PHARMACOLOGICAL, NEUROMODULATION & PSYCHOSOCIAL MANAGEMENT

Negative & Obsessive Symptoms of Schizophrenia

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For MD / DNB / DPM Psychiatry Residents — Departmental Teaching Session

SESSION OVERVIEW

What We'll Cover Today

- Why negative and obsessive symptoms deserve their own lecture — hint: nobody consults you for them at 2 a.m.
- Negative symptoms: how to recognize them, tell them apart from their many impostors, and a full six-step management ladder
- What's genuinely new in the pharmacology — muscarinic drugs, glutamatergic agents, and a fairly crowded drug graveyard
- Neuromodulation and psychosocial care for negative symptoms — not just "add rTMS and hope for the best"
- Obsessive-compulsive symptoms in schizophrenia — the diagnosis your textbook probably glossed over
- An integrated framework, an honest scorecard, and the pitfalls examiners love to ask about

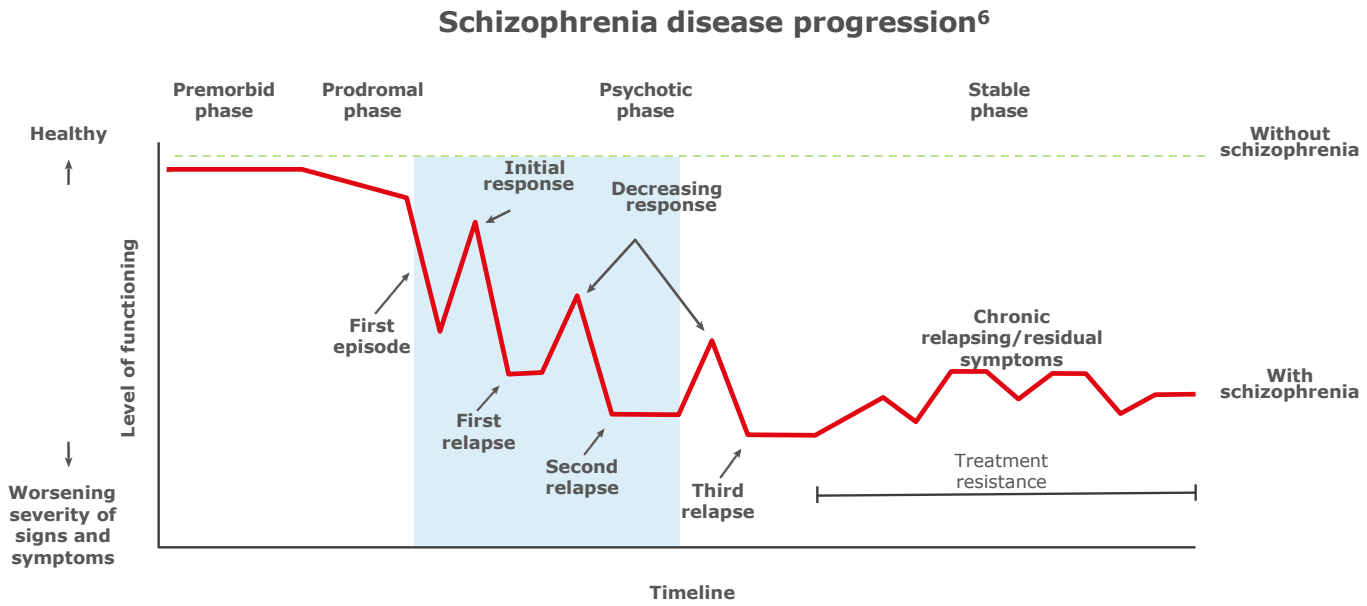
BEFORE WE BEGIN

The Quiet Symptoms

Two symptom domains that rarely make noise on the ward, and rarely get asked about either

- Positive symptoms get you paged at night. Negative and obsessive symptoms get a passing mention in the discharge summary — and yet they drive most of the long-term disability and unemployment in schizophrenia
- Up to 60% of patients with schizophrenia have clinically significant negative symptoms; up to a third have obsessive-compulsive symptoms — neither shows up on a routine mental status exam unless you go looking
- Both domains were, until recently, chronically under-treated, mostly because drug development money went almost entirely toward positive symptoms for the past seventy years
- This talk covers exactly the two domains most likely to be missed on your ward round — and most likely to turn up in your next viva

Negative symptoms are common in schizophrenia and can occur in every phase of the illness



Negative symptoms can occur at any point in the course of illness, although they are reported as the most common first symptom of schizophrenia

Figure adapted from Nasrallah & Smeltzer 2011.

LAT, long-acting therapy.

1. Tandon R et al. *Schizophr Res* 2009; 110(1–3): 1–23; 2. Cahn W et al. *Eur Neuropsychopharmacol* 2009; 19: 147–151; 3. Sullivan EV et al. *Biol Psychiatry* 1996; 39: 234–240; 4. Crespo-Facorro B et al. *Int Rev Psychiatry* 2007; 19: 325–336; 5. Emsley R et al. *Schizophr Res* 2013; 148(1–3): 117–121; 6. Nasrallah HA & Smeltzer DJ. Contemporary diagnosis and management of the patient with schizophrenia, 2nd edn. Newtown, PA: Handbooks in Health Care Co, 2011; 7. Stahl SM. *CNS Spectr* 2014; 19: 3–5.

SECTION 1 OF 6

Negative Symptoms — Recognition & Assessment

Five domains, one shared complaint: none of them make noise on a ward round

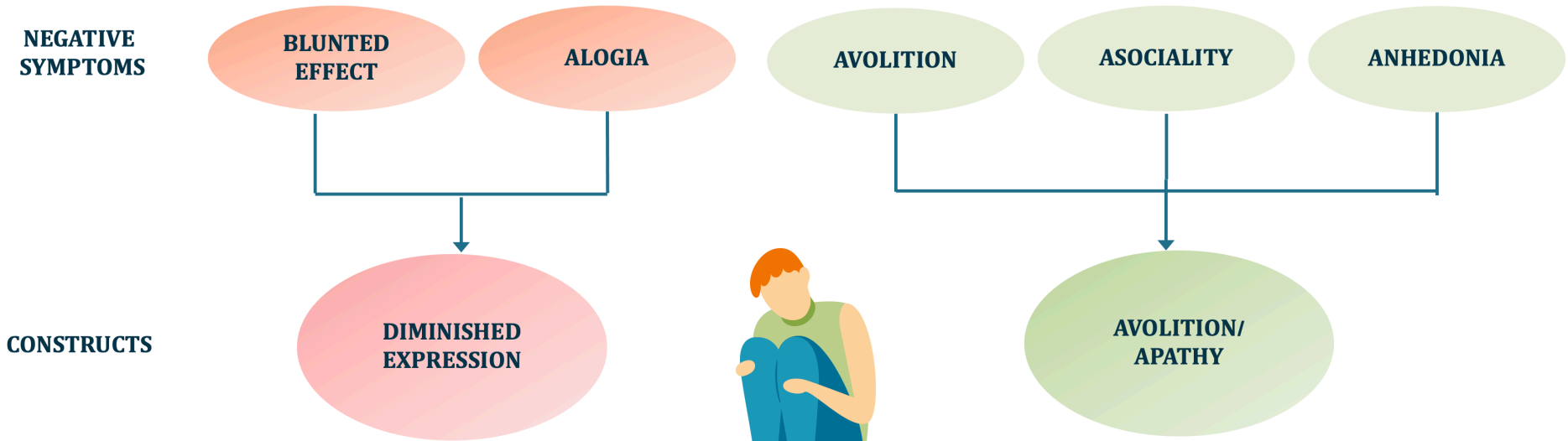
PHENOMENOLOGY

The Five Domains — and the Mnemonic Nobody Asked For

Five domains, one shared complaint: none of them make noise

- Avolition — reduced goal-directed activity; the patient who has quietly decided personal hygiene is somebody else's department
- Anhedonia — reduced capacity for pleasure; consummatory pleasure (enjoying the moment) is often preserved, it's anticipatory pleasure (looking forward to it) that goes missing
- Asociality — reduced interest in social contact, not simply reduced opportunity for it — the distinction matters when the ward itself is understimulating
- Alogia — reduced quantity and spontaneity of speech; on the ward this gets misread as "uncooperative" more often than it should
- Affective blunting — reduced range and intensity of expressed emotion, which is not the same as feeling nothing internally — ask, don't assume
- NIMH-MATRICS consensus groups these into two clusters — motivation/pleasure (avolition, anhedonia, asociality) and diminished expression (alogia, blunted affect) — and the two clusters can respond differently to the same treatment

KEY NEGATIVE SYMPTOM CONSTRUCTS



1. Blunted affect: Decreased expression of emotion
2. Alogia: Reduction in quantity of words spoken
3. Avolition: Reduced initiation and persistence of goal-directed activity due to decreased motivation
4. Asociality: Reduced social interactions and initiative due to decreased interest in relationships with others
5. Anhedonia: Reduced experience of pleasure during an activity or in anticipation of an activity. (Consummatory / Motivational Anhedonia)

Correll, Christoph U., and Nina R. Schooler. "Negative symptoms in schizophrenia: a review and clinical guide for recognition, assessment, and treatment." *Neuropsychiatric disease and treatment* 16 (2020): 519.

THE DISTINCTION THAT MATTERS MOST

Primary (Deficit) vs Secondary Negative Symptoms

PRIMARY / DEFICIT	SECONDARY — TREAT THE CAUSE
Idiopathic and enduring (present for a year or more), persisting even when positive symptoms and mood are well controlled	Due to unresolved positive symptoms (paranoia driving withdrawal) — treat the psychosis, not the "negative symptom"
Deficit schizophrenia: a distinct, more chronic, poorer-prognosis subtype affecting roughly 15–25% of patients	Due to depression — screen with a structured tool; don't assume low mood is "just negative symptoms"
Does not reliably respond to antidepressant augmentation the way secondary symptoms sometimes do	Due to antipsychotic-induced EPS or oversedation — by far the most common reversible mimic on the ward
The population every "new negative-symptom drug" trial is desperately trying to enrich for, and usually fails to isolate cleanly	Due to environmental understimulation (a bare ward is not a stimulating environment) or ongoing substance use

Table 1 Proposed Negative Symptom Terminology

Term	Proposed Definition
Negative symptoms	Broadly defined as a reduction of normal functions either related to motivation and interest (eg, avolition, anhedonia, and asociality) or to expressive functions (eg, blunted affect and alogia)
Deficit syndrome	A symptom complex characterized by primary and enduring negative symptoms that are present for most of the preceding 12 months (including during periods of clinical stability); they are caused by a specific disease process that is separate from the genetic and neurobiological factors that contribute to nondeficit schizophrenia
Predominant negative symptoms	Clinically relevant negative symptoms of greater relative severity than co-occurring positive symptoms; no duration is specified so symptoms could be present for a relatively short time period or they could be long-standing
Prominent negative symptoms	Pronounced and clinically relevant negative symptoms of unspecified duration; reflects the clinical reality of most patients whose illness does not have a clear prominence of either positive or negative symptoms, and may be characterized by both
Primary negative symptoms	Negative symptoms that are thought to be intrinsic to the underlying pathophysiology of schizophrenia
Secondary negative symptoms	Negative symptoms that are thought to be related to other factors, such as psychiatric or medical comorbidities, treatment adverse effects, or environmental factors
Persistent (enduring) negative symptoms	Primary negative symptoms or secondary negative symptoms that have not responded to treatment for a minimum of 6 months, interfere with normal role functioning, and persist during periods of clinical stability

Rating Scales You Should Actually Know

- PANSS Negative subscale — 7 items, widely used because everyone already uses PANSS, but a fairly blunt instrument for this specific job
- SANS (Scale for the Assessment of Negative Symptoms) — the older reference standard, 25 items across 5 domains; thorough, and long enough that nobody uses it at 9 a.m. on a busy OPD day
- BNSS and CAINS — newer MATRICS-consensus instruments built specifically around the two-factor model, now the preferred outcome measures in trials
- None of these substitute for a good clinical interview across two or more visits — negative symptoms need to be observed as a stable trait, not judged from a single bad day on the ward
- Ward-round tip: ask about a typical day, not a checklist — avolition reveals itself in what the patient actually does between 8 a.m. and 8 p.m., not in yes/no answers to a rating scale

THE 4-ITEM NEGATIVE SYMPTOM ASSESSMENT (NSA-4) INSTRUMENT:

A Simple Tool for Evaluating Negative Symptoms in Schizophrenia Following Brief Training

by LARRY ALPHS, MD, PhD; ROBERT MORLOCK, PhD; CHERYL COON, PhD; ARJEN VAN WILLIGENBURG, MS; and JOHN PANAGIDES, PhD

Dr. Alphs is from Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, New Jersey (at the time this research was conducted, Dr. Alphs was employed at Pfizer Global R&D, Ann Arbor, Michigan); Dr. Morlock is from Biogen Idec, La Jolla, California (at the time this research was conducted Dr. Morlock was employed at Pfizer Global R&D, Ann Arbor, Michigan); Dr. Coon is from RTI Health Solutions, Research Triangle Park, North Carolina; Mr. van Willigenburg is from Complete Healthcare Communications Europe, The Netherlands (at the time this research was conducted Mr. van Willigenburg was an employee at Schering Plough Corp, Summit, New Jersey); and Dr. Panagides is from Schering Corp., a division of Merck and Co., Summit, New Jersey.

Psychiatry (Edgemont) 2010;7(7):26–32

ABSTRACT

Objective. To assess the ability of mental health professionals to use the 4-item Negative Symptom Assessment instrument, derived from the Negative Symptom Assessment-16, to rapidly determine the severity of negative symptoms of schizophrenia.

Design. Open participation.

Setting. Medical education conferences.

Participants. Attendees at two international psychiatry conferences.

Measurements. Participants read a brief set of the 4-item Negative Symptom Assessment instructions and viewed a videotape of a patient with schizophrenia. Using the 1 to 6 4-item Negative Symptom Assessment severity rating scale, they rated four negative symptom items and the overall global negative symptoms. These ratings were compared with a consensus rating determination using frequency distributions and Chi-square tests for the proportion of participant ratings

FUNDING: This research was funded by Schering Corp., a division of Merck and Co., and Pfizer, Inc.

FINANCIAL DISCLOSURE: Larry Alphs is the owner of the copyright to the NSA-4. The other authors have no conflicts of interest relevant to the content of this article.

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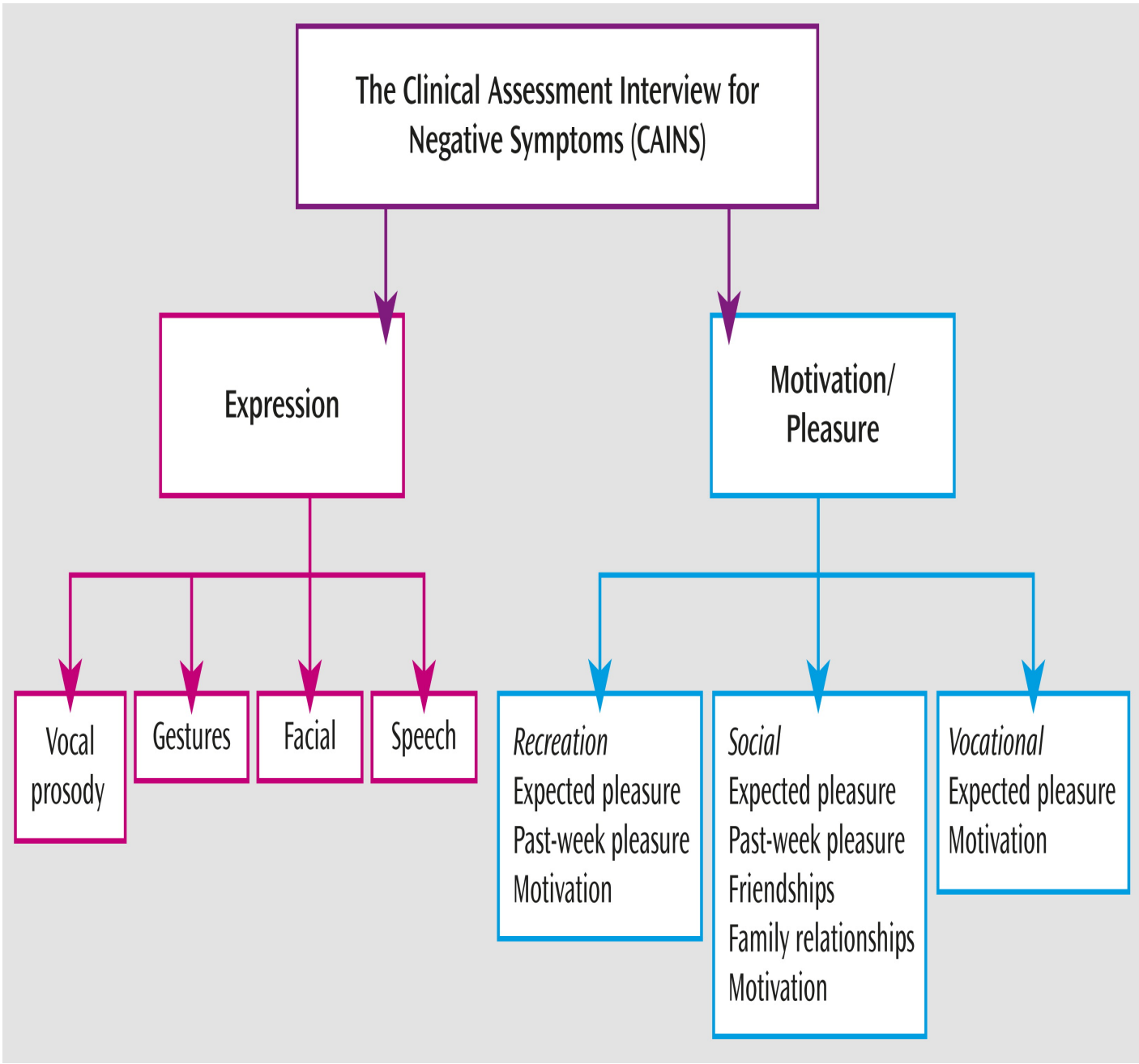
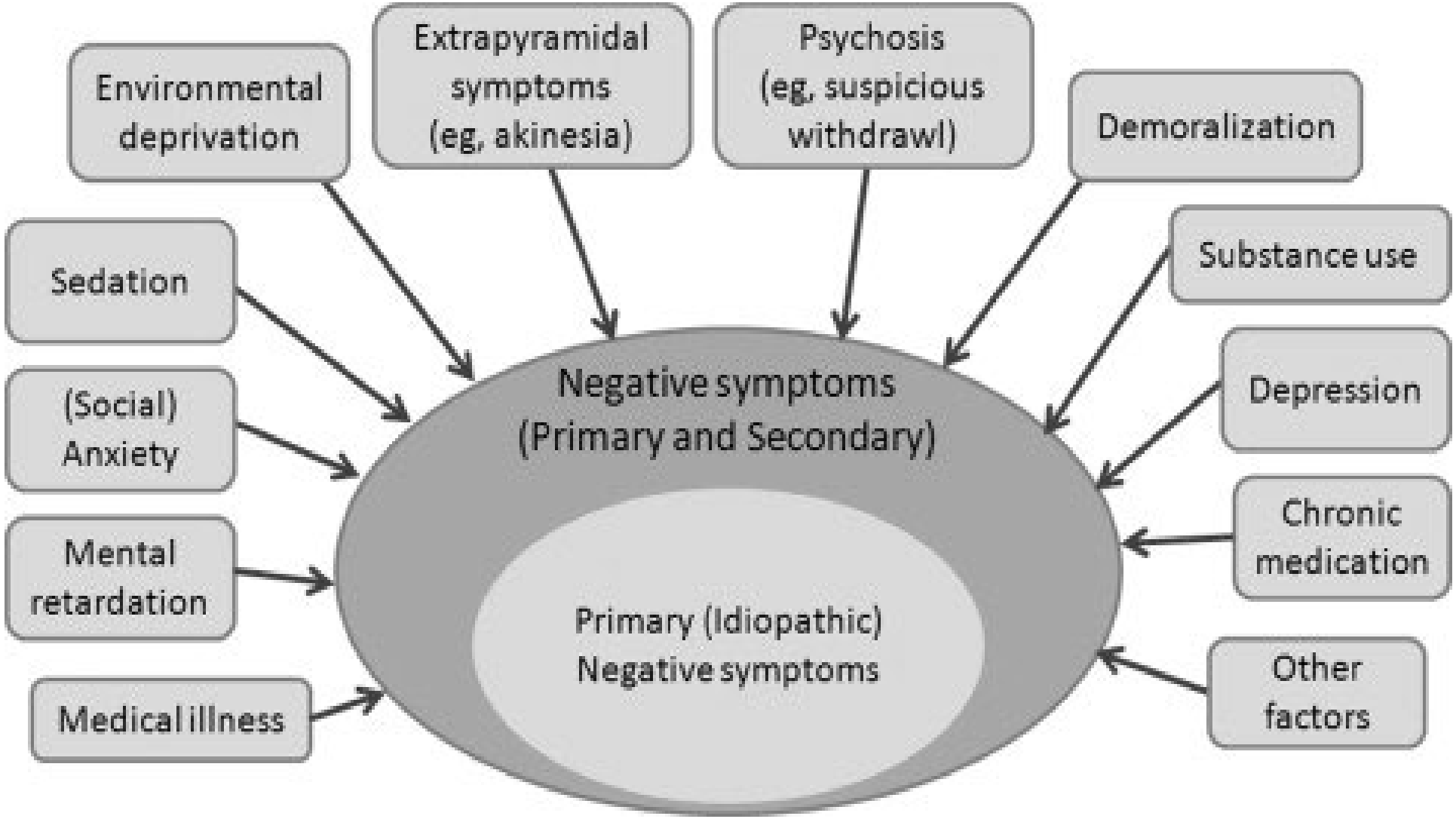
KEY WORDS: schizophrenia, negative symptoms, NSA-4



SECTION 2 OF 6

Managing Negative Symptoms — The Ladder

Six steps, most of which don't involve writing a new prescription


Environmental deprivation
Extrapyramidal symptoms (eg, akinesia)
Psychosis (eg, suspicious withdrawl)
Demoralization
Sedation
Substance use
(Social) Anxiety
Depression
Negative symptoms (Primary and Secondary)
Mental retardation
Chronic medication
Primary (Idiopathic) Negative symptoms
Medical illness
Other factors

A Six-Step Ladder, Not a Single Prescription

- Step 1 — Rule out and treat secondary causes first; this step alone resolves more "negative symptoms" than anything else on this slide
- Step 2 — Optimize the current antipsychotic: lowest effective dose, actively screen for covert EPS
- Step 3 — Consider switching to an antipsychotic with better negative-symptom evidence
- Step 4 — Consider an evidence-based adjunct — an antidepressant, NAC, or one of the newer agents covered ahead
- Step 5 — Add neuromodulation where access allows; rTMS has the strongest evidence base
- Step 6 — Never skip psychosocial treatment — it works, it is underused, and it has no drug interactions to worry about

STEP 1

Find the Secondary Cause Before You Treat It as Primary

- Residual positive symptoms — a suspicious, withdrawn patient may be avoidant, not avolitional; optimize antipsychotic dosing for the psychosis first
- Depression — post-psychotic depression is common and treatable; the Calgary Depression Scale for Schizophrenia is validated specifically to avoid overlapping with negative-symptom items
- Extrapyramidal side effects — bradykinesia, masked facies, and reduced spontaneous movement mimic blunted affect and avolition almost perfectly; a cautious dose reduction can be diagnostic as well as therapeutic
- Sedation — check the drug chart before you write "amotivation" in the notes; a surprising number of "negative symptom" patients are simply oversedated
- Environmental deprivation — an understimulating ward or custodial home environment produces a clinical picture that is very hard to distinguish from primary negative symptoms
- Substance use, especially cannabis — both intoxication and withdrawal blunt affect and motivation

Optimizing and Choosing the Antipsychotic

- Lower the dose where tolerated — excessive D2 blockade in the mesocortical pathway can itself worsen negative symptoms; more antipsychotic is not automatically better antipsychotic
- Avoid high-potency, high-EPS-liability agents wherever an equally effective, lower-EPS option exists
- A handful of agents have modestly better negative-symptom-specific evidence, not just "fewer side effects" in general — worth knowing which ones, and why, rather than switching on reputation alone
- Clozapine remains the answer for treatment-resistant positive symptoms; its effect on primary negative symptoms is underwhelming — don't oversell it on this indication alone

Table

Treatment approaches for negative symptoms of schizophrenia

Treatment	Efficacy
Cognitive-behavioral therapy	Statistically significant but clinically limited
Medications	
Antipsychotics	Limited; second-generation antipsychotics are not superior to first-generation antipsychotics
Antidepressants	Statistically significant but clinically limited. Safe as add-on treatment
Anticonvulsants	No significant evidence
Stimulants	No significant evidence
Glutamate Acetylcholine Minocycline Oxytocin	Further research is needed
Brain stimulation therapies	
tDCS TMS	Meta-analysis of RTCs comparing tDCS and rTMS with sham interventions show that both treatments have significant efficacy
VNS DBS	Further research is needed

DBS: deep brain stimulation; RCTs: randomized controlled trials; tDCS: transdirect current stimulation; TMS: transcranial magnetic stimulation; VNS: vagus nerve stimulation

Source: References 1-3

TWO OLD(ER) FRIENDS, RECONSIDERED

Amisulpride and Cariprazine — Different Mechanisms, Both With Negative-Symptom Data

AMISULPRIDE	CARIPRAZINE
Selective D2/D3 antagonist; at low dose (50–300 mg/day) preferentially blocks presynaptic D2/D3 autoreceptors, increasing dopamine tone rather than simply blocking it	A D3-preferring partial agonist at D2/D3, and a partial agonist at 5-HT1A — a genuinely different mechanism, not just "another SGA"
Head-to-head and meta-analytic data show a modest but real advantage for negative symptoms specifically, at low dose	Head-to-head trial vs risperidone (Németh et al., Lancet 2017) showed superiority specifically in patients with predominant negative symptoms
Cheap, widely available across India, and free of major QTc surprises at usual doses — a genuinely practical first switch	Not marketed in India as of this deck's preparation — worth knowing the evidence even where the drug itself isn't on your formulary yet
Caution: hyperprolactinemia is dose-related and can be clinically prominent	Caution: akathisia is the main tolerability issue to counsel patients about

APPROVED

KarXT (Xanomeline–Trospium) — Cobenfy

The first genuinely non-dopaminergic antipsychotic mechanism to reach the market, after seven decades of D2 blockade being the only game in town

- Xanomeline is a dual M1/M4 muscarinic receptor agonist that modulates dopaminergic and glutamatergic circuits indirectly, without touching D2 at all; trospium (a peripheral anticholinergic) is added purely to mop up xanomeline's peripheral cholinergic side effects
- FDA-approved in September 2024 for adults with schizophrenia, on the strength of the EMERGENT trial programme
- An early, genuine signal for negative-symptom benefit — not just "fewer EPS" — which is exactly what has both residents and consultants paying attention
- Not yet available in India; know the mechanism and the story, because it will come up in every journal club and viva for the next few years regardless

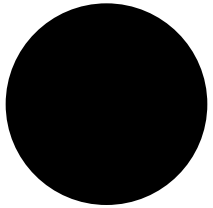
MIXED

KarXT — Reading Past the Headline

- EMERGENT-2 and EMERGENT-3 both met their primary endpoint (PANSS total) convincingly; the adjunctive ARISE trial, adding KarXT onto an existing antipsychotic, also showed benefit
- Negative-symptom improvement has so far been a secondary endpoint — encouraging, but the dedicated negative-symptom trial everyone actually wants is still pending
- GI side effects — nausea, dyspepsia, constipation — from residual muscarinic/anticholinergic activity are common enough to be the leading cause of early discontinuation
- Cost and availability will decide whether this becomes a genuine first-line option or a specialist-only drug for years to come, in India as much as anywhere else

WATCH THIS SPACE

Other Muscarinic Agents Coming Up Behind KarXT



- NBI-1117568 — a selective M4 agonist designed to avoid xanomeline's peripheral side effects by leaving M2/M3 receptors largely alone
- Several other M1/M4-selective molecules are in earlier development across multiple companies — the muscarinic hypothesis has gone from a curiosity to the single most crowded pipeline in schizophrenia drug development in under two years
- Emraclidine, a selective M4 agonist that briefly looked like it might beat KarXT to market for some indications, is a useful cautionary tale — see the next slide

The Drug Development Graveyard, 2023–2025

Every one of these looked genuinely promising in Phase 2. All five met the same fate in Phase 3 — a nicely powered placebo-controlled trial is where good stories go to be tested

RIP

Ulotaront

TAAR1 agonist

DIAMOND-1 and DIAMOND-2 both missed their primary endpoint outright, ending the field's first serious non-dopaminergic hopeful

RIP

Emraclidine

M4 agonist

EMPOWER-1 and EMPOWER-2 both failed to separate from placebo — a genuine shock after strong Phase 1b signal data

RIP

Iclepertin

GlyT1 inhibitor

The CONNEX programme (1,835 patients, 3 trials) found essentially nothing for cognitive impairment

RIP

Luvadaxistat

DAAO inhibitor

The ERUDITE Phase 2 programme could not replicate its own earlier promise and was discontinued

RIP

Pimavanserin (Ph3)

5-HT2A inverse agonist

A strong Phase 2 (ADVANCE) hit single, followed by a Phase 3 that simply didn't happen again

AbbVie press release, Nov 2024; Sumitomo/Otsuka topline 2023–24; Boehringer Ingelheim CONNEX topline, Jan 2025; Takeda/Neurocrine ERUDITE disclosure, Sep 2024; Bugarski-Kirola et al., Schizophrenia Bulletin 2025.

Why Do So Many Phase 3s Fail?

- Escalating placebo response over the past two decades — better-run, more closely monitored trial sites tend to produce better "placebo arm" outcomes too, shrinking the true drug-placebo gap
- Narrow therapeutic windows and inadequate target engagement — several drugs on the graveyard slide never confirmed they were hitting the intended receptor at an adequate brain dose
- Heterogeneous, broadly-defined "negative symptoms" populations dilute a real effect that may exist only in a narrower biological subgroup
- Assay-sensitivity failures can mask a genuine drug-placebo difference — a well-designed Phase 2 does not guarantee a well-designed Phase 3
- The lesson for a resident: read the primary endpoint and the assay-sensitivity data before you get excited about a press release

GLUTAMATE, THE SEQUEL THAT'S STILL PLAYING

IN TRIALS

Evenamide and Sodium Benzoate — the Survivors

- Evenamide — a voltage-gated sodium channel modulator that normalizes glutamate release, added on top of an existing antipsychotic in treatment-resistant schizophrenia
- Open-label extension data show roughly 47% of patients achieving a ≥30% PANSS reduction over 52 weeks of add-on treatment; the Phase 3 ENIGMA-TRS programme began in 2025, results expected 2026
- Sodium benzoate, a DAAO inhibitor, raises NMDA-receptor co-agonist (D-serine) availability; early placebo-controlled trials showed modest but real symptomatic and cognitive benefit at very low cost
- Neither is a dedicated negative-symptom drug — both are being tested mainly in treatment-resistant illness — but the glutamatergic hypothesis is one of the few mechanistic stories still standing after 2023–2025

TWO MORE FROM THE GRAVEYARD ANNEX

Roluperidone and Pimavanserin — Close, but Not Close Enough (Yet)

ROLUPERIDONE	PIMAVANSERIN
Sigma-2/5-HT2A antagonist, with dose-dependent efficacy specifically for negative symptoms across two Phase 2b/3 programmes	5-HT2A inverse agonist, already approved for Parkinson's disease psychosis; repurposed for negative symptoms
FDA issued a Complete Response Letter in 2024 — the data package was judged insufficient, not a clean failure; the sponsor is pursuing a path forward	A genuinely positive Phase 2 (the ADVANCE trial); the Phase 3 topline (2024–25) did not replicate the earlier effect
A textbook example of a drug stuck in regulatory purgatory, rather than either approved or dead	A textbook example of why one good Phase 2 result should never be mistaken for proof
Status in 2026: development continues, approval not guaranteed	Status in 2026: development largely paused, pending a rethink of the target population

Antidepressants, NAC, Cannabidiol, and Anti-Inflammatories

- Antidepressant augmentation (SSRIs, mirtazapine) — meta-analytic evidence is modest and inconsistent; more useful when a secondary depressive component is suspected than as a blanket add-on
- N-acetylcysteine (NAC) — an antioxidant and glutamate-modulating supplement; several small trials, including Indian data (Tharoor et al., 6-month follow-up), suggest a negative-symptom benefit as an adjunct — cheap, well tolerated, worth knowing even while evidence remains preliminary
- Cannabidiol — evidence through 2026 stays mixed: some trials show benefit across positive and negative symptoms combined, others show none; not a default choice, but worth watching
- Anti-inflammatory agents (celecoxib and others) — the "neuroinflammation hypothesis" keeps generating trials with small-to-modest effect sizes; not ready for routine use, but a solid exam answer for "novel mechanisms under investigation"
- The honest summary: none of these are game-changers on their own, but a well-chosen adjunct in the right patient meaningfully adds to an already-optimized antipsychotic regimen

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ORIGINAL ARTICLE

Cognitive and negative symptoms in schizophrenia with L-Carnosine adjuvant therapy – A randomized double-blind placebo-controlled study

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Funding information
Shield Health care

Abstract

The antioxidant L-Carnosine is reported to improve negative and cognitive symptoms in Schizophrenia. A randomized double-blind placebo-controlled study was planned to study the effectiveness of adjuvant L-Carnosine therapy in patients with Schizophrenia. 100 eligible patients with predominant negative symptoms as measured by scale for assessment of negative symptoms (SANS total score ≥ 60) and Schizophrenia diagnosis (International Classification of Disorder-Tenth Edition, ICD-10) were recruited. They were randomly allocated to receive a fixed dose of either 400 mg L-Carnosine or identical placebo for 3 months and increased to 800 mg from 13th week till completion of study. Primary outcome measures assessed changes in SANS scores with L-Carnosine at 24 weeks compared to baseline, 4 and 12 weeks. Secondary outcome measures were done to assess the improvement in cognitive symptoms (executive function, attention, and memory) at 24 weeks using subtests of NIMHANS (National Institute for Mental Health and Neurosciences) cognitive battery. Side effects were assessed using adverse events reporting form. The attention scores (p = .023) showed significant differences in patients receiving 800 mg of L-Carnosine at the end of the study. There were no significant differences in negative symptoms in the two arms at study completion. L-Carnosine dosing of 800 mg may be a promising agent to enhance executive functions in Schizophrenia.

KEYWORDS
antioxidant, antipsychotics, executive function, nutraceutical, psychopathology, supplement

Abbreviations: ANOVA, analysis of variance; ASD, autism spectrum disorder; AVLT, auditory verbal learning test; CGI, clinical global impression; COVID-19, Coronavirus disease; CTRI, Clinical Trial Registry-India; ECG, electrocardiogram; GABA, gamma aminobutyric acid; LOCF, last observation carried forward; NIMHANS, National Institute for Mental Health and Neurosciences; NMDA, N-methyl-D-aspartate receptor; RCT, randomized controlled trial; SANS, scale for assessment of negative symptoms; SAPS, scale for assessment of positive symptoms; SD, standard deviation; TRAIL-A, trail making tests A; TRAIL-B, trail making tests B.

Original Article

Role of Novel Dietary Supplement N-acetyl Cysteine in Treating Negative Symptoms in Schizophrenia: A 6-Month Follow-up Study

YES, THERE'S NOW AN APP FOR THIS TOO

APPROVED

CT-155 — the First Prescription Digital Therapeutic

- A smartphone-delivered digital therapeutic (Click Therapeutics / Otsuka) built around cognitive-behavioural and reward-learning exercises, targeted specifically at negative symptoms
- The Phase 3 CONVOKE trial met its primary endpoint — a statistically significant improvement over an active digital comparator on clinician-rated negative symptoms
- The first prescription-digital-therapeutic pathway built specifically for a negative-symptom domain — a genuinely new category, not just another wellness app with a prescription attached
- Relevant to Indian practice mainly as a sign of where the field is heading; widespread local availability is still some years off

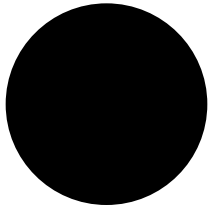
451 Trials, One Sobering Verdict

Intervention class	Effect size (SMD)	Evidence quality
Structured physical activity	0.37	Moderate
Transcranial stimulation (rTMS/tDCS)	0.33	Moderate–high
Integrated psychosocial programmes	0.30	Moderate–high
Antidepressant augmentation	0.19	Moderate
Anti-inflammatory / antioxidant agents	0.15	Low–moderate
Immunomodulators	0.47	Very low (few, small trials)

Interventions for negative symptoms in schizophrenia: efficacy and quality of evidence across 451 randomised controlled trials. Molecular Psychiatry (Nature) 2026.

PAUSE AND TAKE STOCK

Negative Symptoms Pharmacology — What Actually Matters for Your Practice



- Rule out secondary causes before reaching for anything else on this list — this remains the single highest-yield intervention available to you
- Low-dose amisulpride is cheap, available across India, and has genuine if modest negative-symptom evidence — a reasonable first switch
- KarXT is the most mechanistically exciting approved drug in a generation, but it isn't here yet, and its negative-symptom data are still secondary-endpoint level
- No single intervention reliably moves the needle alone; the best-supported strategy combines optimization, one evidence-based adjunct, and non-pharmacological treatment

SECTION 3 OF 6

Neuromodulation & Psychosocial Approaches

The two categories with no pharmacy budget required, and one of the best evidence bases in this entire talk

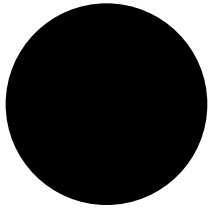
DON'T SKIP THIS SLIDE

Psychosocial Treatment Is Not the Backup Plan

- Cognitive behavioural therapy for psychosis (CBTp), adapted for negative symptoms, has trial-level evidence for improving motivation and function — and needs no pharmacy budget at all
- Social skills training — structured, session-based, with genuine effect sizes in meta-analysis; particularly useful for asociality specifically
- Structured physical activity and exercise programmes — one of the largest effect sizes in the entire literature (see the mega meta-analysis two slides back) and essentially free to deliver
- Vocational rehabilitation and supported employment — restores goal-directed activity in a way no tablet ever will
- Family psychoeducation — reduces expressed emotion, indirectly supporting negative-symptom recovery, and is standard of care that costs nothing but time
- In a resource-limited Indian setting, these are often more feasible to deliver than the newest muscarinic agent — don't let novelty bias crowd them out of your treatment plan

THE PROTOCOL YOU'LL BE ASKED ABOUT

rTMS for Negative Symptoms — Know the Parameters



- Target: left dorsolateral prefrontal cortex (dlPFC) — the same region targeted in treatment-resistant depression, reflecting overlapping hypofrontality
- Standard protocol: high-frequency (10 Hz) stimulation, typically over 3–4 weeks of daily weekday sessions, ideally applied earlier rather than later in the illness course
- Mechanism: increases cortical excitability and downstream dopaminergic tone along the mesocortical pathway — roughly the theoretical opposite of the D2-blockade-driven negative symptoms problem
- This is genuinely examinable: know the target (dlPFC), the frequency (high, around 10 Hz), and that the effect is independent of any change in positive symptoms or antipsychotic dose

THE QUESTION EVERY REFERRING PHYSICIAN ASKS

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rTMS Safety, at Scale

- A 2025 systematic review finds rTMS safe and well tolerated, with numbers reassuring enough for routine departmental use wherever equipment exists
- 126 studies and over 4,000 participants with schizophrenia — among the largest safety evidence bases of any neuromodulation technique in psychiatry
- Seizure risk with standard protocols is extremely low, and comparable to the general population's unprovoked seizure rate
- No signal of worsening psychosis, mood, or cognition; the common side effects are limited to transient scalp discomfort and headache

THE EXPRESS VERSION

Theta-Burst Stimulation: Same Idea, One-Tenth the Time

- Intermittent theta-burst stimulation (iTBS) compresses the protocol without giving up the standard 10 Hz protocol's benefit — roughly 3 minutes standing in for a 37.5-minute conventional session
- Applied to the same left dlPFC target for negative symptoms, with broadly comparable response rates
- A 2024–25 systematic review of the growing iTBS literature in schizophrenia found consistently good feasibility and tolerability, though the evidence base remains modest and heterogeneous in size
- For a busy Indian OPD, the time savings alone make this worth knowing before the evidence fully matures

THE LOW-COST CHALLENGER

tDCS: Cheaper Electrodes, Steadily Growing Evidence

- Anodal stimulation over the left dlPFC, paired with a cathodal reference elsewhere, remains the standard protocol
- Active tDCS continues to outperform sham, with response rates in the 13–20% range — clearly above placebo, though still modest in absolute terms
- Portability and low cost make this the most plausible neuromodulation option for resource-limited settings, including much of routine Indian psychiatric practice

Where Do ECT and MST Actually Fit?

- Two well-established techniques, with a surprisingly thin negative-symptom-specific evidence base
- ECT's strongest schizophrenia evidence remains catatonia and treatment-resistant positive symptoms — usually as an augmentation strategy alongside clozapine, not a stand-alone negative-symptom answer
- Magnetic seizure therapy (MST) offers ECT-like efficacy with a gentler cognitive side-effect profile; its schizophrenia negative-symptom data remain preliminary
- Neither is a dedicated modern negative-symptom option for a resident to reach for first — useful to know they exist, and equally useful to know why they aren't on this shortlist

PAUSE AND TAKE STOCK

Negative Symptoms Neuromodulation — At a Glance

REACH FOR THIS	RESERVE FOR THEIR OWN INDICATIONS
10 Hz rTMS or iTBS, left dlPFC — the best-replicated protocol, with growing access even outside metro centres	ECT — catatonia, treatment-resistant positive symptoms, clozapine augmentation
tDCS — a genuine low-resource option where rTMS equipment is unavailable	MST — promising in broad strokes; schizophrenia negative-symptom evidence not yet mature
Structured exercise — portable, cost-free, and one of the best effect sizes in this entire talk	Digital therapeutics and apps — often the more feasible option remains years away from local availability

SECTION 4 OF 6

Obsessive-Compulsive Symptoms in Schizophrenia

The comorbidity most training programmes mention once, in a footnote, and then never again

A CONFUSING FAMILY TREE

The Many Names of the Same Confusing Comorbidity

- "Schizo-obsessive disorder" — proposed as a distinct subtype with its own course and treatment implications; not formally recognized in DSM-5 or ICD-11
- "OCS" (obsessive-compulsive symptoms) — the pragmatic umbrella term used across most recent literature, deliberately agnostic about mechanism
- "Clozapine-induced" or "clozapine-associated OCS" — the specific, and now best-studied, subtype: symptoms emerging or worsening after clozapine initiation
- Clinical bottom line: label it however your chart template allows, but screen for it — it doesn't announce itself the way psychosis does

HOW COMMON, REALLY?

Epidemiology: More Common Than Most Training Programmes Suggest

- OCS prevalence in schizophrenia overall: 20–76% across studies, median around 30% — an enormous range that reflects inconsistent screening far more than inconsistent biology
- In clozapine-treated patients specifically: 21–76%, median around 45% — clozapine both unmasks and worsens obsessive-compulsive symptoms in a meaningful minority
- New or worsened OCS after clozapine initiation: roughly 10–18% of patients
- Counter-intuitive nugget: one comparative study found clozapine (20%) and haloperidol (23%) produced broadly similar OCS rates — clozapine's reputation as the sole culprit outruns the sample size behind it

Why Does Clozapine Do This?

- The leading hypothesis centres on clozapine's potent 5-HT2A/5-HT2C antagonism, disproportionate to its comparatively weak D2 blockade — the same cortico-striatal circuit implicated in primary OCD
- Downstream glutamatergic dysregulation from this circuit disruption may reflect a genuine deficit-syndrome overlap — some of this may be illness biology expressing itself, not purely a side effect
- Dose and duration both matter clinically, but the mechanism is a circuit-level story, not simply "more drug, more symptoms"
- Exam-relevant takeaway: this is a receptor-pharmacology answer, not a "clozapine is just a dirty drug" hand-wave

THE MISTAKE EVERYONE MAKES AT LEAST ONCE

The Diagnostic Trap — OCS or Negative Symptoms?

LOOKS LIKE NEGATIVE SYMPTOMS	IS ACTUALLY OBSESSIVE-COMPULSIVE
Patient withdrawn, spends hours "doing nothing" in their room	Actually performing lengthy, ego-dystonic checking or ordering rituals in private
Reduced spontaneous speech, poor eye contact on interview	Preoccupied with intrusive thoughts and internal rumination, not primary avolition
Rigid daily routine, read as "lack of initiative" or amotivation	The rigid routine is compulsive — driven by anxiety relief, not an absence of drive
Flat affect; assessed by asking about function and observable behaviour	Flat affect; assessed by asking directly about intrusive thoughts and rituals, not a generic checklist

Assessing OCS in a Patient Who Also Has Psychosis

- Y-BOCS (Yale–Brown Obsessive Compulsive Scale) remains the standard instrument, adapted and validated for use in schizophrenia populations
- Insight is often better preserved for OCS than for the primary psychotic symptoms — many patients recognize their rituals as excessive even while holding fixed delusional beliefs elsewhere; ask directly, most will tell you
- Screen every patient starting clozapine at baseline, and again at 3 and 6 months — post-initiation OCS is common enough to warrant routine screening rather than incidental discovery
- Distinguish OCS from repetitive checking driven by genuine paranoid ideation — the content of the behaviour and the patient's own explanation for it usually separate the two

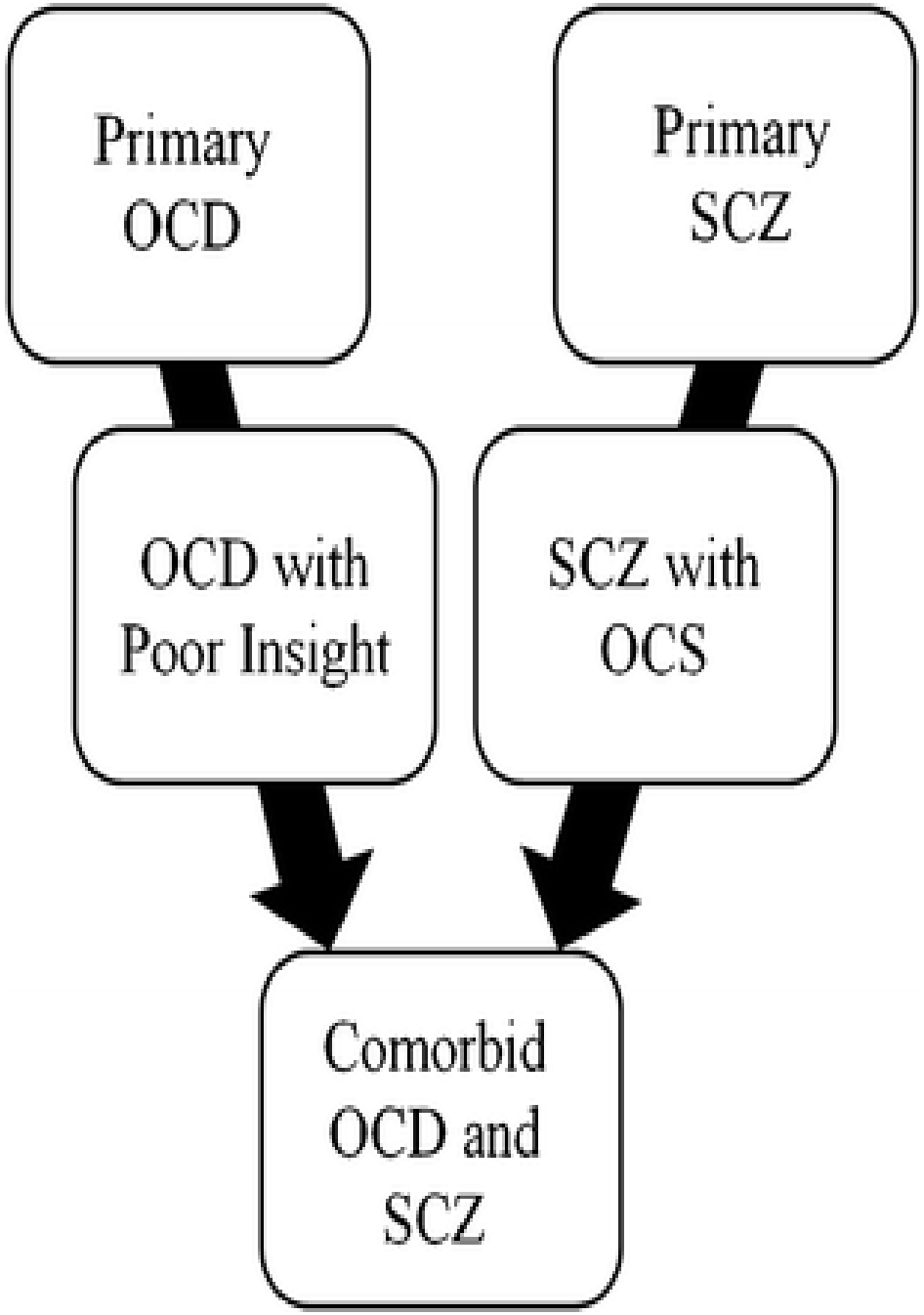
SECTION 5 OF 6

Managing Obsessive-Compulsive Symptoms

A practical algorithm borrowed from OCD, adapted carefully for a patient who also has psychosis

A Practical Algorithm, Not a Formal Guideline

- Step 1 — Confirm the diagnosis; rule out negative symptoms and paranoid ideation dressed up as OCS
- Step 2 — If clozapine-associated, consider a cautious dose reduction or slower titration before adding anything new
- Step 3 — If symptoms persist, consider SSRI/SNRI augmentation — watching closely for the prescribing trap on the next slide
- Step 4 — Aripiprazole augmentation is a reasonable, evidence-informed second-line option, especially where an SSRI is contraindicated or unhelpful
- Step 5 — CBT with exposure and response prevention (ERP), adapted for a patient with psychosis, deserves more use than it currently gets
- Step 6 — Neuromodulation, borrowed from primary OCD circuitry, remains investigational here but is worth knowing about


Primary OCD
Primary SCZ
OCD with Poor Insight
SCZ with OCS
Comorbid OCD and SCZ


SCHIZO OBSESSIVE DISORDER
EPIDEMIOLOGY
Schizophrenia: Approx. 1% in general population.
Obsessive-Compulsive Disorder (OCD): 2%–3% in general population.
Recent studies show higher prevalence of OCS in schizophrenia:
25% have OCS.
12% have comorbid OCD.
17.1% of patients had OCS at first psychotic episode.
ATYPICAL ANTIPSYCHOTICS AND OCS
Broader use of atypical antipsychotics (e.g., clozapine) might have contributed to increased OCS prevalence in recent decades.
INSIGHT IN OCD PATIENTS
Poor insight is common in OCD patients, ranging from 13.8% to 30.7%.
OCD AND SCHIZOTYPAL PERSONALITY DISORDER (SPD) CO-OCCURRENCE
Co-occurrence rates range widely from 5% to 50%.
DIAGNOSTIC RECOGNITION
DSM-IV (1994) allowed dual diagnosis of schizophrenia and OCD.
In the same year (1994), the term "schizo-obsessiveness" was coined by Hwang and Opler.
1994
SPECTRUM PERSPECTIVE
Pogurotsky and Koran proposed the concept of OCD-schizophrenia spectrum disorders, including:
Pure OCD
OCD with poor insight
OCD with schizotypal personality disorder
Schizophrenia with OCS
Schizophrenia with comorbid OCD
Pure schizophrenia
DSM-5 UPDATES
Removed OCD from the anxiety disorders chapter.
Introduced "schizophrenia spectrum disorder."
Recognized obsessions without insight, integrating schizo-obsessive subgroup into a continuum between obsessions and delusions.
Understanding the overlap. Improving the outcomes.

Is It Clozapine, and What Do You Do About It?

- Establish the timeline first — did the OCS emerge or worsen after clozapine initiation or a dose increase? Document it clearly before touching the regimen
- If the clozapine dose or plasma level is high relative to clinical need, a carefully monitored reduction can meaningfully reduce OCS without sacrificing antipsychotic control — always weigh this against relapse risk
- If reduction isn't feasible, or symptoms persist regardless, move on to augmentation strategies rather than chasing dose changes indefinitely
- Document everything — "worsening obsessive symptoms on clozapine" is exactly the kind of finding a future treating team, and your thesis committee, will want to see clearly recorded

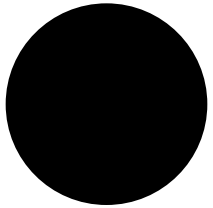
STEP 3

SSRI/SNRI Augmentation — Evidence and a Genuine Prescribing Trap

- SSRIs/SNRIs added to the existing antipsychotic are the most commonly used first-line augmentation strategy for clozapine-associated OCS, supported by case series and small trials
- The trap: fluvoxamine is a potent CYP1A2 inhibitor — exactly the enzyme that metabolizes clozapine — and can push clozapine levels toward toxicity if the dose isn't adjusted downward
- Sertraline or escitalopram are more pharmacologically forgiving choices in this population, even though fluvoxamine's own OCD-specific efficacy makes it tempting to reach for first
- General caution with any SSRI here: a theoretical concern for early activation or symptom flare — start low, go slow, as ever

THE INTERACTION EVERY RESIDENT FORGETS AT LEAST ONCE

Fluvoxamine + Clozapine: A Combination That Ends in a Toxic Level



- Fluvoxamine can raise clozapine plasma levels several-fold through CYP1A2 inhibition — some case reports describe a five- to ten-fold increase
- Clinical consequence: sedation, hypersalivation, seizure risk, and myocarditis risk all climb right along with the level — this is not a theoretical interaction, it's a Monday-morning-clozapine-clinic interaction
- If you do combine them, because fluvoxamine genuinely has good OCD-specific evidence, cut the clozapine dose substantially first, and recheck a trough level before you trust anything
- The honest teaching point: this combination gets prescribed by well-meaning residents more often than it should — usually right before the clozapine level comes back and everyone has a very interesting Monday morning

STEP 4

Aripiprazole Augmentation for Clozapine-Associated OCS

IN TRIALS

- Rationale: aripiprazole's D2/D3 partial agonism and 5-HT1A partial agonism may counteract clozapine's disproportionate serotonergic blockade — a mechanistically coherent, if still small-study, argument
- Small open-label and case-series studies report meaningful reductions in Y-BOCS scores when added at typically 5–15 mg/day
- A welcome secondary effect reported in several series: aripiprazole augmentation also helps offset clozapine-associated weight gain and metabolic burden
- Evidence quality remains modest — no large definitive RCT yet — but this is the augmentation strategy with the most consistent signal in the literature so far

Glutamatergic Agents — Evidence from OCD, Extrapolated With Caution

Agent	Trials	Signal
N-acetylcysteine	4 RCTs	Best-studied of the group; consistent modest benefit
Memantine	3 RCTs	Encouraging NMDA-antagonist add-on signal
Riluzole	2 RCTs	Mixed signal, generally well tolerated as an add-on
Topiramate	3 RCTs	Positive direction, limited by tolerability
Ketamine / minocycline	Small RCTs each	Preliminary, mechanistically appealing

Glutamatergic medications for obsessive-compulsive and related disorders: a systematic review and meta-analysis of 27 RCTs. JAMA Network Open 2024;7. Trials are predominantly in primary OCD/OCD-spectrum populations — dedicated schizophrenia-OCS trials remain scarce.

BEYOND THE PRESCRIPTION PAD

CBT/ERP and Neuromodulation for OCS — Borrowed Circuitry, Real Promise

- CBT with exposure and response prevention (ERP), adapted for patients with coexisting psychosis, has case-series and small-trial support — the biggest barrier is trained-therapist availability, not efficacy
- A more gradual, modified ERP approach — accounting for fluctuating insight and cognitive symptoms — is usually needed; standard OCD-clinic pacing may need adjustment
- Deep brain stimulation (ventral capsule/striatum or subthalamic targets) remains reserved for severe, treatment-refractory primary OCD — not schizophrenia-associated OCS, and not on your ward's differential
- High-frequency dTMS targeting the dorsomedial prefrontal cortex/anterior cingulate circuit implicated in primary OCD is a plausible extrapolated target, but formally studied only in primary OCD so far

A Practical Algorithm for Clozapine-Induced OCS

- 1. Confirm the diagnosis; rule out negative symptoms and paranoid ideation dressed up as OCS
- 2. Establish the timeline against clozapine dose or level changes, and document it clearly
- 3. If clinically feasible and psychosis remains controlled, consider a cautious clozapine dose reduction
- 4. Add SSRI/SNRI (sertraline or escitalopram preferred for CYP1A2 safety) or, alternatively, aripiprazole 5–15 mg/day
- 5. If response is inadequate, consider a glutamatergic adjunct (NAC is the best-tested) and refer for CBT/ERP where available
- 6. For refractory, severe cases, consider a neuromodulation referral and reassess at 8–12 weeks — a specialist decision, not one to make solo as a resident

Take-Home Messages for OCS

- OCS in schizophrenia is common, under-recognized, and worth a specific question at every clozapine review — not an incidental finding
- The diagnostic trap runs both ways: negative symptoms can look like OCS and OCS can look like negative symptoms — ask directly about intrusive thoughts and rituals
- Fluvoxamine and clozapine together demand a dose adjustment and a level check — never combine them casually
- Aripiprazole augmentation currently has the most consistent, if still modest, evidence base for clozapine-associated OCS
- CBT/ERP, adapted for psychosis, is underused relative to its promise — refer for it, don't just medicate around it

SECTION 6 OF 6

Bringing It Together

One integrated framework, one honest report card, and the pitfalls examiners actually ask about

THE CLINICAL SYNTHESIS

An Integrated Framework — Match Mechanism to Phenotype

PREDOMINANTLY NEGATIVE PRESENTATION	PREDOMINANTLY OBSESSIVE PRESENTATION
Rule out secondary causes first — the highest-yield step, every time	Confirm the diagnosis first — is it truly OCS, not negative symptoms or paranoia?
Low-dose amisulpride, or a partial-agonist switch (cariprazine, where available)	SSRI (sertraline/escitalopram) or aripiprazole augmentation; check for a clozapine interaction first
Add rTMS/iTBS where accessible; structured exercise always, regardless of access	Add a glutamatergic adjunct (NAC); refer for CBT/ERP
Layer psychosocial treatment throughout, not as a last resort	Reassess at 8–12 weeks; escalate to specialist or neuromodulation referral if refractory

THE HONEST SCORECARD

Where We Actually Stand in 2026

The whole field would like a residency-style report card, and the fine print is worth remembering on ward rounds

INTERVENTION	GRADE	REPORT-CARD COMMENT
KarXT / Cobenfy	**A-**	*Genuinely new mechanism, real FDA approval — just not on your formulary yet*
Low-dose amisulpride	**B+**	*Unglamorous, cheap, available in India, and it actually works a bit*
Cariprazine	**B**	*Excellent trial data, currently allocated to countries that aren't India*
rTMS / iTBS (left dlPFC)	**B+**	*Best-evidenced neuromodulation option; needs equipment and a referral pathway*
Structured exercise	**A-**	*Free, safe, one of the best effect sizes in this whole talk, chronically under-prescribed*
NAC (adjunct)	**B-**	*Cheap, safe, modest evidence — a reasonable low-risk add-on*
Evenamide, sodium benzoate	**C+**	*A promising story, still waiting on its defining trial*
Emraclidine, ulotaront, iclepertin, luvadaxistat	**F**	*See: the graveyard slide, several slides ago*
Aripiprazole augmentation for OCS	**B**	*Small studies, a consistent direction, still no landmark RCT*
CBT/ERP for OCS	**B+**	*Works very well — when you can actually access a trained therapist*

Grades are this speaker's synthesis of the evidence discussed today, not a formally validated instrument — your consultant is allowed to disagree, loudly.

Common Pitfalls (and Viva Favourites)

- Calling every quiet, withdrawn patient "negative symptoms" without ruling out depression, EPS, or sedation first — the single most common error, on both the ward and the exam table
- Forgetting to ask directly about obsessive-compulsive symptoms in a clozapine clinic — "he's just quiet" is not a screening tool
- Prescribing fluvoxamine with clozapine without adjusting the dose — an examiner will ask about this interaction more often than you'd like
- Confusing primary/deficit negative symptoms (enduring, present even when well) with secondary negative symptoms (reversible, cause-driven) — this distinction is asked constantly, and answered vaguely just as often
- Treating rTMS as exotic or unavailable — it is more accessible across Indian centres than most residents assume, and it remains a genuinely favourite exam topic

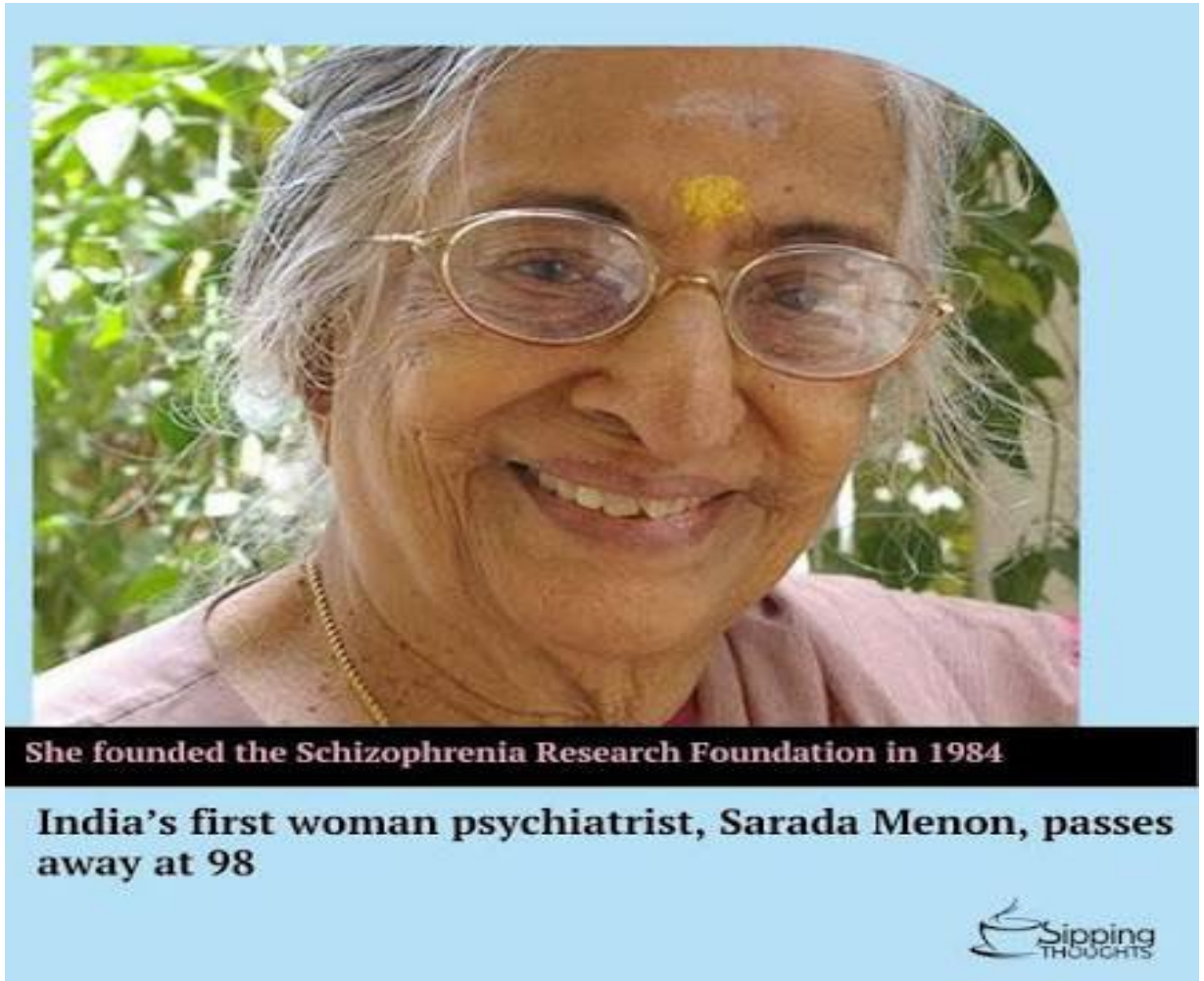
Future Directions Worth Watching

- Biomarker-guided treatment — inflammatory markers, cognitive subtyping, and imaging-defined circuit dysfunction, used to enrich future negative-symptom trials rather than treating everyone as one population
- Digital phenotyping — smartphone-collected passive behavioural data (movement, speech patterns, social contact) as a more sensitive outcome measure than PANSS subscales alone
- Combination strategies designed from the outset — pairing a receptor-level drug with neuromodulation or a digital therapeutic, rather than testing each in isolation
- Dedicated schizophrenia-specific OCS trials — the single biggest evidence gap in this entire talk; nearly everything discussed today was extrapolated, borrowed, or improvised

IF YOU REMEMBER FIVE THINGS FROM TODAY

Take-Home Messages

- Rule out secondary causes before treating either negative symptoms or OCS as "primary" — this single habit will outperform most of the drugs in this talk
- Low-dose amisulpride, rTMS/iTBS, and structured exercise remain your most practical, available negative-symptom tools in India today
- KarXT and the muscarinic story are genuinely new pharmacology — know the mechanism even before it reaches Indian shelves
- Screen every clozapine patient for OCS at baseline and follow-up, and never combine fluvoxamine with clozapine without adjusting the dose
- No single intervention works alone — the evidence consistently favours combining pharmacology, neuromodulation, and psychosocial treatment over any single "magic bullet"


She founded the Schizophrenia Research Foundation in 1984
India's first woman psychiatrist, Sarada Menon, passes away at 98
Sipping THOUGHTS

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Thank You

- Questions, disagreements, and "but what about drug X" are always welcome
- Full reference list and slide deck available on request
- Go screen your next clozapine patient for obsessive-compulsive symptoms — you will probably find some

Somewhere between your thesis defence and your board exam, someone will ask you to define primary negative symptoms in under thirty seconds. This entire talk was that thirty seconds, stretched considerably.