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Posted Date: 20 May 2024

doi: 10.20944/preprints202405.1223.v1

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Review

The Clinical Antipsychotic Effect of Recently Developed Antipsychotic Drugs in Schizophrenia

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Abstract: Schizophrenia and schizoaffective disorder are generally treated with second-generation antipsychotic drugs. These drugs are mostly D_2 and 5-HT_{2A} antagonists. They improve positive schizophrenia symptoms sufficiently well; however, they ameliorate negative schizophrenia symptoms and cognitive functions to a small extent. We review novel antipsychotic drugs exerting a partial agonism at dopaminergic and serotonergic receptors such as cariprazine, brexipiprazole and lumateperone. Besides, the mechanisms of actions of non-anti-dopaminergic antipsychotic drugs are pointed out. Updated neural networks are used to explain the mechanism of action of M_4 and M_1 receptor agonists, for example xanomeline combined with trospium or emraclidine, and trace-amine-associated receptor 1 agonists (TAAR1), for example ulataront. Phase 3 clinical trials of new third generation antipsychotic drugs are presented. Novel antipsychotic drugs with a partial agonism at D_2 and D_3 receptors improve positive and negative schizophrenia symptoms as well as cognitive symptoms better than second generation antipsychotic drugs. Besides, they are well tolerated. M_4 and M_1 receptor agonists, i.e., xanomeline combined with trospium or emraclidine, and TAAR1 agonists, i.e., ulataront, have promising results in clinical trials; they well improve negative schizophrenia symptoms and cognitive functions. Phase 3 clinical trials offer promising results for anti-dopaminergic and non-anti-dopaminergic novel antipsychotic drugs. These new non-anti-dopaminergic antipsychotic drugs better emend negative schizophrenia symptoms, and they better improve cognitive functions than second-generation antipsychotic drugs. Promising new antipsychotic drugs are cariprazine, brexipiprazole, lumateperone, ulataront, and xanomeline combined with trospium. Although phase 3 clinical studies are not yet completed, they showed a therapeutic effect superior to those achieved by second-generation antipsychotic drugs. They are tolerated very well, and they better treat negative schizophrenia symptoms and improve cognitive functions.

Keywords: antipsychotic drug; M4 and M1 receptor agonist; negative schizophrenia symptoms; neural network; schizophrenia; trace-amine-associated receptor 1 agonist; ulataront; xanomeline

1. Introduction

Schizophrenia and schizoaffective disorder are chronic disabling diseases with positive, negative, affective, and cognitive symptoms. Generally, these mental diseases are treated with antipsychotic drugs. Schizophrenic disorders have a genetic etiology in 80% of cases. The disposable antipsychotic drugs have different therapeutic effects on positive and negative schizophrenic symptoms, and they can cause movement disturbances, that is extrapyramidal symptoms (EPS). The often-prescribed antipsychotic drugs have an antagonism at D_2 and 5-HT_{2A} receptors [1,2]. Some new antipsychotic drugs have been developed, among them the third-generation antipsychotic drugs which exert a partial agonism at dopaminergic and serotonergic receptors. Antipsychotic drugs without exerting an antagonism or a partial agonism at dopaminergic receptors are available as well.

 doi:10.20944/preprints202405.1223.v1

Xanomeline, combined with trospium, an anticholinergic drug, and trace-amine associated receptor 1 (TAAR1) agonists, have been developed and are being examined in clinical studies [3]. M4 and M1 receptor agonists, i.e., xanomeline combined with trospium, exert an antipsychotic effect, because an agonism at M_4 and M_1 muscarinic cholinergic receptors promotes the blockade of D_2 dopaminergic receptors. In this review, the neural networks involved in the prefrontal cortex in schizophrenia are updated. Clinical studies should still be carried out to know whether these new antipsychotic drugs are therapeutically comparable or superior to often used antipsychotic drugs [1]. In the first clinical studies performed, cariprazine, brexipiprazole, lumateperone, xanomeline, and ulataront well treated negative schizophrenia symptoms and improved cognitive functions [4,5]. The aim of this review is to update the therapeutic advantages of third-generation antipsychotic drugs in comparison to second-generation antipsychotic drugs and to point out the results of first phase 3 clinical studies.

2. Clinical Antipsychotic Effect of Second-Generation Antipsychotic Drugs

Second-generation antipsychotic drugs such as risperidone, olanzapine, quetiapine, and clozapine are used in the treatment of schizophrenia and schizoaffective disorder in a wide range. Most of these drugs are D_2 and 5-HT_{2A} receptor antagonists and only clozapine has a D_3 and D_4 and 5-HT_{2A} antagonistic effect and a 5-HT_{1A} agonistic effect. Clozapine can be administered in treatment-resistant psychotic disorders. All second-generations antipsychotic drugs can cause movement disturbances, i.e., EPS. Only clozapine does not have these side effects, because it does not block the D_2 receptor [6,7]. These drugs have a good antipsychotic effect, they improve above all positive antipsychotic schizophrenia symptoms, and also negative schizophrenia symptoms, but to a lesser degree. Olanzapine better improves mutism, depression, social withdrawal than other second-generation antipsychotic drugs [7]. Olanzapine, quetiapine and clozapine have a prolactin-sparing effect; risperidone in contrast raises prolactin levels, because it has a high affinity for the D_2 receptor [4–6].

3. Mechanisms of Action of Recently Developed Antipsychotic Drugs

Some third-generation antipsychotic drugs have been developed. Cariprazine, brexipiprazole and lumateperone have a partial agonistic effect at dopaminergic and serotonergic receptors. This partial agonism at D_2 and 5-HT_{2A} receptors might better improve negative schizophrenia symptoms, because these symptoms are associated to hypoactive dopaminergic and serotonergic neurons in the prefrontal cortex [5,8–12]. Three new third-generation antipsychotic drugs do not block dopaminergic receptors, namely TAAR1 agonists, M4 and M1 receptor agonists. The antipsychotic effects of these new drugs appear in Table 1 [13,14].

4. Why Is the Development of Novel Antipsychotic Drugs Necessary, What Are the Missing Clinical Effects in the Efficacy of Second-Generation Antipsychotic Drugs?

Although second-generation antipsychotic drugs are widely used in the treatment of schizophrenia patients, they have lacking therapeutic effects and cause many negative adverse effects. First of all, they do not treat sufficiently negative schizophrenia symptoms such as mutism, social withdrawal and depression. Besides, it could not be shown that these drugs improve cognitive functions. They can cause movement disturbances, and libido is reduced [8]. However, antipsychotic drugs like cariprazine, brexipiprazole, and lumateperone better ameliorate cognitive functions. Besides, they do not reduce libido, and they do not influence movement. Promising new drugs like ulataront and xanomeline combined with trospium have a good therapeutic effect in improving cognitive functions [15].

 doi:10.20944/preprints202405.1223.v1

Table 1. Mechanism of action and therapeutic effects in phase 3 clinical trials of novel antipsychotic drugs.

_	Cariprazine	Brexipiprazole	Luma-teperone	SEP 363856	Xanome-line combined with trospium
Food and Drug Administratio n (FDA) approval	Approved for treatment of schizophrenia and acute mania in bipolar disorder in 2015	Approved for treatment of schizophrenia and as an adjunctive therapy for major depression and for agitated patients with Alzheimer's disease in 2015	Approved for treatment of adult patients with schizo-phrenia in 2019	Ulataront (SEP 363856) has got a break-through therapy designation for treatment of schizophrenia by FDA	The approval of xanomeline, combined with trospium for treatment of schizophrenia is expected in September, 2024
Mecha-nisms of action	A partial agonism at D_2/D_3 receptors with a higher affinity for D_3 receptors and an agonism at 5-HT_{1A} receptors	A partial agonism at D_2/D_3 receptors and has a 5-HT_{1A} agonism	A partial agonism at D_2/5-HT_{2A} receptors; blocks serotonin reuptake, and interferes with glutamate neurotrans-mission	An agonistic effect at TAAR1/5-HT1A receptors. It stabilizes mono-aminergic neurotransmissi on, i.e., dopaminergic and serotonergic neurons	An agonistic effect at M1/M4 receptors. M1/M4 muscarinic cholinergic neurons stimulation leads to the blockade of D_2 dopa-minergic neurons in the prefrontal cortex
Thera-peutic effects	Ameliorates positive and negative schizophrenia symptoms and depressive symptoms	Improves positive and negative schizophrenia symptoms and depressive symptoms	emends well positive and negative schizo-phrenia symptoms and ameliorates social capabilities	emends well positive and negative schizophrenia symptoms and improves cognitive functions	improves well positive and negative schizo-phrenia symptoms and cognitive functions
Thera-peutic effects on positive schizo-phrenia symptoms	Improves	Improves	Ameliorates	Good therapeutic effect	improves well
Thera-peutic effects on negative schizo-phrenia symptoms	Good therapeutic effect	Good therapeutic effect	Ame-liorates	Improves	Improves
Thera-peutic effects on affective symptoms	Good anti-depressive and antimanic effects	Good therapeutic effect on depressive and manic symptoms	Good therapeutic effect on depressive and manic symptoms	Good therapeutic effect on depressive and manic symptoms	Good therapeutic effect on depressive and manic symptoms

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Thera-peutic effects on cognitive symptoms	Improves	Improves	Improves social capabilities	Improves	Improves
Adverse effects	Movement disturbances are reduced; however, akathisia appears in 11% of patients. Metabolic and cardiac adverse effects are reduced	The frequency of movement disturbances, and cardiac and metabolic adverse effects are reduced	Movement disturbances and metabolic and cardiac adverse effects are largely reduced	It caused very few adverse effects, for example movement disturbances or cardiac and metabolic adverse effects	Movement distur-bances and metabolic and cardia adverse effects are seen scarcely and rarely
References	[3,9,10,14,16–19]	[19–22]	[22–25]	[26,27]	[28–36]

4.1. Cariprazine

Cariprazine is a new third-generation antipsychotic drug which was approved by FDA in 2015 for the treatment of schizophrenia and affective disorders. It can be applied for the treatment of acute mania in bipolar disorder [37]. Cariprazine has a partial agonism at D_2 and D_3 receptors with a 10-fold higher affinity for the D_3 receptor. Besides, it has an agonism at 5-HT_{1A} receptors. Its antidopaminergic effects is stronger than with aripiprazole and brexipiprazole [38]. It exerts antipsychotic, antimanic and antidepressive effects. In clinical trials, it showed comparable antipsychotic effects like risperidone. In these trials, cariprazine improved psychotic symptoms, namely positive as well as negative schizophrenia symptoms and cognitive functions. Cariprazine is an activating antipsychotic drug, therefore it can cause sleep disturtances [39]. However, cariprazine can cause akathisia in 11 % of the patients treated. Moreover, cariprazine exerts antimanic and antidepressive actions (see Table 2) Cariprazine can emend psychotic, depressive and manic symptoms, the treatment with this drug better improves quality of life than a pharmacotherapy with risperidone. It can be used in treatment-resistant forms as an alternative of clozapine [2,8,13,15,17,18,37–39].

4.2. Brexipiprazole

Brexipiprazole is a third-generation antipsychotic drug which was approved for the treatment of schizophrenia and major depression bipolar disorder in 2015. It can be used as an augmentation therapy in the treatment of major depression [37].This drug has a partial agonism at D_2 and D_3 receptors and an agonism at 5-HT_{1A} receptors and an antagonism at 5-HT_{2A} receptors. [20,38]. The occurrence of adverse effects is reduced, i.e., movement disturbances and metabolic and cardiac side effects. Brexipiprazole causes adverse effects like akathisia, headache, somnolence, tremor, weight gain. Brexipiprazole is neither sedating nor activating, it seldom causes sleep disturbances [39]. 86 clinical trials were undertaken to study the antipsychotic effects of brexipiprazole; it improved negative schizophrenia symptoms, as well as affective and cognitive symptoms (see Table 2) [20,21,37–40].

4.3. Lumateperone

Lumateperone is a new antipsychotic drug which was approved for the treatment of adult patients suffering from schizophrenia in 2019 [23]. It exerts a partial agonism at D_2 and 5-HT_{2A} receptors, blocks serotonin reuptake and interferes with the glutamatergic neurotransmission [24,25]. Lumateperone reduces dopamine release, therefore dopamine activity is more reduced than with other antipsychotic drugs [40]. It has an antidepressive effects by the blockade of the serotonin release and by the antagonism of 5-HT_{2A} receptors. The occurrence of movement disturbances, i.e., EPS and

 doi:10.20944/preprints202405.1223.v1

metabolic and cardiac side effects have been largely reduced. 20 clinical trials were performed with 1,900 participants, and it was shown that lumateperone improved negative schizophrenia symptoms and social capabilities (see Table 2) The short-term effects of these newer antipsychotic drugs show less adverse effects and a good therapeutic effects on negative schizophrenia symptoms, however long-term studies are very rare. [23–26,39,40].

4.4. TAAR1 Agonists

Trace-amine-associated receptor 1 agonists (TAAR1 agonists) play a key role in the monoamine neurotransmission; through a 5-HT_{1A} agonistic effect and an agonism at trace-amine-associated 1 receptors (TAAR 1), they also might have a therapeutic effect in schizophrenia, anxiety, and addiction. Ulataront (SEP 363856), a TAAR1 agonist, has being examined in clinical trials in phase 3 for the treatment of schizophrenia [27]. In these trials, it improved positive and negative schizophrenia symptoms. Ulataront activates TAAR1 and 5-HT_{1A} receptors. In clinical trials, it also improved positive and negative schizophrenia symptoms in an exacerbation of this disorder. It did not cause movement disturbances nor raised prolactin levels [27]. In the first clinical trial (NCT 02969382) performed with ulataront (SEP 363856), this TAAR1 agonist improved not only positive, but also negative schizophrenia symptoms and cognitive symptoms. This new drug caused very few adverse effects, for example EPS and metabolic and cardiac side effects. An exacerbation of acute schizophrenia can be observed as an adverse effect in the treatment with SEP 363856 [28]. TAAR1 agonists stabilize the monoamine neurotransmission also through a 5-HT_{1A} agonistic effect [28]. By stimulating TAAR 1 and 5-HT_{1A} receptors, monoamine neurons, i.e., dopaminergic and serotonergic neurons are stabilized, namely that a normoactive neurotransmission is enabled (see Table 2) [14].

4.5. Xanomeline Combined with Trospium

M_4 and M_1 receptor agonists are promising antipsychotic drugs that might be used in the treatment of schizophrenia. Xanomeline, an M_4 and M_1 receptor agonist, combined with trospium, an anticholinergic drug, can be approved by FDA for the treatment of schizophrenia patients. The decision about this approval will be taken on September 26, 2024. Dose-dependent cholinergic side effects such as nausea, vomiting, diarrhea, sweating and hypersalivation can be reduced by the administration of the anticholinergic drug trospium [13]. In a phase I trial, a group of healthy volunteers receiving xanomeline alone was compared with a group treated with xanomeline, combined with trospium. The results was that the cholinergic adverse effects were reduced by 49 %, and the antipsychotic effects were not changed [40,41]. The long-term effect of stimulating M1 and M4 receptors indicates a weakening of the receptor occupancy and activation [42,43]. The effect of xanomeline on the sleep architecture was examined in animal experiements. It was found that a direct stimulation of muscarinic cholinergic neurons produces increases in wake and arousal an decreases in the non-rapid eye movement [44].Three clinical studies in comparison with placebo have been performed. Xanomeline, combined with trospium ameliorated positive and negative schizophrenia symptoms, improved cognitive deficits, and it was well tolerated [28–30]. Xanomeline, combined with trospium, improved cognitive and negative schizophrenia symptoms in phase 2 and 3 clinical trials, because in schizophrenia a reduced cholinergic signaling occurs in the hippocampus, dorsolateral prefrontal cortex, and basal ganglia (see Table 2) [31–35]. According to the neural networks involved schizophrenia, a direct interaction between D_2 dopaminergic and M_1 and M_4 muscarinic cholinergic neurons exists in the hippocampus and prefrontal cortex (see Figure 1). M_1 and M_4 muscarinic cholinergic neurons activate medium spiny neurons in the prefrontal cortex, namely GABAergic and somatostatinergic neurons, which strongly presynaptically inhibit D_2 dopaminergic neurons via $GABA_A$ and somatostatin 1 receptors. D_2 dopaminergic neurons activate GABAergic neurons, and the latter neurons inhibit glutamatergic neurons, which transmit an activating potential via NMDA receptors to muscarinic cholinergic neurons [36].

 doi:10.20944/preprints202405.1223.v1

Table 2. Therapeutic effects of second- and third-generation antipsychotic drugs.

Second-generation antipsychotic drugs	
Criterium	**2nd generation antipsychotic drugs**
Therapeutic effect on disorder symptoms	Good therapeutic effect on positive schizophrenia symptoms
Therapeutic effect on negative schizophrenia symptoms	Reduced therapeutic effect on negative schizophrenia symptoms
Therapeutic effect on cognitive symptoms	No therapeutic effect on cognitive symptoms
References	5 - 36
Mechanism of action of 3rd generation antipsychotic drugs	
Antipsychotic drug	**Mechanism of action**
Cariprazine	Partial agonism at D_2 and D_3 receptors and an agonism at 5-HT_{1A} receptors
Brexipiprazole	Partial agonism at D_2 receptors and an agonism at 5-HT_{1A} receptors
Lumateperone	Partial agonism at D_2 and 5-HT_{2A} receptors, blocks serotonin reuptake and interfers with the glutamate neurotransmission
Lumataront	Agonism at TAAR1 receptors and 5-HT_{1A} receptors
Xanomeline	Agonism at M4 and M1 receptors, which interacts with a D_2 receptor blockade
Therapeutic and adverse effects of 3rd generation antipsychotic drugs	
Therapeutic effects on positive schizophrenia symptoms	**Improves well.**
Therapeutic effects on negative schizophrenia symptoms	Improves well.
Therapeutic effects on cognitive symptoms	Exerts a good therapeutic effect.
Movement disturbances	Very reduced
Metabolic and cardiac adverse effects	Very rarely and very reduced
References	5 - 37

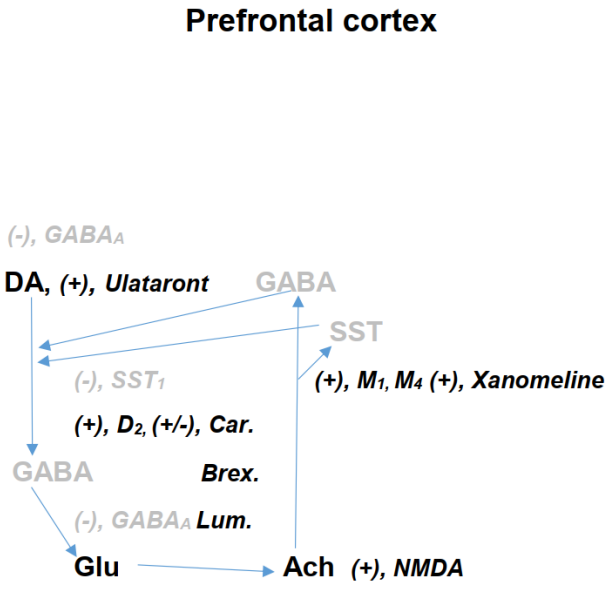

Figure 1. Mechanisms of action of novel antipsychotic drugs in the brain centers involved in schizophrenia.

 doi:10.20944/preprints202405.1223.v1

A positive allosteric modulator of the M_4 receptor is emraclidine, which has been tested in a phase 2 clinical trial in comparison to placebo. In this trial, emraclidine ameliorated positive, negative and cognitive schizophrenia symptoms [37].

Neural pathways involved in schizophrenia in the prefrontal cortex. Classical neurotransmitters and neuropeptides: Ach: acetylcholine; DA: dopamine; GABA: gamma-aminobutyric acid; Glu: glutamate; SST: somatostatin. Specific receptors: D_2: dopaminergic receptor; $GABA_A$: GABAergic receptor; M_1: muscarinic cholinergic receptor; NMDA: ionotropic glutamatergic receptor; SST_1: somatostatin receptor. A minus mark signifies a presynaptic inhibitory potential, and a plus mark signifies a postsynaptic excitatory potential. A minus and plus mark signifies a partial agonism at the specific receptor. The presynaptic inhibitory neurotransmitters and receptors are painted in grey. The therapeutic effect of new antipsychotic drugs, namely the $TAAR_1$ agonist ulataront and the M_1 and M_4 receptor agonist xanomeline combined with trospium, cariprazine (Car), brexipiprazole (Brex) and lumateperone (Lum) are included in the figure.

5. Phase III Clinical Studies

The recently developed second-generation antipsychotic drugs such as cariprazine, brexipiprazole, lumateperone, the non-antidopaminergic antipsychotic drugs such as TAAR1 agonists, and the combination of the M_1 and M_4 receptor agonist xanomeline with trospium, underwent all phase 3 clinical studies. In a phase 3b randomized, double-blind clinical study, cariprazine was compared to risperidone in the treatment of predominant negative schizophrenia symptoms. 227 patients were included in the cariprazine group, and 229 patients belonged to the risperidone group. The treatment was continued for 26 weeks. Cariprazine improved PANSS (Positive and Negative Schizophrenia Syndrome Scale) better than risperidone, above all negative schizophrenia symptoms [45]. A 3 to 8-week pivotal study about the effect of cariprazine on cognitive function was performed, including the Cognitive Drug Research System attention battery. An improvement of cognitive functions in power of attention was observed when 3 mg cariprazine was administered, but not for 6 mg cariprazine. An improvement in continuity of attention was observed with 3 and 6 mg cariprazine [46].

In a retrospective, observational study in Japan, the discontinuation rate was compared in a cohort of 978 patients treated with brexipiprazole and 4898 patients treated with other atypical antipsychotics, for example aripiprazole, olanzapine, quetiapine or risperidone. Patients treated with brexipiprazole were less likely to discontinue the treatment than patients treated with the above mentioned atypical antipsychotics. Consequently, brexipiprazole might contribute to continue antipsychotic treatment [47]. Brexipiprazole, examined in clinical studies, ameliorated positive and negative schizophrenia symptoms, besides depressive and manic and cognitive symptoms [21,22].

In a randomized, placebo-controlled clinical study, 450 patients were enrolled and were treated in a short-term treatment with lumateperone or with placebo. After treatment, the PANSS and the Clinical Global Impression-Severity of Illness (CGI-S) scores were determined. Both scores were improved in comparison to placebo, and no motor, cardiovascular nor endocrine adverse effects were seen [48].

The TAAR1 agonist ulataront has been examined in phase 3 clinical trials, and it improved positive and negative schizophrenia symptoms. Besides, it ameliorated cognitive functions, however an acute schizophrenia exacerbation has been reported as an adverse effect. It did not cause movement disturbances, nor did it raise prolactin levels [27,28].

M1 and M4 subreceptors stimulation in schizophrenia might be a new pharmacological strategy, because a reduced muscarinic cholinergic activity decreased cognitive function and caused negative schizophrenia symptoms [13]. Positive allosteric modulators of M_1 and M_4 receptors exerted antipsychotic activities in amphetamine- and MK 801-induced hyperlocomotion tasks in animal experiments [13]. Emraclidine, a positive allosteric modulator of the M_4 receptor, and xanomeline, combined with trospium were examined in a phase 3 clinical trial. Both compounds improved positive and negative schizophrenia symptoms, as well as depressive and manic and cognitive symptoms [29].

 doi:10.20944/preprints202405.1223.v1

6. Discussion

Schizophrenia and schizoaffective disorder are generally treated with second-generation antipsychotic drugs, which are mostly D_2 and 5-HT_{2A} receptor antagonists. These drugs improve positive schizophrenia symptoms very well; however, they treat negative schizophrenia symptoms to a small extent, nor do they improve cognitive functions. Movement disturbances, i.e., EPS still occur, and raised prolactin levels are often seen. The antipsychotic drug clozapine does not alter movement, nor does it raise prolactin levels, as a consequence of a different mechanism of action. Another question that should be answered in long-term clinical studies, is whether the new antipsychotic drugs are secure in preventing rehospitalization of schizophrenia patients, after psychotic symptoms get worse. Genetic techniques should also be applied to choose the appropriate antipsychotic drug, the SNP's of some important risk genes for schizophrenia should be examined and might be correlated with an improved therapeutic effect of a specific antipsychotic drug. Thus, an antipsychotic drug with a higher therapeutic effect could be selected. Some second-generation antipsychotic drugs such as cariprazine, brexipiprazole and lumateperone have a partial agonism at dopaminergic and serotonergic receptors. In phase 3 clinical studies, it was found that these new drugs better treat positive and negative schizophrenia symptoms, and above all cognitive functions. The discontinuation rate was better than with other second-generation antipsychotic drugs. Some new antipsychotic drugs have been reported, which do not have an antagonism at dopaminergic receptors. The TAAR1 ulataront stimulates TAAR1 receptors and stabilizes the monoamine neurotransmission. In phase 3 clinical trials, it improved positive and negative schizophrenia symptoms, it ameliorated cognitive functions and ameliorated affective symptoms. It did not cause movement disturbances, nor did it raise prolactin levels. An acute schizophrenia exacerbation can occur as an adverse effect. New promising antipsychotic drugs are the M4 and M1 receptor agonist xanomeline, in combination with trospium, and the positive M4 receptor allosteric modulator emraclidine. These drugs exert antipsychotic effects, which can be explained by the neural networks involved in schizophrenia. M_1 and M_4 muscarinic cholinergic neurons and D_2 dopaminergic neurons exert an interaction upon each other in the prefrontal cortex. A stimulation of M_1 and M_4 receptors leads to antagonism at D_2 dopaminergic neurons. Besides, it improves cognitive functions. In phase 3 clinical studies, these new drugs improved positive and negative schizophrenia symptoms well, they improved cognitive functions, and ameliorated depressive and manic symptoms. The occurrence of movement disturbances and endocrine and cardiovascular adverse effects were largely reduced. The approval of xanomeline by FDA is expected in September 2024.

7. Conclusion and Future Perspectives

In order to compare the therapeutic effects of widely used second-generation antipsychotic drugs with novel antipsychotic drugs, more clinical trials should be performed. In these clinical studies, PANSS score should be determined, above all that regarding the negative schizophrenia symptoms. Besides, cognitive functions should be evaluated by an assessment. The results might give a hint to replace the second-generation antipsychotic drugs by novel antipsychotic drugs.

Conflicts of interest: The authors declare that they have no conflicts of interest.

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