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Beyond Delusions and Dopamine:

Negative Symptoms and CIAS—the Forgotten Domains of Schizophrenia

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Learning Objectives

- Describe the unmet disease burden of cognitive impairment associated with schizophrenia (CIAS)
- Differentiate between two underrecognized and undermanaged domains in schizophrenia—negative symptoms and CIAS
- Incorporate an emerging treatment (when available) for patients with CIAS based on clinical trial efficacy, safety, and mechanism of action
- Identify potential benefits and limitations of digital therapeutics in the cognitive and negative domains

An Overview of Schizophrenia

A Topline View of the People Affected by This Disease

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Schizophrenia By the Numbers

- Estimated US prevalence 0.25%–0.64%
- Average age of onset early 20s for men, late 20s to early 30s for women
- Early signs in teenagers vague and nonspecific
  - Sleep problems, irritability, drop in grades
- Many remain permanently disabled following symptom onset

Illustration from NAMI, 2023

NAMI. Schizophrenia. Available at: https://www.nami.org/About-Mental-Illness/Mental-Health-Conditions/Schizophrenia

3 Symptom Domains of Schizophrenia

Positive symptoms:

- Hallucinations
- Delusions
- Disorganized speech
- Agitative/repetitive movements
- Abnormal behavior

Negative symptoms:

Experiential

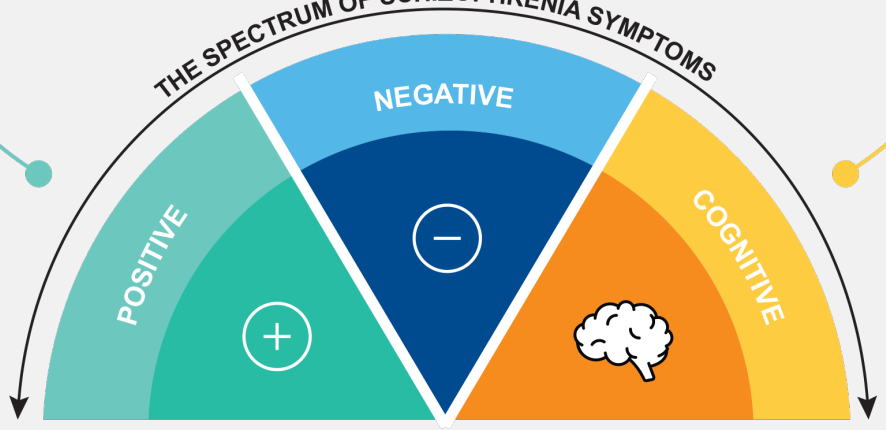
- Avolition (reduced motivation)
- Anhedonia (lack of pleasure)
- Asociality (eg, social isolation)

Expressive

- Flattened affect
- Alogia (lack of speech)

Cognitive symptoms:

- Poor memory
- Disorganized thinking
- Low attention
- Limited social cognition
- Poor working memory and comprehension
- Difficulty expressing thoughts



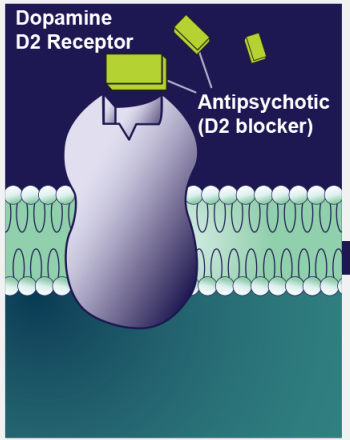
Rosenbrock H, et al. *Eur Arch Psychiatry Clin Neurosci.* 2023;273:1557-1566.

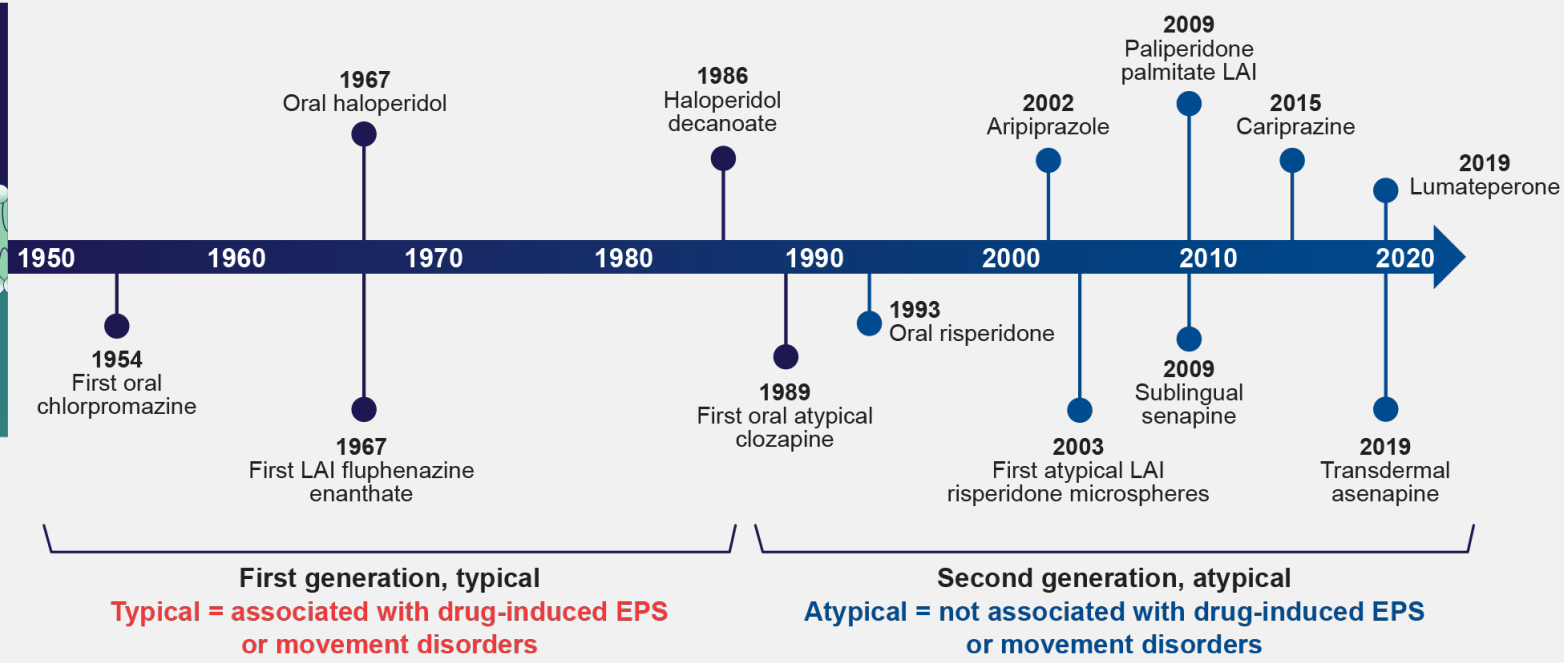
Factors Associated With Increased Mortality

- Life expectancy ~20 years shorter for people with schizophrenia
- Increased rate of suicide early in the illness
  - Related to impulsivity and “urgency”
- Increased modifiable health risk factors later in the illness
  - Obesity, diabetes, hypertension
    - Related to loneliness and sedentary lifestyle
  - Increased cancer due to smoking, alcohol/ substance abuse

Peritogiannis V, et al. *Healthcare*. 2022;10:2366.

Approved Antipsychotics; All Target Dopamine Receptors





EPS, extrapyramidal symptoms; LAI, long-acting injection.

Limitations of Current Antipsychotics

Treatment Resistance

- ~30% of patients with schizophrenia are resistant to D2 antagonism
- 30%–60% have a partial response or intolerability to medications used for treatment
- ~14% achieve recovery (long-term remission + good functional outcome)

Negative & Cognitive Symptoms

- Lower efficacy for addressing negative and cognitive symptoms, though their burden on quality of life may be higher
- Up to 60% of patients have been categorized as having prominent or predominant negative symptoms

Comorbidities

- Current treatments can exacerbate preexisting medical comorbidities
- Current treatments may inadequately address psychiatric comorbidities and >50% of patients have psychiatric comorbidity

Adverse Effects of Medications

- Discontinuation rates in the CATIE trial due to side effects varied from 10%–31%
- Side effects can contribute to reduced life expectancy and stigma
- Contributes to treatment noncompliance

CATIE, Clinical Antipsychotic Trials of Intervention Effectiveness.

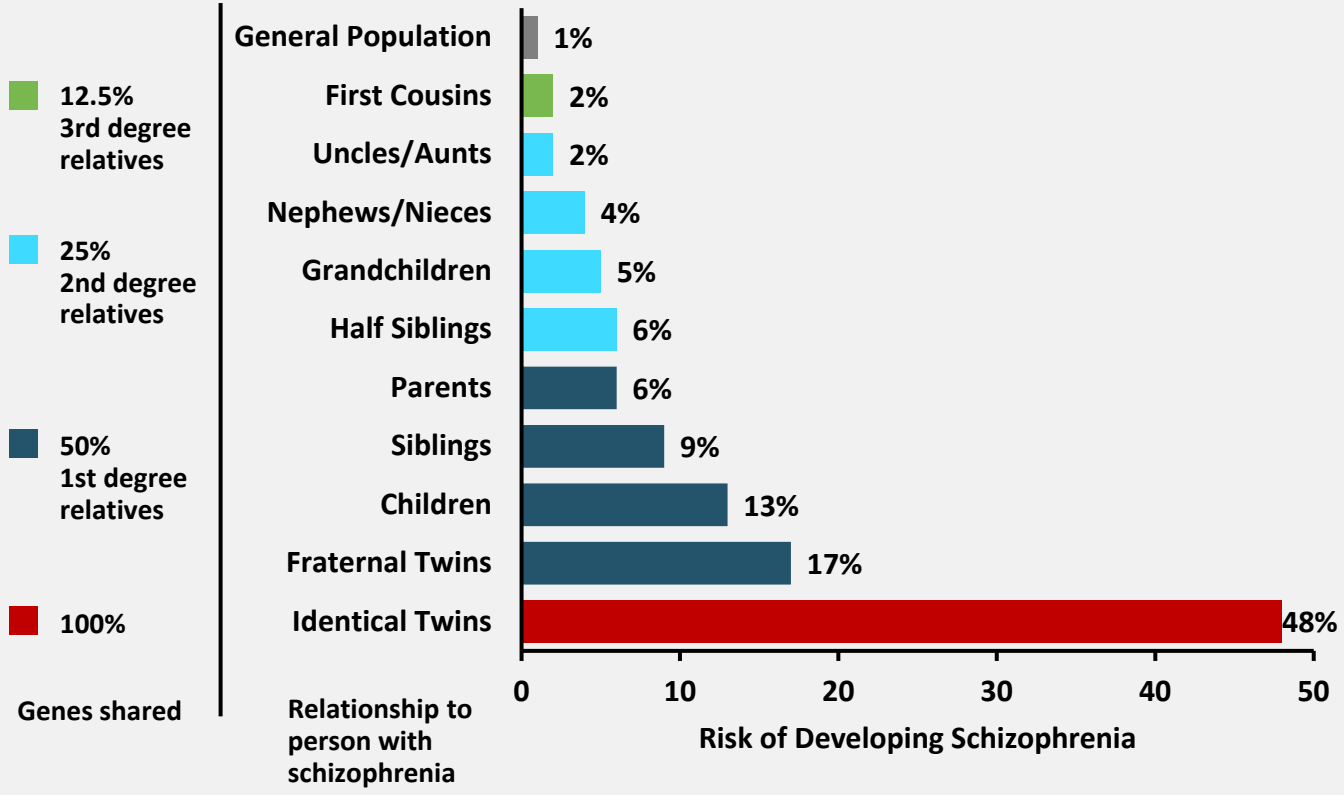
Dedic N, et al. *Int J Mol Sci.* 2021;22:13185; Lieberman JA, et al. *N Engl J Med*. 2005;353:1209-1223; Yeomans D, et al. *Adv Psychiatr Treat.* 2010;16:86-95.

Reviewing the Potential Role of Clozapine

- Clozapine, a serotonin and D4 antagonist, works differently from other dopamine-based antipsychotics
- Currently used almost exclusively for treatment-resistant schizophrenia, largely due to risk for agranulocytosis
  - Recently published systematic review of 14 studies (2,354 patients) found 11 (0.47%) experienced agranulocytosis[1]
- Another recently published study found delayed initiation of clozapine in treatment-resistant schizophrenia worsens long-term outcomes[2]

1. Magistri C, Cristiano M. *J Clin Psychopharmacol*. Sep 29 2023. [Online ahead of print] **2**. Hatano M, et al. *BMC Psychiatry*. 2023;23:673.

Genetics: The Heritability Question



- Genetics affect susceptibility to schizophrenia but does not *cause* it
- Combination genetic/environmental hypotheses most widely accepted
- Genes confer both "risk" and "resilience"

Gottesman II, et al. *Schizophr Res*. 2001;51:93-102.

CIAS and Negative Domains

The “non-positive” symptoms of schizophrenia

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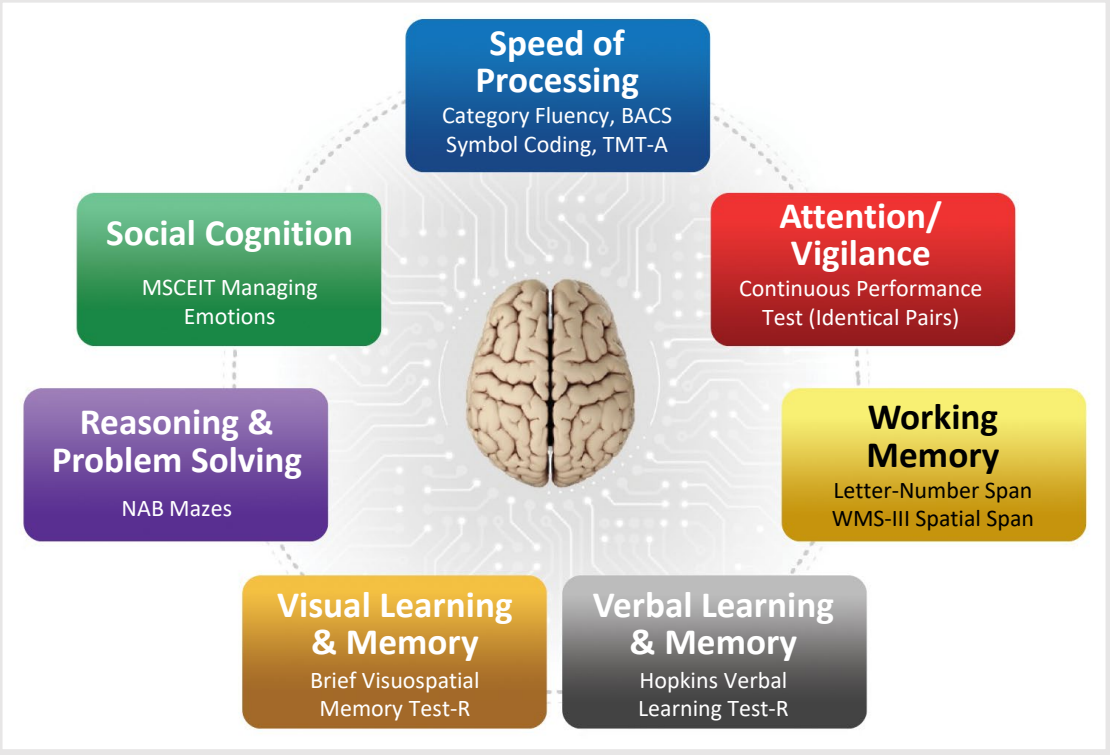
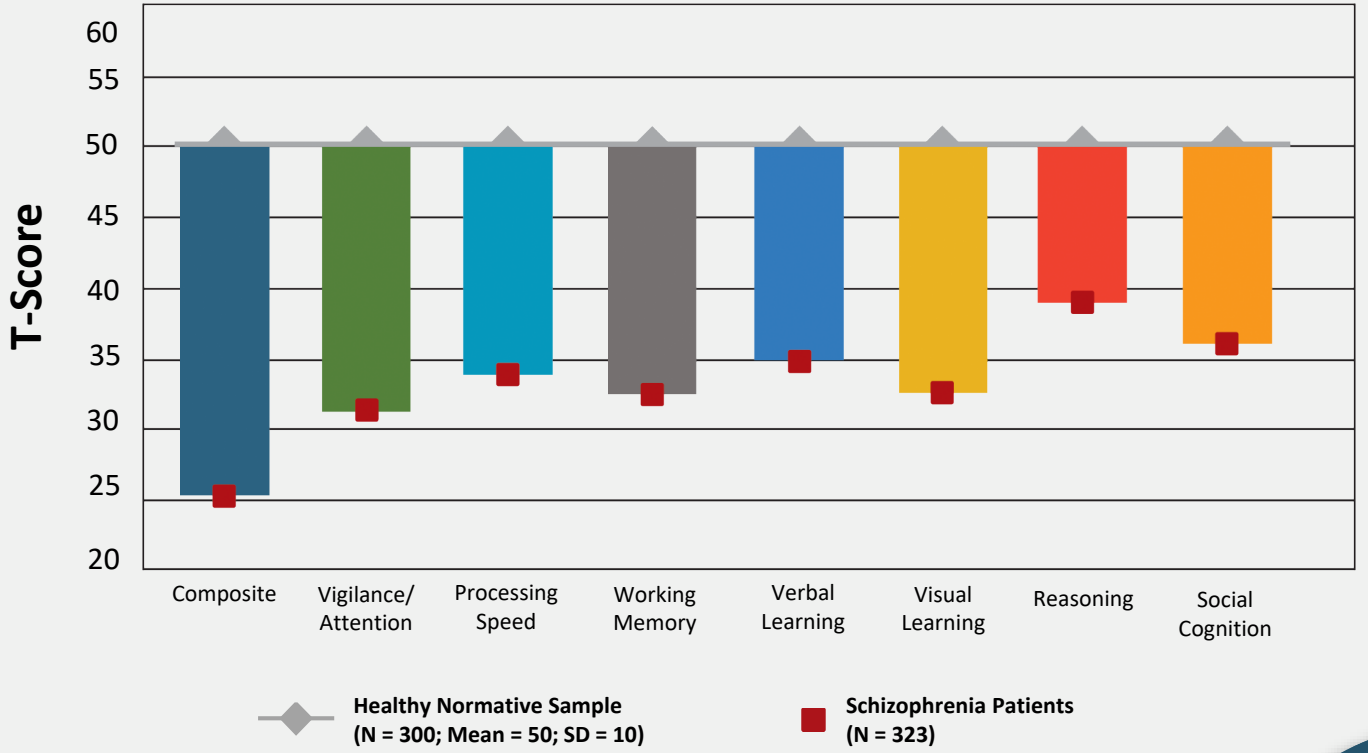
Separate Cognitive Domains Assessed in the MCCB



BACS, Brief Assessment of Cognition in Schizophrenia; MSCEIT, Mayer-Salovey-Caruso Emotional Intelligence Test; NAB, Neuropsychological Assessment Battery; Test-R, revised test; TMT-A, Trial Making Test part A; WMS-III, Wechsler Memory Scale—Third Edition

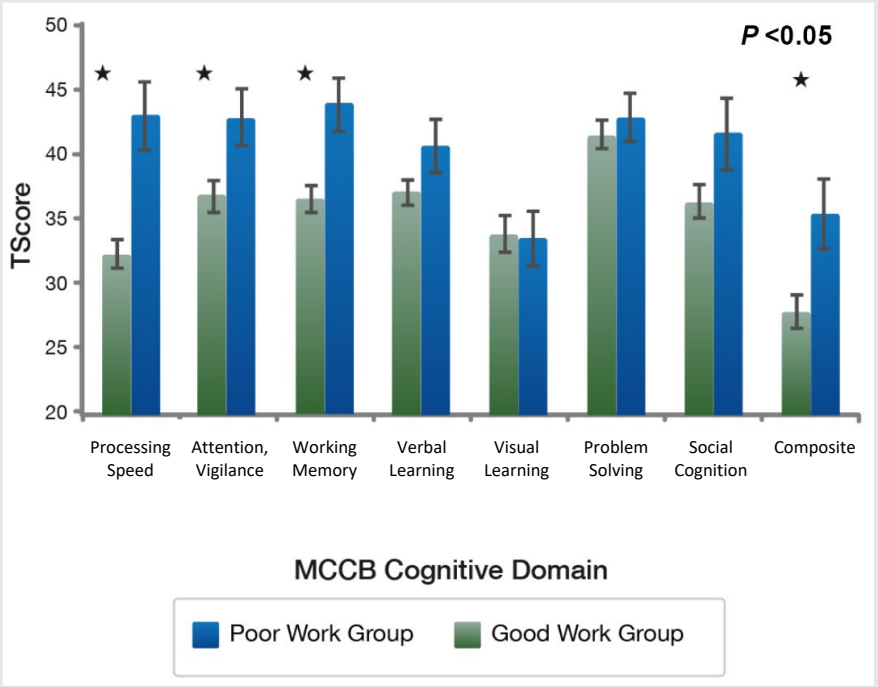
Profile of Cognitive Impairment



Keefe RS, et al. *Schizophr Res.* 2011;125:161-168.

Neurocognitive Deficits and Functional Ability

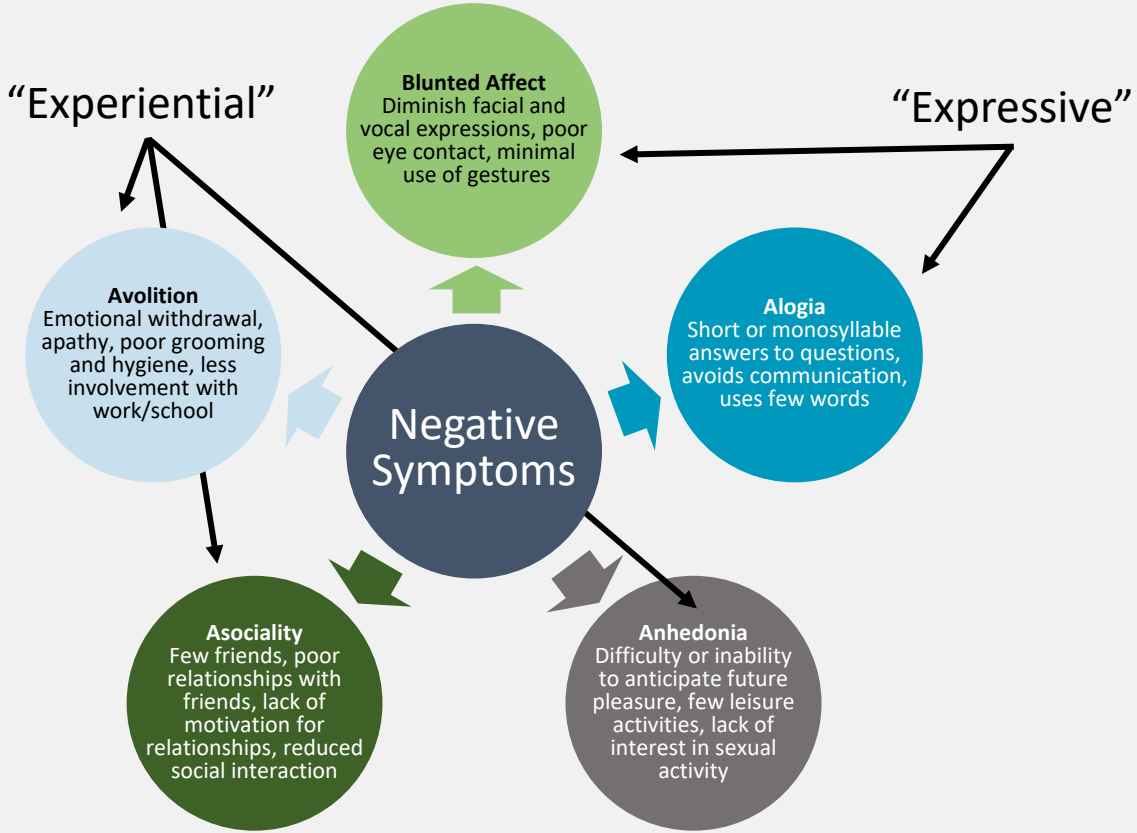
N=117 patients with schizophrenia vs 77 healthy controls[1]



- Patients with schizophrenia have profound and disabling cognitive deficits that interfere with daily functioning, including employment, independent living, and quality of life[2]
- Several neurocognitive domains have been found to be significantly associated with functional outcomes[3]
  - Composite scores demonstrate the strongest correlations with functioning

1. August SM, et al. *Schizophr Res.* 2021;134:76-82; **2.** Bell MD, et al. *Schizophr Bull.* 2001;158:660-661;
3. Green MF, et al. *Schizophr Bull.* 2000;26:119-136.

Detail of Negative Symptoms

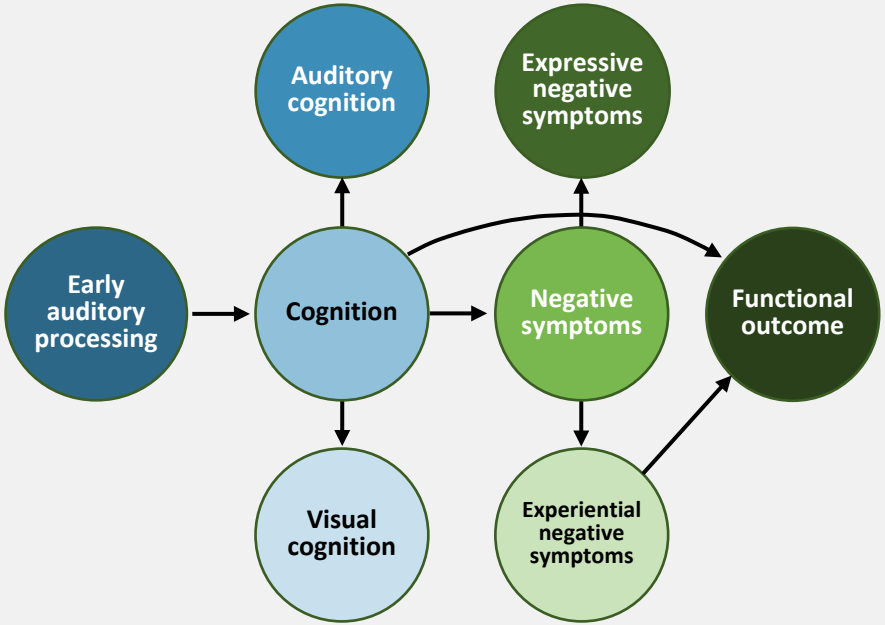


Correll CU, et al. *Neuropsychiatr Dis Treat.* 2020;16:519-534.

Factors Associated With Increased Disability

COGS-2 Study of 1,415 individuals with schizophrenia

M6: Final Model



Domains of Functional Outcome

- Independent living
- Family networks
- Social networks
- **Work productivity**

Thomas ML, et al. *JAMA Psychiatry.* 2017;74:37-46.

Pathophysiology of CIAS and Negative Domains

Genes and molecular pathways

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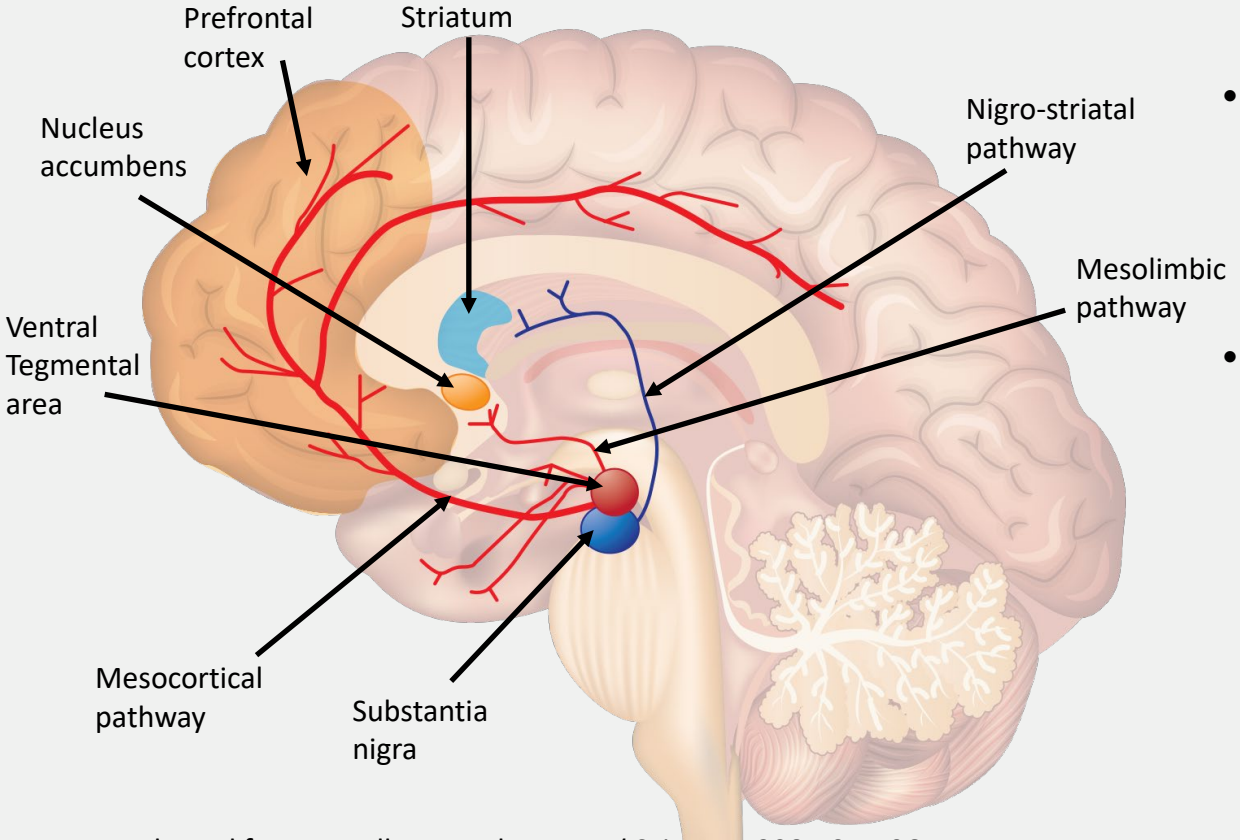
Dopamine and Its Presence and Role in the Brain

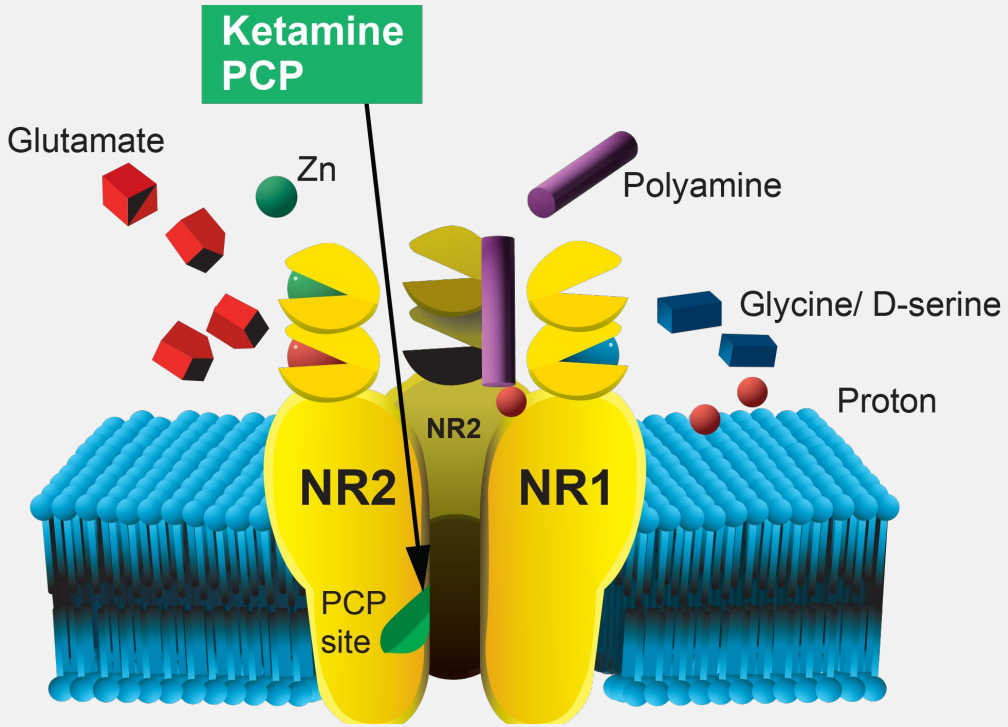


- Multiple dopamine systems in the brain
  - Nigrostriatal
  - Mesolimbic/mesocortical
- Increased salience concept of positive symptoms
  - Dopamine excess increases “salience” of potentially irrelevant events
  - Increased salience leads to paranoia, delusions, increased significance of hallucinations

Image adapted from: Latella D, et al. *J Neurol Sci.* 2019;398:101-106.

Glutamate and NMDAR Receptors

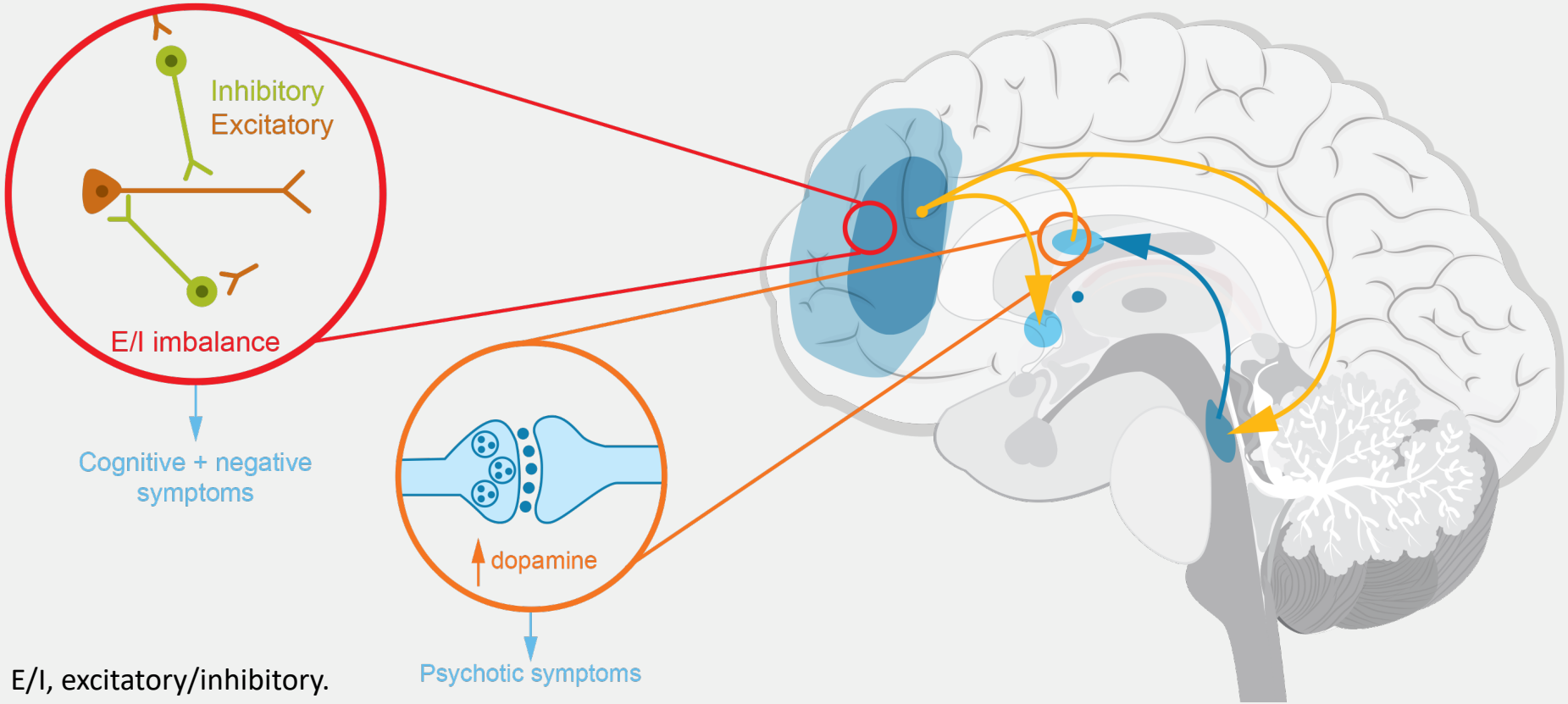
- Glutamate is the main excitatory transmitter in brain (60% of neurons)
- Effects mediated in part by N-methyl-D-aspartate receptors (NMDAR)
- NMDAR antagonists (eg, ketamine, phencyclidine) induce schizophrenia-like symptoms and cognitive impairments
- NMDAR are modulated by other amino acids including glycine and D-serine



PCP, phencyclidine.

Beck K, et al. *JAMA Netw Open.* 2020;3:e204693.

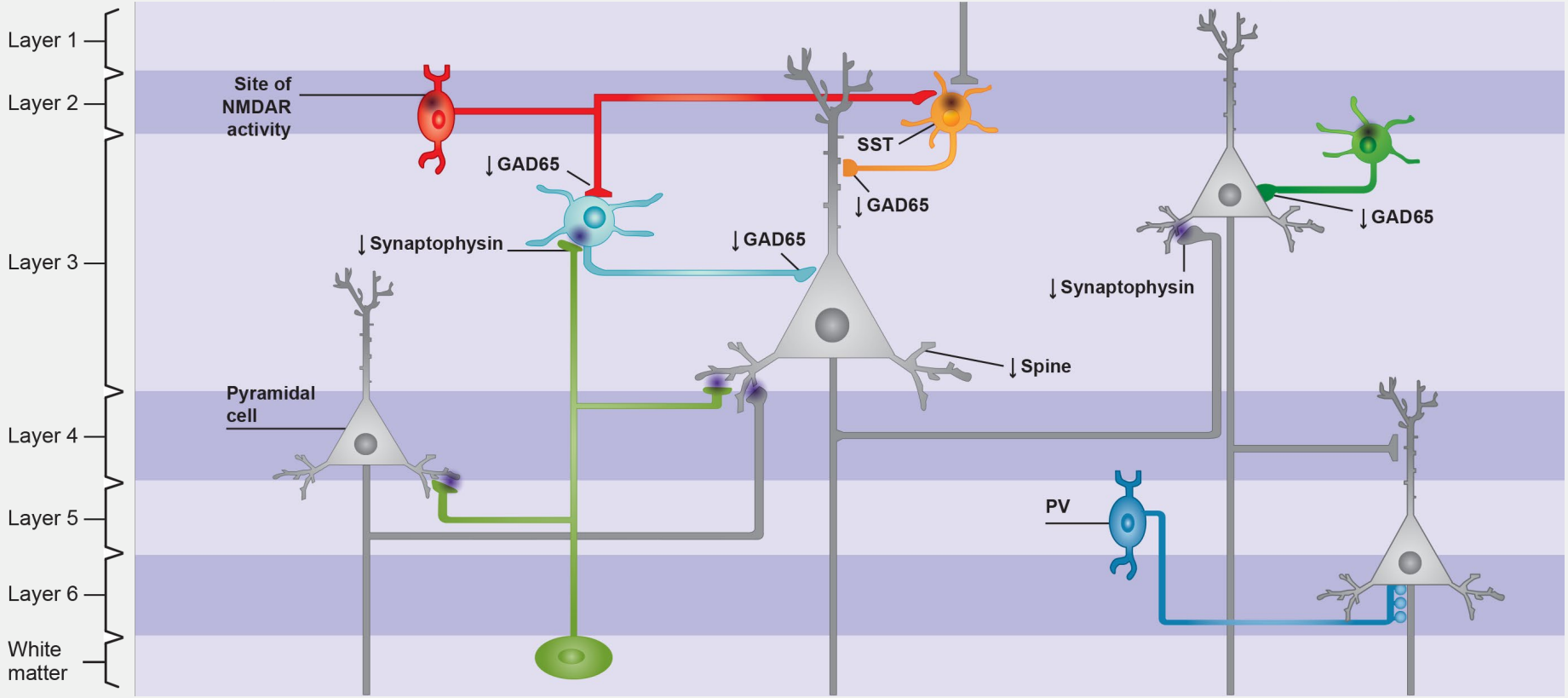
Excitatory, Inhibitory Balance: Prefrontal Cortex



E/I, excitatory/inhibitory.

Adapted from: Howes OD, Shatalina E. *Biol Psychiatry.* 2022;92:501-513.

Excitatory, Inhibitory Balance: Auditory Cortex Neurons

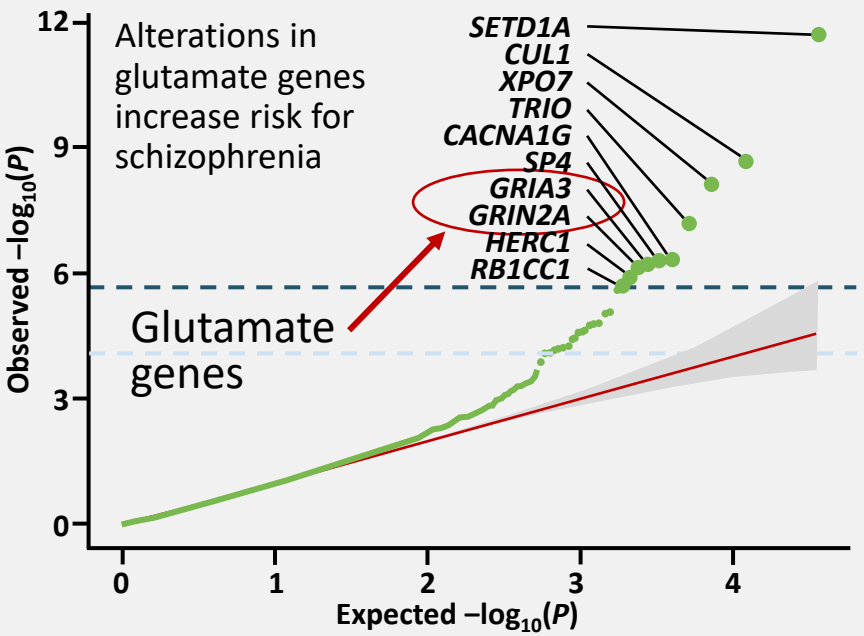


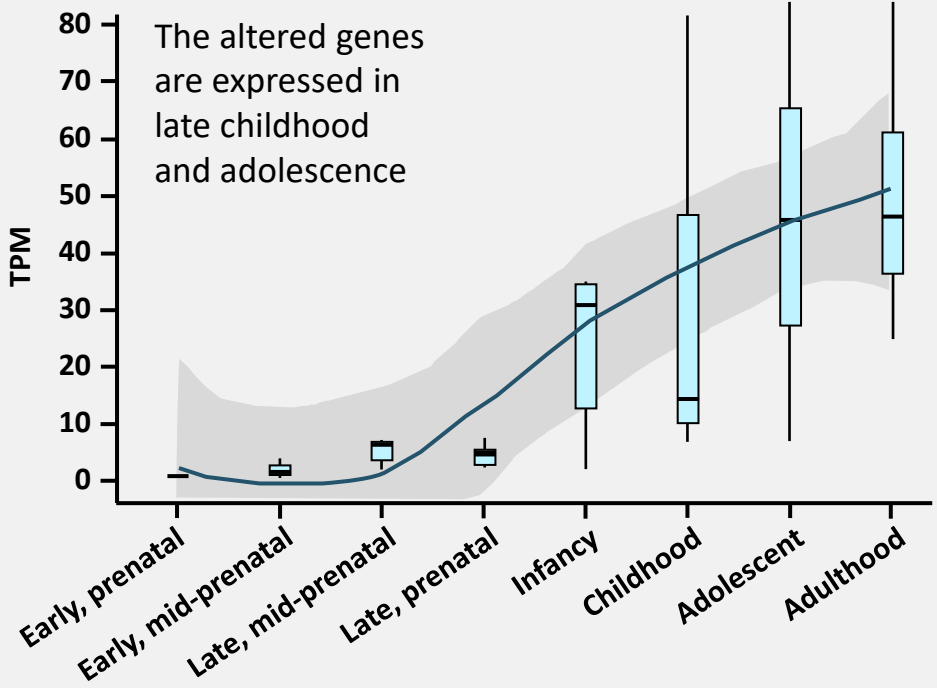
Javitt DC, Sweet RA. *Nat Rev Neurosci.* 2015;16:535-550.

GAD, glutamic acid decarboxylase; PV, parvalbumin; SST, somatostatin.

Why Does Schizophrenia Begin in Late Adolescence?

Largest genetic study of schizophrenia (24,248 schizophrenia and 97,322 controls)





TPM, transcript per million.

Singh T, et al. *Nature.* 2022;604:509-516.

Emerging Treatments

Treatments targeting CIAS and negative symptoms

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CIAS: An Unmet Clinical Need

"Cognitive impairment represents an area of great clinical unmet need, with no approved pharmacologic therapies to treat it. Improved daily functioning, associated with cognitive improvement . . . really should be prioritized."

—John M. Kane, MD
Professor of Psychiatry and Molecular Medicine
Zucker School of Medicine at Hofstra/Northwell
Speaking with Carlos A. Larrauri, MSN
Mental Health Clinician, NAMI Board of Directors Member
Patient diagnosed with schizophrenia at 23 years of age

Larrauri CA, et al. *Neuropsychiatr Dis Treat.* 2023;19:1331-1338.

Why Are There No Approved Treatments for CIAS?

- 200+ CIAS trials listed on ClinicalTrials.gov
- Amount of investment being made in the development of treatments and opportunities for success
  - NIH spends 25x more on cancer than on schizophrenia
  - Industry investment in clinical trials in 2017 was $71.5 billion — dwarfing government efforts
  - There are >1,000 ongoing clinical trials in cancer for every one in CIAS
  - Progress from phase 1 to FDA approval is 5.1% for cancer indications — similar to psychiatry at 6.2%
- Curing cancer is more likely to be personally tangible and may appear to be more morally compelling to investors

Keefe RSE. *World Psychiatry.* 2019;18:167-168.

Emerging Agent for Positive and Negative Symptoms: KarXT*

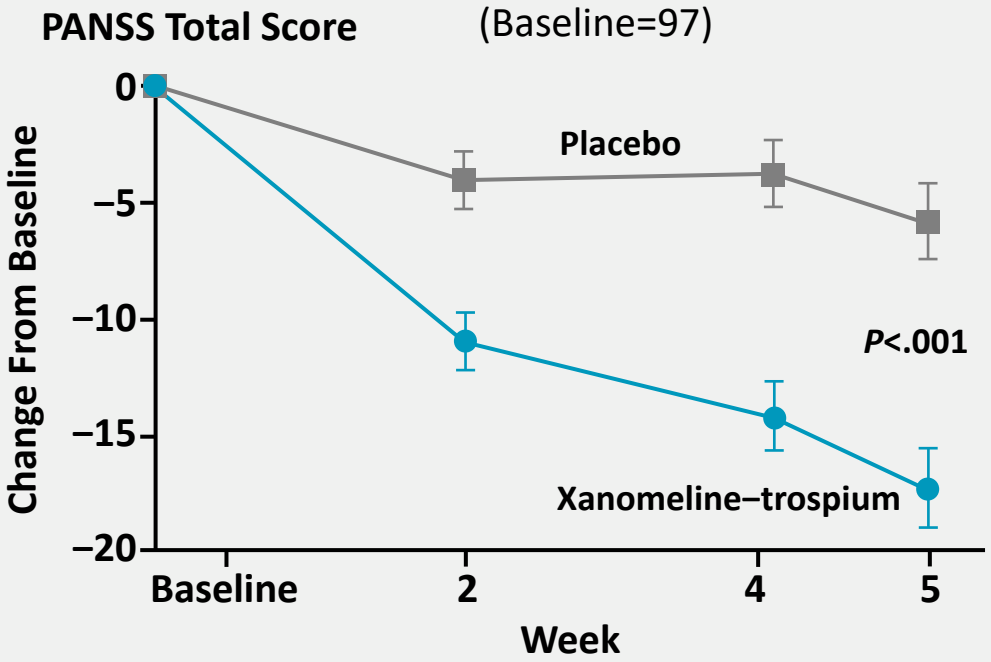
Trial Name ID#	Phase	Trial Focus	Primary Endpoint	Pts	Timeline	Completion
EMERGENT-1 NCT03697252	2	Efficacy, safety, and tolerability in pts with acute exacerbation; KarXT vs PBO	Change from BL in PANSS	182	5 weeks	September 2019
EMERGENT-2 NCT04659161	3	Efficacy and safety in acutely psychotic, hospitalized pts	Change from BL in PANSS	252	5 weeks	May 2022
EMERGENT-3 NCT04738123	3	Efficacy and safety in acutely psychotic, hospitalized pts	Change from BL in PANSS	256	5 weeks	December 2022
EMERGENT-4 NCT04659174	3	Open-label, long-term safety and tolerability†	Incidence of TEAEs	350	53 weeks	December 2023
EMERGENT-5 NCT04820309	3	Open-label, long-term efficacy and safety in adults with schizophrenia	Incidence of TEAEs	586	56 weeks	January 2025
ARISE NCT05145413	3	Add-on for patients with inadequately controlled symptoms	Change in PANSS	400	6 weeks	October 2024

*KarXT, xanomeline + trospium; †Open-label extension trial for EMERGENT-2 or EMERGENT-3 patients. BL, baseline; PANSS, Positive and Negative Syndrome Scale; PBO, placebo; Pts, patients; TEAE, treatment-emergent adverse events.

Source: ClinicalTrials.gov, October 24, 2023.

Efficacy and Safety Results From KarXT Phase 2 Trial

Results from EMERGENT-1 trial (NCT03697252) of KarXT vs placebo (N=182)



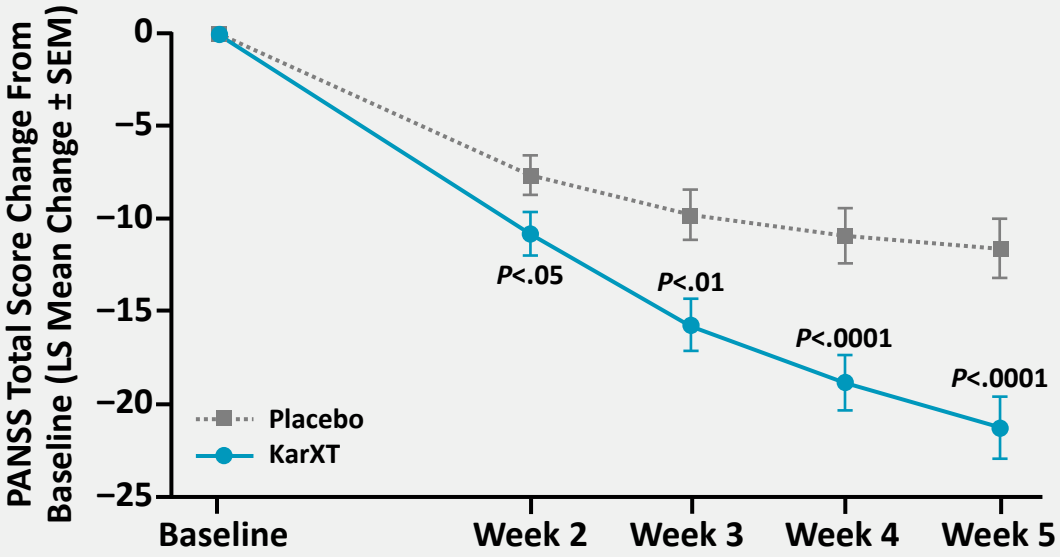
Side Effects	KarXT (n=89)	Placebo (n=90)
Constipation	15 (17%)	3 (3%)
Nausea	15 (17%)	4 (4%)
Dry Mouth	8 (9%)	1 (1%)
Dyspepsia	8 (9%)	4 (4%)
Vomiting	8 (9%)	4 (4%)

Brannan SK, et al. *N Engl J Med*. 2021;384:717-726.

Efficacy and Safety Results From KarXT Phase 3 Trial

Results from EMERGENT-2 Trial (NCT04659161) of KarXT vs placebo (N=251)

Change From Baseline in PANSS Total Score vs Placebo at Week 5



Side Effects	KarXT (n=126)	Placebo (n=125)
Constipation	27 (21%)	13 (10%)
Dyspepsia	24 (19%)	10 (8%)
Nausea	24 (19%)	7 (6%)
Vomiting	18 (14%)	1 (<1%)
Headache	17 (14%)	15 (12%)
Hypertension	12 (10%)	1 (<1%)
Dizziness	11 (9%)	4 (3%)

SEM, standard error of the mean.

Paul SM, et al. ACNP 2022. Abstract M17.

Effect of KarXT on Cognition

Table 2. EMERGENT-2/EMERGENT-3 KarXT Treatment Effect on Cognitive Impairment

Sample	Treatment	LSM Change from Baseline ±SE at Week 5	KarXT vs Placebo		
			LSM Difference ±SE	*P* Value	Cohen's *d*
Full sample	KarXT (n=152)	0.13 ± 0.05	0.06 ± 0.06	0.33	0.12
	Placebo (n=160)	0.07 ± 0.05			
Impaired	KarXT (n=69)	0.41 ± 0.07	0.29 ± 0.10	<0.01	0.52
	Placebo (n=65)	0.13 ± 0.08			

Table 3. EMERGENT-1 KarXT Treatment Effect on Cognitive Impairment

Sample	Treatment	LSM Change from Baseline ±SE at Week 5	KarXT vs Placebo		
			LSM Difference ±SE	*P* Value	Cohen's *d*
Full sample	KarXT (n=60)	0.13 ± 0.11	0.18 ± 0.13	0.16	0.20
	Placebo (n=65)	-0.05 ± 0.11			
Impaired	KarXT (n=23)	0.57 ± 0.19	0.50 ± 0.22	0.03	0.50
	Placebo (n=37)	0.07 ± 0.13			

LSM, least square mean; SE, standard error.

- No significant effect overall
- May improve cognition in a subset of individuals

Horan W, et al. ECNP Congress 2023. Poster P.1232.

KarXT Mechanism of Action

KarXT acts on presynaptic muscarinic receptors M1 and M4; this indirectly regulates dopamine release by reducing acetylcoholine

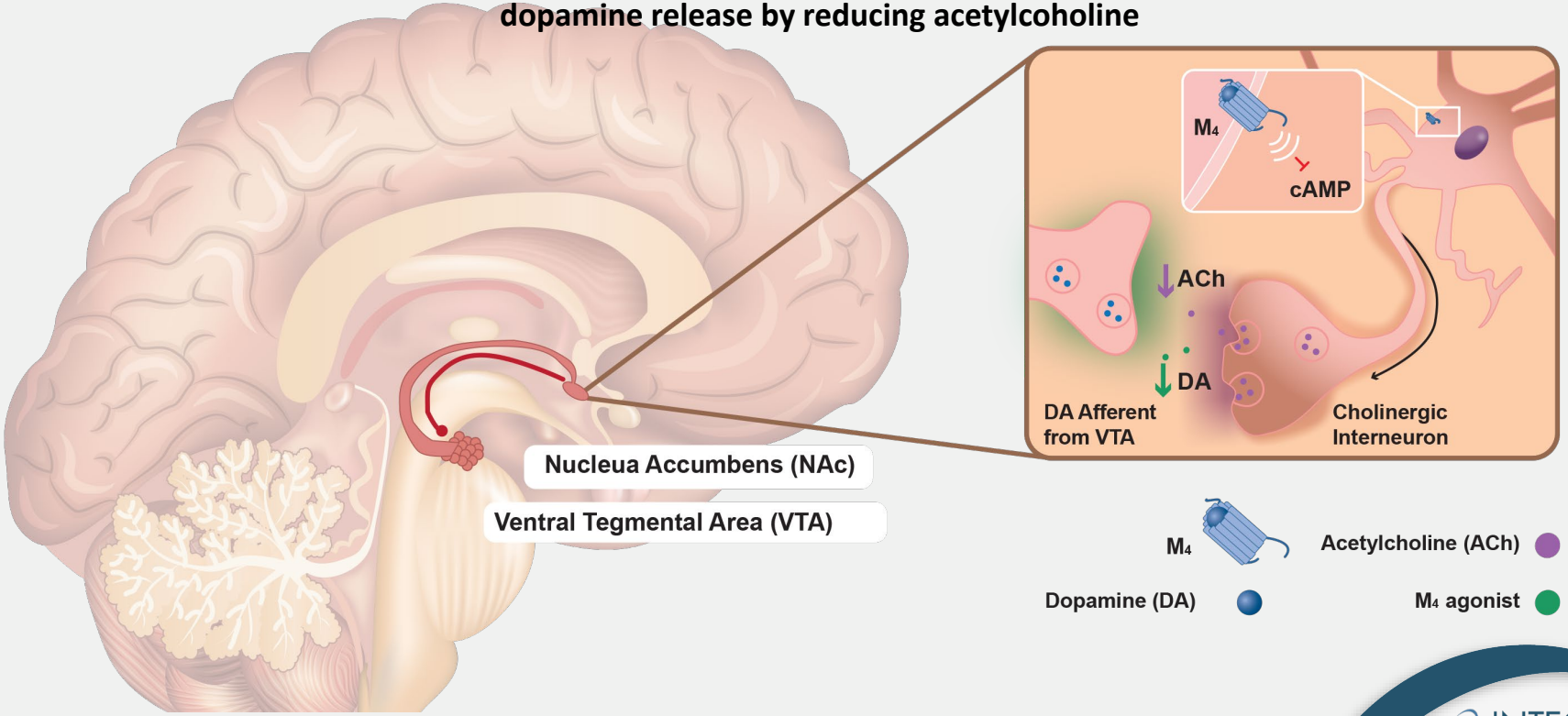
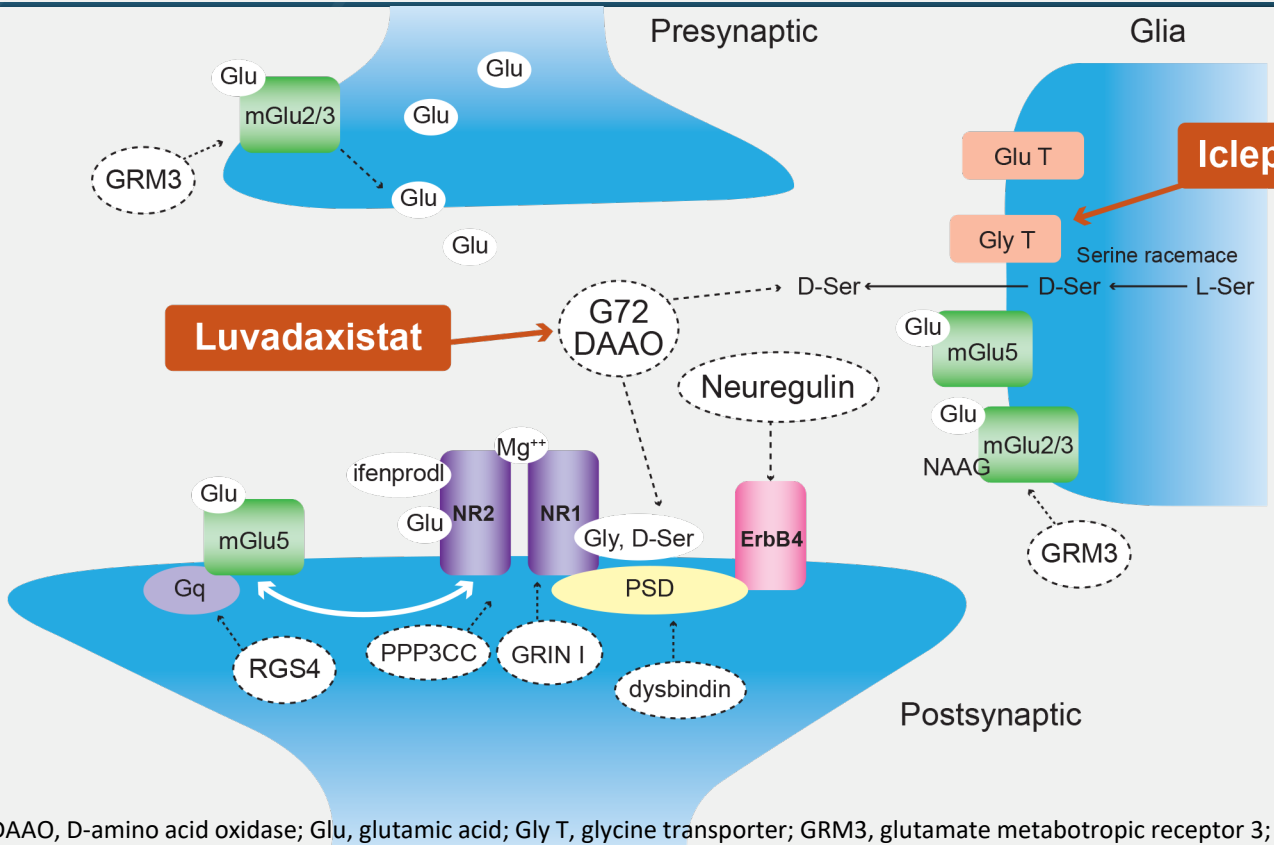


Figure adapted from: Paul SM, et al. *Am J Psychiatry.* 2022;179:611-627.

Emerging Treatments Targeting NMDA Receptors



Strategy

- Glycine and D-serine modulate NMDAR
- Are difficult to administer on their own
- New drugs reduce glycine, D-serine elimination from brain
- "Block the drain" instead of "turn on the faucet"

DAAO, D-amino acid oxidase; Glu, glutamic acid; Gly T, glycine transporter; GRM3, glutamate metabotropic receptor 3; NAAG, N-acetylaspartylglutamatic acid; PSD, postsynaptic density; PPP3CC, protein phosphatase 3 catalytic subunit gamma; RGS4, regulator of G protein signaling 4; Ser, serine.
Figure adapted from: Moghaddam B. *Neuron.* 2003;40:881-884.

Explaining Endpoint Measurement in CIAS Trials

- MATRICS MCCB (Measurement and Treatment Research to Improve Cognition in Schizophrenia; MATRICS Consensus Cognitive Battery)
- Referred to simply as “MCCB,” a rating scale comprising 10 tests assessing 7 cognitive domains
  - Speed of processing
  - Attention vigilance
  - Working memory
  - Verbal learning
  - Visual learning
  - Reasoning and problem solving
  - Social cognition

Horan WP, et al. *Curr Top Behav Neurosci.* 2023;63:407-436; Rosenbrock H, et al. *Eur Arch Psychiatry Clin Neurosci.* 2023;273:1557-1566.

Emerging Agent: Iclepertin in Phase 3 Trials

Trial Name* and/or ID#	Trial Focus	Primary Endpoint	Pts	Timeline	Estimated Completion
CONNEX-1 NCT04846868	Effect of iclepertin on cognition and functional capacity	Change from BL in MATRICS MCCB	586	26 weeks	January 2025
CONNEX-2 NCT04846881	Effect of iclepertin on cognition and functional capacity	Change from BL in MATRICS MCCB	586	26 weeks	January 2025
CONNEX-3 NCT04860830	Effect of iclepertin on learning and memory	Change from BL in MATRICS MCCB	586	26 weeks	January 2025
NCT05211947	LT safety of iclepertin in patients who participated in a CONNEX trial	Occurrence of TEAEs	1401	1 year & 12 days	February 2026

*If assigned.

LT, long-term.

Source: ClinicalTrials.gov, October 24, 2023.

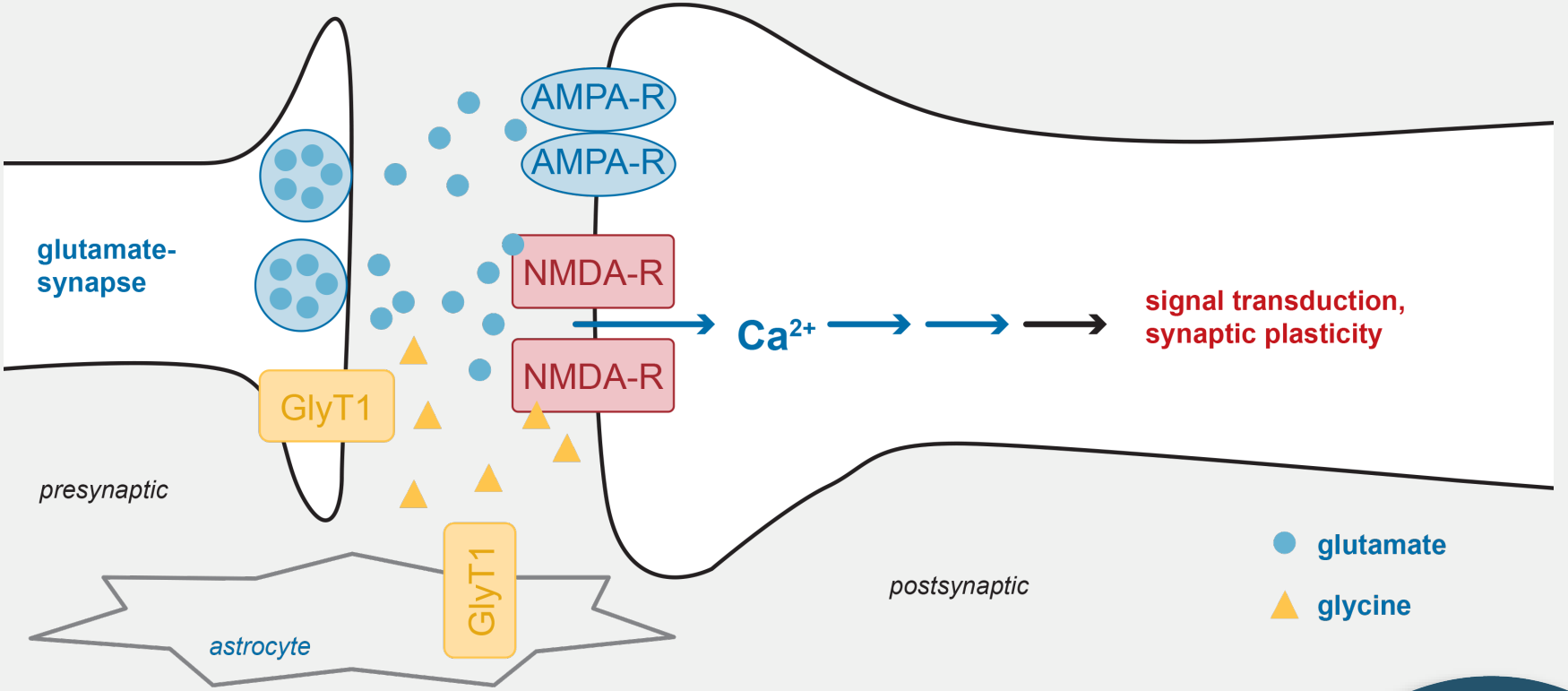
Emerging Agent: Iclepertin Phase 2 Trial Results

- Formerly BI-425809, iclepertin a GlyT1 inhibitor
- Published findings from phase 2 clinical trial (NCT02832037), N=509
  - **Primary endpoint:** Change from baseline in MCCB
  - **Length:** 12 weeks
  - **Dosing:** Once-daily 2 mg, 5 mg, 10 mg, 25 mg, or placebo
  - **Efficacy:** Greater mean improvement in MCCB overall composite score vs placebo; greatest improvements seen with 10 mg and 25 mg doses
  - **Safety:** 41%–59% of patients experienced AEs, depending on dose
    - Most common: Gastrointestinal disorders (11%-2%, depending on dose), headache (8% overall), somnolence (6%-2%)

GlyT1, glycine transporter 1.

Fleischhacker WW, et al. *Lancet Psychiatry.* 2021;8:191-201.

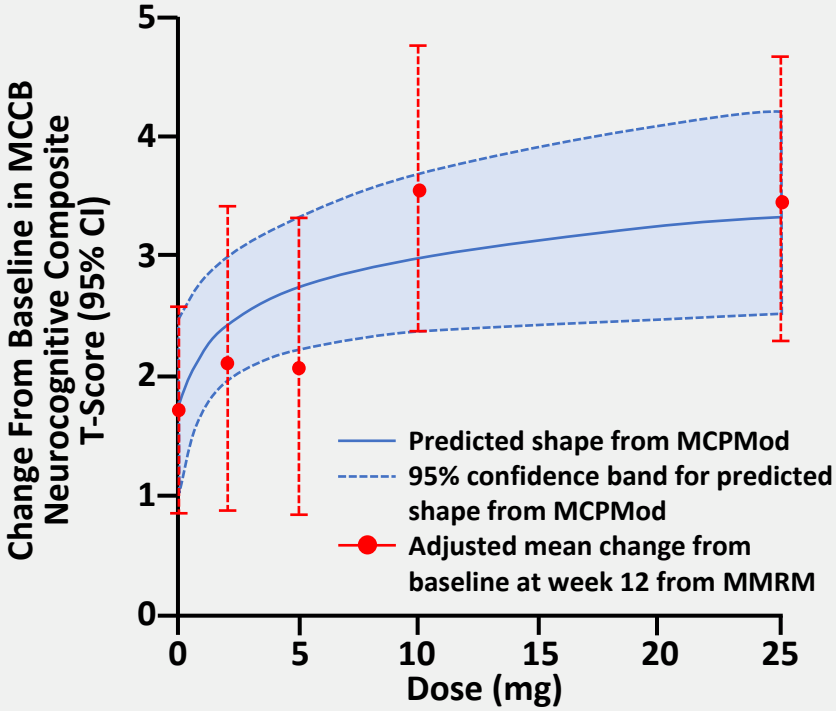
Iclepertin Mechanism of Action

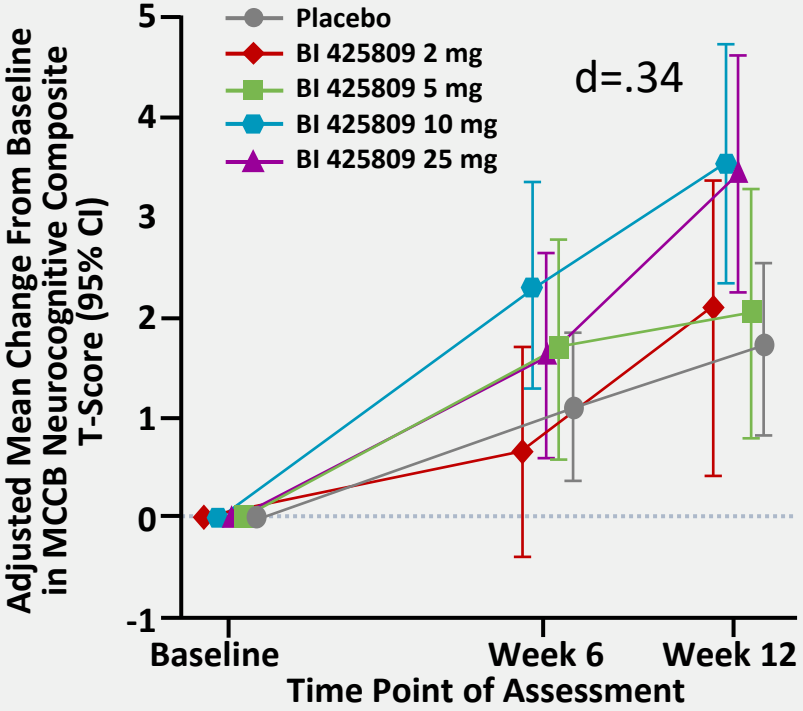


AMPA-R, α-amino-2 hydroxy-5-methyl-4-ixoxazolepropionic acid receptor.

Figure adapted from: Rosenbrock H, et al. *Eur Arch Psychiatry Clin Neurosci.* 2023;273:1557-1566.

Efficacy of Iclepertin





CI, confidence interval; MCPMod, multiple comparison procedure and modeling; MMRM, mixed model repeated measures.

Fleischhacker WW, et al. *Lancet Psychiatry.* 2021;8:191-201.

Emerging Agent: Luvadaxistat* in Phase 2 Trial

Trial Name* and/or ID#	Trial Focus	Primary Endpoint	Pts	Timeline	Estimated Completion
ERUDITE NCT05182476	Efficacy and safety in as add-on treatment for patients with CIAS	Change from BL in BAC	200	98 days	January 2025

Luvidaxistat:

- DAAO inhibitor
- Being developed as adjunctive to antipsychotics
- Increases D-serine levels in the brain
- Improved cognition at low dose
- “Inverted U” shape curve

*Formerly TAK-831.

BAC, Brief Assessment of Cognition in Schizophrenia.

Source: ClinicalTrials.gov, October 24, 2023.

Other Management Considerations

Treatment goals, adherence, concepts in digital therapies

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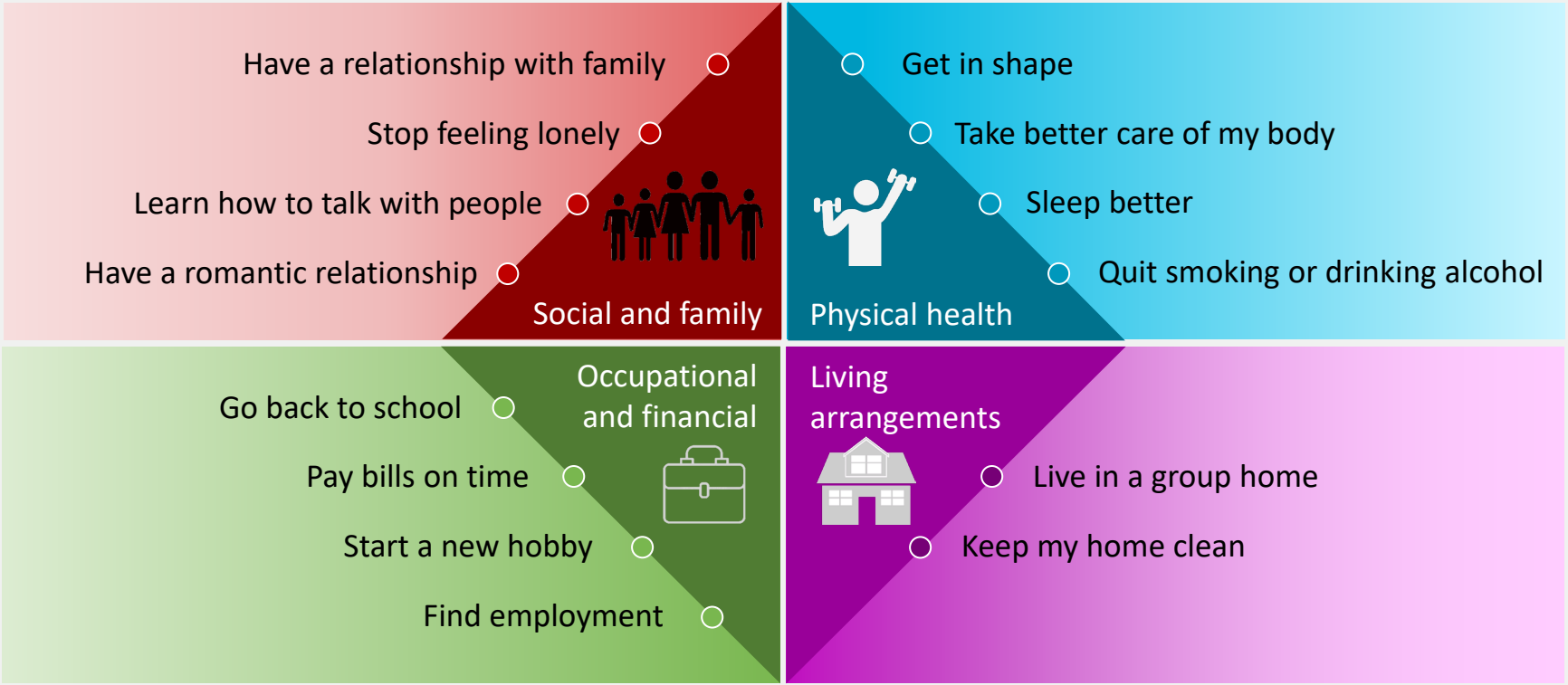
Treatment Goals for Patients With Schizophrenia



Correll CU, et al. *J Clin Psychiatry.* 2022;83:LU21112AH1.

Shared Decision-Making

Provides knowledge about the condition
Including etiology, prognosis, and potential outcomes

Inquires about patient preference
Prior medication trials, lifestyle, and limitations

Shares insight about treatment options
Including risks, benefits, side effects, and alternatives

Shares experience and values
Preferences, socioeconomic circumstances, and experience of illness

Voices their concerns
Including personal risk tolerance and accessibility of treatment

Asks questions of the provider
Regarding treatment options, outcomes, anecdotal experience

Elwyn G, et al. *J Gen Intern Med.* 2012;27:1361-1367; Siafis S, et al. *BMC Psychiatry.* 2022;22:406.

Assessing Adherence

Instead of asking "Are you taking your medications every day?" Try these questions:

Patient's Attitudes

- Do you think you benefit from taking your medication?
- Have you ever decided not to take your medication on purpose?
- What led to that?

Cognitive Impairment

- When do you usually take your medication?
- What reminds you to take it?
- How much do you take?

Home Life

- Does anyone help you remember to take your medication?
- Does anyone think you shouldn't take the medication?

Healthcare Delivery

- How do you get your refills?
- Do you feel that we understand your concerns about treatment?

Kane JM, et al. *J Clin Psychiatry.* 2019;80:IN18031AH1C.

Potential Benefits of Digital Therapeutics

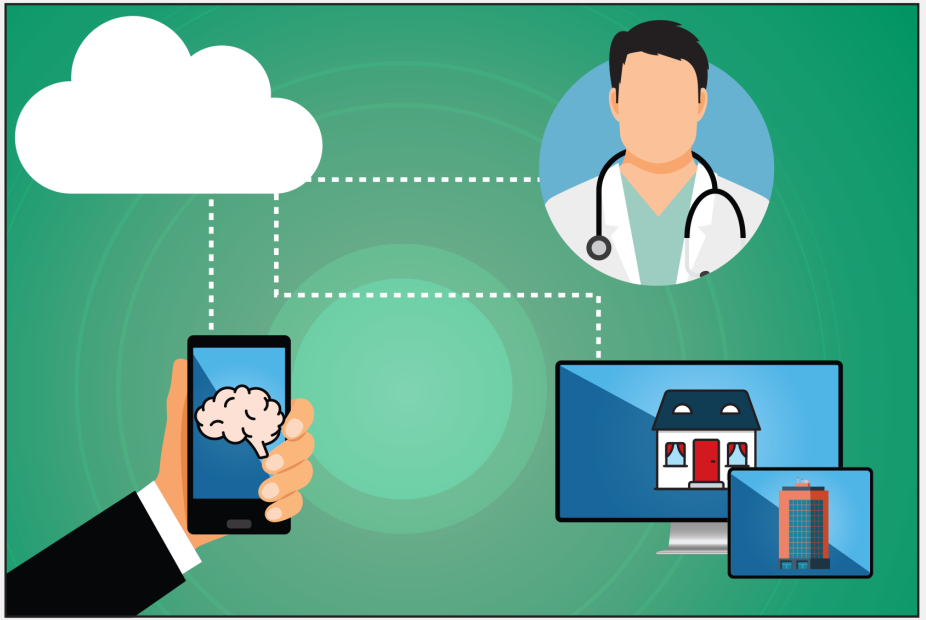
- Digital therapeutics using smartphones, wearable devices expanding throughout medicine
- In psychiatry, these could be harnessed to[1-5]
  - Motivate treatment goals, enhance adherence
  - Individualize treatment, prevent relapse
  - Improve cognition, social deficits
  - Provide real-time assessment of function

- 16-week CONVOKE trial (NCT05838625) now underway in 432 patients using smartphone app to improve negative symptoms[6]

1. Bell I, et al. *Schizophr Res Cogn.* 2022;28:100247. **2**. Chivilgina O, et al. *Sci Eng Ethics.* 2021;27:25. **3**. Curto M, Fazio F, Ulivieri M, et al. *Expert Opin Pharmacother.* 2021;22:1143-1155. **4**. Harvey PD. *Am J Psychiatry.* 2022;179:445-447. **5**. Lal S, et al. *Schizophrenia (Heidelb).* 2023;9:21. **6**. VanDewater K. *Helio Psychiatry*. May 17, 2023.

Exploring the Potential for Digital Therapeutics

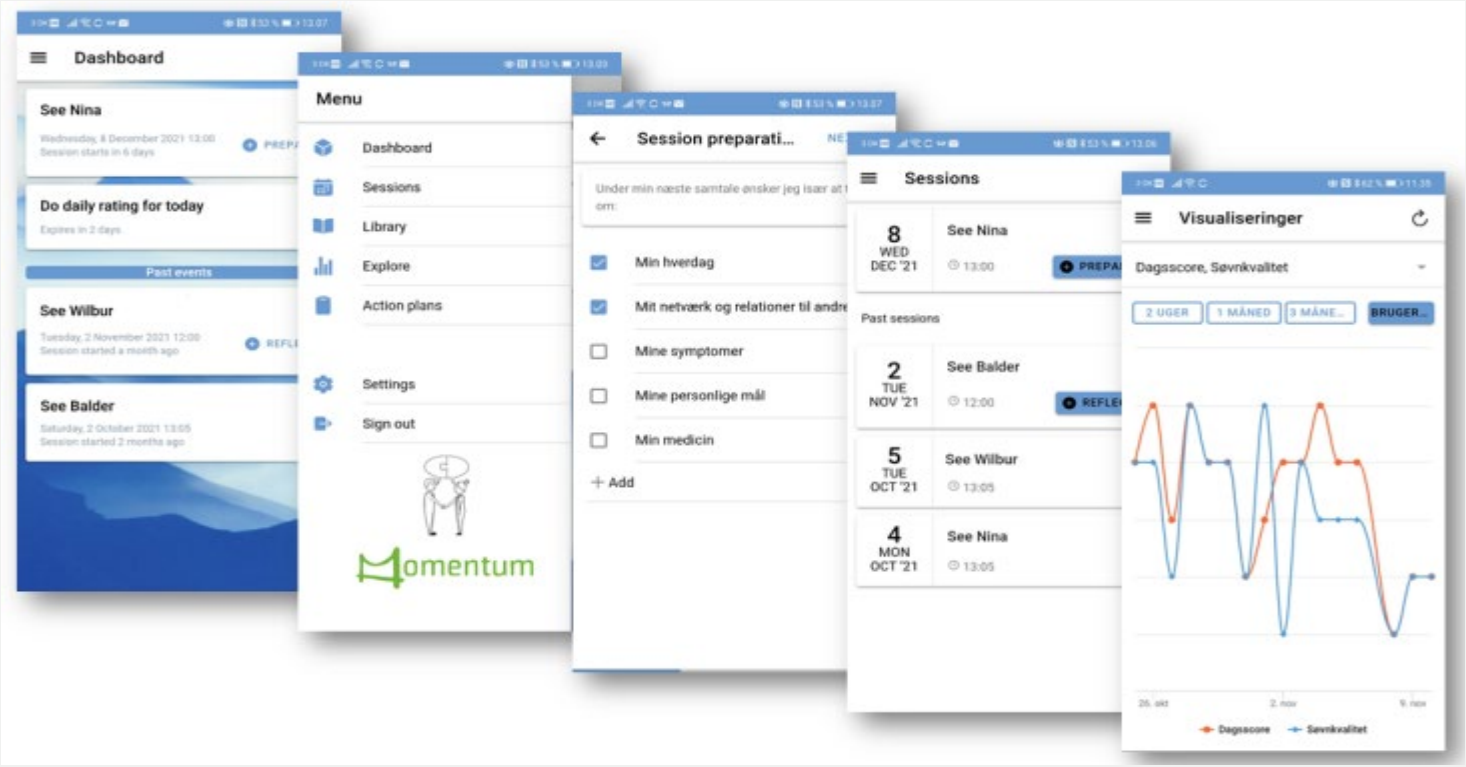
- Ubiquity of smartphones can be harnessed to resolve unmet therapeutic needs
- Top unmet needs per survey of 75 patients with schizophrenia
  - Improving social skills (19%)
  - Reducing stress related to disease (19%)
  - Meeting new people (17%)
  - Difficulty setting goals, completing activities (13%)
  - Sharing progress with healthcare providers



Campellone T, et al. *CNS Spectrums.* 2023;28:263.

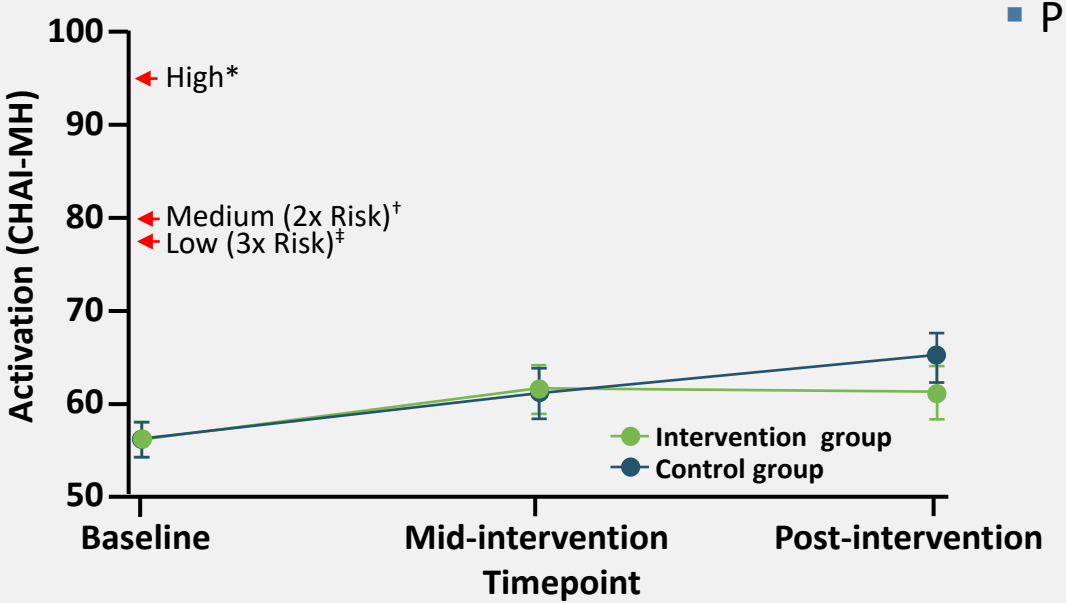
Smartphone App Study for Shared Decision-Making/Adherence

Momentum trial of schizophrenia patients in outpatient setting (N=1)



Vitger T, et al. *J Med Internet Res.* 2022;24:e40292.

Momentum Trial Primary Endpoint Results



- Primary endpoint: Difference in CHAI-MH
  - 10 items assessing health activation
    - Defined as "an individual's willingness to take on the role of managing their health and healthcare"
  - Effect size improvement of 0.42 between intervention and control groups
  - Statistically significant difference of 4.39, 95% CI 0.99–7.79; *P*=.01

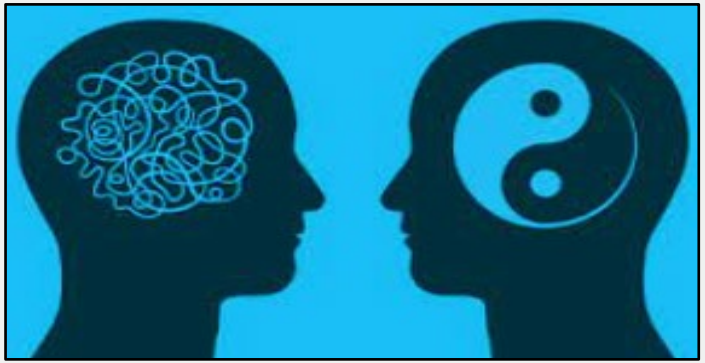
Cutpoints indicate risk for decline over the next 3 years.*Negligible risk for decline; †More than twice the risk for decline between 80 and 95; ‡More than 3 times the risk for decline 79 and below.

CHAI-MH, Consumer Health Activation Index for Mental Health.

Figure adapted from: Vitger T, et al. *J Med Internet Res*. 2022;24:e40292. Wolf MS. *Med Decis Making*. 2018;38:334-343.

Potential Cautions for Digital Therapeutics

- Significant ethical thought and consideration needed when designing these apps to ensure privacy and quality care
- Must be used in conjunction with human support and clinician interaction
- Technology in this space is currently lacking
- Compelling evidence of efficacy
- Data confidentiality
- Clear standards for safety of daily implementation
- Understanding of how these technologies might shift or change responsibilities for clinicians



- User-centric interface that is easy to understand and will meet individualized patient needs

Bell I, et al. *Schizophr Res Cogn*. 2022;28:100247; Chivilgina O, et al. *Sci Eng Ethics*. 2021;27:25; Ghaemi SN, et al. *JMIR Form Res*. 2022;6:e29154; Harvey PD. *Am J Psychiatry*. 2022;179:445-447; 5. Lal S, et al. *Schizophrenia* (Heidelb). 2023;9:21.

Case Study

Married woman with children, struggling with mental processing

INTEGRITY
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Heather: 35-Year-Old Woman

- Onset of schizophrenia and diagnosis at age 28
- Married with 2 children
  - Ages 12 and 10
- Unable to hold down a job
- Struggles with responsibilities of motherhood
  - Found it difficult to keep up with online Zoom classes and schoolwork when children were home during COVID-19 pandemic
- Successfully treated for last 7 years with 2nd-generation antipsychotic
  - But cognitive impairment remains unimproved
  - Husband reports she lacks motivation and has trouble interpreting what others mean when they talk

Summary

- ***All*** currently approved antipsychotics work via dopamine blockade, which doesn't significantly affect CIAS or negative domains
- CIAS and negative symptoms have long-term deleterious impact on education and employment
- Pharmacologic treatments still in development could improve CIAS and negative symptoms
- Digital therapeutic interventions could work synergistically with pharmacologic to improve CIAS and negative domains
- Treatment goals and shared decision-making can improve treatment adherence, cognition, and social deficits