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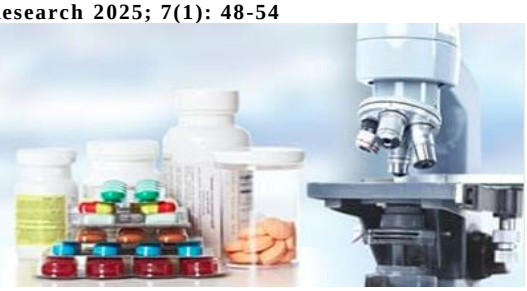

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Comparative analysis between muscarinic and dopamine receptor in antipsychotic activity

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Abstract
Schizophrenia and related psychotic disorders are primarily treated with antipsychotic drugs targeting dopamine and muscarinic receptors. This review presents a comparative analysis of the antipsychotic activity of agents acting on these receptors, including KarXT (*Xanomeline-trospium*) olanzapine, clozapine, betel nut, *Withania somnifera*, haloperidol, chlorpromazine, Ginkgo biloba, and aporphine alkaloids. Dopamine receptor antagonists, such as haloperidol and chlorpromazine, have been the cornerstone of antipsychotic therapy but are associated with extrapyramidal side effects and tardive dyskinesia. Atypical antipsychotics like olanzapine and clozapine exhibit a mixed dopamine and muscarinic receptor profile, offering better symptom control but increasing the risk of metabolic and anticholinergic side effects. KarXT (*Xanomeline-trospium*) a novel muscarinic agonist-antagonist combination, represents a promising approach by bypassing dopamine-related adverse effects while maintaining efficacy. Traditional and plant-based compounds, such as betel nut, *Withania somnifera*, and Ginkgo biloba, modulate muscarinic and dopamine pathways and offer potential adjunctive benefits. Aporphine alkaloids, found in various plant species, exhibit dopamine receptor partial agonist activity and may hold promise for future drug development. This comparative review highlights the therapeutic advantages and limitations of muscarinic and dopamine receptor-targeting drugs, emphasizing the need for novel treatments that balance efficacy and safety in managing psychosis.

Keywords: *Schizophrenia*, muscarinic receptors, dopamine receptors, KarXT, *Withania somnifera*, antipsychotic drugs

Introduction
Schizophrenia is a common and complex mental illness that has three main symptom domains: cognitive symptoms (such as poor attention, concentration, memory, and executive functions), negative symptoms (such as lack of motivation, lack of emotional expression or flat affect, and social withdrawal), and positive symptoms (such as hallucinations, delusions, disordered thinking and speech) [1]. In terms of demographics, between 0.5% and 1.0% of people globally suffer from *Schizophrenia* [2]. It typically shows up in late adolescence or early adulthood. Many individuals with *Schizophrenia* remain incapacitated for the rest of their lives, despite the fact that the disease's natural development varies greatly. *Schizophrenia* really continues to rank among the top 10 global causes of disability [3]. All of the antipsychotics that are currently on the market are either dopamine (DA) D2 receptor antagonists or partial agonists/antagonists [4]. Postsynaptic DA receptor blockage [5]. Current antipsychotics that directly antagonize DA D2 receptors are linked to distinct and predictable adverse effects (AEs), which might range from behavioural toxicities to mobility problems [6]. Although their overall effectiveness and/or side effects may be influenced by other neurotransmitter systems, DA D2 receptors are thought to primarily mediate their good therapeutic effects by lowering positive symptoms of *Schizophrenia* [7, 8]. Antipsychotic medications are also linked to unwanted side effects, such asakathisia, weight gain, metabolic abnormalities, excessive sedation, hyperprolactinemia, extrapyramidal side effects, and the possibility of tardive dyskinesia [9, 10]. More effective treatments based on novel or distinct molecular targets are badly needed, particularly if they have better safety and tolerability profiles and/or are demonstrated to be effective across all three symptom domains [11]. The five muscarinic acetylcholine receptors are members of the superfamily of G protein-coupled neurotransmitter receptors, which are partially responsible for regulating synaptic activity.

Muscarinic receptors, which are anatomically located in cortical and subcortical regions, regulate glutamatergic and dopaminergic neurotransmission, which is believed to be impaired in *Schizophrenia*. According to neurochemical research, muscarinic and dopamine receptors reciprocally affect each other [12]. According to mechanistic research, the M1, M4, and M5 receptor subtypes have the ability to alter the particular brain circuits and physiology that are disturbed in *Schizophrenia* and are believed to be the cause of positive, negative, and cognitive symptoms. Clinical and preclinical research on novel therapeutic approaches that target these receptors is rapidly progressing, and these approaches hold promise for offering more complete relief than antipsychotics already on the market [13]. The safety profile of anti-psychotic medications now in use is not very encouraging given that they must be used for a few years[14]. These anti-psychotics have the potential to irreversibly disrupt the brain's dopaminergic circuits over time[15]. They could result in global cognitive decline and serious movement abnormalities like tardive dyskinesia and tardive psychosis. Delayed dementia [14, 15]. Recent MRI scans of individuals with *Schizophrenia* have provided sufficient evidence that anti-psychotics may even be the cause of the brain's basal ganglia shrinking [15].

Synthetic drugs

KarXT (*Xanomeline-trospium*)

A promising treatment for *Schizophrenia* called KarxT combines trospium, an antimuscarinic drug, with xanomeline, an agonist for muscarinic receptors M1 and M4. Xanomeline can target and excite muscarinic receptors in the brain by efficiently crossing the blood-brain barrier (BBB). This can reduce or eliminate both positive and negative symptoms and improve cognitive function. However, trospium reduces the possible adverse effects of xanomeline because it cannot pass the blood-brain barrier and largely functions as an antimuscarinic agent in peripheral organs. These results highlight KarXT's potential as a successful treatment for *Schizophrenia* [16].

A phase 1 study (NCT02831231) in healthy adults shown that the addition of trospium reduced the incidence of pro cholinergic side effects when compared to xanomeline alone [17]. Emergent-1 Trial (NCT03697252) [18]. In a phase 2 randomized, double-blind, placebo-controlled study of *Schizophrenia* inpatients, KarXT was associated with fewer and milder pro cholinergic side effects over a 5-week treatment period than those previously observed with xanomeline alone [19, 20].

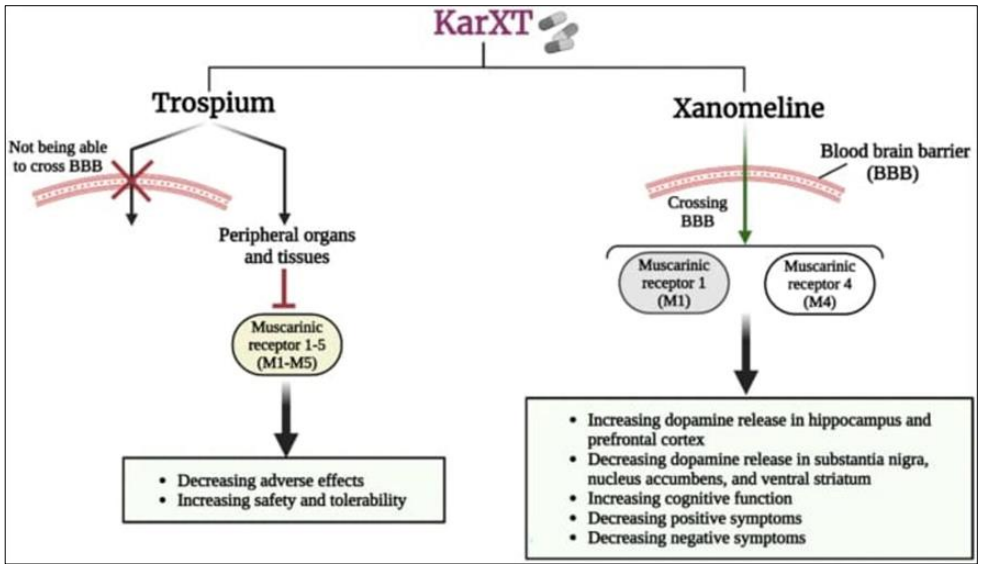

Fig 1: KarXT

Olanzapine

An atypical antipsychotic called olanzapine has strong antagonistic effects on muscarinic acetylcholine receptors, especially the M3 subtype. Weight gain and metabolic abnormalities are among the negative effects of olanzapine that have been linked to this antagonism. According to a study examining olanzapine's effects on muscarinic M3 receptor (M3R) binding density, the drug raised M3R binding density in the brainstem's dorsal vagal complex (DVC), ventromedial nuclei (VMH), and hypothalamus arcuate (Arc). These areas are linked to the control of insulin secretion and food intake. Along with a fall in plasma insulin and glucose levels, the study also found increases in body weight, food consumption, and circulating plasma levels of cholecystokinin (CCK) and ghrelin. Increased M3R density, according to the authors, represents a compensatory up-regulation [21].

One of the most effective antipsychotic drugs for treating *Schizophrenia* is still olanzapine, nonetheless, its weight and metabolic profile raise serious tolerance issues. Lybalvi, a recently FDA-approved formulation of olanzapine-samidorphan combination tablets (OLZ/SAM), is designed to reduce weight gain caused by antipsychotics by modulating the endogenous opioid system with samidorphan [22].

Clozapine

The first atypical antipsychotic created was clozapine [23] has been referred to as atypical because, unlike conventional antipsychotics, it does not cause tardive dyskinesia, raise prolactin levels, or create substantial extrapyramidal adverse effects with prolonged usage [24, 25]. Clozapine seemed to be beneficial in preclinical testing without producing catalepsy, which was unexpected because at the time, catalepsy was thought to be required for efficacy [26]. Unfortunately, 16 individuals in Finland experienced agranulocytosis, which resulted in 8 deaths, while clozapine testing was just being

started in the US. As a result, clozapine was taken off the market in the countries where it was first launched [26, 27].
As the number of patients taking typical antipsychotics increased, more people experienced severe movement abnormalities [27]. Additionally, the unpleasant symptoms improved more with clozapine. Refractory *Schizophrenia* may be effectively treated with clozapine. Clozapine was approved in the US for treating refractory *Schizophrenia* as a result of this study. Nonetheless, the FDA mandated that all clozapine users sign up for a register that includes regular blood checks for agranulocytosis [28].

Herbal drugs

Betel nut

Millions of persons with *Schizophrenia* reside in areas where betel is chewed. According to current research, betel nut alkaloids, which include strong muscarinic cholinomimetics, may have therapeutic potential for *Schizophrenia* [29]. "Betel chewing" refers to the act of masticating a quid of components, such as lime, typically in the form of burnt shell or coral, the leaf of the creeping vine Piper betel, and the seed of the *Areca catechu* palm (betel nut). Millions of people chew betel nuts, which are the fourth most popular narcotic in the world after nicotine, ethanol, and caffeine. They are found between the east coast of Africa and the western Pacific [30]. In betel nut, nine alkaloids are the active components [31]. Arecoline, a strong muscarinic agonist that quickly penetrates the blood-brain barrier and produces a variety of parasympathetic effects, is the most prevalent of these [32]. These cholinergic substances are being considered once more as possible therapies for psychosis [33, 34]. Our main idea is that betel nut's muscarinic activity could help persons with *Schizophrenia* by reducing their symptoms. Clinical treatment should benefit from a better knowledge of the relationship between betel chewing and *Schizophrenia*, as millions of people with *Schizophrenia* reside in areas where betel chewing is common. These findings, along with the muscarinic agonist action of arecoline, the most prevalent betel nut alkaloid, support the main study hypothesis that chewing betel may help reduce the basic symptoms of *Schizophrenia* [18].

Withania somnifera

The adaptogenic qualities of *Withania somnifera*, popularly known as ashwagandha, have long been utilized in Ayurvedic therapy. Recent research has investigated its possible antipsychotic benefits, especially when used as a supplementary treatment for *Schizophrenia*.
A standardized extract of *Withania somnifera* (WSE) was administered at a dose of 1,000 mg per day for 12 weeks to individuals with *Schizophrenia* who were experiencing a worsening of their symptoms. This study was randomized, double-blind, and placebo-controlled. The Positive and Negative Syndrome Scale (PANSS) indicated that WSE considerably decreased negative, general, and total symptoms when compared to a placebo. Participants who received WSE also reported notable reductions in their perceived stress levels. The most frequent side effects were gastrointestinal distress and somnolence, and they were minor and temporary [35].
An additional analysis of the same study concentrated on the symptoms of anxiety and depression in people with *Schizophrenia*. With medium effect sizes favouring WSE over placebo, the results indicated that WSE would be helpful in reducing these symptoms. Although the precise processes causing these benefits are yet unclear, they might entail immune-inflammatory pathway regulation [36].
It is believed that the anti-inflammatory and immunomodulatory qualities of *Withania somnifera* are connected to its possible antipsychotic action. WSE has been shown in preclinical research to suppress nuclear factor kappa-B (NF-kB) activation and regulate the synthesis of pro-inflammatory cytokines, both of which are linked to the pathophysiology of *Schizophrenia* [37].

Draw backs

- **Central nervous system:** Confusion and disorientation may result from blocking the M1, M4, and M5 receptors in the central nervous system (CNS) [38].
- **Cardiovascular effect**: Tachycardia may result from inhibition of M2 receptors in cardiac tissue [38].
- **Gastrointestinal and exocrine effect:** Dry mouth, sore throat, constipation, ileus, and gastroesophageal reflux can all be caused by the antagonistic interaction of M3 receptors in exocrine glands and smooth muscle[38].
- **Ophthalmologic effects:** Mydriasis and photophobia can result from blockage of muscarinic receptors in the eyes [38].

Advancement in antipsychotic drugs acting on muscarinic receptor

Cobenfy

Notable news is that Cobenfy, a medication that targets M1 and M4 muscarinic receptors, has been approved by the FDA. In contrast to conventional antipsychotics that block dopamine receptors, Cobenfy reduces side effects like weight gain and motor problems by indirectly modulating dopamine activity through muscarinic pathways. Its efficacy in reducing both positive and negative symptoms of *Schizophrenia* has been shown in clinical trials [39].

NBI-1117568

NBI-1117568 is a new antipsychotic that targets muscarinic receptors and was created by Neurocrine Biosciences. The medication significantly reduced the intensity of *Schizophrenia* symptoms in a mid-stage clinical trial, with the lowest dose of 20 mg exhibiting the greatest promise. This emphasizes how muscarinic receptor manipulation may be used as a treatment approach [40].

Xanomeline

Recent research has further investigated the therapeutic potential of muscarinic receptor agonists in the treatment of *Schizophrenia*. The 2022 review highlights the antipsychotic effects of muscarinic agonists such as xanomeline and examines how M1 and M4 receptors regulate dopamine circuits linked to psychosis [41].

Dopamine receptor

The catecholamine neurotransmitter dopamine has crucial roles in the peripheral (PNS) and central (CNS) nervous systems. A series of five G-protein-coupled receptors, known as the D1-like and D2-like receptors, mediate dopaminergic activities. While the D2-like group, which includes D2R, D3R, and D4R, largely couples to the inhibitory G protein Gi/o, the D1-like group, which includes D1R and D5R, primarily couples to the stimulatory G protein Gs. The CNS's most prevalent dopamine receptors

are D1R and D2R, particularly in the prefrontal cortex and basal ganglia [42, 43]. Numerous neuropsychiatric conditions, such as Parkinson's disease (PD), *Schizophrenia*, different forms of cognitive impairment, attention-deficit hyperactivity disorder (ADHD), drug misuse, and autism, have been linked to aberrant D1R and D2R signalling [42, 44, 45-49]. It's been suggested that D1R and D2R-mediated dopaminergic pathway activation mediates a number of the rewarding and reinforcing effects of many misused substances [50, 51]. The dopaminergic system is central, and as a result, many ligands targeting D1R and D2R have been developed to treat a variety of CNS disorders by restoring homeostasis in disease states and maintaining normal dopaminergic homeostasis. Because dopamine receptors are highly similar, most dopaminergic drugs are highly polypharmacology, often targeting multiple dopamine receptors and other aminergic GPCRs [52, 53].

D2 Receptor occupancy and clinical implication

The degree of D2 receptor occupancy is closely related to the therapeutic efficacy and side effect profile of antipsychotics Therapeutic Window: Clinical improvement is associated with an optimal D2 receptor occupancy range (usually 60-80%) occupancy below this range may be ineffective, while occupancy above it increases the risk of side effects [54].

Synthetic drugs

Haloperidol

Haloperidol is a first-generation typical antipsychotic that is widely used throughout the world to block the brain's dopamine D2 receptors and produce its antipsychotic effects. The drug is used to treat positive symptoms of *Schizophrenia*, such as delusions and hallucinations. The U.S. Food and Drug Administration (FDA) has approved haloperidol for a variety of therapeutic uses, and it also has off-label usage [55].

Haloperidol is an excellent treatment for explosive and combative hyperexcitability that is not caused by sudden provocation. Only after alternative psychotherapy and non-antipsychotic drugs have failed to elicit a response should haloperidol be considered for usage in children [56].

Children who present with excessive motor activity and conduct disorders that include symptoms such as impulsivity, attention problems, aggression, mood swings, and low frustration tolerance respond well to haloperidol. Only when other psychotherapy and non-antipsychotic drugs have failed should haloperidol be considered for usage in children [57].

First-generation typical antipsychotics like haloperidol work by preventing the brain's dopamine D2 receptors from functioning. When 72 percent of dopamine receptors are inhibited, this medication is at its most effective [58]. The D2 receptor is not the only receptor that haloperidol blocks; noradrenergic, cholinergic, and histaminergic receptors are also affected. Numerous negative medication responses are linked to the blockage of these receptors [59].

Chlorpromazine

As a first-generation antipsychotic from the phenothiazine class, chlorpromazine has been used extensively since the 1950s to treat psychotic illnesses. Its main mode of action is dopamine D2 receptor antagonism, which is essential to its antipsychotic properties. By blocking dopamine D2 receptors in different dopaminergic pathways of the brain, chlorpromazine alleviates symptoms like hallucinations, delusions, and thought disorders that are typical of psychosis. By blocking dopamine at the postsynaptic D2 receptors, chlorpromazine lowers excessive dopaminergic activity [60].

The development of the dopamine hypothesis of *Schizophrenia* was based on the effectiveness of antipsychotics such as chlorpromazine in reducing psychotic symptoms. According to this theory, hallucinations and delusions two positive symptoms of *Schizophrenia* are caused by the hyperactivity of dopaminergic pathways, especially the mesolimbic pathway. Apathy and social disengagement, on the other hand, are linked to unpleasant symptoms when the mesocortical circuit is hypoactive. Chlorpromazine helps to balance dopamine activity in these circuits by blocking D2 receptors, which lessens psychotic symptoms [61].

Herbal drugs

Ginko biloba

Studies have looked into the possible effects of ginkgo biloba, especially its standardized extract EGb 761®, on the dopaminergic system, which is intimately related to antipsychotic action. Studies reveal that long-term EGb 761® treatment can improve dopaminergic transmission in the PFC. According to a study, EGb 761® increased dopamine levels in the rat PFC significantly after 14 days of subchronic administration, whereas a single dose had no effect on basal extracellular dopamine levels. The flavonoid components of the extract were mainly responsible for this action [62]. According to the rise in dopamine levels, EGb 761® may influence dopaminergic activity by inhibiting monoamine oxidase B (MAO-B) and having antioxidant qualities. These processes could contribute to its apparent effects in neuropsychiatric disorders [63]. In clinical settings, Ginkgo biloba extract has been explored as an adjunct therapy for *Schizophrenia*. A meta-analysis concluded that Ginkgo, when added to standard antipsychotic treatment, ameliorates the symptoms of chronic *Schizophrenia* [64]. The effects of EGb 761® on tardive dyskinesia, a movement disorder linked to long-term antipsychotic usage, have also been investigated. In a randomized, double-blind, placebo-controlled study, EGb 761® successfully decreased tardive dyskinesia symptoms in patients with *Schizophrenia*, indicating a possible use in treating side effects brought on by antipsychotics [65].

Aporphine alkaloids

Aporphine alkaloids, a subclass of isoquinoline alkaloids, acting on dopamine receptors have been studied in relation to their antipsychotic properties. These substances are commonly found in many different plant families and are distinguished by their tetracyclic backbone [66]. Notably, several derivatives of aporphines have a strong affinity for dopamine receptors. Dopamine D1 and D2 receptors, for example, It have been found to be antagonistic to (R)-aporphine, with binding affinities (K_i) of 717 nM and 527 nM, respectively. Potential antipsychotic qualities are suggested by this antagonistic activity [67]. Additionally, a number of aporphine alkaloids, including corytuberine, bulbocapnine, boldine and glaucine, have shown neuroleptic like effects, including anticonvulsant, antipsychotic and

antinociceptive properties. It is thought that interactions with dopamine receptors mediate these effects [67].

Draw backs of dopamine receptor:

- **Extrapyramidal symptoms:** These are movement disorders brought on by drugs, and they include acute symptoms like parkinsonism (tremors and stiffness), akathisia (restlessness), and dystonia (muscle contractions). Blockade of the dopamine D2 receptor in the nigrostriatal pathway causes EPS [68].
- **Tardive Dyskinesia:** Involuntary, repetitive movements, usually of the face and tongue, are the hallmark of this late-onset movement disease. It causes receptor super sensitivity and is linked to long-term dopamine receptor antagonism [69].
- **Neuroleptic Malignant syndrome**: A rare but potentially fatal illness that manifests as fever, autonomic instability, muscle rigidity, and altered mental status. NMS is associated with widespread blockage of dopamine receptors [69].
- **Metabolic side Effects:** Certain antipsychotics, especially atypical ones, raise the risk of cardiovascular illnesses by causing weight gain, insulin resistance, and dyslipidaemia. The dual antagonism of serotonin and dopamine receptors is assumed to be responsible for these effects [70].
- **Hyperprolactinemia:** Blocking dopamine D2 receptors can result in increased prolactin levels, which can cause galactorrhoea (milk production), gynecomastia (male breast growth), and irregular menstruation since dopamine controls the release of prolactin [71].
- **Cognitive and Emotional Blunting:** The quality of life of patients may be impacted by excessive dopamine blocking, which can diminish emotional reactivity and impair cognitive abilities [69].

Advancement in antipsychotic activity acting on dopamine receptor

- **Dopamine D3 Receptor partial agonist:** To treat both positive and negative symptoms of *Schizophrenia*, ariprazine, a partial agonist that prefers the D3/D2 receptor for dopamine D3, has been created. It is believed to be effective in alleviating negative feelings in part because of its preferential binding to D3 receptors [72].
- **Serotonin Dopamine activity modulators:** Rexpiprazole, an SDAM, interacts with serotonin 5-HT1A and dopamine D2 receptors as a partial agonist and serotonin 5-HT2A receptors as an antagonist. The goal of this receptor activity profile is to balance serotonin and dopamine regulation, which could increase tolerability and efficacy [72].
- **Phosphodiesterase:** Phosphodiesterase inhibitors are being researched for their ability to modify dopamine receptor-related intracellular signalling pathways, which could alleviate negative and cognitive symptoms in *Schizophrenia* [73].

Trace Amine Associated receptor 1(TARR1) Agonist

Ulotaront, a TAAR1 agonist, is a novel strategy that indirectly modulates glutamatergic and dopaminergic function. A positive side effect profile and possible antipsychotic benefits are suggested by early trials, although more research is required [72].

Conclusion

In comparing muscarinic and dopamine receptor mechanisms in antipsychotic activity across KarXT, olanzapine, clozapine, betel nut, *Withania somnifera*, haloperidol, chlorpromazine, Ginkgo biloba, and aporphine alkaloids, distinct advantages and limitations emerge. Dopamine receptor-targeting drugs, such as haloperidol and chlorpromazine, effectively reduce psychotic symptoms but often cause extrapyramidal side effects and tardive dyskinesia. Atypical antipsychotics like clozapine and olanzapine, which also act on muscarinic receptors, offer better tolerability but may lead to metabolic disturbances. KarXT represents a novel approach leveraging muscarinic receptor modulation to minimize dopamine-related side effects. Natural compounds like betel nut, *Withania somnifera*, Ginkgo biloba, and aporphine alkaloids provide alternative mechanisms, potentially balancing efficacy and safety. A muscarinic-based strategy may offer a promising future for antipsychotic therapy, though further studies are needed to optimize efficacy and minimize side effects.

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