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REVIEW ARTICLE

Review of Next-Generation Non-Dopaminergic Antipsychotic Agents Targeting Central Muscarinic Receptors

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Abstract: Schizophrenia treatment is mainly hindered by exclusive therapeutic dependence on postsynaptic dopamine receptor blockade. While first- and second-generation antipsychotics show measurable efficacy against acute positive symptoms, their therapeutic impact on negative symptoms and cognitive deficits remains profoundly limited. Their adverse effects include metabolic syndromes, extrapyramidal motor dysfunction, hyperprolactinemia, and tardive dyskinesia. The clinical approval of xanomeline-trospium indicates the first novel pharmacological mechanism for schizophrenia in over seven decades. Central muscarinic acetylcholine receptor subtypes, predominantly M_1 and M_4, modulate frontostriatal and mesolimbic circuitry without direct antagonism of postsynaptic dopamine D_2 receptors. Agonism of striatal M_4 receptors mobilize postsynaptic 2-arachidonoylglycerol synthesis, which acts via retrograde presynaptic cannabinoid CB_1 receptor signaling to attenuate hyperactive mesolimbic dopamine release. Cortical and hippocampal M_1 receptor activation potentiates N-methyl-D-aspartate receptor conductance, ameliorating prefrontal microcircuit hypofunction and supporting cognitive processing. Co-formulation of the centrally active, non-selective M_1/M_4 preferring agonist xanomeline with trospium chloride, a quaternary ammonium peripheral anticholinergic that does not cross the blood-brain barrier, mitigates dose-limiting peripheral cholinergic adverse effects. Pivotal Phase 2 and Phase 3 trials have confirmed significant reductions in positive and negative symptoms alongside favorable metabolic, motor, and prolactin profiles. Translation into real-world clinical practice necessitates close attention to transient autonomic alterations, dosing schedules, somatic comorbidities, and global access paradigms. Muscarinic receptor therapeutics introduce a vital non-dopaminergic paradigm shift, repositioning neurochemical balancing across cortico-striato-thalamic circuits.

Keywords: Schizophrenia; Muscarinic Receptors; Xanomeline-Trospium; Antipsychotic Drugs; Endocannabinoid Signaling.

1. Introduction

Schizophrenia is a severe, chronic neuropsychiatric disorder characterized by profound disruptions in perception, inferential thinking, affective processing, volition, and cognitive organization [1]. Global epidemiological surveys indicate a lifetime prevalence approaching 0.7% to 1.0% across diverse populations, conferring substantial long-term functional impairment, reduced quality of life, and disproportionate socioeconomic burden [2, 3]. Longitudinal disability analyses consistently rank schizophrenia among the leading global causes of severe neuropsychiatric disability [4]. The therapeutic ceiling of conventional antipsychotic pharmacotherapy constitutes an unresolved clinical problem. Approximately 30% to 40% of patients fail to achieve symptomatic remission despite sustained treatment with standard postsynaptic dopamine D_2 receptor antagonists or partial agonists [5, 6]. Treatment-resistant schizophrenia, formally operationalized by the Treatment Response and Resistance in Psychosis consensus criteria, affects 20% to 30% of all diagnosed individuals [7, 8]. These clinical realities highlight the fundamental limitation of focusing interventions exclusively on dopamine receptor antagonism [9, 10].

The modern era of psychopharmacology began with the serendipitous observation of chlorpromazine's tranquilizing properties in the early 1950s, which subsequently led to the formulation of the classic dopamine hypothesis of schizophrenia [11]. Early iterations posited that generalized cerebral hyperdopaminergia underlay all symptomatic domains of the illness [12]. Subsequent neurochemical, neuroimaging, and pharmacological investigations refined this model into a more known dual-deficit pathway: subcortical mesolimbic hyperdopaminergia drives positive psychotic symptoms, whereas mesocortical hypodopaminergia within the prefrontal cortex contributes to primary negative symptoms and cognitive dysfunction [13, 14].

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Both first-generation antipsychotics, typified by haloperidol and chlorpromazine, and second-generation atypical antipsychotics, such as risperidone, olanzapine, and quetiapine, share an obligate reliance on binding and blocking postsynaptic dopamine D_2 receptors [15]. Positron emission tomography studies indicate that clinical antipsychotic efficacy requires occupying approximately 65% to 80% of striatal D_2 receptors [16]. However, exceeding an 80% striatal D_2 receptor occupancy threshold markedly increases the risk of motor adverse events, including drug-induced parkinsonism, acute dystonia, and akathisia [17]. Long-term continuous blockade of striatal D_2 receptors induces homeostatic receptor upregulation and postsynaptic dopamine supersensitivity, predisposing patients to tardive dyskinesia—a frequently irreversible choreoathetoid movement disorder [18, 19]. Second-generation antipsychotics reduced motor liability through combined serotonin 5-HT2A receptor antagonism or dopamine D_2 partial agonism [20]. Nevertheless, these atypical agents introduced extensive metabolic toxicities. Weight gain, peripheral insulin resistance, new-onset type 2 diabetes mellitus, and atherogenic dyslipidemia occur with substantial frequency, driven by potent off-target antagonism at histamine H_1, serotonin 5-HT2C, and peripheral muscarinic receptors [21, 22]. These cardiometabolic derangements contribute directly to a 15- to 20-year reduction in life expectancy among individuals with schizophrenia compared to the general population, with cardiovascular disease indicating the primary cause of excess premature mortality [23].

Standard dopaminergic agents display limited therapeutic efficacy against negative symptoms, such as blunted affect, alogia, asociality, anhedonia, and avolition, as well as neurocognitive deficits across executive function, working memory, and processing speed [24]. Because subcortical dopamine blockade does not address prefrontal cortical network dysconnectivity or NMDA receptor-mediated synaptic hypofunction, persistent negative and cognitive symptoms remain the most reliable predictors of long-term functional disability and unemployment in chronic schizophrenia [25]. Recognition that standard antipsychotics fail to restore prefrontal microcircuit computation prompted investigation into alternative neurotransmitter systems, specifically glutamate and acetylcholine [26, 27]. The cholinergic hypothesis of schizophrenia originated from early observations of cognitive disruption following central anticholinergic administration, alongside post-mortem brain tissue analyses demonstrating marked reductions in muscarinic acetylcholine receptor density across the dorsolateral prefrontal cortex, hippocampus, and striatum of patients with schizophrenia [28, 29].

Muscarinic acetylcholine receptors comprise five distinct G-protein-coupled receptor subtypes (M_1 through M_5), divided functionally into two families based on downstream G-protein coupling. The M_1, M_3, and M_5 subtypes couple preferentially to $G_{q/11}$ proteins to stimulate phospholipase C, generating inositol 1,4,5-trisphosphate and diacylglycerol, which mobilizes intracellular calcium stores and activates protein kinase C [26]. Conversely, M_2 and M_4 receptors couple to $G_{i/o}$ proteins, inhibiting adenylyl cyclase, lowering intracellular cyclic adenosine monophosphate (cAMP), and gating inward-rectifying potassium channels [27]. Centrally expressed M_1 and M_4 receptors occupy several important nodes that modulate frontostriatal and mesolimbic neurotransmission. Postsynaptic M_1 receptors are concentrated on pyramidal neurons and GABAergic interneurons in the prefrontal cortex and hippocampus, where their activation enhances NMDA receptor conductance and sustains long-term potentiation [30, 31]. Conversely, M_4 receptors are localized within the striatum, primarily on striatonigral and striatopallidal medium spiny neurons, functioning as an upstream modulatory gate over subcortical dopamine release [32]. Pharmacological stimulation of these central muscarinic receptors modulates subcortical dopamine release and restores cortical microcircuit balance without binding directly to postsynaptic dopamine receptors, introducing a distinct non-dopaminergic therapeutic paradigm.

2. Role of Muscarinic Receptors in Schizophrenia

2.1. Molecular Pharmacology and Differential Receptor Distribution

The five muscarinic receptor subtypes exhibit distinct anatomical distributions and physiological profiles within the central nervous system and peripheral tissues. Understanding their spatial organization is essential for dissecting both therapeutic antipsychotic actions and peripheral tolerability liabilities.

Postsynaptic M_1 receptors are broadly expressed across the cerebral cortex, hippocampus, and amygdala, regions governing working memory, cognitive flexibility, sensory gating, and emotional regulation [26]. Within prefrontal layer V pyramidal neurons, M_1 receptor signaling enhances cellular excitability by suppressing slowly activating voltage-gated potassium currents (M-currents) and facilitating glutamatergic neurotransmission through intracellular protein kinase C-dependent phosphorylation of NMDA receptor subunits GluN2A and GluN2B [30]. This interaction potentiates NMDA receptor-mediated inward currents, stabilizing dendritic spines and maintaining synchronous gamma-band oscillatory activity essential for working memory operations [31].

The M_4 receptor subtype is prominently expressed within the basal ganglia, exhibiting high density in the dorsal striatum and nucleus accumbens, with moderate expression in cortical and hippocampal layers [27]. Within striatal microcircuits, M_4 receptors are located postsynaptically on dopamine D_1-receptor-expressing medium spiny neurons that project via the direct basal ganglia pathway, as well as presynaptically on cholinergic interneuron axon terminals [32]. Activation of M_4 autoreceptors on cholinergic interneurons

suppresses local acetylcholine release, whereas their heteroreceptor activation on medium spiny neurons triggers an intracellular cascade that directly modulates striatal dopaminergic tone [32].

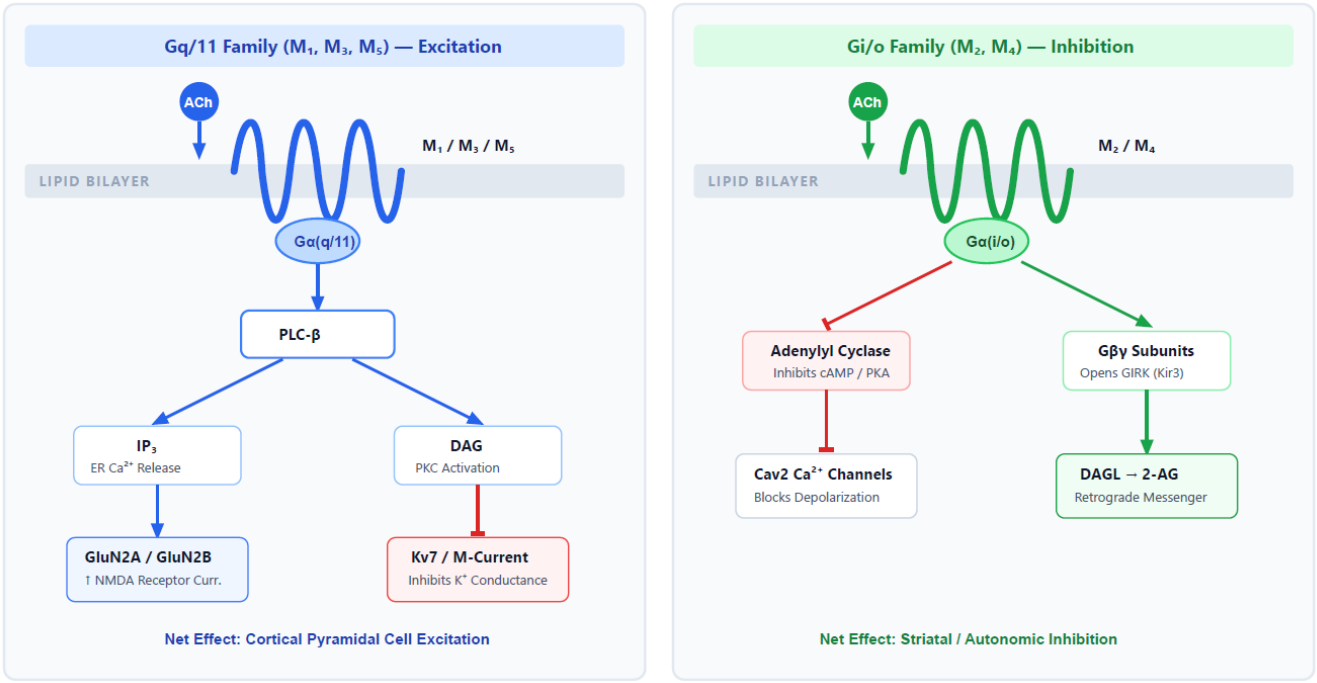

Figure 1. Muscarinic Receptor Subtypes and Their Targets

The remaining subtypes exhibit distinct regional distributions. The M_2 subtype is expressed predominantly in cardiac muscle, smooth muscle, and centrally within the brainstem and basal forebrain, where it functions primarily as an autoreceptor limiting cholinergic output [26]. The M_3 subtype is distributed across visceral smooth muscle, bronchial tissue, exocrine glands (including salivary, lacrimal, and sweat glands), and endocrine pancreatic beta cells, regulating smooth muscle contraction, glandular secretion, and insulin release [27]. Centrally, M_3 expression is minimal. The M_5 subtype displays restricted central localization, expressed at low levels within the ventral tegmental area and substantia nigra pars compacta, where it facilitates dopamine neuron firing via microvascular dilation and local paracrine mechanisms [26].

2.2. Striatal Dopamine Regulation via Retrograde Endocannabinoid Signaling

The central mechanism by which muscarinic agonists suppress mesolimbic dopamine release was historically attributed to indirect polysynaptic feedback pathways. However, electrophysiological and neurochemical investigations by Foster and colleagues (2016) demonstrated that striatal M_4 receptor activation modulates dopamine efflux through an on-demand retrograde endocannabinoid signaling mechanism [32].

Striatal medium spiny neurons receive convergent glutamatergic afferents from the cerebral cortex and dopaminergic projections from the substantia nigra pars compacta and ventral tegmental area. Stimulation of postsynaptic M_4 receptors on striatal medium spiny neurons couples to $G_{i/o}$ proteins, inhibiting adenylyl cyclase and dampening protein kinase A activity. M_4 receptor activation stimulates intracellular phospholipase C pathways, generating diacylglycerol, which is subsequently converted into the endocannabinoid 2-arachidonoylglycerol (2-AG) by the enzyme diacylglycerol lipase [32].

Once synthesized on demand within the postsynaptic dendritic spine, 2-AG is released into the synaptic cleft and travels retrogradely across the synapse to bind selectively to presynaptic cannabinoid CB_1 receptors localized on dopaminergic axon terminals. Activation of these presynaptic CB_1 receptors couples to inhibitory $G_{i/o}$ proteins, suppressing voltage-gated calcium channel opening and activating presynaptic inwardly rectifying potassium channels. This inhibits calcium influx into the terminal, suppressing exocytotic dopamine release into the dorsal and ventral striatum [32]. Pharmacological disruption of diacylglycerol lipase or selective antagonism of presynaptic CB_1 receptors abolishes M_4 agonist-induced suppression of striatal dopamine efflux, confirming this retrograde endocannabinoid loop as the primary pathway through which M_4 receptor agonists reduce subcortical dopamine hyperfunction without occupying dopamine D_2 receptors [32].

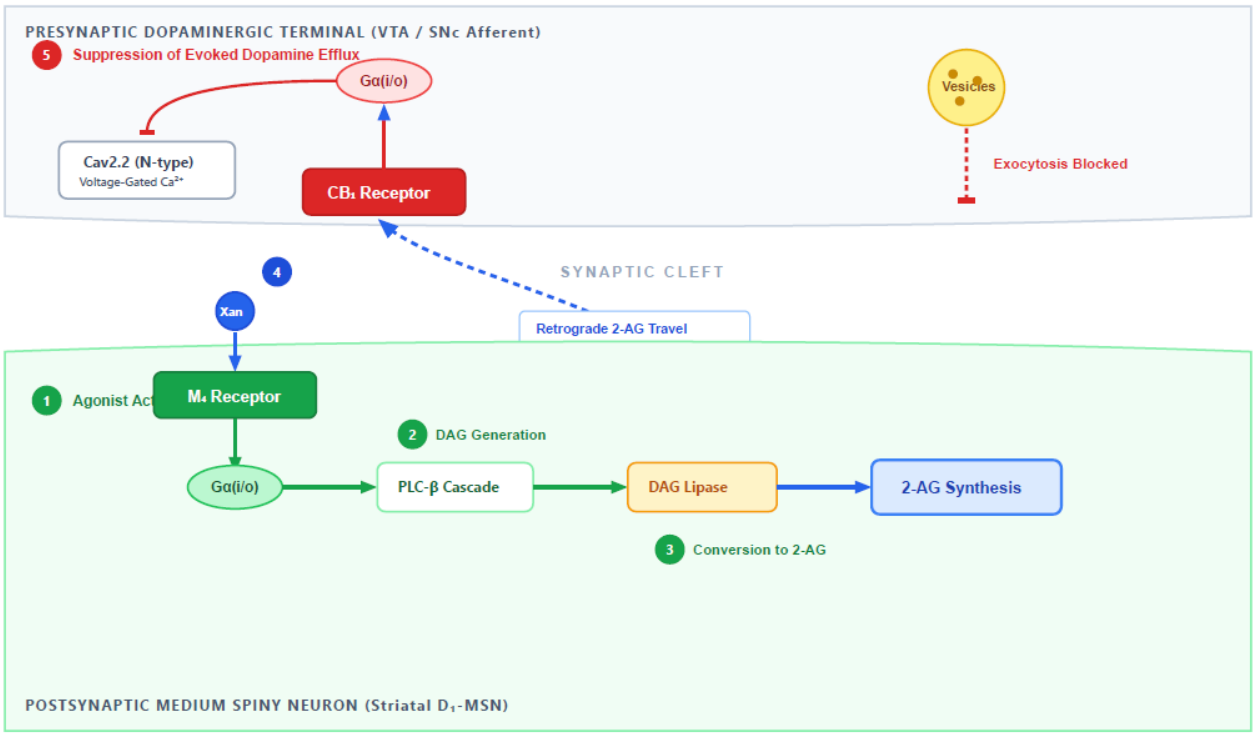

Figure 2. Striatal M_4 Activation and Retrograde 2-AG Suppression of Presynaptic Dopamine Efflux

Table 1. Neurobiological, Pharmacological, and Circuit-Level Properties of Central Muscarinic Receptor Subtypes Involved in Antipsychotic Mechanisms.

Parameter / Feature	M1 Receptor Subtype	M2 Receptor Subtype	M3 Receptor Subtype	M4 Receptor Subtype	M5 Receptor Subtype
Canonical G-Protein Coupling	$G_{q/11}$	$G_{i/o}$	$G_{q/11}$	$G_{i/o}$	$G_{q/11}$
Primary Downstream Effector Cascade	Phospholipase Cβ activation; ↑ IP_3 /DAG; ↑ $[Ca^{2+}]_i$; PKC activation; inhibition of K_v7/M-current	Adenylyl cyclase inhibition (↓ cAMP); activation of GIRK ($K_{ir}3$) channels; inhibition of Ca_v2 channels	Phospholipase Cβ activation; ↑ IP_3 /DAG; ↑ $[Ca^{2+}]_i$; calmodulin/MLCK and PKC activation	Adenylyl cyclase inhibition (↓ cAMP); DAG lipase activation → 2-AG synthesis; GIRK opening	Phospholipase Cβ activation; ↑ IP_3 /DAG; ↑ $[Ca^{2+}]_i$; endothelial NO synthase activation
Primary CNS Neuroanatomical Distribution	High in cerebral cortex (layers III/V), hippocampus (CA1/CA3), striatum, and amygdala	High in basal forebrain, brainstem motor nuclei; moderate in cortex and hippocampus	Very low/sparse central expression; detected in hypothalamus and solitary tract	High in striatum (caudate, putamen, nucleus accumbens); moderate in cortex and hippocampus	Restricted expression; localized primarily to substantia nigra pars compacta and VTA
Peripheral Tissue Localization	Exocrine glands, autonomic ganglia, gastric parietal cells	Cardiac tissue (SA/AV nodes, atria), smooth muscle, presynaptic autonomic terminals	Visceral smooth muscle (GI, bladder, bronchi), salivary and lacrimal glands, pancreatic β-cells	Low peripheral expression; sympathetic postganglionic terminals, secretory glands	Systemic and cerebral microvasculature endothelium

Parameter / Feature	M1 Receptor Subtype	M2 Receptor Subtype	M3 Receptor Subtype	M4 Receptor Subtype	M5 Receptor Subtype
Cellular & Circuit Actions in Psychosis	Potentiates NMDA receptor conductance (GluN2A/B) on pyramidal cells; enhances cortical signal-to-noise ratio and gamma oscillations	Functions as inhibitory autoreceptor on cholinergic terminals; modulates hippocampal acetylcholine tone	Minimal direct role in central psychosis circuitry; drives peripheral visceral adverse events	Heteroreceptors on direct-pathway MSNs drive retrograde endocannabinoid (2-AG) inhibition of dopamine release	Facilitates dopamine neuron burst firing via local microvascular nitric oxide dilation and direct excitation
Target Relevance to Antipsychotic Action	Primary pro-cognitive & negative symptom target (restores prefrontal cortical computation)	Tolerability/autonomic liability (bradycardia when engaged centrally/peripherally)	Primary dose-limiting peripheral adverse event mediator (GI hypermotility, salivation)	Primary antipsychotic target (suppresses hyperactive mesolimbic dopamine tone)	Theoretical modulator of reward; current lack of subtype-selective pharmacology

3. The Development of Muscarinic Therapeutics

3.1. Xanomeline-Trospium

The development of muscarinic agonists for neuropsychiatric disorders was historically limited by severe peripheral cholinergic toxicities. Xanomeline was originally synthesized as an orally bioavailable, non-quaternary azacyclic derivative that selectively activates M_1 and M_4 muscarinic receptor subtypes with minimal affinity for dopamine, serotonin, or adrenergic receptors [33]. In early clinical evaluations for Alzheimer's disease, xanomeline crossed the blood-brain barrier and produced substantial improvements in cognitive performance. Unexpectedly, it also markedly reduced psychotic symptoms, hallucinations, and behavioral agitation in patients with dementia [34].

Table 2. Pharmacokinetic Parameters, Bioavailability, Transporter Interactions, and Tissue Partitioning of Xanomeline and Trospium Chloride

Pharmacokinetic & Physicochemical Parameter	Xanomeline	Trospium Chloride
Chemical Structure	Synthetic 3-(hexyloxy)-1,2,5-thiadiazole azacyclic ether	Quaternary ammonium derivative of nortropane (azoniabicyclo-octane ester)
Molecular Weight	281.42 g/mol; uncharged lipophilic tertiary base at physiological pH	427.96 g/mol; permanently ionized, positively charged quaternary cation
Lipophilicity ($\log P$ / $\log D_{7.4}$)	$\log P \approx 3.2$ (highly lipophilic)	$\log D_{7.4} \approx -1.2$ to -0.5 (highly hydrophilic)
Oral Absolute Bioavailability (F)	Low to moderate (~10%–20% due to extensive first-pass hepatic metabolism)	Low (~10% under fasted conditions; drops to <3% with high-fat meals)
Time to Peak Concentration (T_{max})	Approximately 1.5 to 2.5 hours	Approximately 4.0 to 5.0 hours
Terminal Elimination Half-Life ($t_{1/2}$)	Approximately 5 to 7 hours	Approximately 18 to 20 hours
Apparent Volume of Distribution (V_d/F)	High (>1500 L), indicating deep peripheral and central tissue distribution	Moderate (~400 to 600 L), largely restricted to extracellular/peripheral compartments
Plasma Protein Binding	Approximately 90% bound to plasma albumin and α_1-acid glycoprotein	Approximately 50% to 85% bound primarily to plasma albumin
Blood–Brain Barrier (BBB) Permeability	Extensive passive transcellular diffusion; rapid CNS accumulation	Negligible passive diffusion; restricted by permanent positive ionic charge
Membrane Transporter Interactions	Non-substrate for P-glycoprotein (P-gp); passive diffusion dominates	High-affinity substrate for P-gp and organic cation transporters (OCT2); actively effluxed at BBB
Primary Clearance & Metabolic Pathways	Extensive hepatic metabolism via CYP2D6, CYP3A4, and flavin monooxygenases (N-oxidation)	Minimal hepatic CYP metabolism (<10%); largely cleared via non-enzymatic ester hydrolysis

Pharmacokinetic & Physicochemical Parameter	Xanomeline	Trospium Chloride
Excretion Routes	$> 80\%$ eliminated via renal excretion as inactive metabolites; $< 1\%$ unchanged drug	~80% excreted in urine via glomerular filtration and active tubular secretion (OCT2); 60% unchanged parent
Food Effect & Administration Rule	Minimal impact on total AUC, but food reduces peak gastrointestinal tolerability	Significant food effect (AUC decreased by 70%–80%); mandatory dosing 1 h before or 2 h after meals

However, the clinical translation of xanomeline monotherapy was arrested by dose-limiting peripheral adverse effects. Because xanomeline non-selectively stimulates peripheral M_2 and M_3 receptors in visceral smooth muscle and secretory glands, patients experienced high rates of gastrointestinal toxicity, including nausea, intractable vomiting, profuse diaphoresis, diarrhea, hypersalivation, and abdominal cramping, resulting in treatment discontinuation rates exceeding 50% in early trials [34, 35].

To resolve this central-peripheral paradox, Karuna Therapeutics developed the dual-agent co-formulation KarXT (xanomeline-trospium chloride; Cobenfy). Trospium chloride is an established pan-muscarinic receptor antagonist containing a fully ionized quaternary ammonium moiety [36]. This permanent positive charge confers high water solubility and prevents passive diffusion across the lipophilic blood-brain barrier. Trospium is a substrate for the active efflux transporter P-glycoprotein at the human brain capillary endothelium, ensuring that its pharmacological actions remain restricted to peripheral tissues [37].

Co-administration of trospium chloride alongside centrally penetrating xanomeline, trospium competitively blocks peripheral M_2 and M_3 muscarinic receptors in the gastrointestinal tract, salivary glands, and autonomic ganglia. Meanwhile, xanomeline enters the central nervous system unhindered to engage cortical M_1 and striatal M_4 receptors. Clinical pharmacology studies established that an empirical fixed-dose ratio of xanomeline to trospium chloride effectively mitigates peripheral cholinergic side effects while preserving central therapeutic efficacy [38].

4. The EMERGENT Clinical Trial Program

The clinical efficacy, safety, and durability of xanomeline-trospium for schizophrenia were systematically evaluated through the comprehensive EMERGENT clinical trial development program, which spanned early proof-of-concept testing, pivotal Phase 3 registration studies, and long-term open-label extensions.

4.1. EMERGENT-1

The clinical validity of dual muscarinic modulation was established in EMERGENT-1 (Brannan et al., *New England Journal of Medicine*, 2021) [39]. This study was a 5-week, multicenter, randomized, double-blind, placebo-controlled Phase 2 trial conducted in an acute inpatient setting. The trial evaluated 182 hospitalized adult patients meeting DSM-5 criteria for schizophrenia who were experiencing an acute psychotic relapse characterized by a baseline Positive and Negative Syndrome Scale (PANSS) total score between 80 and 120. Patients were randomized in a 1:1 ratio to receive either twice-daily oral KarXT (titrated from xanomeline 50 mg/trospium 20 mg twice daily up to a maximum dose of xanomeline 125 mg/trospium 30 mg twice daily) or matching placebo. The primary efficacy endpoint was the change from baseline to week 5 in the PANSS total score. At the conclusion of the 5-week intervention, patients in the KarXT cohort demonstrated a statistically significant and clinically robust reduction in PANSS total score compared to placebo (least-squares mean change: -17.4 points vs. -5.9 points, indicating a treatment difference of -11.5 points; 95% confidence interval, -16.4 to -6.6; $p < 0.001$; Cohen's d=0.75) [39, 40].

Secondary outcome measures in EMERGENT-1 showed parallel improvements. KarXT produced significant reductions in both the PANSS positive symptom subscale (-5.4 points vs. -2.2 points; $p < 0.001$) and the PANSS negative symptom subscale (-3.2 points vs. -1.7 points; $p < 0.01$). Additionally, significant improvements were documented on the Clinical Global Impression-Severity (CGI-S) score (-1.0 point vs. -0.4 points; $p < 0.001$). Importantly, the incidence of treatment-emergent extrapyramidal symptoms, assessed using the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale, was comparable between the active KarXT and placebo arms, with no signals of drug-induced parkinsonism, akathisia, or acute dyskinesia [39].

4.2. EMERGENT-2 and EMERGENT-3 (Phase 3)

The registrational Phase 3 trials, EMERGENT-2 and EMERGENT-3, were designed to confirm the efficacy and safety profile of KarXT in independent, adequately powered patient cohorts presenting with acute schizophrenia exacerbations [41, 42].

EMERGENT-2 enrolled 252 acutely hospitalized adults randomized 1:1 to flexible-dose KarXT (xanomeline 100/20 mg up to 125/30 mg twice daily) or placebo for 5 weeks [41]. At week 5, KarXT treatment achieved a statistically significant 9.6-point greater reduction in PANSS total score compared to placebo (-21.2 points vs. -11.6 points; $p < 0.0001$; Cohen's d=0.61). Significant reductions were demonstrated across all key secondary endpoints, including the PANSS positive subscale (-3.5 point difference; p<0.0001), PANSS negative subscale (-1.4 point difference; p=0.006), and the PANSS Marder negative factor score.

EMERGENT-3 enrolled 256 acute psychiatric inpatients across global investigative sites under a fixed-dose paradigm [42]. At week 5, the KarXT group demonstrated an 8.4-point greater reduction in PANSS total score relative to placebo (-20.6 points vs. -12.2 points; p<0.0001; Cohen's $d = 0.60$). KarXT also produced a significant reduction in the PANSS positive subscore (-3.0 point difference; p<0.0001). The primary safety and tolerability observations in EMERGENT-3 aligned closely with EMERGENT-2, confirming consistency across independent trials.

Table 3. EMERGENT Clinical Trial Program Results (Phase 2 and Phase 3)

Trial	Phase	Study Design and Duration	Patient Population (N)	Primary Efficacy Endpoint (PANSS Total Change vs. Placebo)	Effect Size (Cohen's d)	Adverse Events and Safety Findings
EMERGENT-1	Phase 2	Randomized, double-blind, placebo-controlled; 5 weeks	Acute inpatient schizophrenia (N=182)	-11.5 points ($p < 0.001$)	0.75	Mild-to-moderate nausea, constipation, dyspepsia; no motor EPS; no weight gain
EMERGENT-2	Phase 3	Randomized, double-blind, placebo-controlled; 5 weeks	Acute inpatient schizophrenia (N=252)	-9.6 points ($p < 0.0001$)	0.61	Transient GI effects, modest elevations in pulse rate; no prolactin elevation
EMERGENT-3	Phase 3	Randomized, double-blind, placebo-controlled; 5 weeks	Acute inpatient schizophrenia (N=256)	-8.4 points ($p < 0.0001$)	0.60	Nausea, vomiting, dyspepsia; minimal shifts in glycemic or lipid measures
EMERGENT-4	Phase 3 (OLE)	Outpatient open-label extension; up to 52 weeks	Completers of EMERGENT-2 / EMERGENT-3 ($N \approx 110$)	Sustained PANSS improvement from acute baseline	N/A (Open-label)	Durable therapeutic effect; stable metabolic profile; low motor adverse event incidence
EMERGENT-5	Phase 3 (OLE)	Outpatient open-label safety study; 52 weeks	Stable or subacute outpatients ($N = 566$)	Mean PANSS reduction >20 points over 52 weeks	N/A (Open-label)	Discontinuation due to AEs approximately 11%; minimal weight shifts; no EPS signals

4.3. EMERGENT-4 and EMERGENT-5 (Phase 3 Open-Label Extensions)

Because acute registration trials are limited to 5-week intervals in strictly monitored inpatient environments, evaluating long-term safety, durability of efficacy, and metabolic impact necessitated extended outpatient trials. The Phase 3 open-label extension studies, EMERGENT-4 and EMERGENT-5, assessed treatment outcomes over 52 weeks [43, 44].

EMERGENT-4 enrolled patients who successfully completed the acute 5-week treatment period in either EMERGENT-2 or EMERGENT-3, monitoring long-term durability. Participants maintained continuous, stable reductions in PANSS total scores, with sustained improvements in both positive and negative symptoms throughout the 52-week period [43]. EMERGENT-5 enrolled 566 clinically stable outpatients who transitioned either from prior oral antipsychotics or entered de novo to evaluate 52-week safety

and tolerability. Over one year of continuous treatment, patients experienced mean reductions in PANSS total score exceeding 20 points from their original baseline, alongside high retention rates [44].

Across both Phase 3 open-label extension cohorts, KarXT demonstrated negligible liability for the adverse effects that classically compromise standard antipsychotics: there was no evidence of treatment-emergent parkinsonism, akathisia, tardive dyskinesia, weight gain, dyslipidemia, insulin resistance, or clinically significant prolactin elevation [43, 44].

5. Clinical Safety, Tolerability, and Adverse Effects

5.1. Gastrointestinal Tolerability and Autonomic Effects

Although trospium chloride successfully neutralizes severe systemic cholinergic toxicity, gastrointestinal adverse effects remain the most commonly observed treatment-emergent events with KarXT [39, 41, 42]. In pooled analyses of the EMERGENT acute trials, nausea occurred in approximately 19% to 20% of KarXT-treated patients compared to 3% to 4% receiving placebo, dyspepsia in 17% to 19% versus 3% to 5%, constipation in 13% to 15% versus 4% to 6%, and vomiting in 11% to 13% versus 2% to 3%.

These gastrointestinal effects are primarily mild to moderate in severity, dose-dependent, and transient. Peak incidence occurs within the first 1 to 2 weeks of treatment, coinciding with dosage titration, followed by substantial attenuation as neuroadaptive and peripheral tolerance develop. The overall rate of trial discontinuation directly attributable to gastrointestinal adverse events remained below 5% across the Phase 3 trials, confirming that peripheral muscarinic receptor blockade by trospium renders the co-formulation clinically tolerable for most patients [41, 42].

5.2. Cardiovascular and Autonomic Effects

Safety analyses from the EMERGENT clinical program and clinical pharmacology reviews indicate that xanomeline-trospium treatment induces modest, dose-dependent hemodynamic shifts [45, 46]. Patients receiving KarXT experienced mean resting heart rate increases of 4 to 6 beats per minute (bpm) relative to placebo, alongside small mean elevations in systolic blood pressure of approximately 1.5 to 2.5 mmHg.

Mechanistically, these hemodynamic variations do not stem purely from peripheral anticholinergic blockade by trospium chloride. While quaternary trospium limits vagal parasympathetic transmission at peripheral cardiac muscarinic receptors, it is dosed at levels calibrated to mitigate visceral cholinergic tone without inducing complete peripheral autonomic denervation [47]. Instead, these cardiovascular manifestations is a complex autonomic relationship: centrally penetrating xanomeline elicits sympathoexcitation and modulates central muscarinic baroreflex and vasomotor control, operating alongside an incomplete peripheral muscarinic blockade by trospium [48, 49]. Clinicians should obtain baseline blood pressure and pulse readings, screen for preexisting cardiovascular disease or rhythm disturbances, and monitor heart rate and blood pressure periodically, particularly during dose titration [50].

5.3. Motor, Endocrine, and Metabolic Effects

The clinical differentiation of xanomeline-trospium from conventional first- and second-generation antipsychotics is most evident across motor, metabolic, and endocrine parameters. Because KarXT does not antagonize postsynaptic dopamine D_2 receptors, it avoids the neurological and endocrine toxicities associated with direct nigrostriatal and tuberoinfundibular dopamine pathway blockade [21, 22].

Pooled motor safety assessments from the EMERGENT program, using standardized scales including the Simpson-Angus Scale, Barnes Akathisia Rating Scale, and Abnormal Involuntary Movement Scale, showed no statistically significant differences between KarXT and placebo in rates of treatment-emergent extrapyramidal symptoms, akathisia, or parkinsonism [41, 42]. Anticholinergic rescue medication use was similarly balanced between treatment arms. Because it lacks postsynaptic striatal D_2 receptor occupancy, KarXT does not induce receptor upregulation, minimizing the long-term risk of dopamine supersensitivity and tardive dyskinesia [18, 19].

Similarly, KarXT exhibits endocrine and metabolic neutrality. Standard antipsychotics that block D_2 receptors in anterior pituitary lactotrophs disinhibit prolactin secretion, leading to hyperprolactinemia, gynecomastia, galactorrhea, amenorrhea, and long-term osteopenia [21]. In contrast, serum prolactin levels in KarXT-treated patients remained stable, with mean changes comparable to placebo. Evaluations across the 52-week EMERGENT extension studies showed stable fasting glucose, glycated hemoglobin (HbA1c), total cholesterol, low-density lipoprotein, and triglyceride profiles, without the weight gain or metabolic shifts characteristic of agents like olanzapine or clozapine [22, 43, 44].

Table 4. Comparative Safety Matrix Between First-Generation Antipsychotics, Second-Generation Antipsychotics, and Xanomeline-Trospium (KarXT)

Clinical Safety & Tolerability	First-Generation Antipsychotics (e.g., Haloperidol, Chlorpromazine)	Second-Generation Antipsychotics (e.g., Olanzapine, Risperidone)	Xanomeline-Trospium (KarXT / Cobenfy)
Extrapyramidal Symptoms (EPS)	High (parkinsonism, acute dystonia, rigidity secondary to striatal D_2 blockade $> 80\%$)	Low to moderate (dose-dependent; mitigated by 5-HT_{2A} antagonism or D_2 partial agonism)	Negligible / Placebo-level (no direct dopamine D_2 receptor binding or antagonism)
Akathisia	High (frequently severe, dose-limiting, and distressing)	Low to moderate (notably elevated with partial agonists like aripiprazole)	Placebo-level (incidence comparable to placebo across Phase 2/3 trials)
Tardive Dyskinesia Risk	High (~5% annualized cumulative incidence via postsynaptic D_2 supersensitivity)	Low to moderate (~0.5%–1.5% annualized risk; lower than FGA class)	Theoretical minimum / Absent (no chronic upregulation of striatal D_2 receptors)
Weight Gain Liability	Low to moderate (chlorpromazine moderate; haloperidol negligible)	Moderate to severe (highest with olanzapine and clozapine via H_1/5-HT_{2C} antagonism)	Neutral / Negligible (slight weight loss observed in 52-week extension cohorts)
Metabolic Derangements (Lipids / Glucose)	Generally low (modest with low-potency phenothiazines)	Moderate to severe (insulin resistance, diabetic ketoacidosis risk, atherogenic dyslipidemia)	Metabolically neutral (no deleterious alterations in HbA1c, fasting glucose, or lipid panels)
Hyperprolactinemia	Severe (uninhibited prolactin secretion via tuberoinfundibular D_2 receptor blockade)	High with risperidone/paliperidone; sparing with aripiprazole/quetiapine	Absent (serum prolactin concentrations track placebo levels)
Sedation & Somnolence	High with low-potency FGAs (central H_1 and α_1-adrenergic antagonism)	Moderate to high (prominent with clozapine, olanzapine, quetiapine)	Low (sedation rates comparable to placebo; non-sedating profile)
Anticholinergic Central Adverse Effects	Variable (high with low-potency FGAs; impairs cognition and memory)	Variable (high with clozapine and olanzapine; cognitive blunting)	None (trospium does not cross the BBB; centrally active xanomeline is pro-cholinergic)
Gastrointestinal Toxicity	Low (occasional constipation secondary to low-potency antimuscarinic action)	Low to moderate (constipation common; clozapine hypomotility/ileus risk)	Moderate to high (transient nausea, dyspepsia, vomiting, constipation via peripheral balancing)
Cardiovascular & Hemodynamic Effects	High QTc prolongation risk (thioridazine, haloperidol IV); orthostatic hypotension (α_1)	Variable QTc liability (ziprasidone); orthostatic hypotension; tachycardia	Modest heart rate increase (4–6 bpm) and mild BP elevation (1.5–2.5 mmHg); minimal QTc liability
Hepatic / Renal Precautionary Demands	Routine monitoring; dose adjustments for advanced organ failure	Routine baseline liver enzyme tests; weight/metabolic monitoring schedules	Contraindicated in moderate-to-severe hepatic impairment; dose titration required in renal failure

6. Positive Allosteric Modulation at Muscarinic Receptors

The therapeutic validation of xanomeline-trospium has catalyzed drug discovery efforts targeting the muscarinic cholinergic system, focusing on positive allosteric modulators (PAMs) designed to bypass the need for a peripheral antagonist companion [51, 52].

Figure 3. Orthosteric Agonism versus Positive Allosteric Modulation at Muscarinic Receptors

Table 5. Developmental of Muscarinic-Targeted and Non-Dopaminergic Antipsychotic Agents in Clinical Trials.

Compound Name	Primary Molecular Mechanism	Sponsor	Developmental Phase & Status	Study Indicators & Published Outcomes	Clinical Indications Targeted
Xanomeline-Trospium (KarXT / Cobenfy)	Orthosteric dual M_1/M_4 preferring agonist + peripheral quaternary antimuscarinic	Karuna Therapeutics / Bristol Myers Squibb	FDA Approved (Sept 2024); Phase 3 ongoing for adjunct / AD psychosis	Met primary endpoints in EMERGENT-1, -2, -3; sustained efficacy in EMERGENT-4, -5	Acute schizophrenia; adjunctive schizophrenia; Alzheimer's disease psychosis
Emraclidine (CVL-231)	Highly selective positive allosteric modulator (PAM) of M_4 receptors	Cerevel Therapeutics / AbbVie	Phase 2 completed (Program under strategic review)	Did not achieve statistical separation on PANSS total change in EMPOWER-1 and EMPOWER-2	Acute schizophrenia; non-motor neuropsychiatric symptoms
NBI-1117568	Selective oral orthosteric M_4 receptor agonist	Neurocrine Biosciences / Sosei Heptares	Phase 2 completed (Advancing to Phase 3)	Phase 2 dose-finding trial met primary endpoint at 20 mg once-daily (8.4-point PANSS reduction vs. placebo)	Acute schizophrenia; cognitive impairment in schizophrenia
Anavex 3-71 (AF710B)	Dual agonist at sigma-1 (σ_1) receptor and positive allosteric modulator of M_1	Anavex Life Sciences	Phase 2 ongoing	Phase 1 demonstrated safety, oral bioavailability, and dose linearity; favorable CNS pharmacodynamics	Schizophrenia; Frontotemporal dementia; Alzheimer's disease
MK-7622	Highly selective positive allosteric modulator (PAM) of M_1 receptors	Merck & Co.	Phase 2 discontinued	Failed to demonstrate robust pro-cognitive separation in clinical cognitive impairment trials	Adjunctive cognitive impairment associated with schizophrenia
Ulotaront (SEP-363856)	Trace amine-associated receptor 1 (TAAR1) agonist with 5-HT_{1A} partial agonism	Sunovion / Sumitomo Pharma	Phase 3 ongoing / Re-evaluating	Initial pivotal DIAMOND-1/-2 trials missed primary endpoints; secondary analyses exploring titration profiles	Acute and maintenance schizophrenia; Parkinson's disease psychosis
Ralmitaront (RO6889450)	Highly selective trace amine-associated receptor 1 (TAAR1) partial agonist	Roche	Phase 2 discontinued	Terminated following interim futility analysis evaluating efficacy in negative symptoms and acute psychosis	Negative symptoms of schizophrenia; acute exacerbations
Pimavanserin (ACP-103)	Selective 5-HT_{2A} receptor inverse agonist / antagonist	Acadia Pharmaceuticals	FDA Approved for PDP; Phase 3 evaluated for schizophrenia	Failed to meet primary endpoint as adjunctive therapy for negative symptoms (ADVANCE-2)	Approved for Parkinson's disease psychosis; investigational in schizophrenia

6.1. Selective Muscarinic Allosteric Modulators

Orthosteric muscarinic agonists bind to the endogenous acetylcholine binding pocket, which is highly conserved across all five receptor subtypes (M_1 through M_5), presenting challenges for subtype selectivity. Conversely, positive allosteric modulators bind to less-conserved allosteric pockets topographically distinct from the orthosteric binding site, enhancing receptor affinity and efficacy only in the presence of endogenous acetylcholine [51, 52].

Emraclidine (formerly CVL-231) was developed as an orally bioavailable, highly selective positive allosteric modulator targeting the M_4 receptor subtype [53]. Preclinical models showed that emraclidine selectively potentiated M_4 signaling, attenuated dopamine efflux, and reversed amphetamine-induced hyperlocomotion without provoking peripheral cholinergic adverse events or requiring co-administration of an anticholinergic agent [54]. Following favorable Phase 1b safety and pharmacodynamic outcomes in patients with schizophrenia [55], two pivotal registration-directed Phase 2 trials, EMPOWER-1 and EMPOWER-2, were initiated.

In November 2024, topline data from EMPOWER-1 and EMPOWER-2 showed that neither trial achieved its primary efficacy endpoint of a statistically significant reduction in the PANSS total score compared to placebo at week 6 [56, 57]. While emraclidine revealed a favorable safety profile devoid of typical cholinergic or motor adverse effects, the absence of acute antipsychotic separation highlighted key pharmacological distinctions. These outcomes suggest that pure allosteric modulation of M_4 receptors alone may be insufficient to achieve acute antipsychotic efficacy, or that dual M_1 and M_4 orthosteric agonism—as provided by xanomeline—is required to generate clinical antipsychotic separation in acute relapse paradigms [58].

6.2. Selective M1 Agonists and Adjunctive Pipelines

Selective M_1 receptor agonists, such as NBI-1117568, continue under clinical evaluation, aimed primarily at cognitive impairment associated with schizophrenia (CIAS) and primary negative symptom domains [59]. Because cortical M_1 receptor signaling enhances NMDA receptor conductance and prefrontal microcircuit firing, selective M_1 activation indicate a strategy for targeting cognitive deficits that do not respond to dopamine D_2 receptor blockade [30, 31].

Other non-dopaminergic trials are investigating trace amine-associated receptor 1 (TAAR1) agonists (e.g., ulotaront) and selective 5-HT2A receptor inverse agonists, expanding options beyond the classic monoaminergic pathways [60, 61].

7. Clinical Applications

7.1. Dosing, Titration Schedules, and Contraindications

The United States Food and Drug Administration (FDA) approved xanomeline-trospium chloride (Cobenfy) in September 2024 for the treatment of schizophrenia in adults, establishing it as the first approved antipsychotic operating through a non-dopaminergic mechanism [38].

Clinical administration of KarXT requires careful adherence to titration protocols to establish gastrointestinal and autonomic tolerability. Therapy is initiated at an oral dose of 50 mg xanomeline / 20 mg trospium chloride twice daily for the first two days. On day 3, the dose is escalated to 100 mg xanomeline / 20 mg trospium chloride twice daily. Based on clinical efficacy and individual tolerability, the dose may be titrated after a minimum of one week to the maximum recommended dose of 125 mg xanomeline / 30 mg trospium chloride twice daily. To minimize food-effect variability in gastrointestinal transit and absorption, KarXT must be taken with water at least one hour before meals or at least two hours following meals [38].

Because trospium chloride exerts peripheral anticholinergic effects, KarXT is contraindicated in patients with urinary retention, gastric retention, or uncontrolled narrow-angle glaucoma. Additionally, because both xanomeline and trospium undergo hepatic and renal clearance pathways, it is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh Class B or C) and requires careful dosage adjustment in patients with moderate renal impairment (estimated glomerular filtration rate < 60 mL/min/1.73 m^2) [38, 47].

7.2. Patient Selection

Real-world clinical implementation requires systematic patient selection criteria. Primary candidates for KarXT include:

1. Patients who have developed severe metabolic complications on second-generation antipsychotics, including rapid weight gain, insulin resistance, or dyslipidemia [21, 22].

2. Patients experiencing distressing motor adverse events, such as parkinsonism, akathisia, or emergent tardive dyskinesia [18, 19].
3. Patients with persistent negative symptoms or cognitive deficits that have shown minimal response to standard D_2 receptor antagonists [24, 25].

Cross-titration and switching from established dopaminergic antipsychotics to KarXT must be managed cautiously. Sudden discontinuation of standard antipsychotics risks precipitating rebound psychosis, cholinergic rebound, or withdrawal akathisia due to unmasked, upregulated dopamine D_2 receptors [17]. A gradual cross-titration schedule over 2 to 4 weeks is recommended, steadily introducing and titrating KarXT while progressively tapering the preceding dopaminergic agent.

7.3. Global and the Indian Healthcare

Translating muscarinic therapeutics into clinical practice within low- and middle-income countries, including India, introduces unique logistical and economic considerations [62]. Schizophrenia in India is managed within a complex, highly heterogeneous healthcare infrastructure characterized by significant disparities between urban psychiatric centers and resource-constrained rural clinics [23].

In India, the implementation of the Mental Healthcare Act (MHCA) 2017 legally mandates access to mental healthcare and essential psychotropic medications for all individuals with mental illness [62]. However, resource constraints and public healthcare spending limit the immediate adoption of novel, branded therapeutics. Generic second-generation antipsychotics—primarily olanzapine, risperidone, and aripiprazole—remain the primary treatment modalities across public hospital formularies and rural healthcare centers due to their low cost and wide availability [62].

Clozapine remains underutilized across Indian clinical practices despite its documented efficacy in treatment-resistant schizophrenia, constrained by mandatory absolute neutrophil count monitoring logistics, limited laboratory infrastructure in secondary centers, and clinical hesitancy [7]. If introduced at standard global patent pricing, KarXT will face substantial affordability barriers, likely confining its initial clinical use to the private healthcare sector. Addressing these disparities will require value-based pricing, regional manufacturing partnerships, and integration into the National List of Essential Medicines to ensure equitable access across diverse socioeconomic populations [23, 62].

8. Limitations

8.1. Receptor Target Specificity and the Need for Dual M1/M4 Activation

The failure of selective M_4 positive allosteric modulators, such as emraclidine in the EMPOWER-1 and EMPOWER-2 Phase 2 trials, raises critical theoretical questions regarding receptor target requirements in schizophrenia [56, 57]. Preclinical literature posited that selective M_4 receptor potentiation would suffice to normalize subcortical dopamine release without generating peripheral side effects [53, 54]. However, the negative Phase 2 results indicate that unconstrained allosteric modulation may provide insufficient tone during acute psychopathology, or that simultaneous M_1 and M_4 receptor activation is necessary to achieve clinical efficacy [58].

Dual M_1/M_4 activation provides a synergistic mechanism: striatal M_4 stimulation suppresses subcortical dopamine efflux through retrograde 2-AG/CB_1 signaling, while cortical M_1 stimulation enhances prefrontal NMDA receptor-mediated pyramidal cell firing and improves signal-to-noise ratios [30, 32]. Whether selective M_4 PAMs can produce maintenance efficacy in stable outpatients or prevent relapse remains an open question, but current evidence supports orthosteric dual M_1/M_4 agonism as the primary validated muscarinic antipsychotic strategy.

8.2. Autonomic Shifts and Long-Term Cardiovascular Safety

The cardiovascular effects of xanomeline-trospium require careful evaluation across long-term real-world populations. Although mean increases of 4 to 6 bpm in heart rate and 1.5 to 2.5 mmHg in systolic blood pressure are clinically manageable in clinical trial cohorts, their cumulative impact over years of continuous exposure in patients with preexisting cardiovascular disease remains unknown [45, 46].

Because individuals with schizophrenia display higher baseline rates of smoking, physical inactivity, obesity, and hypertension, persistent tachycardia and blood pressure elevations could theoretically accelerate cardiovascular morbidity [23]. Determining

whether these autonomic shifts persist, attenuate, or interact with autonomic aging will require systematic post-marketing surveillance and dedicated registry studies [50].

8.3. Therapeutic Role in Treatment-Resistant Schizophrenia

A critical question is whether muscarinic agonists show clinical efficacy in treatment-resistant schizophrenia (TRS). Clozapine remains the sole evidence-based pharmacotherapy for TRS, yet up to 40% to 70% of treatment-resistant patients exhibit incomplete response or clozapine intolerance [7]. Clozapine possesses an intricate polypharmacological profile, including active metabolite actions at muscarinic receptor subtypes (N-desmethylclozapine is an M_1 partial agonist and M_4 agonist), suggesting that muscarinic modulation may contribute to its clinical efficacy [28, 29]. Dedicated randomized clinical trials evaluating KarXT in strictly defined treatment-resistant cohorts, both as monotherapy and as an adjunctive treatment to clozapine, is an essential next step in clinical schizophrenia research.

9. Conclusion

The clinical development and regulatory approval of xanomeline-trospium marks a major shift in psychiatric therapy, establishing the first non-dopaminergic mechanistic class for schizophrenia in over seventy years. This treatment addresses acute positive and negative symptoms while avoiding the motor, metabolic, and endocrine adverse events associated with postsynaptic dopamine D_2 receptor blockade by targeting frontostriatal and mesolimbic circuits through dual M_1 and M_4 muscarinic acetylcholine receptors. The striatal M_4 receptor retrogradely regulates subcortical dopamine release via 2-arachidonoylglycerol synthesis and presynaptic cannabinoid CB_1 receptor activation, and the cortical M_1 receptor enhances NMDA receptor-dependent prefrontal computational performance. The success of dual muscarinic modulation provides a foundation for exploration of cholinergic, allosteric, and neuromodulatory mechanisms, expanding pharmacological options beyond monoaminergic receptor blockade.

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