Partners for Advancing Clinical Education EFFICIENT



SCHIZOPHRENIA
CLINICAL COURSE



Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

★ FIRST EPISODE OF PSYCHOSIS[1-3]

- Attributed to **dopamine dysregulation**
- **Generally, most apparent** schizophrenia symptoms
- Often preceded by negative and cognitive symptoms
- May occur abruptly even in high-functioning individuals
- Early age of onset is a **poor prognostic indicator**

★ *Patient was not identified until these symptoms developed*

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. **2.** Faden J et al. Schizophrenia: One Name, Many Different Manifestations. *Med Clin North Am*. 2023;107(1):61-72. **3.** Immonen J et al. Age at onset and the outcomes of schizophrenia: A systematic review and meta-analysis. *Early Interv Psychiatry*. 2017;11(6):453-460.

SCHIZOPHRENIA

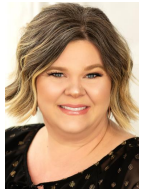
NEW DOPAMINE STORY[1,2]

- Multiple pathways contribute to the clinical spectrum of SZ
  - **Mesocortical** (hypoactive)
  - **Mesolimbic** (hypoactive)
  - **Nigrostriatal pathway #1** (hyperactive)

OVERALL GOAL OF TREATMENT:

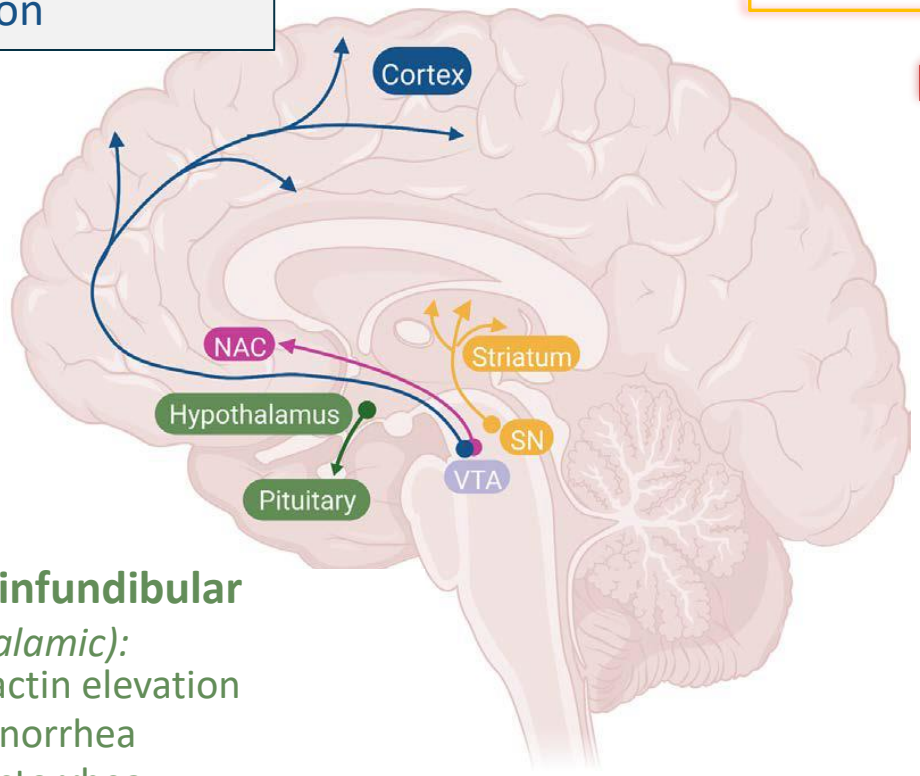
- Reduce hyperactive pathways
- Increase hypoactive pathways

DOPAMINERGIC PATHWAYS



Mesocortical:
- Negative symptoms
- Cognitive impairment
- Depression

Nigrostriatal #1
(associative striatum):
Psychosis



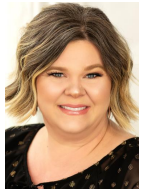
Mesolimbic
(limbic striatum):
Negative symptoms

Nigrostriatal #2
(sensorimotor striatum):
- Dystonia
- Akinesia
- Rigidity
- Tremor
- Dyskinesia

Tuberoinfundibular
(hypothalamic):
- Prolactin elevation
- Amenorrhea
- Galactorrhea
- Sexual dysfunction

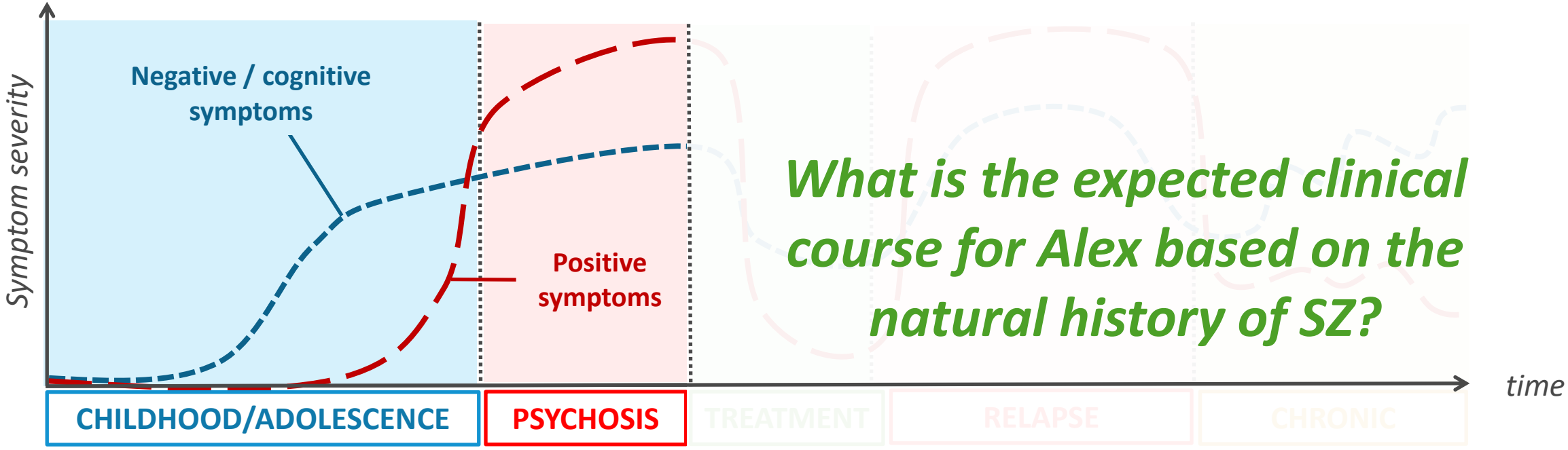
From Xu H et al. *Transl Psychiatry*. 2022;12(1):464

1. Correll CU et al. Emerging Treatments in Schizophrenia. *J Clin Psychiatry*. 2022;83(1):SU21024IP1. 2. Xu H et al. The interplay of dopamine metabolism abnormalities and mitochondrial defects in the pathogenesis of schizophrenia. *Transl Psychiatry*. 2022;12(1):464



SCHIZOPHRENIA

CLINICAL COURSE

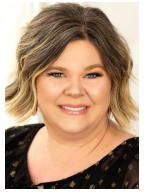


What is the expected clinical course for Alex based on the natural history of SZ?

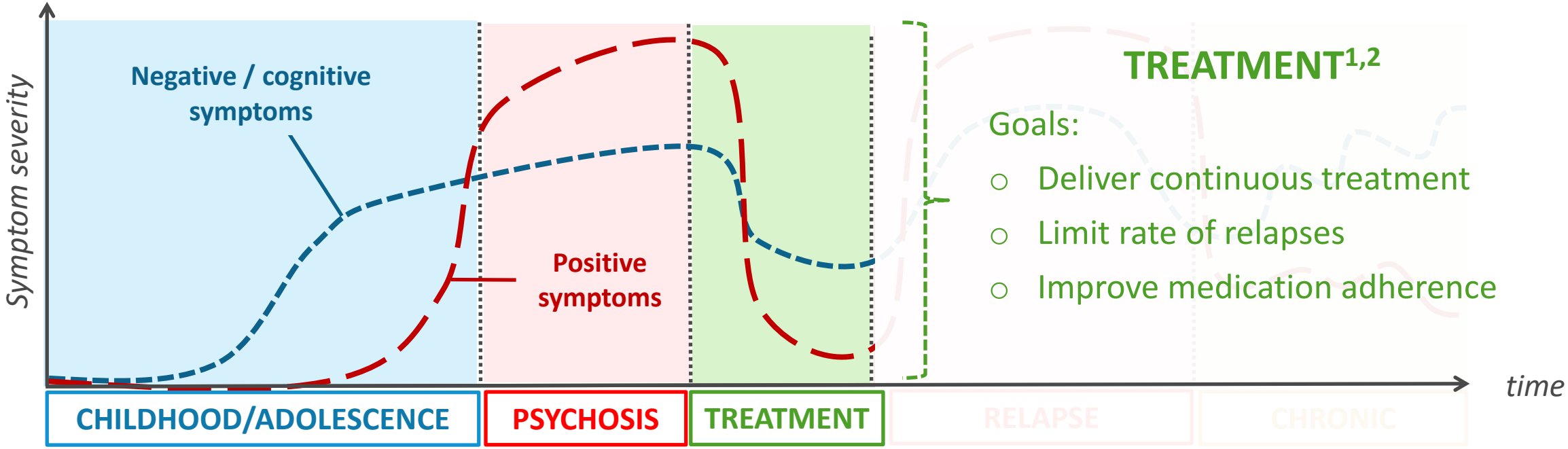
Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210.

PACE Partners for Advancing Clinical Education EFFICIENT



SCHIZOPHRENIA
CLINICAL COURSE



TREATMENT[1,2]

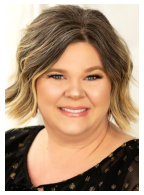
Goals:

- Deliver continuous treatment
- Limit rate of relapses
- Improve medication adherence

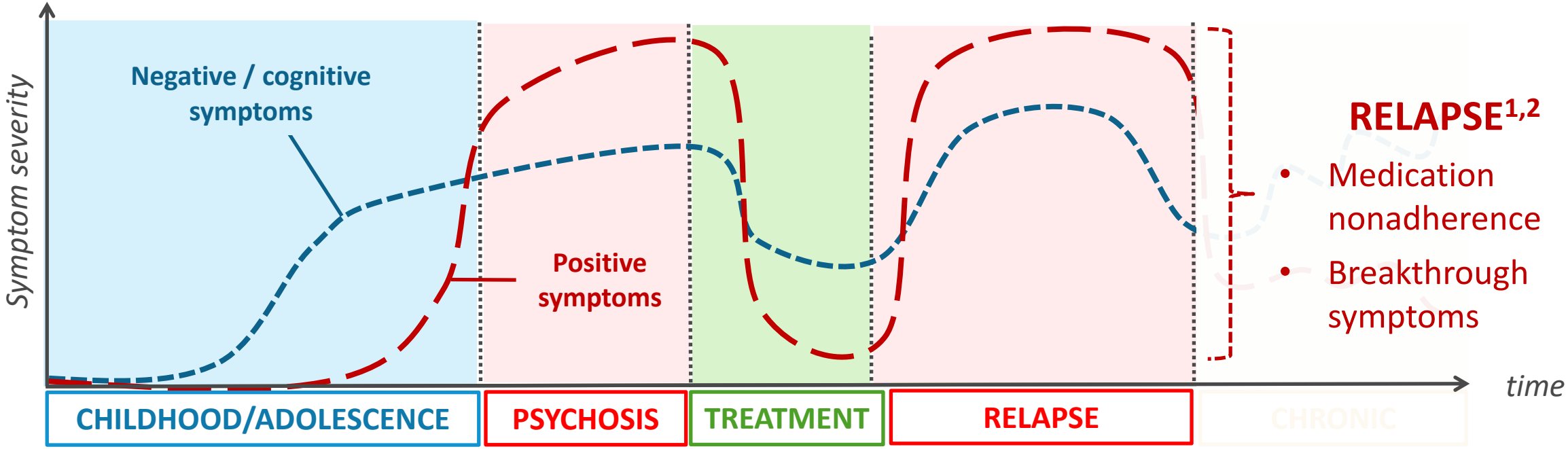
Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. **2.** Faden J et al. Schizophrenia: One Name, Many Different Manifestations. *Med Clin North Am*. 2023;107(1):61-72.

PACE Partners for Advancing Clinical Education EFFICIENT



SCHIZOPHRENIA
CLINICAL COURSE



RELAPSE[1,2]

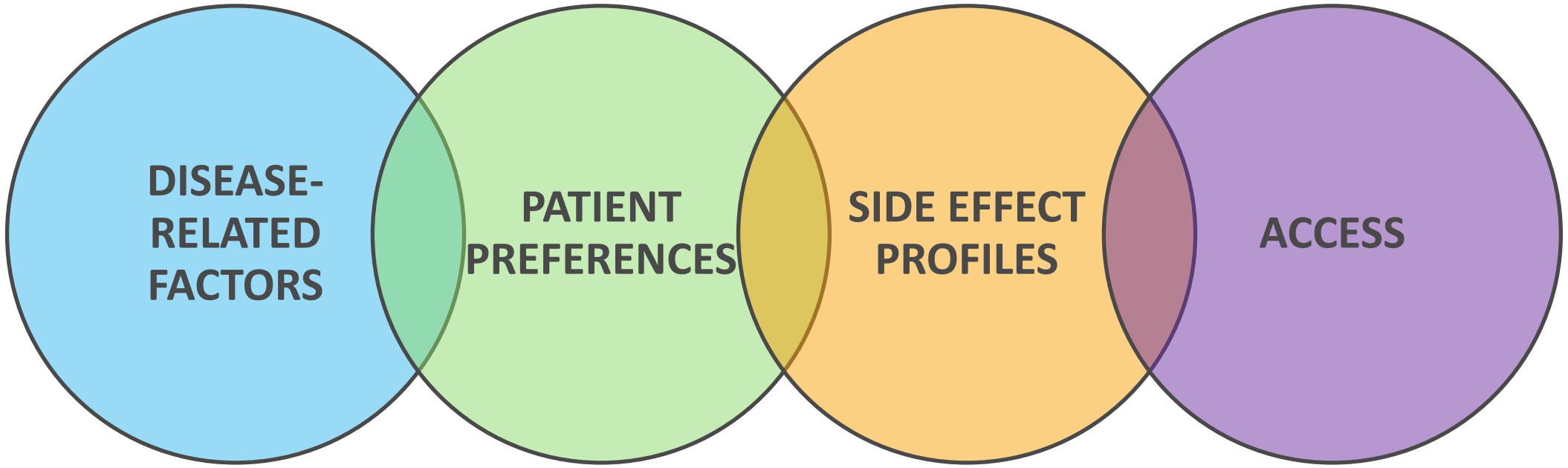
- Medication nonadherence
- Breakthrough symptoms

Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. **2.** Faden J et al. Schizophrenia: One Name, Many Different Manifestations. *Med Clin North Am*. 2023;107(1):61-72.

SCHIZOPHRENIA
NONADHERENCE

Medication nonadherence to antipsychotics *is a major challenge for schizophrenia management*



- *Poor insight*
- *Poor social functioning*
- *Negative attitudes toward medications*
- *Metabolic dysfunction*
- *Movement disorders*
- *Cost*
- *Complicated treatment regimens*

1. Cahaya N et al. Interventions to Improve Medication Adherence in People with Schizophrenia: A Systematic Review. *Patient Prefer Adherence*. 2022;16:2431-2449.

PACE Partners for Advancing Clinical Education EFFICIENT

SCHIZOPHRENIA

BREAKTHROUGH SYMPTOMS

BREAKTHROUGH SYMPTOMS

OVERT PSYCHOSIS

- Delusions
- Hallucinations
- Disorganized speech / behavior

PSYCHOSIS-RELATED

- Anxiety
- Depression

SIDE-EFFECT RELATED

- Negative symptoms
- Agitation (secondary to akathisia)

Breakthrough symptoms are not always due to treatment failure

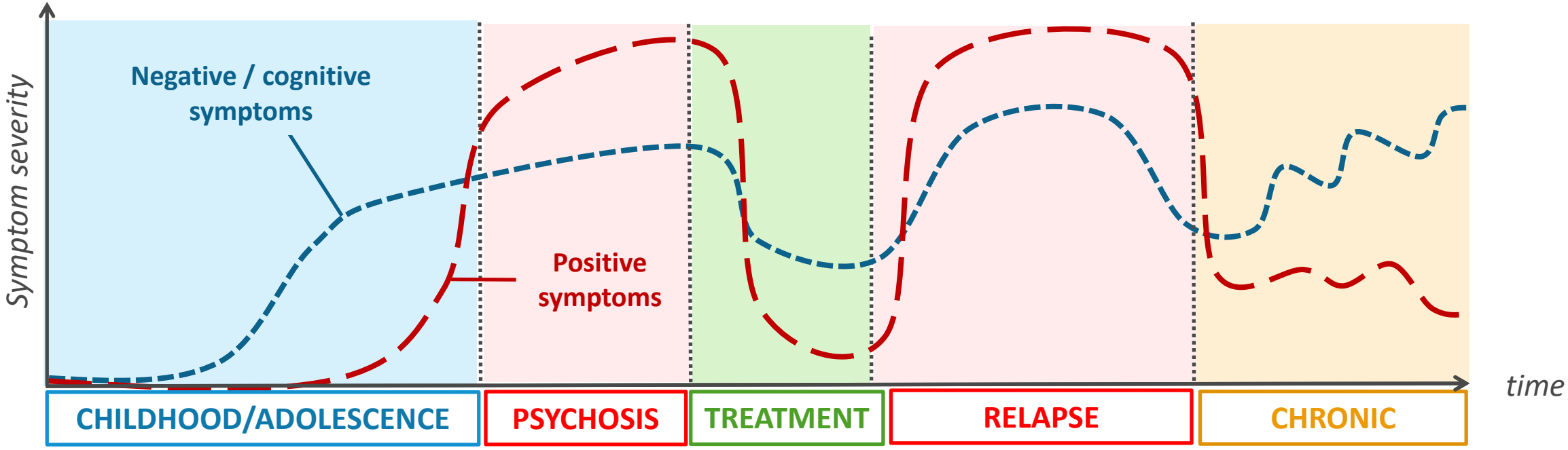
External factors (substance use, legal issues, interpersonal stresses)

Natural course of the disease?

1. Correll CU et al. Practical considerations for managing breakthrough psychosis and symptomatic worsening in patients with schizophrenia on long-acting injectable antipsychotics. *CNS Spectr*. 2019;24(4):354-370.

SCHIZOPHRENIA

CLINICAL COURSE[1,2]



Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

- *Treatment resistance*
- *Progression of negative and cognitive symptoms*

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210. **2.** Faden J et al. Schizophrenia: One Name, Many Different Manifestations. *Med Clin North Am*. 2023;107(1):61-72.

PACE Partners for Advancing Clinical Education EFFICIENT

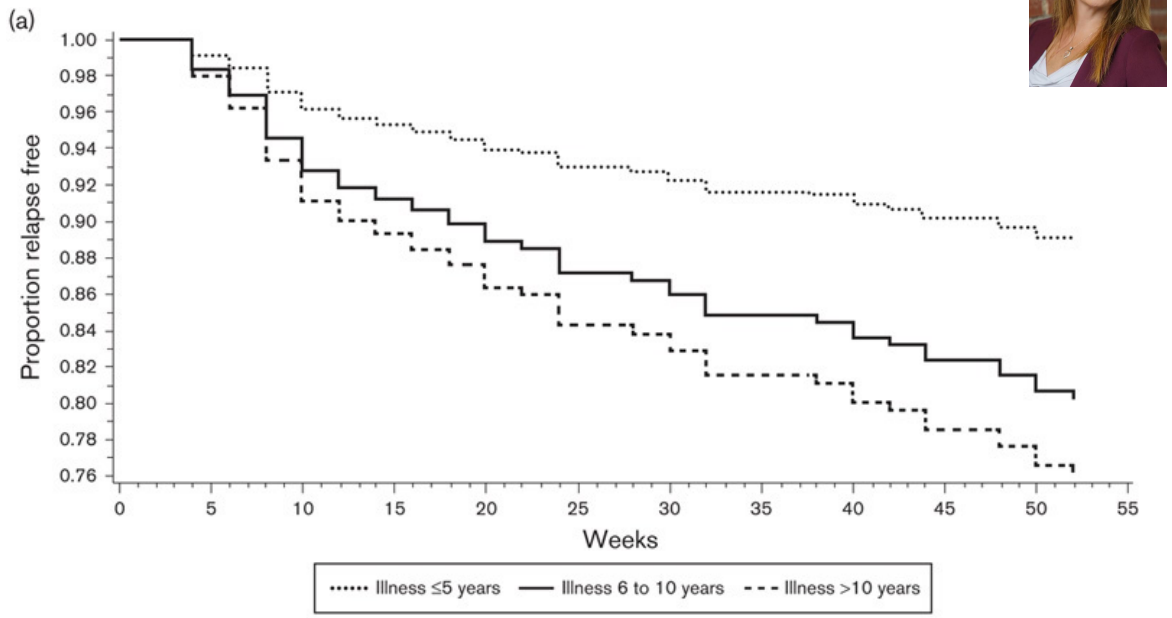
CHRONICITY
RELAPSE RATE

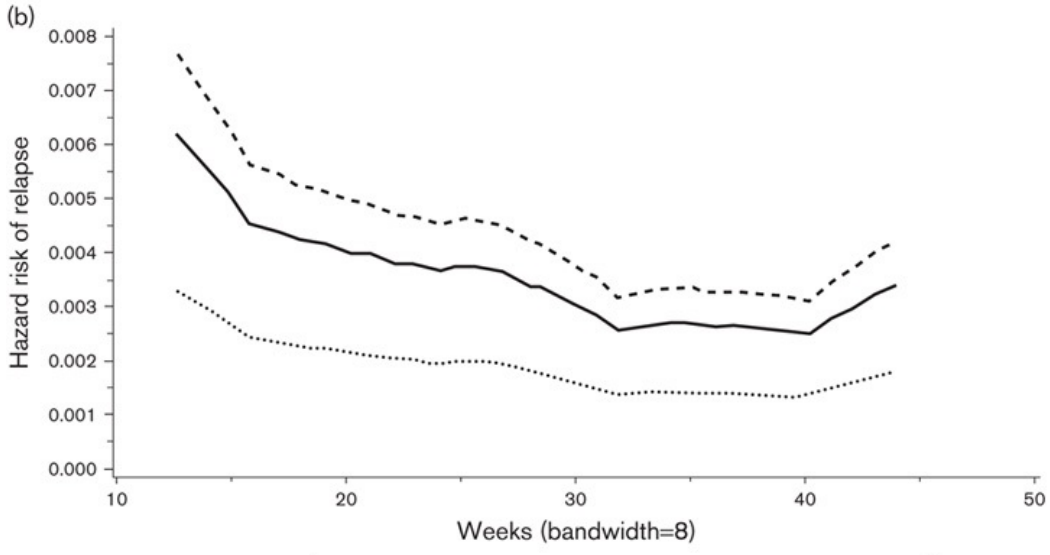
STUDY DESIGN/METHODS
- Post hoc exploratory analysis
- 323 patients with stable SZ or schizoaffective disorder switched to biweekly LAI risperidone for 52 weeks

RESULTS
- **18.3% of patients relapsed** despite continuous LAI antipsychotics
- **6.0% increase in relapse risk** for each year of illness (*P*=0.003)
- **4.4-fold increase in relapse risk** for illness duration >10 years vs. ≤5 years (*P*=0.0181)

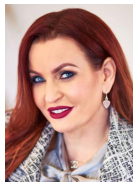
CONCLUSION
- **Chronicity (illness duration)** independent of medication nonadherence is a risk factor for relapse activity

LAI: long-acting injectable

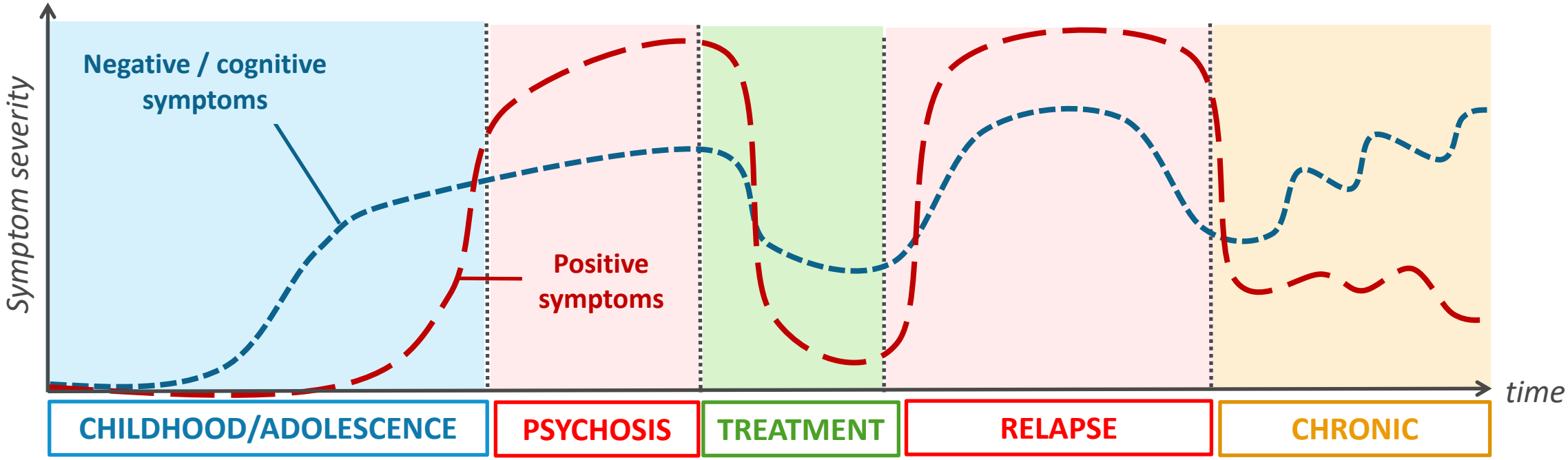




1. Alphs L et al. Factors associated with relapse in schizophrenia despite adherence to long-acting injectable antipsychotic therapy. *Int Clin Psychopharmacol*. 2016;31(4):202-209.



SCHIZOPHRENIA
CLINICAL COURSE

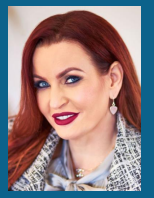


Adapted from McCutcheon RA. *JAMA Psychiatry*. 2020;77(2):201-210.

EXPERT INSIGHT: *What variations in clinical course do you commonly see?*

1. McCutcheon RA et al. Schizophrenia-An Overview. *JAMA Psychiatry*. 2020;77(2):201-210.

CASE 1*
DISCUSSION



RECAP:

Alex is a 23-year-old male who initially presented with auditory hallucinations. Additional inquiry revealed a history of paranoid thinking, social withdrawal, cognitive impairment, and negatively impacted family relationships. Alex is diagnosed with schizophrenia.

Alex and his family are counseled on his SZ diagnosis and prognosis

NEXT STEPS: *TREATMENT*

*Fictional case.

PACE EFFICIENT

MODULE
— 2 —

DATA-DRIVEN DECISION-MAKING

PACE
Partners for Advancing Clinical Education
EFFICIENT

AUDIENCE POLL

Which of the following clinical symptoms do most antipsychotics (including first-generation and second-generation) primarily target?

a) Positive symptoms
b) Negative symptoms
c) Cognitive impairment
d) All the above
e) A & C
f) I do not know/I am unsure.

AUDIENCE POLL

Which of the following clinical symptoms do most antipsychotics (including first-generation and second-generation) primarily target?

a) Positive symptoms
b) Negative symptoms
c) Cognitive impairment
d) All the above
e) A & C
f) I do not know/I am unsure.

CASE 1*
TREATMENT

RECAP:

Alex is a 23-year-old male diagnosed with schizophrenia. In addition to auditory hallucinations, he presents with negative and cognitive symptoms.

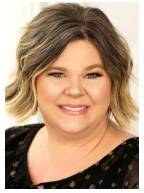
WHICH ANTIPSYCHOTIC WOULD YOU CONSIDER TREATING THIS PATIENT WITH AS FIRST-LINE THERAPY?

*Fictional case.

AUDIENCE POLL

Which antipsychotic would you use as first-line therapy for this patient?

a) Amisulpride
b) Cariprazine
c) Clozapine
d) Lumateperone
e) Olanzapine
f) Quetiapine
g) Risperidone
h) Another antipsychotic (not listed above)
i) I do not know/I am unsure.



TRADITIONAL ANTIPSYCHOTICS
LIMITATIONS

TRADITIONAL ANTIPSYCHOTICS

↓

Dopamine modulation

↙ ↓ ↘

ADDRESSED:
- Positive symptoms
- Agitation

Primary target of FDA-approved agents

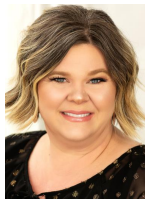
UNADDRESSED:
- Negative symptoms
- Cognitive symptoms

No FDA-approved treatments for cognitive impairment associated with schizophrenia (CIAS)

Unfavorable side effect profile:
- Extrapyramidal symptoms
- Metabolic changes
- Sedation

Despite current limitations, how can we optimize therapeutic management of negative / cognitive symptoms with currently available antipsychotics?

1. Cerveri G et al. Pharmacological treatment of negative symptoms in schizophrenia: update and proposal of a clinical algorithm. *Neuropsychiatr Dis Treat*. 2019;15:1525-1535.

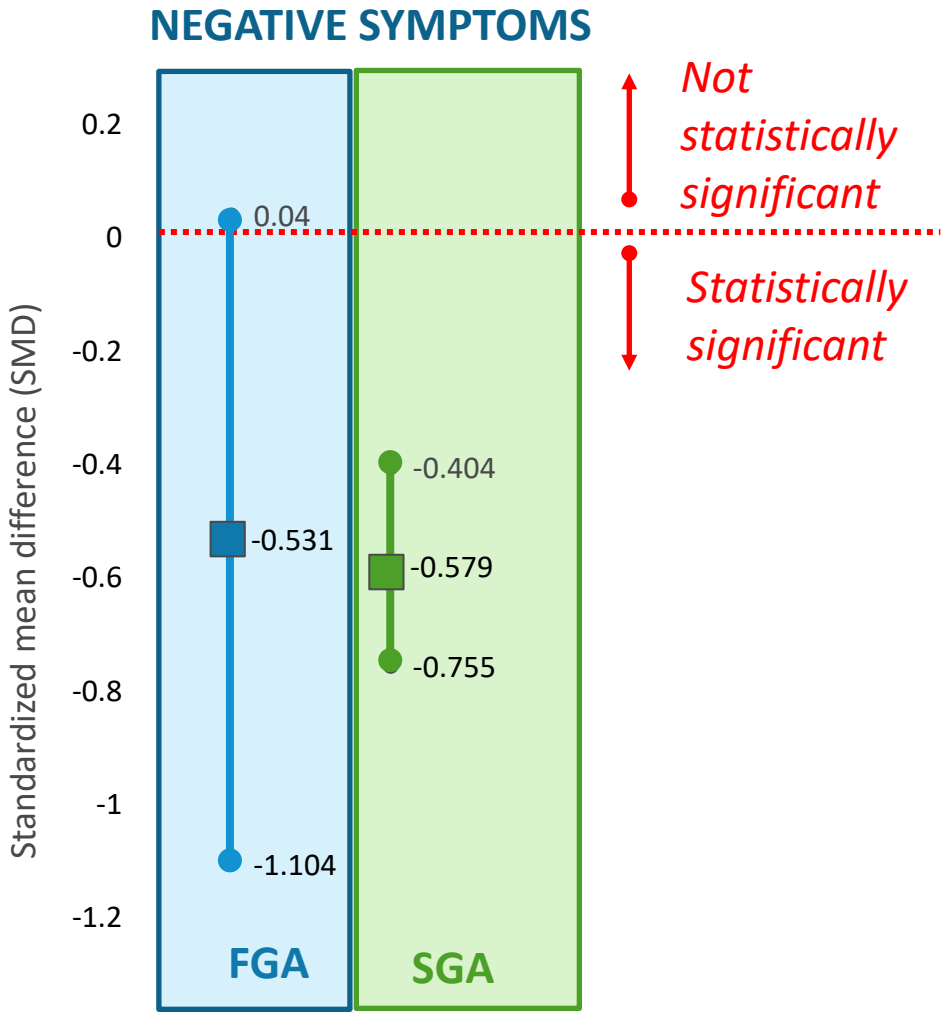


NEGATIVE SYMPTOMS
ANTIPSYCHOTIC GENERATIONS

STUDY DESIGN
- 2015: Meta-analysis (168 RCTs, 5,815 patients)

RESULTS
- SGA antipsychotics associated with modest reductions in negative symptoms. Most were **not considered clinically meaningful** on the CGI scales.
  - **FGA:** SMD= **−0.531** (*P*=0.069, **not significant**) (95%CI, −1.104 to 0.04)
  - **SGA:** SMD= **−0.579** (*P*<0.001, **significant**) (95%CI, −0.755 to −0.404)

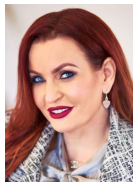
Are certain SGAs more efficacious than others for this purpose?



CGI: Clinical Global Impression scale; **FGA**: first-generation antipsychotic; **SGA:** second-generation antipsychotic

Adapted from Fusar-Poli P et al. Schizophr Bull. 2015;41(4):892-899.

1. Fusar-Poli P et al. Treatments of Negative Symptoms in Schizophrenia: Meta-Analysis of 168 Randomized Placebo-Controlled Trials. *Schizophr Bull*. 2015;41(4):892-899.



NEGATIVE SYMPTOMS
COMPARING ATYPICAL ANTIPSYCHOTICS

STUDY DESIGN

2018 systematic review and meta-analysis (21 RCTs, 3,451 patients) evaluating the impact of 34 antipsychotics on negative symptoms

RESULTS

META-ANALYSIS

Only amisulpride > impact than placebo

(SMD=0.47 [95% CI, 0.27-0.71); *P*=0.0001)

Is this reflective of your practice?

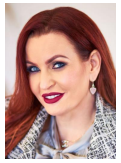
SYSTEMATIC REVIEW

Olanzapine and quetiapine superior to risperidone (single trials)

What about newer agents?

RCT: randomized controlled trial

1. Krause M et al. Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2018;268(7):625-639.



NEGATIVE SYMPTOMS
CARIPRAZINE

STUDY DESIGN

- Phase 3 randomized controlled trial
- Patients with stable SZ (N=461) randomized 1:1 to either oral cariprazine (n=230) or oral risperidone (n=231) for 26 weeks

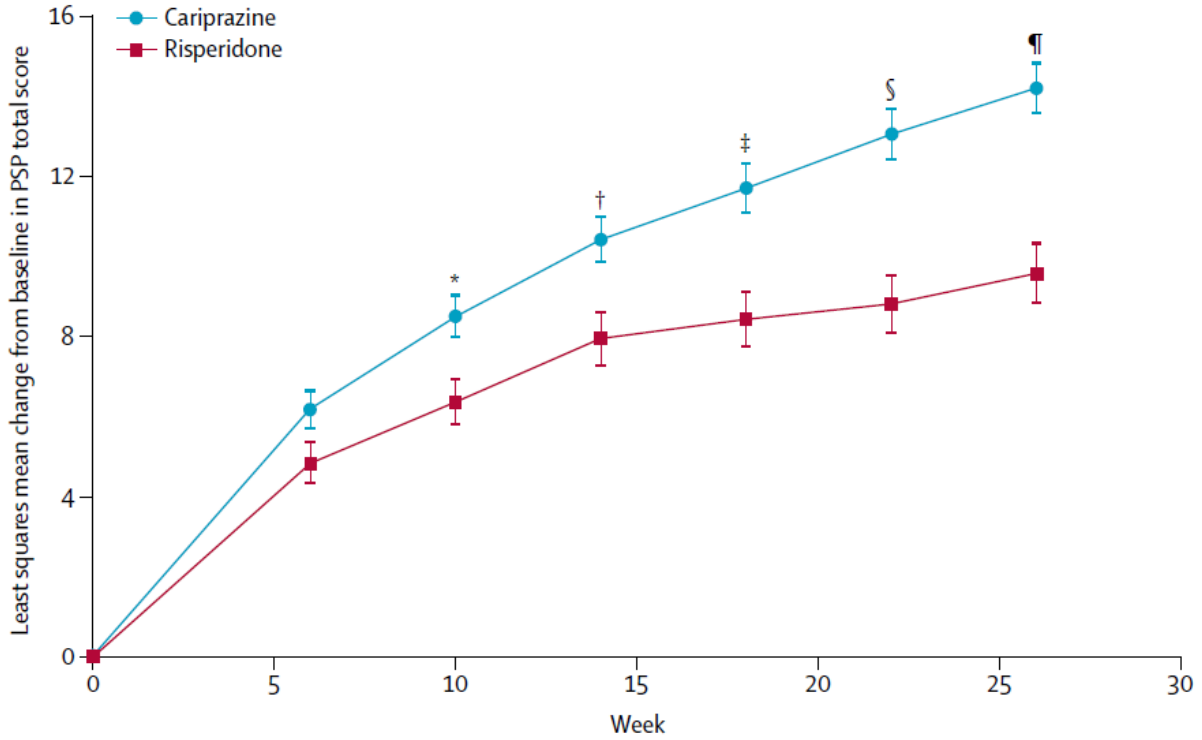
RESULTS

- **Cariprazine demonstrated greater improvement in negative symptoms** vs risperidone (*P*=0.0022)
  - LSMD for PANSS-FSNS: – 1.46 points [95% CI: –2.39 to – 0.53]

INTERPRETATION

Cariprazine may be considered for patients with predominantly negative symptoms of schizophrenia

MEAN CHANGE IN PERSONAL AND SOCIAL PERFORMANCE TOTAL SCORE

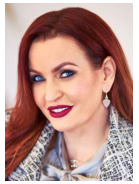


What about cognitive symptoms?

1. Németh G et al. Cariprazine versus risperidone monotherapy for treatment of predominant negative symptoms in patients with schizophrenia: a randomised, double-blind, controlled trial. *Lancet*. 2017;389(10074):1103-1113

LSMD: least squares mean difference; **PANSS-FSNS**: Positive and Negative Syndrome Scale factor score for negative symptoms

PACE Partners for Advancing Clinical Education EFFICIENT



COGNITIVE SYMPTOMS
CARIPRAZINE

STUDY DESIGN[1]

- Post-hoc analysis of cariprazine vs risperidone trial

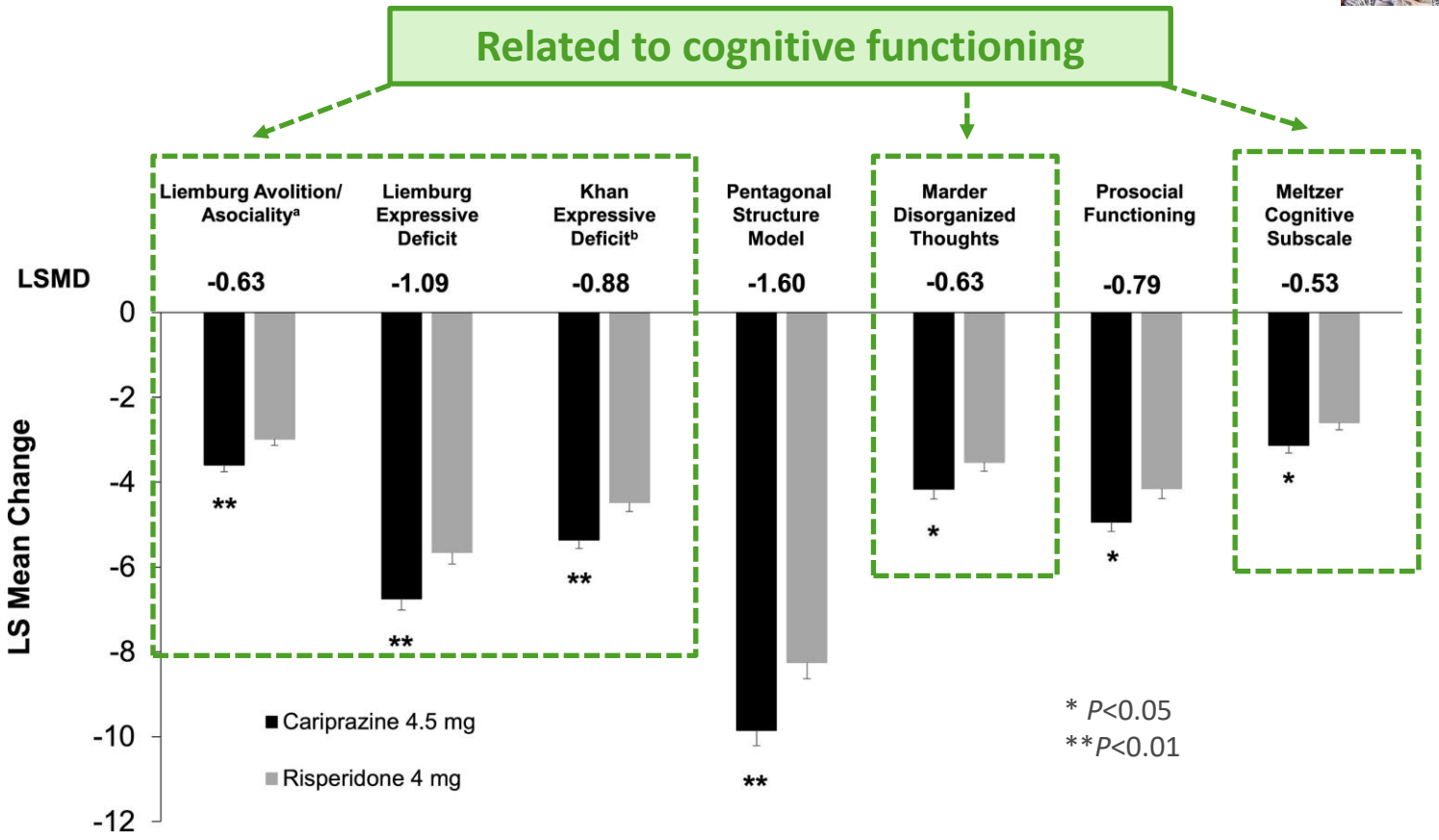
RESULTS[1]

- Cariprazine associated with significant improvement in multiple symptom domains including ***disorganized thoughts, prosocial function, and cognition***

CONCLUSION/INTERPRETATION[1]

- Cariprazine may also be ***efficacious against cognitive impairment* in SZ***

REMEMBER: *No FDA-approved agents for CIAS*



From Fleischhacker W et al. *Eur Psychiatry*. 2019;58:1-9

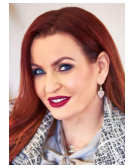
Believed to be due to **D_3 partial agonism*

Remember from antipsychotic talk: 10-fold greater binding affinity vs D_2[2]

1. Fleischhacker W et al. The efficacy of cariprazine in negative symptoms of schizophrenia: Post hoc analyses of PANSS individual items and PANSS-derived factors. *Eur Psychiatry*. 2019;58:1-9. 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.

PACE Partners for Advancing Clinical Education EFFICIENT

SZ CLINICAL SPECTRUM
LUMATEPERONE



STUDY DESIGN/INTERVENTIONS

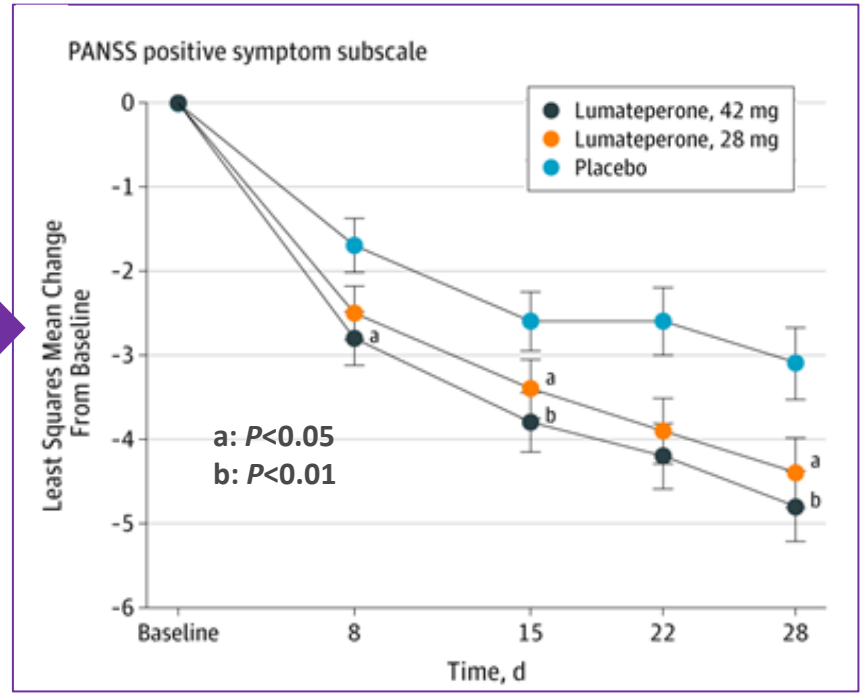
- Phase 3 RCT of patients with SZ (N=450)
- Randomized 1:1:1 for 4 weeks to lumateperone 42mg, 28mg, or placebo

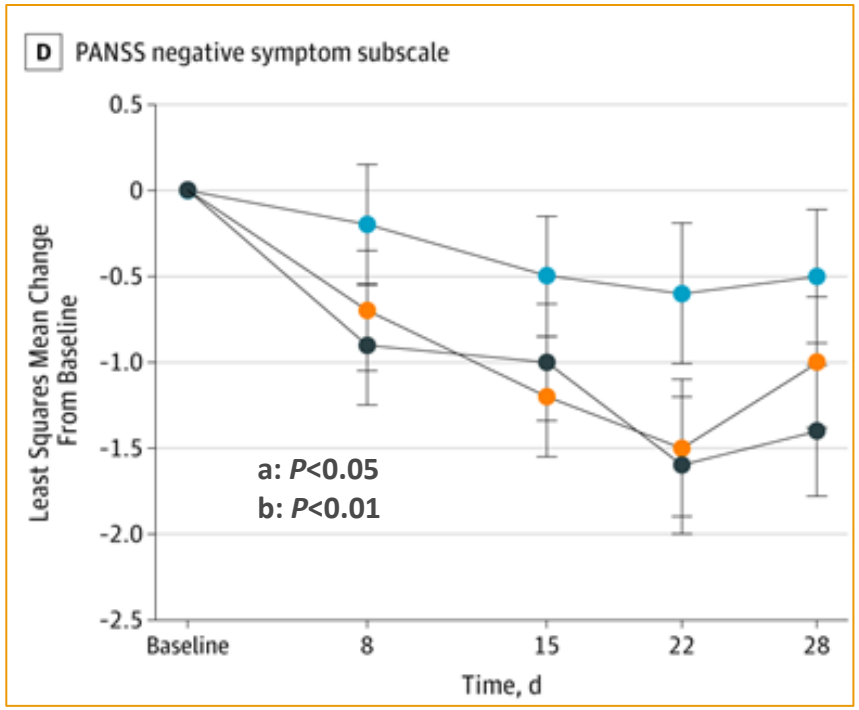
RESULTS

- **Lumateperone 42 mg** reduced total PANSS (LSMD=−4.2 points [95% CI, −7.8 to −0.6]; ***P* = 0.02**)
  - **Effect size = – 0.30**
- PANSS symptom subscale breakdown
  - **Positive symptoms:** statistically significant
  - **Negative symptoms:** not statistically significant

INTERPRETATION

- Did not significantly reduce negative symptoms
- However, ***similar effect size for PANSS total score to cariprazine***





RCT: randomized controlled trial; **PANSS**: Positive and Negative Syndrome Scale

1. Correll CU et al. Efficacy and Safety of Lumateperone for Treatment of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry*. 2020;77(4):349-358

CASE 1*
TREATMENT

RECAP:

Alex is a 23-year-old male diagnosed with schizophrenia. In addition to auditory hallucinations, he presents with negative and cognitive symptoms.

The patient is treated with LAI risperidone

What other agents would you consider for this patient?

LAI: long-acting injectable

*Fictional case.

PACE EFFICIENT

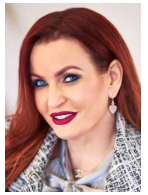
CASE 2*
INTRODUCTION

Paul is a 21-year-old male who was hospitalized 2 months ago after attempting to stab his mother because “voices in my head were telling me to do it.”

Six months prior to his hospitalization, Paul was diagnosed with schizophrenia due to a several-month history of hearing voices telling him to “hurt himself.” He was prescribed **oral risperidone,** which helped his symptoms initially, but after 3 months, it began to lose efficacy. Upon further questioning, he **admitted missing several doses**.

What treatment strategy would best help this patient?

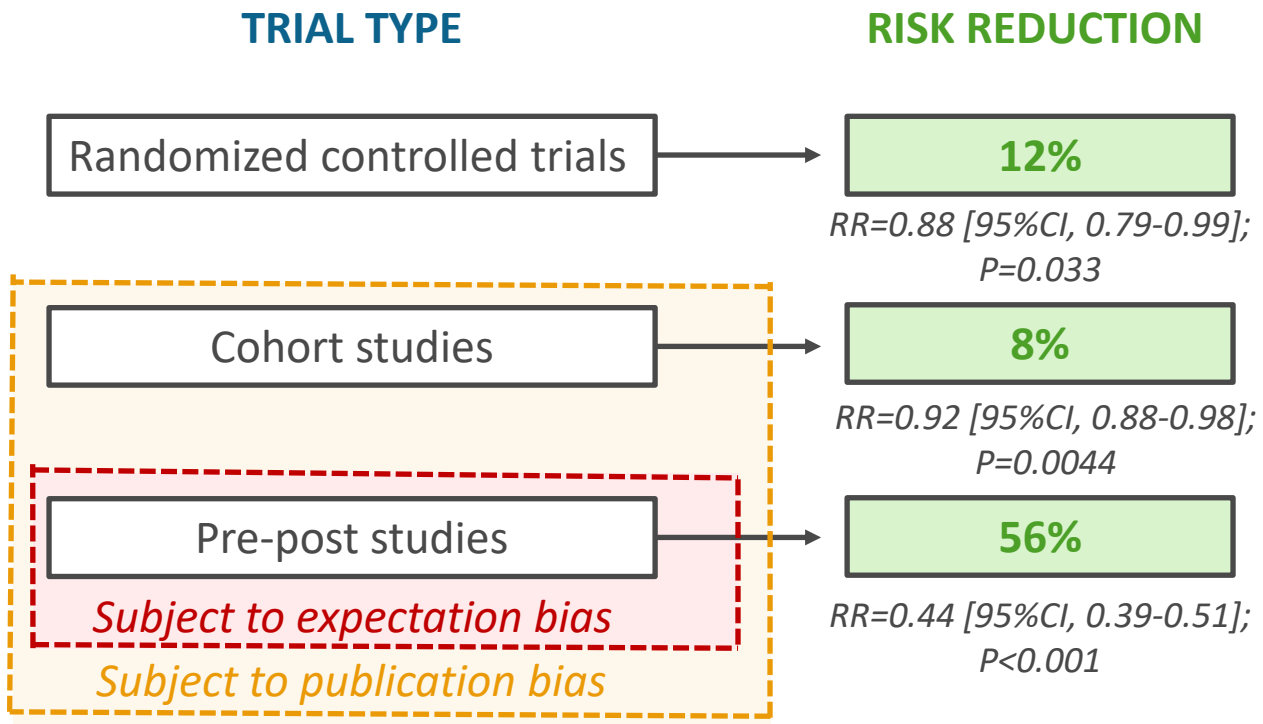
*Fictionalized representation based on a real medical case.



LONG-ACTING INJECTABLES
MEDICATION ADHERENCE

STUDY DESIGN
- Comparative meta-analysis (32 RCTs, 65 cohort studies, 40 pre-post studies)

RESULTS
- **Statistically significant lower risk of hospitalization or relapse** for LAI vs. oral antipsychotics

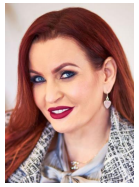


*LAIs are shown to **decrease risk of hospitalization or relapse** for schizophrenia relative to oral agents*

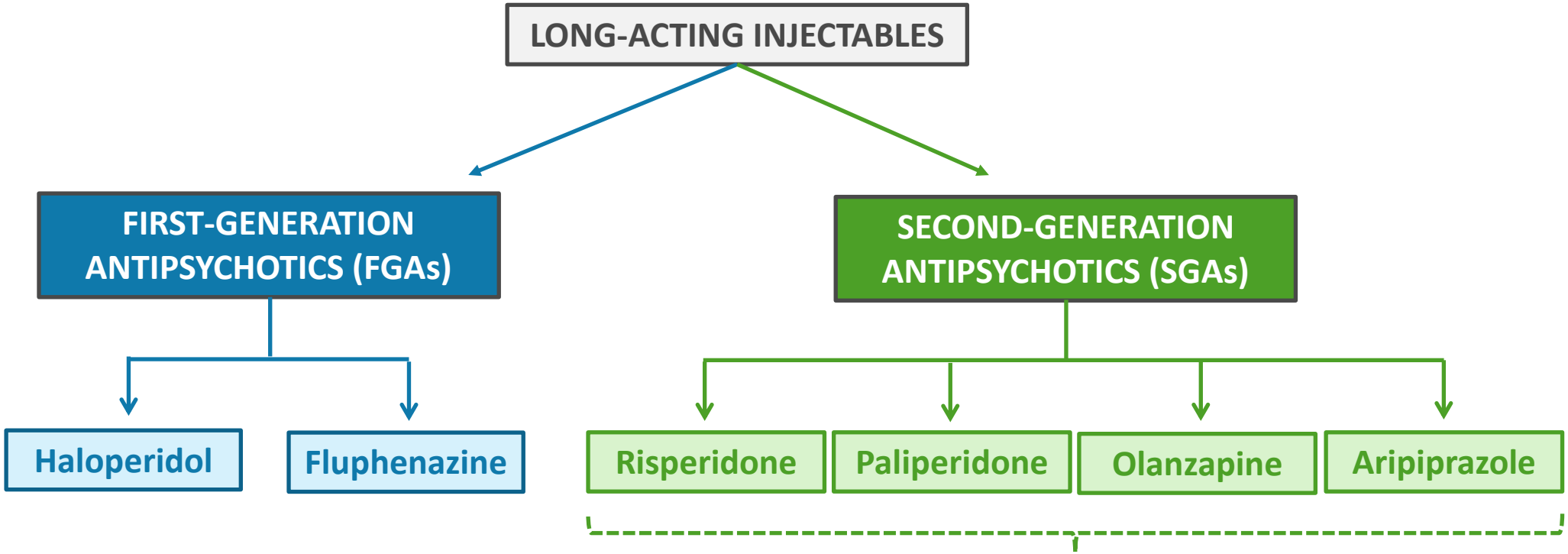
1. Kishimoto T et al. Long-acting injectable versus oral antipsychotics for the maintenance treatment of schizophrenia: a systematic review and comparative meta-analysis of randomised, cohort, and pre-post studies. *Lancet Psychiatry*. 2021;8(5):387-404.

LAI: long-acting injectable; **RCT:** randomized controlled trial; **RR:** risk reduction

PACE Partners for Advancing Clinical Education EFFICIENT



LONG-ACTING INJECTABLES
FORMULATIONS



*Remember **Atypical Antipsychotics** lecture for the differences between FGAs and SGAs!*

1. Correll CU et al. Pharmacokinetic Characteristics of Long-Acting Injectable Antipsychotics for Schizophrenia: An Overview. *CNS Drugs*. 2021;35(1):**39-59.**

CASE 2*
RESOLUTION

RECAP:

Paul is a 21-year-old male with SZ who was hospitalized for auditory hallucinations that led to an attempted stabbing of his mother. Previously, he **noted symptom improvement with oral risperidone but was nonadherent** to his regimen. Both Paul and his mother want to restart treatment so Paul can return to school.

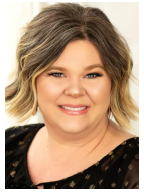
Already established tolerability with oral risperidone

Paul is switched to LAI risperidone and is doing well with no relapses or hospitalizations

*Fictionalized representation based on a real medical case.

PACE EFFICIENT

PHARMACIST QUICK TIP



EMERGING TREATMENTS

OLDER AGENTS[1,2]

- First-generation antipsychotics
- Second-generation antipsychotics

NEWER AGENTS[1,2]

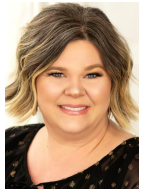
- Cariprazine
- Lumateperone

EMERGING AGENTS[1,2]

- *Ulotaront*
- *Xanomeline-trospium*
- *Emraclidine*
- *Pimavanserin*

No D_2 activity!

1. Correll CU et al. Emerging Treatments in Schizophrenia. *J Clin Psychiatry*. 2022;83(1):SU21024IP1. **2.** Correll CU et al. Pharmacologic Treatment of Schizophrenia Beyond Dopamine Receptor Blockade-Has Its Time Come Yet? JAMA Psychiatry. Published online December 13, 2023. doi:10.1001/jamapsychiatry.2023.4353



ULOTARONT
MECHANISM OF ACTION

TAAR1: Modulates monoaminergic neurotransmission (dopamine, serotonin, norepinephrine)

- **TAAR1 agonist**[1,2]
  - Modulates ***hyperdopaminergic circuits***
  - Modulates ***glutamate neurotransmission***
- **5-HT_{1A} agonist**[1,2]

May reduce movement-related side effects

- Presynaptic dopamine regulation without postsynaptic D_2 antagonism

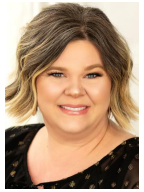
May help with negative and cognitive symptoms

- Regulates striatal and hippocampal excitatory neurotransmission

Ulotaront demonstrates ***antipsychotic effects with an absence of D_2 or 5-HT_{2A} receptor activity***[1,2]

1. Heffernan MLR et al. Ulotaront: A TAAR1 Agonist for the Treatment of Schizophrenia. *ACS Med Chem Lett*. 2021;13(1):92-98.
2. Yang SM et al. TAAR1 agonist ulotaront modulates striatal and hippocampal glutamate function in a state-dependent manner. *Neuropsychopharmacology*. Published online December 19, 2023. doi:10.1038/s41386-023-01779-x

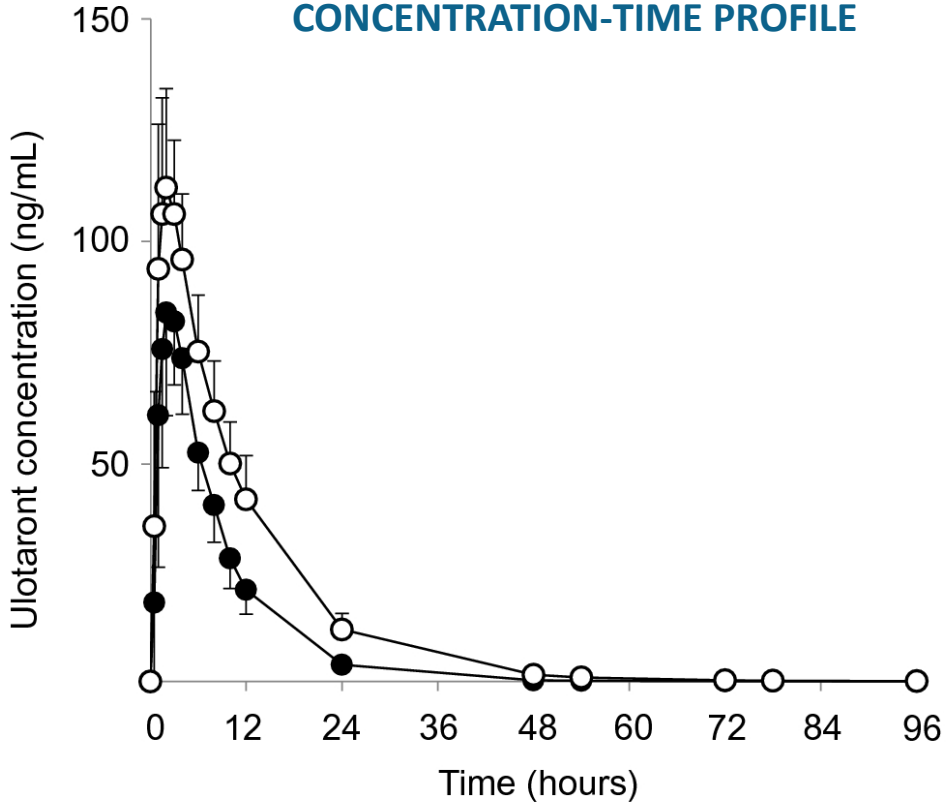
TAAR1: trace amine-associated receptor 1



ULOTARONT
PHARMACOKINETICS

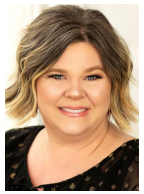
- **Half-life** = ~7 hours
- **T_{max}** = 2.8 hours
- **Metabolism**: primarily CYP2D6
  - Weak drug-drug interactions when combined with paroxetine (strong CYP2D6 inhibitor)

ULOTARONT PLASMA CONCENTRATION-TIME PROFILE



From Tsukada H et al. *Clin Pharmacokinet*. 2023;62(12):1755-1763.

1. Tsukada H et al. A Phase I, Open-Label, Fixed Sequence Study to Investigate the Effect of Cytochrome P450 2D6 Inhibition on the Pharmacokinetics of Ulotaront in Healthy Subjects. *Clin Pharmacokinet*. 2023;62(12):1755-1763.



ULOTARONT

CLINICAL EFFICACY / SAFETY

- **EFFICACY:** conflicting data

PHASE 2 / OLE[1,2]	PHASE 3 (2 trials)[3]
Significant reductions in *PANSS total score*[1]	**No significant reductions in** *PANSS total score*
Positive symptom subscale[2] *Negative symptom subscale*[2] *MADRS*[2]	**Not included** *Positive/negative symptom subscale and MADRS*

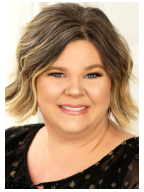
Both phase 3 clinical trials had an unusually high placebo response

- **SAFETY**[1-3]
  - Minimal motor side effects and weight changes
  - Common side effects: worsening SZ, headache, insomnia

Although phase 3 data did not find a significant reduction in PANSS total score, high placebo responses may contribute to such discrepancies

1. Koblan KS et al. A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia. *N Engl J Med*. 2020;382(16):1497-1506 2. Correll CU et al. Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: results of a 6-month, open-label extension study. *NPJ Schizophr*. 2021;7(1):63. 3. Kane J et al. Efficacy and Safety of Ulotaront in the Treatment of Schizophrenia: Results of Two 6-Week, Randomized, Double- Blind, Placebo-Controlled, Phase 3 Trials. Neuropsychopharmacology (2023) 48:211 – 354

MADRS: Montgomery–Åsberg Depression Rating Scale; **OLE**: open-label extension; **PANSS**: Positive and Negative Syndrome Scale



XANOMELINE-TROSPIUM
MECHANISM OF ACTION

XANOMELINE[1,2]

Central muscarinic acetylcholine agonist

M_1/M_4 agonists

Potential benefits of M_1/M_4 agonism

Modulates negative/cognitive symptoms

Modulates psychotic and behavioral disturbances

PITFALLS

Severe peripheral cholinergic side effects

TROSPIUM[1,2]

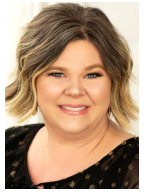
Peripheral muscarinic antagonist that does not cross the blood-brain barrier

Reduces cholinergic side effects

Therapeutic benefit of xanomeline with reduced risk of cholinergic effects

1. Singh A. Xanomeline and Trospium: A Potential Fixed Drug Combination (FDC) for Schizophrenia-A Brief Review of Current Data. *Innov Clin Neurosci*. 2022;19(10-12):43-47.
2. Gomes FV et al. Beyond Dopamine Receptor Antagonism: New Targets for Schizophrenia Treatment and Prevention. *Int J Mol Sci*. 2021;22(9):4467.

PACE Partners for Advancing Clinical Education EFFICIENT



XANOMELINE-TROSPIUM

PHARMACOKINETICS

XANOMELINE[1]

T_{max} = 2.5 hours
Half-life = 1.25 hours

Limited oral bioavailability (<1%)
Extensive first-pass metabolism

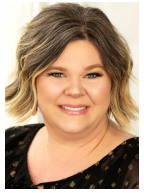
TROSPIUM[1,2]

T_{max} = 4-5 hours
Half-life = 20 hours

Oral bioavailability = 10%
Decreased with food intake

*Some continued potential for **anticholinergic effects** possibly due to large discrepancies in half-life of both agents[1]*

1. Singh A. Xanomeline and Trospium: A Potential Fixed Drug Combination (FDC) for Schizophrenia-A Brief Review of Current Data. *Innov Clin Neurosci*. 2022;19(10-12):43-47. **2.** Doroshyenko O et al. Clinical pharmacokinetics of trospium chloride. *Clin Pharmacokinet*. 2005;44(7):701-720.



XANOMELINE-TROSPIUM

CLINICAL EFFICACY / SAFETY

STUDY DESIGN/INTERVENTION

- Pooled analysis of three 5-week double-blind, placebo-controlled trials evaluating xanomeline-trospium

RESULTS

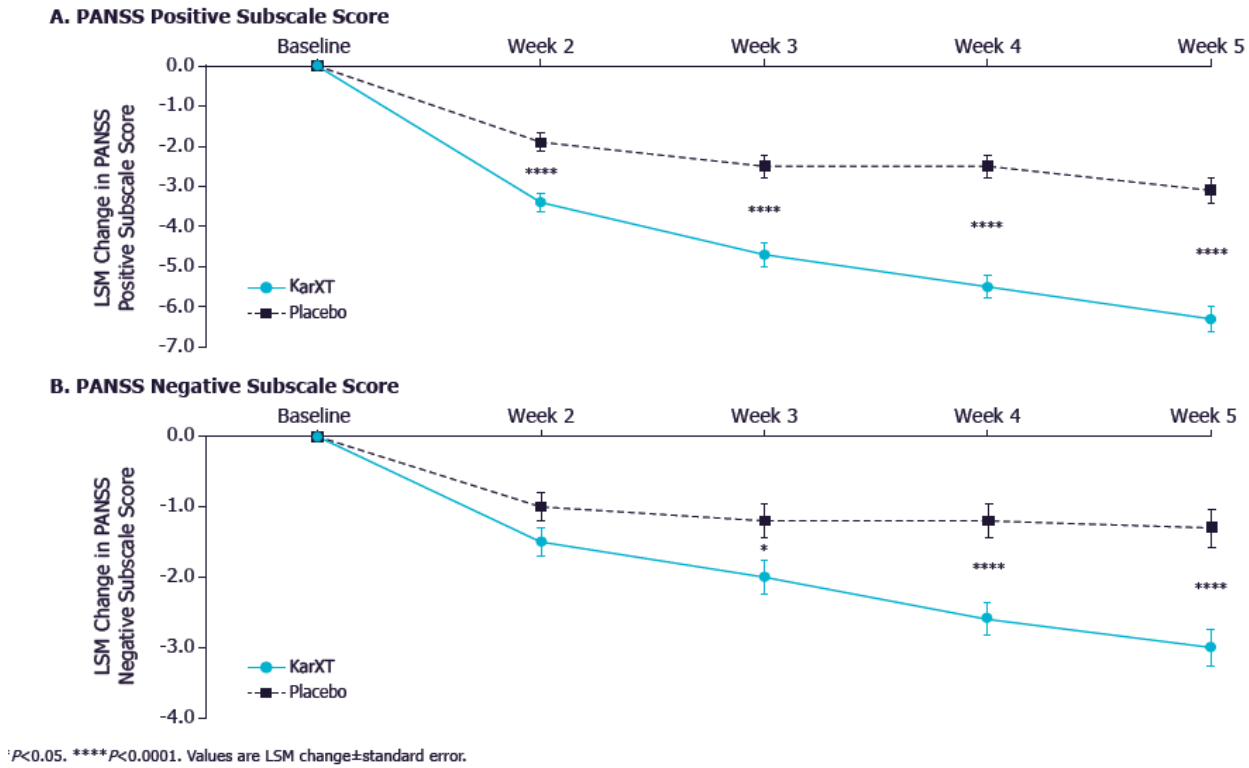
	LSMD	P-value	Effect size
PANSS total score	–9.9 points	*P*<0.0001	0.65
Positive subscale	–3.2 points		0.67
Negative subscale	–1.7 points		0.40

SAFETY

- Weight and motor side effect neutral; no sedation
- Peripheral anticholinergic side effects common

CONCLUSION

- Xanomeline-trospium *is effective for* ***positive and negative symptoms*** but risks peripheral anticholinergic effects

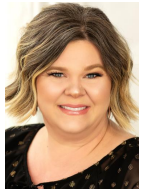


*P<0.05. ****P<0.0001. Values are LSM change±standard error.

LSMD: least squares mean difference; **MADRS**: Montgomery–Åsberg Depression Rating Scale; **PANSS**: Positive and Negative Syndrome Scale

1. Kaul I et al. Efficacy of KarXT (Xanomeline–Trospium) in Schizophrenia: Pooled Results From the Randomized, Double-Blind, Placebo-Controlled EMERGENT Trials. Poster presented at: Neuroscience Education Institute (NEI) Congress; November 9-12, 2023; Colorado Springs, Colorado

PACE Partners for Advancing Clinical Education EFFICIENT



XANOMELINE-TROSPIUM
COGNITIVE IMPAIRMENT

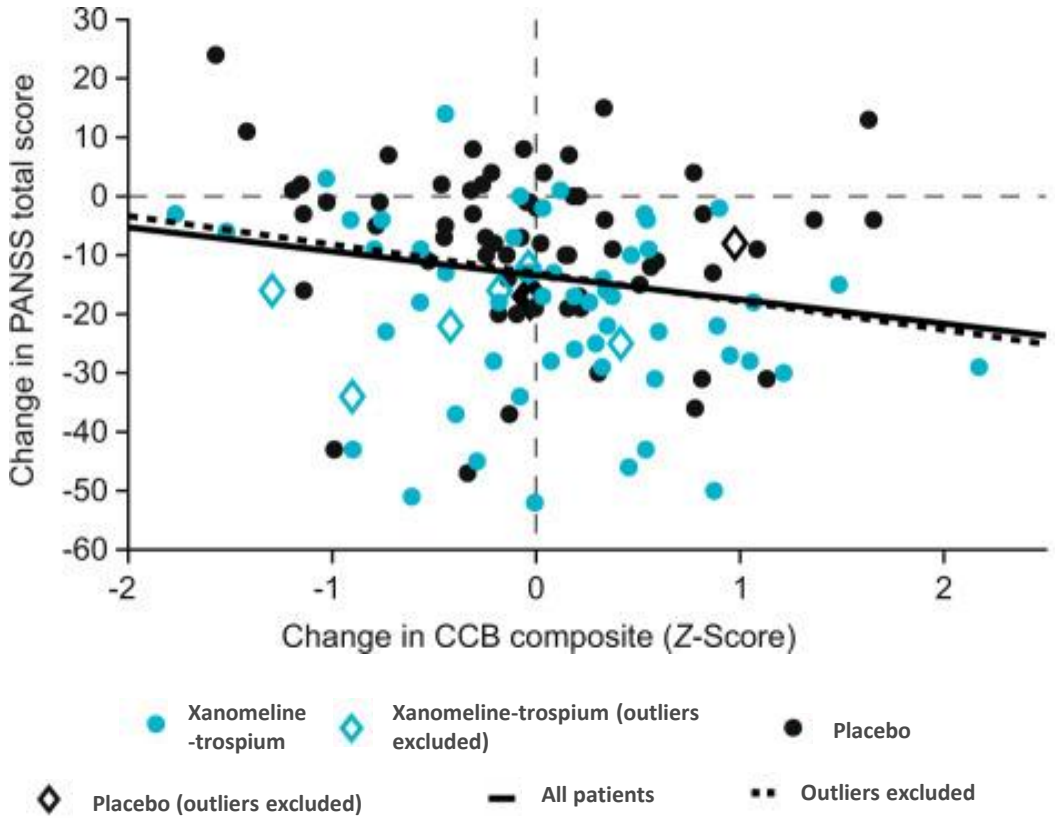
STUDY DESIGN
- Post-hoc analysis of previous 5-week study EMERGENT-1 trial of xanomeline-trospium (n=54) vs placebo (n=63)
- Cognitive impairment measured using Cogstate Brief Battery (CBB)

STUDY RESULTS
- **Improved cognitive performance** for xanomeline-trospium vs placebo (LSMD=0.27; *P*=0.04)
- Greater improvement for patients with baseline impairment (LSMD=0.50; *P*=0.03)
- Cognitive improvement not correlated with total PANSS

INTERPRETATION
- Xanomeline-trospium may provide potential benefit for treating neurocognitive impairments in SZ

FDA set to make a decision on approval by 9/26/24

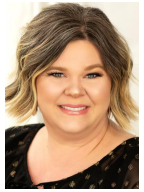
CORRELATION BETWEEN PANSS TOTAL SCORE AND COGNITIVE IMPAIRMENT



1. Sauder C et al. Effectiveness of KarXT (xanomeline-trospium) for cognitive impairment in schizophrenia: post hoc analyses from a randomised, double-blind, placebo-controlled phase 2 study. *Transl Psychiatry*. 2022;12(1):491.

PANSS: Positive and Negative Syndrome Scale

PACE Partners for Advancing Clinical Education EFFICIENT



EMRACLIDINE

MECHANISM OF ACTION

Selective positive allosteric M_4 modulator

Proposed antipsychotic mechanisms

M_4 receptors primarily located in the striatum on ***D_1 projection neurons***

Reduce release of dopamine in basal ganglia

M_4 receptors also located in the striatum on the terminals of glutamate neurons

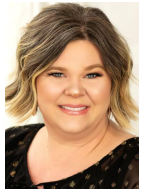
Reduce signaling in the D_1 receptor signaling pathway

Modulates dopamine without D_2 postsynaptic antagonism

STAY TUNED: Undergoing large clinical trials

1. Cookson J et al. A new cholinergic mechanism for antipsychotics: emraclidine and M4 muscarinic receptors. *Lancet*. 2022;400(10369):2159-2161.

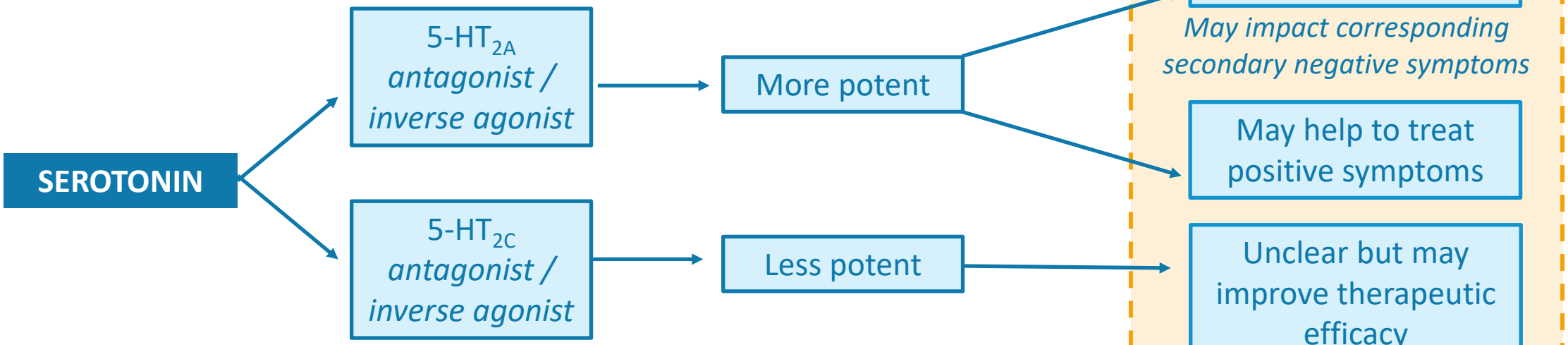
PACE Partners for Advancing Clinical Education EFFICIENT



PIMAVANSERIN

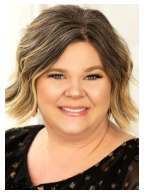
MECHANISM OF ACTION

- No activity against dopamine!
  - Avoid metabolic and motor side effect profile
- Targets serotonin receptors



DIMDs: drug-induced movement disorders

1. Davis J et al. Evaluating pimavanserin as a treatment for psychiatric disorders: A pharmacological property in search of an indication. *Expert Opin Pharmacother*. 2021;22(13):1651-1660.



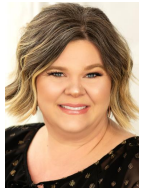
PIMAVANSERIN

PHARMACOKINETICS[1,2]

Oral administration without titration or impact by food

		CLINICAL IMPLICATION
Half-life	57 hours	May help with issues of ***nonadherence***
T_{max}	~ 6 hours	Impact seen relatively quickly
Time to steady state	12 days	
Metabolism	hepatic (CYP3A4, CYP3A5, CYP2D6, CYP2J2)	Always consider the impact of ***inducers/inhibitors*** if an agent is hepatically metabolized

1. Davis J et al. Evaluating pimavanserin as a treatment for psychiatric disorders: A pharmacological property in search of an indication. *Expert Opin Pharmacother*. 2021;22(13):1651-1660. **2.** Kitten AK et al. Pimavanserin: A Novel Drug Approved to Treat Parkinson's Disease Psychosis. *Innov Clin Neurosci*. 2018;15(1-2):16-22.



PIMAVANSERIN

CLINICAL EFFICACY / SAFETY

STUDY DESIGN/INTERVENTIONS

- Phase 2 randomized-controlled trial
- Patients with schizophrenia underwent 1:1 randomization to pimavenserin (n=201) and placebo (n=202) for 26 weeks

RESULTS

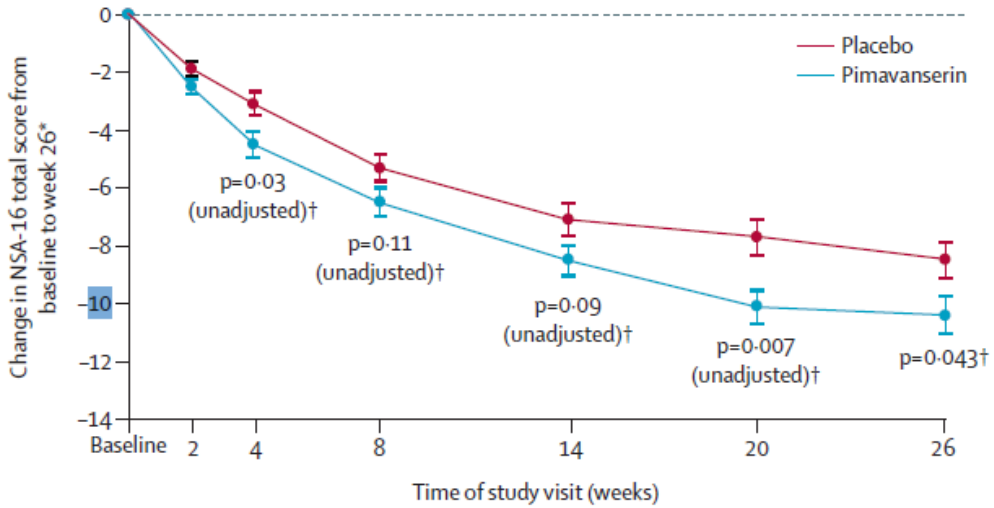
- **Pimavenserin improved negative symptoms** on NSA-16 vs placebo (–10.4 points vs –8.5 points; *P*=0.043; effect size = 0.211)

SAFETY

- Weight and motor side effect neutral
- May impact QT_c interval but no cases of prolongation
- Common symptoms: headache and somnolence

INTERPRETATION

- Pimavanserin showed a reduction in negative symptoms but given small effect size, additional research is needed



Number of patients

Placebo	201	201	197	192	184	179	173
Pimavanserin	199	199	193	191	185	180	174

Phase 3 clinical trials ongoing

Currently FDA-approved for hallucinations and delusions associated with Parkinson's disease psychosis

1. Bugarski-Kirola D et al. Pimavanserin for negative symptoms of schizophrenia: results from the ADVANCE phase 2 randomised, placebo-controlled trial in North America and Europe. *Lancet Psychiatry*. 2022;9(1):46-58

NSA-16: Negative Symptom Assessment- 16 item

PACE Partners for Advancing Clinical Education EFFICIENT


Q&A