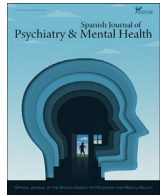




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New interventions for schizophrenia: Navigating the treatment landscape

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ABSTRACT

For over half a century, antipsychotic efficacy for schizophrenia treatment has been tied to dopamine D2 receptor antagonism, with predictable trade-offs: limited impact on negative and cognitive symptoms, and substantial metabolic, endocrine, and motor adverse effects. In the past few years, schizophrenia drug development has re-accelerated, including the first US approval of a non-D2 antipsychotic mechanism (xanomeline–trospium), and several late-stage programmes aiming to treat symptom domains that matter most to long-term functioning. At the same time, several high-profile “dopamine-sparing” agents have failed in phase 2 and 3 trials, underscoring that mechanistic novelty alone is insufficient. Successful translation requires alignment among biological targets, trial design, and patient phenotypes. In this review, we examine emerging interventions and propose a pragmatic translational framework centered on domain-specific prescribing, earlier implementation of measurement-based care, and biomarker-informed stratification.

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The schizophrenia treatment landscape is changing

Schizophrenia remains a disorder in which clinicians can often ameliorate acute psychosis yet struggle to deliver sustained functional recovery. The predominant pharmacologic strategy – dopamine D2 receptor antagonism or partial agonism – has demonstrated clear efficacy for positive symptoms but has not consistently improved negative symptoms or cognitive impairment. Moreover, it is associated with well-recognized metabolic, endocrine, and extrapyramidal adverse effects.¹

Over the past decade, academia and industry have increasingly focused on (1) symptom domains not adequately addressed by existing treatments; and (2) mechanisms that move beyond direct D2 antagonism. As these approaches mature, clinical practice is likely to shift toward greater personalisation based on symptom profile, tolerability, and comorbidity risk.²

Below (Table 1) we summarise interventions with novel or differentiated mechanisms that have either reached licensing approval, are in active late-stage development, or have shown early

promise but not translated into phase 3 success. Together, these advances give a practical overview of where the field is heading.

Muscarinic agonism reaches clinical practice

Xanomeline–trospium (cobenfy; formerly KarXT)

Xanomeline is an orthosteric muscarinic receptor agonist with functional preference for M1 and M4 signalling. M1 receptors are widely expressed in cortex and hippocampus and are implicated in cortical processing relevant to cognition and psychosis.³ M4 receptors, enriched in striatal circuitry, modulate dopaminergic tone indirectly, one plausible route to antipsychotic effects without direct D2 antagonism.

The historic limitation of muscarinic agonism has been peripheral cholinergic adverse effects (e.g., nausea, vomiting/diarrhoea, sweating/salivation, bradycardia).⁴ Trospium chloride is a peripherally acting muscarinic antagonist with limited CNS penetration; the combination aims to preserve central muscarinic signalling while attenuating peripheral toxicity. In practice, clinicians should still anticipate a mixed “cholinergic/anticholinergic” profile (e.g., nausea and dyspepsia; constipation and urinary retention risk depending on the individual).

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Table 1
Summary of the new treatments for schizophrenia treatment.

Intervention	Core mechanism (simplified)	Key evidence signal	Status (US)	Status (EU/Spain in sources reviewed)
Xanomeline–trospium (COBENFY)	Central M1/M4 agonism + peripheral antimuscarinic to reduce peripheral AEs	Two placebo-controlled acute psychosis trials; EMERGENT-2 phase 3 positive	FDA-approved for schizophrenia (2024)	No marketing authorisation identified
Lumateperone (CAPLYTA)	Multi-system modulation (serotonin/dopamine/glutamate); mechanism not fully established	Short-term efficacy trials in label; relapse-prevention programmes reported	FDA-approved for schizophrenia (2019)	No marketing authorisation identified
Pimavanserin	5-HT _{2A} inverse agonist/antagonist	Mixed: earlier negative-symptom signal; later phase 3 negative	FDA-approved for Parkinson's disease psychosis; not schizophrenia	No marketing authorisation identified
Ulotaront (SEP-363856)	TAAR1 + 5-HT _{1A} agonism (non-D ₂)	NEJM acute trial positive; later phase 3 mixed/negative; new phase 3 ongoing	Investigational	Investigational
Roluperidone	Sigma-2/5-HT _{2A} antagonist (non-D ₂)	Regulatory setback; more evidence requested	Not approved (CRL)	Investigational
Emraclidine	M4 receptor PAM	Phase 1b signal; later phase 2 negative	Investigational	Investigational
F17464	Preferential D ₃ antagonism + 5-HT _{1A} partial agonism	Phase 2 completed; wider dissemination awaited	Investigational	Investigational
Valbenazine	VMAT2 inhibitor (TD)	RCTs reduce AIMS	FDA-approved for TD	EU/Spain status not confirmed in reviewed sources
Deutetrabenazine (Austedo)	VMAT2 inhibitor (TD)	Two RCTs reduce AIMS	FDA-approved for TD	Authorised for TD in EU (2026)
Iclepertin (BI 425809)	Glycine transporter-1 (GlyT1) inhibitor	Positive phase 2 RCT, but three negative phase 3 RCT	Investigational	Investigational
Evenamide	Voltage-gated sodium channel inhibitor	Positive phase 2 RCT, phase 3 ongoing	Investigational	Investigational
LB-102 (n-methyl amisulpride)	Dopamine D _{2/3} and 5-HT ₇ inhibitor	One positive phase 2 RCT	Investigational	Investigational

Following positive placebo-controlled trials,⁵ the FDA approved cobenfy for the management of schizophrenia in adults in September 2024, making it the first approved antipsychotic drug with a primarily cholinergic (rather than dopaminergic) target. While its overall efficacy profile relative to placebo is clear, its risks and benefits relative to D₂ antagonists, its benefits for negative and cognitive symptoms and the position of this drug in treatment algorithms are yet to be established.

Emraclidine (CVL-231): M4 positive allosteric modulation

Emraclidine is a brain-penetrant M4 positive allosteric modulator, designed to amplify endogenous acetylcholine signalling selectively at M4. This approach has the potential to retain striatal circuit benefits while improving tolerability vs broader muscarinic agonism. A 2-part randomised, double-blind, placebo-controlled phase 1b trial reported an antipsychotic-like signal⁶ and informed subsequent phase 2 development. However, 2 phase 2 trials (EMPOWER-1/EMPOWER-2) did not meet their primary endpoints, despite tolerability consistent with former studies.^{7,8}

This outcome raises a clinically important possibility: M4-only potentiation may be insufficient for robust antipsychotic efficacy in heterogeneous acute schizophrenia populations, and M1 engagement (or combined muscarinic signalling) may be more important than initially anticipated.

Targeting excitation–inhibition balance and glutamatergic circuitry

A major strand of contemporary schizophrenia drug development aims to tackle cortical microcircuit instability, often framed as an imbalance between excitatory pyramidal activity and inhibitory interneuron control (E/I balance).⁹ NMDA-receptor hypofunction, particularly on fast-spiking interneurons, leads to impaired inhibitory gain control, increased cortical noise, and disrupted

synchrony. Downstream consequences plausibly include degraded cognitive computations and, via cortico-striatal pathways, secondary effects on dopaminergic signalling.

Iclepertin (BI 425809): GlyT1 inhibition

A wide variety of compounds have been investigated as potential candidates for enhancing NMDA-related signalling, often by increasing synaptic availability of NMDA co-agonists. Iclepertin is a glycine transporter-1 (GlyT1) inhibitor designed to increase synaptic glycine availability, thereby augmenting glycine-site NMDA receptor signalling.¹⁰ Initial promise from phase 2 did not translate to success in three large phase 3 trials in the CONNEX phase 3 programme which reported no benefit vs placebo on the primary cognitive endpoint at 26 weeks.¹¹ This failure echoes bitopertin, an earlier GlyT1 inhibitor that generated early promise but ultimately failed in phase 3 programmes for negative symptoms when used adjunctively.

Evenamide: voltage-gated sodium channel inhibition to normalise activity-dependent glutamate release (add-on strategy)

Evenamide is a selective inhibitor of voltage-gated sodium channels with minimal activity across a broad range of other central nervous system targets. It is proposed to attenuate aberrant, high-frequency neuronal firing, thereby normalizing excessive, activity-dependent glutamate release without reducing basal glutamate levels. This distinction is conceptually important, as the therapeutic goal is to reduce pathological hyperexcitability without impairing normal cortical processing. Preclinical studies also suggest that evenamide may modulate aberrant dopaminergic signaling.¹²

Clinically, evenamide has been developed as an adjunct for patients with persistent positive symptoms despite adequate

antipsychotic treatment, a population in whom repeated switching among D2-based drugs often yields limited incremental benefit.

An initial randomised, double-blind, placebo-controlled, add-on to a stable second-generation antipsychotic, evenamide 30 mg twice daily produced a statistically significant reduction in PANSS total at 4 weeks, with a modest effect size (reported Cohen's $d \approx 0.33$) and good tolerability.¹³ Phase 3 trials are ongoing, and success here would provide a valuable therapeutic option for a patient group where evidence-based treatments beyond clozapine are limited.

Tuning the serotonin system

Pimavanserin (NUPLAZID): selective 5-HT2A inverse agonism

Pimavanserin is a selective 5-HT2A inverse agonist/antagonist with minimal direct dopamine receptor activity.¹⁴ Its development in schizophrenia has largely targeted negative symptoms as an adjunct to background antipsychotic therapy, based on the hypothesis that serotonergic modulation might improve motivation, affective flattening, and social engagement without worsening motor or metabolic burden.

An earlier phase 2 study (ADVANCE) reported improvement in negative symptoms vs placebo when added to a stable antipsychotic treatment.¹⁵ However, subsequent late-stage work failed to confirm benefit, and public reporting indicates that further schizophrenia trials were stopped after a negative phase 3 outcome.¹⁶

In this context, pimavanserin has demonstrated efficacy for psychosis associated with Parkinson disease and is approved in the United States for this indication. This experience suggests that achieving trial endpoints based on overall symptom burden may be more feasible than demonstrating efficacy for narrowly defined, domain-specific targets.

Roluperidone (MIN-101): sigma-2/5-HT2A antagonism

Roluperidone is a D2-sparing compound with reported sigma-2 receptor and 5-HT2A antagonism, among other receptor effects, developed for predominant negative symptoms.^{17,18} The translational appeal is clear: if negative symptoms are partly dissociable from dopaminergic psychosis mechanisms, then a non-D2 approach might produce benefit without EPS/prolactin liabilities.

While phase 2–3 programmes have been pursued,^{19,20} the US FDA issued a Complete Response Letter indicating the application did not provide substantial evidence of effectiveness in negative symptoms and requesting additional supportive data (including around concomitant antipsychotic use and safety).²¹ New trial is likely.

Novel approaches to dopamine modulation

Ulotaront (SEP-363856): TAAR1/5-HT1A agonism

Ulotaront acts as an agonist at TAAR1 and 5-HT1A, offering a mechanistic route to modulate monoaminergic systems indirectly rather than blocking D2 receptors. In both human and rodent studies it has been shown to reduce presynaptic dopamine synthesis capacity,²² particularly in states where it is raised.

An initial placebo-controlled trial in acute schizophrenia showed a greater reduction in PANSS total score over 4 weeks vs placebo, with a tolerability profile consistent with low D2-mediated motor/endocrine effects.²³ However, later phase 3 work has not been positive, although at least in part this has been due to extremely high placebo responses. Recent work suggests that

efficacy may be primarily limited to those with raised dopamine synthesis capacity.²²

Valbenazine and deutetrabenazine: VMAT2

Tardive dyskinesia (TD) is not only an adverse effect, but also a driver of discontinuation, dose limitation, and reluctance to use clozapine or long-term antipsychotic strategies. Treating TD effectively can preserve antipsychotic continuity and reduce functional stigma-related harms. VMAT2 inhibitors reduce vesicular packaging of monoamines (especially dopamine) within presynaptic terminals, leading to reduced dopaminergic signalling in relevant motor circuits.²⁴ This offers symptomatic reduction in involuntary movements without requiring antipsychotic changes.

Both valbenazine²⁵ and deutetrabenazine²⁶ have multiple randomised placebo-controlled trials supporting reduction in AIMS scores and are established as a pharmacological option for TD in the US. Deutetrabenazine has received EMA recommendation for marketing authorisation in the EU.

Optimising dopamine antagonism

Despite significant advances, there is still room for optimising classical dopamine antagonism.

F17464: preferential D3 antagonism plus 5-HT1A partial agonism

F17464 has been described as a dopamine receptor antagonist with high affinity for D3 receptors relative to D2, alongside 5-HT1A partial agonist properties.²⁷ The translational hypothesis is that D3-biased antagonism might influence cognition, motivation, and salience attribution, with a differentiated adverse-effect profile vs classic D2 antagonists. A phase 2 randomised placebo-controlled study in acute schizophrenia has been completed, and demonstrated efficacy on PANSS scores with good tolerability.²⁸

LB-102 (N-methyl amisulpride)

Amisulpride is one of the most efficacious antipsychotics available. LB-102 is an N-methylated analogue of amisulpride being developed as a once-daily agent, described as a dopamine D2/3 and 5-HT7 inhibitor with improved pharmacokinetics/brain exposure compared with parent compounds. PET work has characterised its D2 occupancy profile in humans. In January 2025, the company reported positive topline phase 2²⁹ results in acutely exacerbated schizophrenia and signalled plans toward phase 3.

Lumateperone (CAPLYTA): a serotonin–dopamine–glutamate modulator

Lumateperone is an atypical antipsychotic with effects across serotonergic, dopaminergic, and glutamatergic systems. Conceptually, it represents an effort to reduce the metabolic and motor costs of antipsychotic treatment while retaining efficacy, and it has been positioned clinically for patients where tolerability is the limiting factor rather than acute symptom control. The FDA approval for schizophrenia reflects short-term placebo-controlled evidence summarised in the prescribing information.³⁰ More recent industry-facing materials also describe relapse-prevention programmes (randomised withdrawal designs).

What this new landscape implies: from monotherapy to treatment packages

Three shifts follow from the pattern above. First, new mechanisms raise the hope that treatment of to date neglected treatment

domains may be on the horizon. The key “new” outcome is not a better PANSS total score in acute psychosis, though that remains essential, but credible interventions for negative symptoms, maintenance, and adverse-effect management. This aligns better with what patients and carers describe as recovery.

Second, tolerability is no longer a footnote: it is part of mechanism selection. A non-D2 strategy can still have burdens (e.g., GI, urinary, cognitive effects). The pragmatic clinical question is which adverse-effect class is acceptable for a given patient at a given stage.

Third, replication and design quality will decide winners. Emraclidine, ulotaront, and roluperidone each show, in different ways, how easily an early mechanistic narrative can outpace reproducible clinical benefit. We need trials that reduce heterogeneity (especially for negative symptoms), measure function, and incorporate meaningful anchors beyond symptom scales alone.

A pragmatic translational agenda for the next 5 years

For schizophrenia pharmacotherapy is moving from the one size fits all approach of D2 antagonism to a personalised toolbox additional advances in our understanding are needed in addition to novel treatments. Four priorities look practical now:

1. Better phenotyping in routine care. Services need a reliable way to distinguish predominant negative symptoms, cognitive impairment, affective comorbidity, and medication side effects – because each may map to different interventions and combinations.
2. Measurement-based prescribing. As options diversify, routine symptom-domain measures and adverse-effect monitoring become part of rational prescribing rather than research culture.
3. Combination logic that is explicit (and testable). If we are entering an era of adjunctive strategies, the field needs combination trials that are designed and analysed as combination trials, rather than post hoc “add-on” assumptions.
4. Whole-person outcomes as endpoints. Schizophrenia is lived in bodies as well as minds: cardiometabolic risk, sleep, substance use, and iatrogenic movement disorders shape long-term outcome. Pharmacological innovation should not distract from integrating physical health and prevention into schizophrenia treatment pathways; it should support it.

Conclusions

The most important development in schizophrenia therapeutics is not that there are “more drugs”; it is that there are *more mechanisms and more intended outcomes*. COBENFY makes the post-D2 era tangible, while other programmes demonstrate how hard translation remains. The clinical opportunity now is to move from a single-axis model of antipsychotic choice toward domain-informed, measurement-based treatment packages – without overselling novelty, and without forgetting that tolerability and physical health remain decisive for long-term recovery.

Declaration of Competing Interest

The authors report no declarations of interest.

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