Review

Novel Compounds for the Treatment of Schizophrenia – A Narrative Review

Kalliopi Diakaki * , Apostolos Miliaras , Evangelia Maria Tsapakis , Konstantinos N Fountoulakis

Posted Date: 4 July 2023

doi: 10.20944/preprints202307.0143.v1

Keywords: schizophrenia; schizophrenia theories; novel antipsychotics

Review

Novel Compounds for the Treatment of Schizophrenia—A Narrative Review

Kalliopi Diakaki [1,*,†], Apostolos Miliaras [1,†], Evangelia Maria Tsapakis [2] and Konstantinos N. Fountoulakis [2]

[1] 3rd Department of Academic Psychiatry, AHEPA General Hospital, Thessaloniki, Greece; apomiliaras@gmail.com
[2] Department of Psychiatry, Academic General Hospital, Heraklion, Crete, Greece; emtsapakis@doctros.org.uk & kostasfountoulakis@gmail.com
* Correspondence: kaldia91@gmail.com
† KD & AM share first authorship.

Abstract: Schizophrenia is a chronic neuropsychiatric syndrome with a significant impact on daily function and quality of life. All available guidelines suggest a combined treatment approach with pharmacologic agents and psychological interventions. However, one in three patients is a non-responder, the effect on negative and cognitive symptoms is limited, and many drug-related adverse effects complicate clinical management. As a result, discovering novel drugs for schizophrenia presents a significant challenge for psychopharmacology. This narrative review of the literature aims to present recently approved and newly discovered pharmacological substances for the treatment of schizophrenia as well as their suggested mechanism of action. We discuss seven novel drugs, three of which have been approved by the FDA (Olanzapine/Samidorphan, Lumateperone, and Pimavanserin). The rest are under clinical trial investigation (Ulotaront, CVL-231, Xanomeline/Trospium, Brilaroxazine). Additional basic and clinical research is, however, required not only to improve our understanding of the neurobiology and potential novel targets in schizophrenia treatment but also to establish modern and more effective therapeutical interventions with friendlier side-effect profiles.

Keywords: schizophrenia; schizophrenia theories; novel antipsychotics

1. Introduction

Schizophrenia is a neuropsychiatric disorder, most likely due to neurodevelopmental reasons arising from abnormalities in different circuits and neurotransmitter systems. This developmental process includes uncontrolled synaptic pruning, deriving from gene-environment interaction [1]. Numerous studies suggest that a synaptic pathology, rather than a loss of neurons, is at the forefront [2]. In addition to the reduction of the number of synapses, multiple findings suggest that both synapse structure and function are affected. For example, a decrease in cortical pyramidal neuron dendritic spine density and dendritic branching, especially in layer III, has been a consistent finding in schizophrenia [3]. Besides, most loci from GWAS studies on the genetics of schizophrenia encode structurally and functionally critical synaptic proteins [4].

The dopamine (DA) hypothesis of psychosis is one of the most enduring ideas in psychopharmacology. Undeniably, one central dysfunction stems from dopaminergic abnormalities, but in a different way than initially thought (updated DA hypothesis-the mesostriatal hyperdopaminergia) [5]. Moreover, DA is not the only neurotransmitter linked to psychosis since many other neurotransmitter systems are dysregulated. Today, numerous alternative neurotransmitter theories are complementary rather than contradictory to the DA hypothesis. Moreover, diverse hypotheses are interconnected rather than conflicting. For example, the loss of dendritic spines in cortical layer III is linked to the DA hypothesis. Loss of dendritic spines and NMDAR hypofunction in inhibitory interneurons cause an excitatory/inhibitory (E/I) imbalance and

 doi:10.20944/preprints202307.0143.v1

a decrease in γ-aminobutyric acid (GABA)ergic transmission resulting in cortical E/I imbalance. This imbalance leads to overstimulation of subcortical areas and overactivation of the mesolimbic pathway, inducing positive symptoms [6].

Increasing evidence implicates glutamate, cholinergic, and serotonin neuronal networks, trace amines, and their TAAR receptors. Focusing on these alternative neurotransmitters/receptors is critical to fully understand the underlying pathophysiology of the psychoses in addition to developing drugs with novel mechanisms of action other than DA receptor antagonism; the latter results from the necessity for safer, more tolerable, and more effective medications [7]. Improved efficacy includes the control of DA receptor blocking-resistant positive symptoms and the unmet need to alleviate negative and cognitive symptoms.

2. Neurotransmitter System Aetiopathogenesis of Schizophrenia

2.1. Dopamine

2.1.1. The Classic Dopamine Hypothesis

The classic dopamine (DA) hypothesis suggests that hyperactivity of the mesolimbic DA pathway ("hyperdopaminergia") accounts for positive psychotic symptoms as the final common pathway for psychosis, whether those symptoms are part of the syndrome of schizophrenia or part of drug-induced psychosis or appear in mania, depression, Parkinson's disease, or dementia. Hyperactivity of mesolimbic DA neurons may also play a role in causing impulsive, agitated, aggressive, and hostile symptoms in any of the illnesses associated with positive symptoms of psychosis. Finally, it is associated with drug-induced highs and the evolution of abuse and dependence.

This hypothesis also suggests that hypoactivity of the mesocortical DA pathway mediates cognitive, affective, and negative symptoms. The cognitive and some negative symptoms of schizophrenia may be due to a deficit of DA activity in mesocortical projections to the dorsolateral prefrontal cortex. In contrast, affective and other negative symptoms of schizophrenia may be due to a deficit of DA activity in mesocortical projections to the ventromedial prefrontal cortex [8].

2.1.2. New concepts concerning DA dysfunction

It has been suggested that the overproduction of DA rather than a dysfunction of postsynaptic DA receptors occurs in hyperactive pathways. This is known as the dopamine synthesizing capacity (DSC) theory. According to this theory, in refractory schizophrenia, there is no overproduction of DA vs non-resistant schizophrenia [9].

DA receptors in the prefrontal cortex (PFC) maintain a balance of excitation/inhibition (E/I) by modulating glutamate neurotransmission and GABAergic interneuron function. In schizophrenia, this DA-induced fine-tuning in cortical activity is underactive. Moreover, the loss of dendritic spines in layer III of the PFC secondary to abnormal pruning is also thought to lead to cortical E/I imbalance [10].

The classic concept of striatal functioning proposes that the dorsal striatum regulates motor movement, and the ventral striatum regulates emotions via the nigrostriatal and the mesolimbic pathway, respectively. The latest data, however, suggest that, in untreated schizophrenia, dopaminergic activity is unaltered in the ventral striatum or even reduced and related to negative symptoms. However, in the associative striatum, an intermediate structure receiving input from the substantia nigra rather than the ventral tegmental area (VTA), it is overactive. Consequently, rather than separate nigrostriatal and mesolimbic projections, an improved concept may be that of a mesostriatal pathway arising from the VTA–substantia nigra complex and projecting to the associative striatum [11].

 doi:10.20944/preprints202307.0143.v1

2.2. Serotonin

The serotonin theory of psychosis proposes that hyperactivity/imbalance of serotonin (5-HT) activity, particularly at serotonin receptors that regulate glutamate release, can result in psychosis. In turn, glutamate neuron dysregulation, mediated by serotonin, results in the dysregulation of various other neurotransmitter systems. This effect on specific DA pathways is associated with the so-called 'serotoninergic' psychosis. Disruption of 5-HT function, leading to positive symptoms of psychosis, may hypothetically be due to the neurodevelopmental abnormalities in schizophrenia, the neurodegeneration in Parkinson's and Alzheimer's disease, and other dementias [12], and psychedelic drug-induced psychosis [13].

The cortico-brainstem glutamate pathways innervate the neurons of the mesostriatal DA pathway directly. When these glutamatergic neurons are hyperactive, they stimulate too much DA release from the mesostriatal projections of this pathway. As a result, hyperactive glutamate output from the prefrontal cortex could explain the origin of positive symptoms.

On the other hand, a second group of glutamate neurons projects to a different set of ventral tegmental area (VTA) neurons, namely, the mesocortical pathway neurons. This circuit inhibits DA release due to the presence of a key GABA interneuron in VTA for mesocortical dopamine projections to the prefrontal cortex. The same indirect synapses subsite in the substantia nigra (SN), where prefrontal cortex (PFC) glutamate neurons innervate the DA neurons of the nigrostriatal pathway. Hyperactivity of the glutamate neurons innervating mesocortical and nigrostriatal dopamine neurons leads to opposite effects to those of the population of glutamate neurons innervating mesostriatal DA neurons, i.e., reduced DA release [14].

In these circuits, the key receptors are the serotonin 5-HT1A and 5HT2A receptors. The 5-HT1A are inhibitory and are located on glutamate neurons that project to the VTA or the SN. When activated by serotonin or a 5-HT1A agonist, they inhibit the glutamate neuron, enhancing mesocortical and nigrostriatal DA pathways. Moreover, the 5-HT1A receptors are located on GABA interneurons in the PFC and indirectly regulate the release of norepinephrine (NE), DA, and acetylcholine (ACh). Serotonin or an external agonist binding at these receptors could reduce GABA output and, in turn, disinhibit NE, DA, or ACh release, improving negative and cognitive symptoms. This explains the putative role of 5-HT1A agonists and partial agonists [15].

The 5-HT2A receptors are located on glutamate neurons. They are excitatory, leading to excitatory glutamate release on downstream targets, thus to hyperactivation of the mesostriatal pathway and hypoactivation of the mesocortical pathway, as stated above. The serotonin hyperfunction hypothesis of psychosis suggests that psychosis may be caused by an imbalance in excitatory 5-HT2A receptor stimulation on the glutamate pyramidal neurons discussed above, which directly innervate mesostriatal DA neurons and visual cortex neurons, inducing delusions and hallucinations. This theory explains the psychotic symptoms in PD dementia and also the psychotic effect of 5-HT2A agonists such as psilocybin and LSD. Moreover, it indicates the promising role of pure 5-HT2A antagonists in psychosis [16].

2.3. Glutamate

The glutamate theory of psychosis proposes that the NMDA glutamate receptor is hypofunctional at critical synapses in the PFC [17]. Disruption of NMDA glutamate functioning may be secondary to neurodevelopmental abnormalities in schizophrenia [18], due to the neurodegenerative abnormalities in Alzheimer's disease or other dementias, or due to the NMDA receptor-blocking actions of drugs such as ketamine or PCP [19].

The key NMDA receptors are those of the indirect cortico-cortical glutamate pathways. Through a cascade of events, one pyramidal neuron inhibits another indirectly via GABA interneurons. More specifically, the first pyramidal neuron excites the GABA interneuron via NMDA receptors located upon the latter. The GABA interneuron inhibits the second pyramidal neuron, and so on. The glutamate hypothesis suggests that psychosis may be caused by the dysfunction of glutamate synapses at the PFC GABA interneurons. NMDA dysfunction in the PFC leads to the loss of function

 doi:10.20944/preprints202307.0143.v1

of the inhibitory GABA interneurons. Thus, the glutamate neurons become 'disinhibited' hence, hyperactive, leading to the downstream effects on the different DA pathways [20].

2.4. Acetylcholine

We have now discussed the dopaminergic, serotoninergic, and glutamatergic hypotheses of schizophrenia. There is also growing evidence that inhibitory GABA signalling is dysregulated in schizophrenia, particularly in the cortex. Dopaminergic, GABAergic, and glutamatergic signalling are all modulated by the cholinergic system. Thereby, modulating ACh receptors represent an exciting new target. Muscarinic ACh receptors (mAChR) appear to be suitable for interventions. In particular, M1, M4, and M5 mAChR subtypes can all modulate schizophrenia-related circuitry and are intriguing targets for novel schizophrenia treatments [21].

Using traditional therapies that lack specificity among mAChR subtypes requires drug tailoring to hit a therapeutic window between beneficial effects (e.g., pro-cognitive efficacy) and classical cholinergic side-effects. These side-effects are mediated by peripherally expressed M2 and M3 receptors, making selective targeting of M1, M4, and M5 therapeutically desirable. The location on the mAChRs where ACh binds, known as the orthosteric binding pocket, is a specific area on each subtype of mAChR, making it challenging to create molecules specifically targeting this site with high subtype selectivity. However, some agonists have been developed that, while lacking complete subtype-selectivity, exhibit preferential activation for certain subtypes over others. Allosteric agents have proved easier in targeting binding pockets outside the orthosteric binding pocket binding ACh. In particular, selective positive allosteric modulators (PAMs) have significantly advanced subtype-selectivity [21].

Substantial evidence supports that the cholinergic system robustly modulates striatal DA signalling through the activation of both mAChRs and nicotinic ACh receptors (nAChRs) via cholinergic projections from the brainstem to the midbrain, where they stimulate DA neurons in SN and the VTA.

The M4 receptor is among the best-studied muscarinic targets for psychosis. In the striatum, the M4 subtype is primarily expressed postsynaptically on direct pathway spiny projection neurons (GABAergic receptors of the 'go-signal'), on cholinergic interneurons, where it acts as an autoreceptor, and on glutamatergic inputs where it acts as a heteroreceptor.

The M4 receptors on cholinergic interneurons and spiny projection neurons modulate DA signalling through different mechanisms. Activation of M4 autoreceptors on cholinergic interneurons reduces ACh release. Typically, ACh induces striatal DA release by activating nAchR on the DA axonal projection, arriving from the VTA/SN complex. Consequently, an M4-mediated decrease in ACh secretion leads to a reduction in DA output. Furthermore, activation of M4 receptors on spiny projection neurons leads to an endocannabinoid-dependent blockade of DA release independent of nAChRs. Beyond its role at the striatum, the M4 receptor regulates hippocampal circuitry involved in cognitive processes. Recent findings suggest that M4 activation (by PAMs) alleviates cognitive deficits and positive symptom reduction.

The M1 receptor is the other well-studied muscarinic receptor. There is robust evidence that M1 activation leads to pro-cognitive effects and alleviates negative-type symptoms. This effect is mediated mainly via cortical and hippocampal M1 receptors. Both regions are highly involved in memory processing and express M1 receptors known to modulate neuronal function. Data suggests that M1 receptor expression is reduced in approximately 25% of schizophrenia patients.

Moreover, deficits in M1 receptor expression are brain region-specific. In schizophrenia, M1 receptor-expressing neurons are reduced in the cortex but not the thalamus or the hippocampus. As for the M1-selective compounds, pure PAMs seem superior in pro-cognitive efficacy and exhibit fewer adverse side effects. Although M1 is primarily considered a target for enhancing cognition, there are indications that M1 activation is associated with an antipsychotic effect. Such implications derive from animal studies where M1 PAMs have demonstrated efficacy in positive symptoms [22]. The norclozapine issue also raises the possibility of an M1-mediated antipsychotic effect. Norclozapine is clozapine's primary metabolite, an agonist at mAChRs with robust activity at the M1

 doi:10.20944/preprints202307.0143.v1

receptor. No other currently used antipsychotics or metabolites are known to act as mAChR agonists. It was assumed that this agonist activity of norclozapine may be one of the unique properties distinguishing clozapine from other atypical antipsychotics in terms of efficacy in cognitive deficits and resistant positive symptoms [23].

The M5 receptors need to be better studied, and data are scarce. However, they modulate DA signalling via actions at DA terminals and DA cell bodies, making them an interesting target for the future [24]. The advent of highly M5-selective compounds with acceptable central nervous system (CNS) penetration brings new knowledge on this receptor and its potential to regulate substance abuse disorders. The discovery of new, improved molecules targeting selectively M5 could help elucidate the potential efficacy of M5-selective NAMs and PAMs in positive and negative symptoms of schizophrenia [21].

2.5. Trace Amines and the TAAR Receptors

Trace amines are endogenous substances found in trace levels in the body. They are formed from amino acids inside CNS during the synthesis of monoamines when certain enzymatic steps are omitted. They are also abundant in common foodstuffs and can be produced and degraded by the microbiota. These molecules do not act as typical neurotransmitters. Namely, they are not released upon nerve firing. There are five main human trace amines: β-Phenylethylamine, p-Tyramine, Tryptamine, p-Octopamine and p-Synephrine [25].

Trace amine-associated receptors (TAARs) are G-protein receptors. There are six isoforms in humans, and TAAR1 is the most studied. Except for TAAR1, all other TAAR subtypes are expressed only in olfactory neurons. TAAR1 are present in multiple CNS areas including several monoamine brainstem centers and projection areas. They are also expressed in the periphery, where they may have a role in nutrient-induced hormone secretion [26]. A cross-talk between TAAR1 and principal neurotransmittory systems has been demonstrated, so that TAAR1 seem to act as a rheostat of DA, Glu and 5-HT [27]. As a result, trace amines acting upon these receptors are thought to retain neurotransmission within "physiological" limits of function, in line with the TAAR1 localization in critical regions of the relative neurotransmitter pathways.

TAAR1 are predominantly located intracellularly. The putative mechanism of DA rheostasis is the following: When the TAARs are occupied by an endogenous or an exogenous agonist, the derivative complex is translocated to the cell surface, where it couples with D2 DA receptors. This heterodimerization directs the second-messenger pathway to move preferentially towards the inhibitory G (Gi) protein signal transduction cascade, inhibiting the synthesis and release of DA, rather than towards the *β*-arrestin-2 excitatory pathway (production of GSK-3 and overstimulation). Presynaptically, amplification of the Gi pathway leads to inhibition of DA release, while postsynaptically, amplification of the Gi pathway can lead to reduced production of GSK-3 and, therefore, to less stimulation. Consequently, drugs that target TAAR1 constitute a promising field of indirect dopamine modulation [28,29].

3. New Agents for the Treatment of Schizophrenia

3.1. Olanzapine/Samidorphan

The FDA approved the combination of Olanzapine/Samidorphan (OLZ/SAM) for adults with schizophrenia or bipolar disorder type I in June 2021. This treatment can be used for maintenance monotherapy or the acute treatment of manic or mixed episodes. Olanzapine is a second-generation (atypical) antipsychotic (SGA). It has approval for treating schizophrenia and bipolar disorder type I. Olanzapine acts primarily on DA and 5-HT receptors. Samidorphan is a 3-carboxamido-4-hydroxynaltrexone, acting as an opioid antagonist, preferentially on the μ-opioid receptor.

Enlighten-1 was a 4-week, phase 3, randomized, double-blind, placebo- and olanzapine-controlled study conducted in patients with schizophrenia in acute exacerbation [30]. It aimed to evaluate the antipsychotic efficacy and safety of OLZ/SAM. In a 4-week study with 352 participants, OLZ/SAM treatment showed significant improvement compared to placebo. Measured by PANSS

 doi:10.20944/preprints202307.0143.v1

score change, OLZ/SAM was as effective as olanzapine versus placebo. The combination was well tolerated and had a similar safety profile to olanzapine. The most common adverse events for both were weight gain, somnolence, and dry mouth.

Enlighten-2 evaluated the weight gain profile of OLZ/SAM versus olanzapine over 6 months in 561 patients with stable schizophrenia [31]. Compared to olanzapine, the combination of OLZ/SAM resulted in less weight gain and a smaller increase in waist circumference. Interestingly, the efficacy of the combination was similar to that of olanzapine alone. Moreover, the group taking olanzapine had a higher weight gain percentage at 6 months. Specifically, the olanzapine group had a higher number of patients who gained 10% or over of their baseline body weight ($p=0.003$). The combination was well tolerated, and the most common adverse events were weight gain, somnolence, and dry mouth.

A systematic review of literature in 2022 [32] highlighted the positive impact of samidorphan supplementation to olanzapine, on its overall tolerability, and especially on olanzapine-induced weight gain, without differences in the antipsychotic efficacy. However, an earlier meta-analysis [33] comparing the short-term effect of OLZ/SAM to olanzapine monotherapy on weight and cardiometabolic parameters did not support a positive effect of samidorphan on weight and the cardiometabolic profile and underlined the need for further research.

3.2. Lumateperone

Lumateperone is a butyrophenone atypical antipsychotic approved by the FDA in 2019 for the treatment of schizophrenia. Lumateperone simultaneously modulates 5-HT, DA, and glutamate neurotransmission. Lumateperone acts as an antagonist on both DA D2 and 5-HT2A receptors. It also indirectly modulates AMPA and NMDA currents and blocks the serotonin transporter (SERT). Its approval was based on results from two placebo-controlled Phase 2 and 3 clinical trials in which lumateperone showed efficacy as an antipsychotic agent [34,35].

Specifically, there was a 4-week, phase II randomized, double-blind, placebo- and risperidone-controlled clinical trial in 2013, with 335 patients with schizophrenia in acute exacerbation [36]. Another study, conducted in 2015, was a 4-week, randomized, double-blind, placebo-controlled, phase III clinical trial with 450 adults with schizophrenia in acute exacerbation.

Both studies aimed to assess the efficacy of lumateperone, using baseline difference in PANSS scores and its subscales. Lumateperone at 42mg showed significant antipsychotic efficacy, with a statistically significant change from PANSS baseline scores compared to placebo. Lumateperone demonstrated a favourable safety profile without association with extrapyramidal side effects, weight gain, or changes in metabolic parameters [37].

A systematic review in 2022 [38] indicates lumateperone as an effective antipsychotic agent, appropriate as a first-line choice for patients with schizophrenia. Additionally, it underlines its possible long-term positive impact on cognitive and negative symptoms. Another systematic review included 5 clinical trials on lumateperone's effect on body weight [39], demonstrating minimum impact on weight gain.

3.3. Brilaroxazine (RP5063)

Brilaroxazine is an antipsychotic agent under development with a unique binding profile [40,41]. It acts as a partial agonist at DA D2, D3 and D4 receptors and at 5-HT1A and 5-HT2A receptors. It is also an antagonist at 5-HT2B, 5-HT6 and 5-HT7 receptors and a full agonist at nAChR $\alpha 4\beta 2$ receptors. In addition, it modulates SERT with moderate affinity. It differs from other antipsychotics as it combines potent affinity and selectivity for specific targets implicated in schizophrenia. As a result, brilaroxazine may be used as an antipsychotic with limited side-effects otherwise associated with commonly used antipsychotics.

In 2018, Cantillon and colleagues [42] published the results of a phase-I, double-blind, ascending-dose randomized clinical trial aiming to assess the safety of RP5063 in 4 cohorts, treated with 10, 20, 50, and 100 mg/day. In the single-dose, used in healthy volunteers, orthostatic hypotension, nausea, and dizziness were the most common side-effects, while in the multiple-dose,

 doi:10.20944/preprints202307.0143.v1

used in clinically stable patients with schizophrenia, akathisia, and somnolence were the most frequently reported side-effects. In addition, there were no significant changes in lipid or prolactin levels, weight, and electrocardiograph (ECG) recordings. In the same study, significant improvements in positive symptoms were shown with brilaroxazine compared to placebo in individuals with a baseline PANSS score higher than or equal to 50. Furthermore, promising preliminary findings of its efficacy on cognition were reported in patients under 50mg of brilaroxazine.

A phase II, 4-week, double-blind, placebo- and aripiprazole-controlled clinical trial evaluated the safety and efficacy of brilaroxazine (15, 30, or 50 mg) in 234 patients with schizophrenia or schizoaffective disorder in acute episodes. It demonstrated that brilaroxazine at 15 mg and 50 mg significantly improved PANSS total score compared to placebo [43]. The most prevalent side-effects were insomnia and agitation. There were no metabolic deficits, abnormalities in ECG recordings or risk of hypotension. Another interesting finding was improved cognitive and negative symptoms in the brilaroxazine groups. Further phase II and phase III clinical trials have since been initiated.

3.4. Xanomeline/Trospium Combination (Kar-XT)

Xanomeline is a muscarinic ACh receptor agonist with reasonable selectivity for the M1 and M4 subtypes and an M5 receptor antagonist studied for the treatment of both Alzheimer's disease and schizophrenia, particularly for the cognitive and negative symptoms [44,45]. Due to gastrointestinal side-effects, there was a high drop-out rate in clinical trials. Trospium is a peripherally restricted muscarinic receptor antagonist that reduces the peripheral cholinergic effects of xanomeline. Since it does not cross the blood-brain-barrier (BBB), it does not act as an antagonist to xanomeline's effect in the brain [46].

A recent phase II, 5-week, double-blind, randomized, placebo-controlled clinical trial evaluated the combination of xanomeline/trospium in 182 patients with schizophrenia in acute episodes [47]. The xanomeline/trospium combination resulted in greater reduction in psychotic symptoms compared to placebo. However, treatment with the combination resulted in cholinergic adverse events. There were no reports of an association between a higher incidence of extrapyramidal symptoms or weight gain.

The results of a phase III, randomized, double-blind, placebo-controlled clinical trial in 252 in-patients with schizophrenia have been presented as a poster [48]. Patients on the xanomeline/trospium combination demonstrated significant improvement by the end of week 5 ($p < 0.0001$). In the xanomeline/trospium group, improvement in negative symptoms was slight but significant. Xanomeline/trospium was well tolerated, with the most prevalent side-effects being cholinergic. Furthermore, there were no reports of any common side-effects associated with atypical antipsychotics.

3.5. Emraclidine (CVL-231)

Emraclidine is an M4-selective positive allosteric modulator (PAM) currently in development as a novel antipsychotic drug for the treatment of schizophrenia [49]. It selectively targets activation of the M4 receptor in the brain resulting in reduced dopaminergic activity without direct DA receptor antagonist activity. Thus, emraclidine could have an antipsychotic effect while minimizing the side-effects commonly linked to other antipsychotics.

The results of a two-part, phase Ib, randomized, placebo-controlled clinical trial were published in 2022 [50]. In part A, the safety and tolerability profile of emraclidine was assessed in patients with stable schizophrenia, randomized in emraclidine 5-40mg or placebo. In Part B, the safety and tolerability were evaluated in patients with schizophrenia in the acute phase, randomized in emraclidine 30 or 40mg or placebo. Both doses of emraclidine showed a favourable safety and tolerability profile and significant improvement in psychotic symptoms, as reflected by a reduction in the PANSS total score (emraclidine 30 mg qd, $p= 0.023$; emraclidine 20 mg bid, $p= 0.047$). At present, phase II and phase III clinical trials are ongoing to confirm the efficacy, safety, and tolerability of the emraclidine. Primary results are expected by the end of 2023.

 doi:10.20944/preprints202307.0143.v1

3.6. Ulotaront (SEP363856)

Ulotaront is a novel compound with antipsychotic activity independent of D2 binding, confirmed in vivo in mice and by PET in non-human primates and developed using SmartCube technology [51]. Ulotaront activates TAAR1 receptors and ameliorates presynaptic DA dysfunction without D2 receptor binding. Ulotaront also seems to reverse glutamate hypofunction and activates 5-HT1A receptors.

The results of a phase II, 4-week, randomized, double-blind, flexible-dose (50 mg/day or 75 mg/day) aimed to evaluate the efficacy and safety of SEP 363856 in adults with schizophrenia in acute relapse were published in 2020 [52]. Ulotaront demonstrated significant superiority in improving the PANSS total score compared to placebo (p= 0.001). Furthermore, it showed a favourable safety and tolerability profile. A six-month extension study followed up recruited patients who completed the initial study to evaluate the safety and efficacy of long-term ulotaront treatment. Ulotaront use was associated with continued improvement in the PANSS total and BNSS total scores [53]. The most frequently reported side-effects were headache, insomnia and anxiety, while treatment with ulotaront was associated with minimal risk of extrapyramidal symptoms, weight gain, and prolactinaemia. Ulotaront is in phase III clinical development for further evaluation of efficacy, safety, and tolerability.

A population analysis [54] of the pharmacokinetics of ulotaront based on eight studies concluded that ulotaront shows a good absorption profile and exhibits dose-dependency at 10 to 100 mg. The median time for maximum concentration and the median effective half-life were estimated to be 2.8 and 7 hours, respectively. Race, age, gender, drug formulation, or clinical status (healthy volunteer versus patient with schizophrenia) did not significantly impact ulotaront pharmacokinetics. A recent systematic review [55] evaluated the available data on the safety, efficacy, and tolerability of ulotaront as a treatment for schizophrenia and suggested it is a potentially effective antipsychotic agent with a good safety profile.

3.7. Pimavanserin (ACP-103)

Pimavanserin is an inverse agonist and antagonist at the 5-HT2A, and to a lesser extent, at the 5-HT2C, which lacks binding affinity for DA receptors, including the DA D2 [56], histamine, muscarinic and adrenergic receptors. It is the first FDA-approved drug for the treatment of psychotic symptoms in patients with Parkinson's disease. Pimavanserin is currently evaluated as an alternative agent for the treatment of schizophrenia, mainly focused on negative symptoms.

ADVANCE-II, a phase II, 26-week, randomized, double-blind, placebo-controlled, multi-centre, international study, assessed the efficacy and safety of pimavanserin in 403 patients with predominantly negative symptoms of schizophrenia while being on stable antipsychotic therapy [57]. Pimavanserin was well-tolerated, with a similar profile to placebo regarding side-effects (39.8% versus 35.1%, respectively). As for its efficacy, pimavanserin demonstrated a statistically significant improvement in the Negative Symptom Assessment-16 total score, while patients receiving pimavanserin at 34mg showed significant improvement in the NSA-16 total score.

ENHANCE-III, a phase III, 6-week, randomized, double-blind, placebo-controlled clinical trial, assessed pimavanserin as an adjunctive treatment in resistant-to-treatment out-patients with schizophrenia [58]. The study's primary endpoint was reduction in the PANSS total score, which failed to occur. However, pimavanserin demonstrated superiority regarding changes in the PANSS Negative Symptoms subscale and the Marder Negative Symptom Factor score compared to placebo. Furthermore, pimavanserin showed a similar safety profile, and without higher rates of side-effects compared to placebo. The most common adverse events were headache, somnolence, and insomnia.

A 2019 study found that pimavanserin improved symptoms of schizophrenia and schizoaffective disorder in patients with refractory hallucinations and delusions who did not respond to clozapine or multiple antipsychotics. All ten patients showed significant improvement within 4-8 weeks of taking 34 mg/day of pimavanserin, and some experienced improvements in negative symptoms and social functioning as well. Further research is needed to confirm the effectiveness of pimavanserine compared to clozapine [56].

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 4 July 2023 doi:10.20944/preprints202307.0143.v1

3.8. Table

Table 1. The pharmacological binding profile of novel antipsychotics.

Compound/Target	Dopamine	Serotonin	Noradrenaline	Histamine	Acetylcholine	TAAR
Olanzapine/ Samidorphan	D4 D2 D3 D1	5HT2A 5HT6 5HT2B 5HT2C 5HT3 5HT7 5HT1B 5HT1D	α2C α1A α2B α2A α1B	H1	M1 M3 M2 M4	
Lumateperone	D2 D1	5HT2A 5HT2c SERT 5HT1D	α1			
Xanomeline/ Trospium	D3	5HT2B 5HT2C 5HT1B 5HT1A 5HT2A 5HT4 5HT1E			M4 M3 M1 M2	
Brilaroxazine	D2 D3 D4	5HT1A 5HT2A 5HT2B 5HT6 5HT1A 5HT7			nAChR α4β2	
Ulotaront		5HT6 5HT1A 5HT1D 5HT1B 5HT7				TAAR1
Emraclidine					M4	
Pimavanserin		5HT2A 5HT2C				

4. Conclusions

The treatment of schizophrenia is still a significant challenge in clinical practice, despite the enormous progress in psychopharmacological research. The complexity of aetiopathogenesis leads to high variability in medication response across patients with schizophrenia and schizoaffective disorder. While a multitude of psychotropic drugs is presently available, one out of three patients remain a non-responder, the effect on negative and cognitive symptoms is limited, and there are still debilitating residual symptoms, such as extrapyramidal side-effects and other drug-related adverse effects. As a result, it is crucial to strengthen clinical research on novel antipsychotic agents.

Author Contributions: Conceptualization, E.M.T.; methodology, E.M.T, K.D., and A.M.; validation, K.N.F.; investigation, E.M.T., K.D., A.M.; writing—original draft preparation, K.D., and A.M.; writing—review and editing, E.M.T. and K.N.F.; supervision, K.N.F. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding, and The APC was funded by *Brain Sciences*.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: None.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Mısır, E.; Akay, G. G. Synaptic dysfunction in schizophrenia. *Synapse* **2023**, e22276.
2. Berdenis van Berlekom, A.; Muflihah, C. H.; Snijders, G. J.; MacGillavry, H. D.; Middeldorp, J.; Hol, E. M.; Kahn, R. S.; De Witte, L. D. Synapse pathology in schizophrenia: a meta-analysis of postsynaptic elements in postmortem brain studies. *Schizophr Bull* **2020**, 46, 374-386.
3. MacDonald, M. L.; Alhassan, J.; Newman, J. T.; Richard, M.; Gu, H.; Kelly, R. M.; Sampson, A. R.; Fish, K. N.; Penzes, P.; Wills, Z.P.; Lewis, D.A.; Sweet, R. A. Selective loss of smaller spines in schizophrenia. *Am J Psychiatry* **2017**, 174, 586-594.
4. Hall, J.; Bray, N. J. Schizophrenia genomics: convergence on synaptic development, adult synaptic plasticity, or both? *Biol Psychiatry* **2022**, 91, 709-717.
5. McCutcheon, R. A.; Abi-Dargham, A.; Howes, O. D. Schizophrenia, dopamine, and the striatum: from biology to symptoms. *TINS* **2019**, 42, 205-220.
6. Howes, O. D.; Shatalina, E. Integrating the neurodevelopmental and dopamine hypotheses of schizophrenia and the role of cortical excitation-inhibition balance. *Biol Psychiatry* **2022**, 92, 501-513.
7. Granger, K. T.; Sand, M.; Caswell, S.; Lizarraga, L.; Barnett, J. H.; Moran, P. M. A new era for schizophrenia drug development–Lessons for the future. *Drug Discov Today* **2023**, 28, 103603.
8. Weinstein, J. J.; Chohan, M. O.; Slifstein, M.; Kegeles, L. S.; Moore, H.; & Abi-Dargham, A. Pathway-specific dopamine abnormalities in schizophrenia. *Biol Psychiatry* **2017**, 81, 31-42.
9. Howes, O. D.; Bose, S. K.; Turkheimer, F.; Valli, I.; Egerton, A.; Valmaggia, L. R.; Murray, R. M.; McGuire, P. Dopamine synthesis capacity before onset of psychosis: a prospective [18F]-DOPA PET imaging study. *Am J Psychiatry* **2011**, 168, 1311-1317.
10. de Jonge, J. C.; Vinkers, C. H.; Hulshoff Pol, H. E.; & Marsman, A. GABAergic mechanisms in schizophrenia: linking postmortem and in vivo studies. *Front Psychiatry* **2017**, 8, 118.
11. Stahl, S.S. *Stahl's Essential Psychopharmacology*, 5th ed.; Cambridge University Press: Cambridge, UK, **2021**; pp. 92-93.
12. Stahl, S. M. Parkinson's disease psychosis as a serotonin-dopamine imbalance syndrome. *CNS Spectr* **2016**, 21, 355-359.
13. López-Giménez, J. F.; & González-Maeso, J. Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways. *Curr Top Behav Neurosci* **2018**, 36, 45-73.
14. Paz, R. D.; Tardito, S.; Atzori, M.; Tseng, K. Y. Glutamatergic dysfunction in schizophrenia: from basic neuroscience to clinical psychopharmacology. *Eur Neuropsychopharmacol* **2008**, 18, 773-786.
15. Alex, K. D.; Pehek, E. Pharmacologic mechanisms of serotonergic regulation of dopamine neurotransmission. *Pharmacol Therap* **2007**, 113, 296-320.
16. Stahl, S. M. Mechanism of action of pimavanserin in Parkinson's disease psychosis: targeting serotonin 5HT2A and 5HT2C receptors. *CNS Spectr* **2016**, 21, 271-275.
17. Uno, Y.; Coyle, J. T. Glutamate hypothesis in schizophrenia. *Psychiatry Clin Neurosci* **2019**, 73, 204-215.
18. Egerton, A.; Grace, A. A.; Stone, J.; Bossong, M. G.; Sand, M.; McGuire, P. Glutamate in schizophrenia: Neurodevelopmental perspectives and drug development. *Schizophr Res* **2020**, 223, 59-70.
19. Frohlich, J.; Van Horn, J. D. Reviewing the ketamine model for schizophrenia. *J Psychopharmacol* **2014**, 28, 287-302.
20. Stahl, S.S. *Stahl's Essential Psychopharmacology*, 5th ed.; Cambridge University Press: Cambridge, UK, **2021**; pp. 106-109.
21. Foster, D. J.; Bryant, Z. K.; Conn, P. J. Targeting muscarinic receptors to treat schizophrenia. *Behav Brain Res* **2021**, 405, 113201.
22. Dean, B.; Scarr, E. (2020). Muscarinic M1 and M4 receptors: Hypothesis driven drug development for schizophrenia. *Psychiatr Res* **2020**, 288, 112989.
23. Li, Z.; Huang, M.; Ichikawa, J.; Dai, J.; Meltzer, H. Y. N-desmethylclozapine, a major metabolite of clozapine, increases cortical acetylcholine and dopamine release in vivo via stimulation of M1 muscarinic receptors. *Neuropsychopharmacol* **2005**, 30, 1986-1995.
24. Shin, J. H.; Adrover, M. F.; Wess, J.; Alvarez, V. A. Muscarinic regulation of dopamine and glutamate transmission in the nucleus accumbens. *PNAS* **2015**, 112, 8124-8129.

25. Gainetdinov, R. R.; Hoener, M. C.; Berry, M. D. Trace amines and their receptors. *Pharmacol Rev* **2018**, 70, 549-620.
26. Liberles, S. D. Trace amine-associated receptors: ligands, neural circuits, and behaviors. *Curr Opin Neurobiol* **2015**, 34, 1-7.
27. Rutigliano, G.; Accorroni, A.; Zucchi, R. The case for TAAR1 as a modulator of central nervous system function. *Front Pharmacol* **2018**, 8, 987.
28. Stahl, S.S. *Stahl's Essential Psychopharmacology*, 5th ed.; Cambridge University Press: Cambridge, UK, 2021; pp. 241-242.
29. Berry, M. D.; Gainetdinov, R. R.; Hoener, M. C.; Shahid, M. Pharmacology of human trace amine-associated receptors: Therapeutic opportunities and challenges. *Pharmacology & Therapeutics* **2017**, 180, 161-180.
30. Potkin, S.G.; Kunovac, J.; Silverman, B.L.; Simmons, A.; Jiang, Y.; DiPetrillo, L.; McDonnell D. Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia: Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study. *J Clin Psychiatry* **2020**, 81, 19m12769.
31. Correll, C.U.; Stein, E.; Graham, C.; DiPetrillo, L.; Akerman, S.; Stanford, A.D.; Jiang, Y.; Yagoda, S.; McDonnell, D.; Hopkinson, C. Reduction in Multiple Cardiometabolic Risk Factors With Combined Olanzapine/Samidorphan Compared With Olanzapine: Post Hoc Analyses From a 24-Week Phase 3 Study. *Schizophr Bull*. **2023**, 49, 454-463.
32. Jawad, M.Y.; Alnefeesi, Y.; Lui, L.M.W.; Ceban, F.; Chen-Li, D.C.J.; Teopiz, K.; Jaberi, S.; Gillissie, E.S.; Vincenzo, J.D.D.; Rosenblat, J.D.; McIntyre, R.S. Olanzapine and samidorphan combination treatment: A systematic review. *J Affect Disord* **2022**, 301, 99-106.
33. Srisurapanont, M.; Suttajit, S.; Likhitsathian, S.; Maneeton, B.; Maneeton, N. A meta-analysis comparing short-term weight and cardiometabolic changes between olanzapine/samidorphan and olanzapine. *Sci Rep* **2021**, 11, 7583.
34. Correll, C.U.; Davis, R.E.; Weingart, M.; Saillard, J.; O'Gorman, C.; Kane, J.M.; Lieberman, J.A.; Tamminga, C.A.; Mates, S.; Vanover, K.E. Efficacy and Safety of Lumateperone for Treatment of Schizophrenia: A Randomized Clinical Trial. *JAMA Psychiatry* **2020**, 77, 349-358.
35. Lieberman, J.A.; Davis, R.E.; Correll, C.U.; Goff, D.C.; Kane, J.M.; Tamminga, C.A.; Mates, S.; Vanover, K.E. ITI-007 for the Treatment of Schizophrenia: A 4-Week Randomized, Double-Blind, Controlled Trial. *Biol Psychiatry* **2016**, 79, 952-961.
36. Edinoff, A.; Wu, N.; deBoisblanc, C.; Feltner, C.O.; Norder, M.; Tzoneva, V.; Kaye, A.M.; Cornett, E.M.; Kaye, A.D.; Viswanath, O.; Urits, I. Lumateperone for the Treatment of Schizophrenia. *Psychopharmacol Bull* **2020**, 50, 32-59.
37. Jawad, M.Y.; Alnefeesi, Y.; Ceban, F.; Lui, L.M.W.; Jaberi, S.; Di Vincenzo, J.D.; Amirbeik, L.; Chen-Li, D.C.J.; Teopiz, K.; Phan, L.; Cao, B.; Ho, R.; Rosenblat, J.D.; McIntyre, R.S. Lumateperone for the Treatment of Adults With Schizophrenia: a Systematic Review. *Curr Psychiatry Rep* **2022**, 24, 359-368.
38. Satodiya, R.M.; Brown, V.R.; Njuguna, S.W.; Bied, A.M. A Systematic Review of Clinical Trials on Lumateperone and Its Effects on Body Weight. *J Clin Psychopharmacol* **2022**, 42, 495-499.
39. Cantillon, M.; Prakash, A.; Alexander, A.; Ings, R.; Sweitzer, D.; Bhat, L. Dopamine serotonin stabilizer RP5063: a randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophr Res* **2017**, 189, 126-133.
40. Rajagopal, L.; Kwon, S.; Huang, M.; Michael, E.; Bhat, L.; Cantillon, M.; Meltzer, H.Y. RP5063, an atypical antipsychotic drug with a unique pharmacologic profile, improves declarative memory and psychosis in mouse models of schizophrenia. *Behav Brain Res* **2017**, 332, 180-199.
41. Cantillon, M.; Ings, R.; Bhat, L. Pharmacokinetics of RP5063 following single doses to normal healthy volunteers and multiple doses over 10 days to stable schizophrenic patients. *Clin Transl Sci* **2018**, 11, 378-386.
42. Cantillon, M.; Prakash, A.; Alexander, A.; Ings, R.; Sweitzer, D.; Bhat, L. Dopamine serotonin stabilizer RP5063: A randomized, double-blind, placebo-controlled multicenter trial of safety and efficacy in exacerbation of schizophrenia or schizoaffective disorder. *Schizophr Res* **2017**, 189, 126-133.
43. Bodick, N.C.; Offen, W.W.; Levey, A.I.; Cutler, N.R.; Gauthier, S.G.; Satlin, A.; Shannon, H.E.; Tollefson, G.D.; Rasmussen, K.; Bymaster, F.P.; Hurley, D.J.; Potter, W.Z.; Paul, S.M. Effects of xanomeline, a selective muscarinic receptor agonist, on cognitive function and behavioral symptoms in Alzheimer disease. *Arch Neurol* **1997**, 54, 465-473.
44. Shekhar, A.; Potter, W.Z.; Lightfoot, J.; Lienemann, J.; Dubé, S.; Mallinckrodt, C.; Bymaster, F.P.; McKinzie, D.L.; Felder, C.C. Selective muscarinic receptor agonist xanomeline as a novel treatment approach for schizophrenia. *Am J Psychiatry* **2008**, 165, 1033-1039.
45. Rovner, E. S. Trospium chloride in the management of overactive bladder. *Drugs* **2004**, 64, 2433-2446.
46. Brannan, S.K.; Sawchak, S.; Miller, A.C.; Lieberman, J.A.; Paul, S.M.; Breier, A. Muscarinic cholinergic receptor agonist and peripheral antagonist for schizophrenia. *New England Journal of Medicine* **2021**, 384, 717-726.

47. Correll, C.U.; Miller, A.C; Sawchak, S; Kaul, I.; Paul, S.M.; Brannan, S.K. Safety and efficacy of KarXT (xanomeline-trospium) in schizophrenia in the phase 3 randomized, double-blind, placebo-controlled EMERGENT-2 trial. Presented at the 28th Annual National Psychopharmacology Update of the Nevada Psychiatric Association (NPA); Las Vegas, Nevada, USA, 15-18 February **2023**.
48. Yohn, S.E.; Weiden, P.J.; Felder, C.C.; Stahl, S.M. Muscarinic acetylcholine receptors for psychotic disorders: bench-side to clinic. *Trends Pharmacol Sci* **2022**, 43, 1098-1112.
49. Krystal, J.H.; Kane, J.M.; Correll, C.U.; Walling, D.P.; Leoni, M.; Duvvuri, S.; Patel, S.; Chang, I.; Iredale, P.; Frohlich, L.; Versavel, S.; Perry, P.; Sanchez, R.; Renger, J. Emraclidine, a novel positive allosteric modulator of cholinergic M4 receptors, for the treatment of schizophrenia: a two-part, randomised, double-blind, placebo-controlled, phase 1b trial. *Lancet* **2022**, 400, 2210-2220.
50. Dedic, N.; Jones, P.G.; Hopkins, S.C.; Lew, R.; Shao, L.; Campbell, J.E.; Spear, K.L.; Large, T.H.; Campbell, U.C.; Hanania, T.; Leahy, E.; Koblan, K.S. SEP-363856, a Novel Psychotropic Agent with a Unique, Non-D2 Receptor Mechanism of Action. *J Pharmacol Exp Ther* **2019**, 371, 1-14.
51. Koblan, K.S.; Kent, J.; Hopkins, S.C.; Krystal, J.H.; Cheng, H.; Goldman, R.; Loebel, A. A Non-D2-Receptor-Binding Drug for the Treatment of Schizophrenia. *N Engl J Med* **2020**, 382, 1497-1506.
52. Correll, C.U.; Koblan, K.S.; Hopkins, S.C.; Li, Y.; Dworak, H.; Goldman, R.; Loebel, A. Safety and effectiveness of ulotaront (SEP-363856) in schizophrenia: results of a 6-month, open-label extension study. *NPJ Schizophr*. **2021**, 7, 63.
53. Galluppi, G.R.; Polhamus, D.G.; Fisher, J.M.; Hopkins, S.C.; Koblan, K.S. Population pharmacokinetic analysis of ulotaront in subjects with schizophrenia. *CPT Pharmacometrics Syst Pharmacol* **2021**, 10, 1245-1254.
54. Le, G.H.; Gillissie, E.S.; Rhee, T.G.; Cao, B.; Alnefeesi, Y.; Guo, Z.; Di Vincenzo, J.D.; Jawad, M.Y.; March, A.M.; Ramachandra, R.; Lui, L.M.W.; McIntyre, R.S. Efficacy, safety, and tolerability of ulotaront (SEP-363856, a trace amine-associated receptor 1 agonist) for the treatment of schizophrenia and other mental disorders: a systematic review of preclinical and clinical trials. *Expert Opin Investig Drugs* **2023**, 32, 401-415.
55. Nasrallah, H.A.; Fedora, R.; Morton, R. Successful treatment of clozapine-nonresponsive refractory hallucinations and delusions with pimavanserin, a serotonin 5HT-2A receptor inverse agonist. *Schizophrenia Research* **2019**, 208, 217-220.
56. Bugarski-Kirola, D.; Arango, C.; Fava, M.; Nasrallah, H.; Liu, I.Y.; Abbs, B.; Stankovic, S. Pimavanserin for negative symptoms of schizophrenia: results from the ADVANCE phase 2 randomised, placebo-controlled trial in North America and Europe. *The Lancet Psychiatry* **2022**, 9(1), 46-58.
57. Bugarski-Kirola, D.; Bitter, I.; Liu, I.Y.; Abbs, B.; Stankovic, S. ENHANCE: phase 3, randomized, double-blind, placebo-controlled study of adjunctive pimavanserin for schizophrenia in patients with an inadequate response to antipsychotic treatment. *Schizophrenia Bulletin Open* **2022**, 3, sgac006.