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Fourth-Generation Antipsychotics: novel mechanism of action and clinical indication

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ABSTRACT

Fourth-generation or novel-mechanism antipsychotics are characterized by distinctive pharmacological profiles that are largely dopamine-sparing or dopamine-independent in their mechanisms of action. Unlike traditional agents that primarily target D_2 receptors, these compounds modulate serotonergic, muscarinic, sigma, and trace amine-associated receptor pathways. These mechanisms represent a paradigm shift toward circuit-level modulation in antipsychotic drug development. Fourth-generation antipsychotics achieve antipsychotic effectiveness while improving cognition and tolerability. Their dopamine-independent actions promote restoration of neural network balance and neuroplasticity. This article summarizes pimavanserin, roluperidone, KarXT, emraclidine, brilaroxazine, and ulotaront, and highlights their clinical relevance for improving negative and cognitive symptoms with minimal risk of extrapyramidal symptoms, metabolic disturbances, and prolactin elevation

Keywords: *Novel antipsychotics, Dopamine-sparing agents, TAAR1 agonists, Negative symptoms, Schizophrenia*

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1. INTRODUCTION

Over the past decade, fourth-generation or novel-mechanism antipsychotics have been introduced, characterized by distinctive pharmacological profiles that are largely dopamine-sparing or dopamine-independent in their mechanisms of action (1–3,6). These include mechanisms involving serotonergic inverse agonism, sigma receptor modulation, muscarinic receptor activation, and TAAR1 stimulation (3–6). Collectively, these mechanisms represent a paradigm shift toward circuit-level modulation in antipsychotic drug development (6). As a result, these agents show promise in addressing the unmet needs in schizophrenia treatment, offering a favorable tolerability profile with minimal risk of extrapyramidal symptoms, metabolic disturbances, and prolactin elevation, while demonstrating strong potential to improve cognition and effectively alleviate negative psychotic symptoms (6).

2. PIMAVANSERIN – 5-HT_2A Inverse Agonism

Pimavanserin is the first-in-class selective serotonin 5-HT_2A receptor inverse agonist and antagonist, notable for its lack of dopamine D_2 receptor affinity (1–3). By inhibiting 5-HT_2A-mediated cortical hyperactivity, it inhibits glutamate activation and interrupts hallucination-related circuits (2–3). The blockade of 5-HT_2A receptors also indirectly increase dopaminergic tone in the prefrontal cortex to enhance mood and cognition without motor effects aggravation (2–3). Pimavanserin has been approved by the United States Food and Drug Administration (FDA) in 2016 for Parkinson's disease psychosis (1).

3. ROLUPERIDONE (MIN-101) – Sigma-2 and 5-HT_2A Antagonism

Roluperidone was specifically developed to target the negative and cognitive symptoms of schizophrenia (4). Through 5-HT_2A antagonism, it reduces cortical hyperexcitability and glutamate-driven psychosis while indirectly improving

mesocortical dopamine transmission (4). By acting as a σ_2 receptor antagonist, it supports mitochondrial productivity and synaptic elasticity, promoting neuroplasticity and neuroprotection (5–6). Additionally, 5-HT_7 receptor antagonism regulates circadian rhythm and balance serotonergic–glutamatergic signaling, contributing to cognitive and mood stabilization (5–6). Roluperidone is currently undergoing phase 3 clinical evaluation for its efficacy in treating the negative symptoms of schizophrenia (4).

4. KarXT (XANOMELINE–TROSPIUM) – Muscarinic M_1/M_4 Activation

KarXT is a dual-component antipsychotic therapy that combines xanomeline, a central muscarinic M_1/M_4 receptor agonist, with trospium chloride, a peripheral muscarinic antagonist (7–9). Through M_1 receptor agonism, it enhances mesocortical glutamate and NMDA activity, leading to improved cognition and reduction of negative symptoms (8). Its M_4 receptor agonist action suppresses mesolimbic dopamine release, thereby suppressing positive psychotic symptoms without directly blocking D_2 receptors (8). Trospium chloride acts peripherally to prevent excessive cholinergic stimulation in the gastrointestinal and cardiovascular systems while maintaining central efficacy (7). KarXT has been approved by the US FDA in 2024 for the treatment of schizophrenia (7,9).

5. EMRACLIDINE (CVL-231) – Muscarinic M_4 Positive Allosteric Modulator

Emraclidine is an investigational positive allosteric modulator (PAM) of the muscarinic M_4 receptor (10–12). By enhancing M_4 receptor activity in mesolimbic regions, it decreases dopamine release in the nucleus accumbens through Gi-protein signaling, thereby reducing positive psychotic symptoms (12). Within mesocortical circuits, emraclidine surges acetylcholine and glutamate production to enhance cognition and mood (10–11). Currently in phase 2 clinical trials for schizophrenia, it demonstrates strong potential as a dopamine-independent therapeutic strategy (10–11).

6. BRILAROXAZINE (RP5063)

Brilaroxazine acts as a multimodal neuromodulator inducing dopaminergic, serotonergic, and adrenergic systems (13,6,14). It functions as a partial agonist at D_2, D_3, and D_4 receptors with moderate efficacy and behaves as an antagonist in hyperdopaminergic mesolimbic regions (14). Through serotonergic modulation, partial agonism at 5-HT_1A promotes dopamine release in cortical areas, while antagonism at 5-HT_2A, 5-HT_2B, 5-HT_6, and 5-HT_7 receptors contributes to mood regulation, neuroprotection, and improved sleep–wake balance (6,14). Additionally, it modulates α_1A and α_2A adrenergic receptors, while upregulating BDNF and NGF expression to support neurogenesis and decrease neuroinflammation (13). Brilaroxazine is currently in phase 3 evaluation and has shown consistent efficacy in improving both positive and negative symptoms (13,6,14).

7. ULOTARONT (SEP-363856)

Ulotaront is the first-in-class antipsychotic drug acting as a full agonist at TAAR1 and 5-HT_1A receptors, with no affinity for dopamine D_2 receptors (15–16). Through TAAR1 activation, it modulates intracellular cAMP signaling and regulates dopamine transporters (15). In mesolimbic pathways, this mechanism reduces dopamine surge to alleviate positive symptoms, whereas in mesocortical circuits it enhances dopaminergic and glutamatergic activity (15). Its 5-HT_1A agonist activity further increases prefrontal dopamine release, generating anxiolytic and antidepressant effects alongside cognitive boost (16). Ulotaront is currently undergoing phase 3 clinical trials for schizophrenia (15–16).

8. CLINICAL AND MECHANISTIC IMPLICATIONS

Fourth-generation antipsychotics represent a major advancement in psychiatric pharmacology by moving beyond dopamine receptor blockade to engage alternative molecular pathways (6). Their dopamine-independent actions promote restoration of neural network balance and neuroplasticity (6). This paradigm shift emphasizes targeted modulation of glutamatergic and cholinergic systems, supporting mood regulation, cognitive enhancement, and overall functional recovery (6). These agents establish a precision-based therapeutic framework focused on circuit-level stabilization for comprehensive and individualized management of schizophrenia and related disorders (6).

9. CONCLUSION

The emergence of fourth-generation antipsychotics signals a critical shift from dopamine-centric models toward broader, more integrative neurobiological targets (6). These agents target serotonergic, muscarinic, sigma, and trace amine pathways and promote circuit-level stabilization, neuroplasticity, and improved cognition (3–6). Their favorable tolerability profile and minimal risk of extrapyramidal symptoms, metabolic disturbances, and prolactin elevation highlight their potential to address persistent negative and cognitive symptoms (6). Fourth-generation antipsychotics represent an important advance

toward individualized and mechanistically precise treatment strategies for schizophrenia.

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Declarations

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Tables

Table. Fourth-Generation Antipsychotics

Generic Name	FDA Status	Therapeutic Indications	Primary Mechanism of Action
Pimavanserin	FDA-approved (2016)	Parkinson's disease psychosis (PDP)	Selective 5-HT$_2$A inverse agonist / antagonist
Roluperidone (MIN-101)	Phase 3	Negative symptoms of schizophrenia	σ_2 receptor antagonist, 5-HT$_2$A antagonist, 5-HT$_7$ antagonist
KarXT (Xanomeline–Trospium)	FDA-approved (2024)	Schizophrenia	M$_1$/M$_4$ muscarinic receptor agonist + M$_2$/M$_3$ antagonist
Emraclidine (CVL-231)	Phase 2	Schizophrenia	Positive allosteric modulator (PAM) of muscarinic M$_4$ receptor
Brilaroxazine (RP5063)	Completed Phase 3	Schizophrenia	Partial agonist at D$_2$/D$_3$/D$_4$, 5-HT$_2$A/5-HT$_7$ antagonist, α_1A/α_2Amodulation, anti-inflammatory
Ulotaront (SEP-363856)	Phase 3	Schizophrenia	TAAR1 full agonist, 5-HT$_1$A agonist