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Novel Antipsychotic Drugs Approved in 2015: Brexpiprazole, Cariprazine, Aripiprazole Lauroxil

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Abstract

Antipsychotic agents, highly benefit for the treatment of a range of psychiatric disorders and act by blocking dopamine receptors in the brain and interfering with dopaminergic transmission. Schizophrenia and mania which are psychosis are treated by antipsychotic drugs. These medicines are classified as typical or atypical antipsychotic drugs. The recently developed drugs which are named 'atypical antipsychotics' are useful in patients that do not respond to treatment with other typical antipsychotics. This review puts emphasis on the recent progress in therapeutically attractive piperazine derivatives being novel atypical antipsychotics that were apporved in 2015. Differences in safety-tolerability, affected receptors, activity, side effects are displayed in this review.

Keywords: Antipsychotic; Brexpiprazole; Cariprazine; Aripiprazole lauroxil

Introduction

This review consists of novel antipsychotics that approved in 2015, brexpiprazole, cariprazine, and aripiprazole lauroxil. All of the compounds are piperazine derivatives, their affects, affected receptors, and adverse effects are just about same. Differences in safety-tolerability, affected receptors, activity, side effects are displayed in this review (Table 1).

All antipsychotic medications in current clinical use act primarily on the dopamine system (most are D_2 antagonists) and are only efficacious for positive symptoms with little efficacy for all eviating the negative or cognitive symptoms [1]. They act by blocking dopamine receptors in the brain and interfering with dopaminergic transmission and they are used to treat psychosis, including schizophrenia and mania [2].

Schizophrenia is a psychiatric disorder that affects approximately 0.4% of individuals in the adult population worldwide that significantly impedes on normal vocational and social functioning [3-5]. Evidence for this disorder was first reported in humans as deficits in prepulse inhibition (PPI=Percentage pre-pulse inhibition) of the startle response, which serves as an operational measure of sensorimotor gating [6,7].

Schizophrenia is characterized by a constellation of signs and symptoms. It is aheterogeneous clinical syndrome, with no single symptom being pathognmonic of the disorder. Despite it being almost 100 years since [8] seminal description of dementia prae-cox, effective management of all of the symptoms of schizophreni are mains elusive.

Neuroleptic treatment can cause numerous side effects, including the often irreversible movement disorder tardive dyskinesia except for aripiprazole (they are rare) [9]. Many of the therapeutic actions and side effects of antipsychotics can take days to weeks, and in some cases months, to develop [10]. Because of that, basic research has turned increasingly toward an investigation of the effects of chronic neuroleptic treatment on neuronal systems. In addition, most second-generation antipsychotics are antagonists of serotonin 5-HT_{2A} receptors and α-1-adrenoreceptors, and individual compounds have a variety of effects on other monoamine receptors, such as 5-HT_{1A} receptors. These broad target effects have the objective of either improving antipsychotic efficacy (with additional effects on affective symptoms or cognitive deficits) or mitigating adverse effects like, extrapyramidal symptoms (EPS) [11,12].

If the D_2 intrinsic activity is too high, this can lead to lack of robust antipsychotic activity as well as pronounced adverse effects related to increased D_2 receptor tonus, like, nausea, vomiting, and motor side effects, such as hyperkinesias and restlessness [13-15], where as D_2 antagonist activity leads to an increased risk of EPS and increased prolactin secretion [16]. Akathisia (the movement disorder) is another common side effect associated with dopamine receptor antagonists, and may be associated with subjective distress in patients [17].

Classification of Antipsychotics

Antipsychotics are classified both typical/atypical and first/second generation. Atypical antipsychotics are the recently developed drugs that are useful in patients that do not respond to treatment with other typical antipsychotics. Atypical antipsychotics have a pharmacological profile different from typical antipsychotic drugs that being primer generation. They cause less extrapyramidal side effects compared to the older typical antipsychotic drugs. Atypicals are more effective in treatment-resistant patients and have a greater efficacy to treat negative symptoms than typical antipsychotics [18].

Atypical antipsychotics are called as second generation and they act on many receptor types including dopamine and serotonin, by the way, they are more selective for dopamine receptors [19].

Atypical second generation antipsychotics (SGAs) appear to have broadly similar efficacy as FGAs against the manic symptoms of bipolar disorder, but there are important differences in their tolerability profiles, which are likely to be of particular relevance during long-term treatment [20]. Almost all have received regulatory approval for use in mania, including aripiprazole [21].

Approved Antipsychotics in 2015

Brexpiprazole, cariprazine, aripiprazole lauroxil are novel atypical antipsychotics. Aripiprazole, approved by the United States Food and

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Antipsychotic Agent	Brexpiprazole	Cariprazine	Aripiprazole lauroxil
Generic name	Rexulty®	Vrayla®	Aristada®
Date of approval	2015 July	2015 September	2015 October
Chemical Structure	phenyl piperazine	phenyl piperazine	phenyl piperazine
Classification	atypical antipsychotic, Second generation	atypical antipsychotic, Second generation	atypical antipsychotic, Second generation
Affected receptor	Serotonin-dopamine activity modulator, partial agonist at 5-HT_{1A} and dopamine D_2 receptors, and antagonist at 5-HT_{2A} and noradrenaline α_{1B} and α_{2C} receptors, all at similar potency	Dopamine D_2 parcial agonist agonism at 5-HT_{1A} D_3-preferring D_3/D_2-receptor partial agonist	Dopamine D_3/D_2 parcial agonist Parcial agonism at 5-HT_{1A} and 5-HT_{2c}
Usage for	Schizophrenia, major depressive disorder	Schizophrenia, bipolar disorder	Acute schizophrenia bipolar disorder schizophrenia, bipolar disorder
Adverse effects	Akathisia, gastrointestinal side effects, moderate weight gain, increases in serum CPK agitation, distress restlessness weight gain, agitation, distress, and restlessness Tardive Dyskinesia Leukopenia, Neutropenia, and Agranulocytosis	neuroleptic malignant syndrome tardive dyskinesia Sleepiness high blood sugar diabetes Uncontrolled movements of the face and body Stiff muscles Indigestion Vomiting Restlessness	Akathisia weight gain, sleepiness, drooling and tremors headache, agitation or anxiety, insomnia, constipation, lightheadedness hypersexuality binge eating compulsive shopping
Recommended oral dose	2-4 mg/day in schizophrenia, 2-3 mg/day in major depression	an oral capsule available in 4 dosage strengths: 1.5 mg, 3 mg, 4.5 mg, and 6 mg.	every four to six weeks every 6 weeks for the 882 mg dose as an injection

Table 1: Novel antipsychotics.

Drug Administration in 2002, appears to have fewer metabolic adverse effects than other atypical antipsychotics [22], by the way, aripiprazole lauroxil is approved in 2015. So far, aripiprazole is the only one D_2 partial agonist, with moderate D_2 intrinsic activity, has reached the market [23], whereas other compounds with higher D_2 intrinsic activity are in development [24] or have been discontinued during development, often because of lack of sufficient clinical efficacy, like, bifeprunox [13].

Brexpiprazole is a novel serotonin dopamine activity modulator. It combines 5-HT_{1A} receptor partial agonism and low-intrinsic activity D_2 receptor partial agonism with antagonist activity on a variety of 5-HT and a-adrenergic receptors. The main focus of this article is the receptors that are most influenced by brexpiprazole at clinically and pharmacologically relevant plasma exposures. The pharmacological effects of brexpiprazole in test models of positive symptoms of schizophrenia and of cognitive impairment [25,26].

For brexpiprazole, the most common treatment-emergent adverse events were headache, insomnia and agitation; incidences of akathisia were lower in the brexpiprazole treatment groups (4.2%-6.5%) versus placebo (7.1%). There were no clinically relevant changes in laboratory parameters and vital signs. Brexpiprazole 4 mg is an efficacious and well-tolerated treatment for acute schizophrenia in adults [27].

For Cariprazine, the most commonly encountered adverse events in the mania trials were extrapyramidal disorder, akathisia, insomnia, vomiting, restlessness, sedation, vision blurred, and akathisia, extrapyramidal disorder, tremor, dyspepsia, vomiting, dizziness, diarrhea, and somnolence.

Cariprazine is a dopamine D_3-preferring D_3/D_2 receptor partial agonist in late-stage clinical development for the treatment of schizophrenia, as well as for bipolar disorder (manic/mixed and depressive episodes), and as an adjunctive agent for the treatment of major depressive disorder [28].

Cariprazine differs from aripiprazole in terms of dopamine D_3 receptor selectivity. In short-term, randomized controlled trials, cariprazine does not appear to adversely impact metabolic variables, prolactin, or the electrocardiogram (ECG) QT interval. In the fixed-dose study of cariprazine that tested 1.5, 3.0, and 4.5 mg/day, the most commonly encountered adverse events were insomnia, extrapyramidal disorder, sedation, akathisia, nausea, dizziness, vomiting, anxiety, and constipation. However, the differences in incidence versus placebo for these events were generally small [28].

Although aripiprazole has offered a new approach to stabilizing the dopaminergic system, an improvement could potentially be made by developing a novel compound that maintains significant partial agonist activity at D_2 receptors, but with lower intrinsic activity. In addition to the issue of optimal D_2 intrinsic activity, optimization of the pharmacological profile by a combination of additional target effects is a well known strategy to improve the clinical efficacy and tolerability of antipsychotics.

Aripiprazole monohydrate (AM) and aripiprazole lauroxil (AL) are two different long-acting injectable formulations of aripiprazole. AL is a prodrug of aripiprazole and available in 441 mg, 662 mg or 882 mg strengths, also led to approval of dosing intervals of every 6 weeks for the 882 mg dose [24].

Side effects of aristada (aripiprazole lauroxil): Akathisia, contraindication Cerebrovascular Adverse Reactions (Including Stroke), Neuroleptik Malignant Syndrome, Tardive Dyskinesia, metabolic changes, hyperglycemia / diabetes mellitus, dyslipidemia, weight gain, orthostatic hypotension, leukopenia, neutropenia, agranulocytosis, seizures, potential for Cognitive and Motor Impairment, difficulties with body temperature regulation, dysphagia, Injection-Site Reactions (rash, swelling, redness, irritation at the point of injection), distonia and pregnancy and nursing complications [29].

Fountoulakis and Vieta published that aripiprazole appears effective for the treatment and prophylaxis against mania. The data on bipolar depression are so far negative; however there is a need for further study at lower dosages. The most frequent adverse effects are extrapyramidal signs and symptoms, especially akathisia, without any significant weight gain, hyperprolactinaemia or laboratory test changes [30].

On October 5, the U.S. Food and Drug Administration approved Aristada extended release injection to treat adults with schizophrenia. Aristada is administered by a health care professional every four to six weeks using an injection in the arm or buttocks. The efficacy of Aristada was demonstrated in part by a 12-week clinical trial in 622 participants. In participants with acute schizophrenia who had been stabilized with oral aripiprazole, Aristada was found to maintain the treatment effect compared to a placebo.

Aristada and other atypical antipsychotic drugs used to treat schizophrenia have a Boxed Warning alerting health care professionals about an increased risk of death associated with the off-label use of these drugs to treat behavioral problems in older people with dementia-related psychosis. No drug in this class is approved to treat patients with dementia-related psychosis. Aristada must be dispensed with a patient Medication Guide that describes important information about the drug's uses and risks [31].

Atypical Antipsychotics and Related Receptors

Most atypical antipsychotics more fully block dopamine receptors in the brain, while aripiprazole only partially blocks the activity of these receptors.

The role of serotonin in depression has also been well documented, and the affinity of atypical antipsychotics for the serotonin transporter as well as post-synaptic serotonin receptors suggests a role for this neurotransmitter [32]. Brexpiprazole has potent activity at the serotonin $5HT_{1A}$ (partial agonist) and noradrenergic alpha-1 and alpha-2 (antagonist) receptors [33]. It exhibits moderate antagonist activity at the serotonin $5HT_{7}$ and $5HT_{2C}$ and histamine H_1 receptors and negligible activity at the muscarinic cholinergic M_1 receptor.

Brexpiprazole displayed almost equal subnanomolar affinities for several cloned human receptors, including h5-HT_{1A}, hD_{2L}, and 5-hHT_{2A} receptors, as well as hα1B- and hα2C-adrenoceptors. Although both brexpiprazole and aripiprazole showed high affinities for h-$5HT_{1A}$ and hD_2 receptors, brexpiprazole had a slightly higher affinity for h5-HT_{1A} receptors than hD_2 receptors, whereas the reverse was true for aripiprazole. Furthermore, brexpiprazole bound with about ten times higher affinity to h5-HT_{1A} and h5-HT_{2A} receptors and much higher affinity to hα1B- and hα2C-adrenoceptors than aripiprazole. The consequences of the high affinities of brexpiprazole for (and antagonist effects on) α1B- and α2C-adrenoceptors are more difficult to predict because of a lack of selective compounds for studying the functional importance of these receptors [26].

Cariprazine is one such orally active, putative antipsychotic which is described as a dopamine D_3 receptor preferring D_3/D_2 receptor partial agonist [34,35].

Although both brexpiprazole and aripiprazole showed high affinities for h-$5HT_{1A}$ and hD_2 receptors, brexpiprazole had a slightly higher affinity for h5-HT_{1A} receptors than hD_2 receptors, whereas the reverse was true for aripiprazole [25,26].

In particular, based on a lower intrinsic activity at D_2 receptors and higher binding affinities for 5-$HT_{1A/2A}$ receptors than aripiprazole, brexpiprazole would have a favorable antipsychotic potential without D_2 receptor agonist and antagonist-related adverse effects. Brexpiprazole is a serotonin-dopamine activity modulator with a unique pharmacology, which may offer novel treatment options across a broad spectrum of central nervous system disorders [25].

Cariprazine has more moderate affinity for human 5-HT_{1A} receptors (Ki 3 nM) and acts as a partial agonist at this receptor. Affinity at other receptors is weaker. This includes human 5-HT_{2A} (Ki 19 nM), histamine H_1 (Ki 23 nM), 5-HT_7 (111 nM), and 5-HT_{2C} (134 nM) receptors. Low affinity was observed for all tested adrenergic receptors [20].

There is a lack of understanding of the pharmacological mode of action of most psychoactive drugs. Many have similar 3D structures so that it is not easy to rationalize their differing relative potency in different clinical settings. However, significantly SAR for different degrees of internal mobility suggests that molecular dynamics should be an additional factor considered when trying to understand the mode of action of this clinically important family of molecules [36].

Results

All of the novel antipsychotics (brexpiprazole, cariprazine, aripiprazole lauroxil) are pheylpiperazine derivatives. At the same time, they are partial agonist at the dopamine D_2 receptor.

It is apparent that the molecules, pathways, and systems thought to be involved in anxiety and depression are interconnected. The pharmacological profiles of psychoactive drugs are complex and, since they interact with many receptor sites, they often result in numerous side effects. Because of the side effects, more selective antipsychotic are needed.

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