LATEST ANTIPSYCHOTICS TREATMENT UPDATES

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ABSTRACT

The world of psychiatrists and pharmacologists is increasingly striving to find new methods of intervention and treatment to improve the quality of life of patients with chronic psychiatric diseases and also to make them more functional and better integrated into society. Thus, more and more molecules are discovered and approved by the Food and Drug Administration in order to achieve these purposes. In this paper, we made a descriptive research of four of the newest antipsychotics, randomly chosen. We selected 38 articles and focused on the forms of presentation, the mechanism of action, the side effects, the drug interaction and the tolerance profile. Thus, we intend to offer new perspectives on how diseases such schizophrenia, treatment-resistant depression, bipolar disorder can be psychopharmacologically approached. The Authors declare that there is no conflict of interest.

Keywords: schizophrenia, antipsychotics, cognitive symptoms, bipolar disorder, resistant depression.

INTRODUCTION

In the late years, pharmaceutical studies were focused on finding new treatments for schizophrenia, treatment-resistant depression or bipolar disorder since they are still a challenge even for modern psychiatry. Main targets would be negative and cognitive symptoms in psychosis that are so difficult to treat until the present days. Asenapine, brexpiprazole, cariprazine and lurasidone were four of the news drugs developed to treat the above mental illnesses and will be presented in these review.

MATERIALS AND METHODS

The electronic database PubMed was searched for the most significant articles on the latest news about drugs studied for schizophrenia. We choose four of they to be presented in this research, thus asenapine, brexpiprazole, cariprazine and lurasidone. We observed a high interest in the study of new treatments for schizophrenia, major depressive disorder and bipolar disorder which are well known to be difficult to treat in some cases.

Asenapine

Asenapine is an atypical antipsychotic (serotonin-dopamine antagonist) derived from the tetracyclic antidepressant mianserin. This molecule was approved by FDA (Food and Drinks Association) in august 2009. The drug is available as sublingual tablets (5 mg and 10 mg). It is prescribed in Europe (as Sycrest) for the treatment of moderate to severe manic episodes in bipolar I disorder and in US (as Saphris) for the acute treatment of schizophrenia and bipolar I disease - with or without psychotic symptoms in adults and adolescents (10-17 yo). The drug may be administered as monotherapy or adjunctive therapy [1-5].

The results of clinical trials conducted so far show considerable difference between

Asenapine and placebo group in patients with manic episode in bipolar I disorder after 2 days of treatment, substantial reduction in symptoms at 3weeks that have been assessed with Young Mania Rating Scale (YMRS) and apparent maintenance of results in 40 weeks [5].

Other studies show that asenapine is also effective in managing acute schizophrenia. It has significantly reduced from baseline the scores assessed with Positive and Negative Syndrome Scale (PANSS) at 6 weeks [6, 7].

Even though Asenapine has shown promising results, further research may be needed to demonstrate a potential role in managing borderline personality disorder and its possible association in treatment of post-traumatic stress disorder [3].

Asenapine binds with high affinity and specificity to numerous serotonin (5HT2A, 5HT2B, 5HT2C, 5HT6 and 5HT7), dopamine (D2, D3 and D4), noradrenaline (α1A and α2) and histamine receptor subtypes (H1 and H2). It has a considerably higher affinity for 5HT2A receptors than D2 receptors [1-4].

As an α2 adrenoceptors antagonist, Asenapine has not only the potential to improve the negative symptoms in schizophrenia but also the cognitive function [7].

Its antagonism at the α1 adrenoceptor causes orthostatic hypotension. It must be mentioned that Asenapine action at H1 receptors causes sedation and is predicted to cause weight gain. In the therapeutic dose range, Asenapine has relatively no impact on muscarinic receptors and thus it has little anticholinergic side effects [4, 6, 8].

Asenapine was formulated as a sublingual fast dissolving tablet. The starting dose is 5 mg, the effective dose between 5-10 mg and the maximum daily dose is 20mg divided into two doses a day in the morning and in the evening. Its bioavailability is 35% when administered by transmucosal absorption, while by oral intake it decreases under 2%. This is caused due to the high hepatic first pass metabolism of this drug. Food and liquids intake, immediately after a taking the drug, can affect the bioavailability, by increasing the hepatic blood flow and clearance. Hence eating and drinking should be avoided for 10 minutes after its administration [1, 6, 9].

Asenapine has fast completely dissolution (within seconds) and absorption and reaches the peak plasmatic concentration in 30 -90 min and a high plasmatic protein binding 95%.[1] Asenapine is mainly metabolized in the liver by CYP1A2 oxidation, UGT1A4 glucuronidation and to a lesser extent by CYP3A4 and CYP2D6. Asenapine itself is the active compound, while its nearly 38 metabolites do not have any considerable effect. They do not cross blood brain barrier and they have very low affinity for receptors [6]. Asenapine half time is about 13-39 h. The routes of elimination of this drug are both through urine (50%) and (50%) feces [1, 2].

The most common adverse reactions associated with asenapine administration are well known for atypical antipsychotics such as: somnolence, sedation, extrapyramidal symptoms (other than akathisia), orthostatic hypotension (dizziness pre-syncope, syncope vasovagal syncope) except for oral hypoesthesia which is a curious, particular side effect of asenapine. Patients should be informed that after Asenepine intake may have temporary (for about 1 h) sensations of numbness or tingling of the mouth or throat [2].

Asenapine has a more favorable weight gain profile than the other atypical antipsychotics. It has low susceptibility to determine serious imbalances of metabolic syndrome such as dysregulation in plasma glucose, increase of lipid and prolactin level. As about its pro arrhythmogenic potential, Asenapine has a mild impact on cardiac function, with little QTc prolongation [6]. Must be mentioned that the side effects mentioned during

acute phase of Asenapine administration did not worsen on long term monotherapy [10].

Drug interactions change how the prescribed medication works or increase the side effects risk. Because Asenapine is metabolized in the liver so it is not recommended for patients with important hepatic dysfunction because of the excessive increase of its plasma concentration. On the other hand it is considered to be safe when used in patients with renal dysfunction. Because asenapine is a potent antagonist of alpha 1 adrenergic receptor thus causing orthostatic hypotension it is advised not to be used with antihypertensive drugs with adrenergic type of action [1, 6, 11].

Concomitant prescription of Asenapine with CYP1A2 inhibitors such as Fluvoxamine must be made wit caution, because it also can increase plasma concentration. The same is to be considered when deciding to associate other concurrent CYP2D6 substrates molecules such as paroxetine or fluoxetine. Carbamazepine is a potent CYP450 inducer, increasing hepatic clearance; thus it decreases plasma concentration of other drugs to subtherapeutic levels. Concomitant intake with other substances that cause dizziness should be avoided such as opioid cough and pain relievers, alcohol, marijuana, muscle relaxants and antihistamines [12].

Existing data suggest that asenapine is a potent atypical antipsychotic drug with a favorable tolerance profile. It is a option to consider for the acute and maintenance treatment of schizophrenia and for the treatment of acute manic or mixed episodes of bipolar I disorder especially in patients where weight gain, dyslipidemia, and endocrine abnormalities are a concern. Further studies should be performed to demonstrate the therapeutic benefit of asenapine in other psychiatric disorders such as PTSD or borderline personality disorder. However, as with other antipsychotics, its administration should be closely monitored for drug-related side effects and an adequate therapeutic response achievement.

Brexpiprazole

Brexpiprazole has been approved for the treatment of schizophrenia in adults by the Food and Drug Administration (FDA) on 2015, and in the European Union by the European Medicines Agency (EMA) on 2018. It is a partial D_2 agonist similar to aripiprazole, but the difference consists in the fact that brexpiprazole is a stronger D_2 antagonist compared to aripiprazole, being situated towards the left, closer to the zone that depicts total antagonism [13-15].

Brexpiprazole was found to have an equal high affinity for serotonin 5-$HT_{1A, 2A}$ and D_2 receptors. Compared to aripiprazole, it has stronger antagonist properties for $5HT_{2A}$ receptors, partial agonist for $5HT_{1A}$ receptors and $\alpha 1$ antagonist to its D_2 partial agonism. These actions should demonstrate its properties as an atypical antipsychotic and to reduce extrapyramidal syndrome, despite the fact that its D_2 antagonism is stronger than that of aripiprazole. Therefore, brexpiprazole is expected to have higher antipsychotic properties for positive and negative symptoms, to reduce side effects such as akathisia, insomnia, restlessness and nausea, to have positive effects on cognitive impairment, a frequent trait in psychotic pacients, and to improve sleep disorders, as well as affective symptoms that also can occur in schizophrenia [14-17].

The effectiveness of brexpiprazole is demonstrated in acute schizophrenia, particularly on improvement of negative symptoms, scattered thoughts and hostility. Studies found that compared to aripiprazole, it has significant amelioration of cognitive impairment. Moreover, it was discovered that brexpiprazole improves personal and social functioning, meaning better relationships and self-care as well as less aggressive behavior. Another benefit compared

to aripiprazole was the decrease in impulsivity, thus decreasing the risk for suicide and drug use encountered in psychosis. Concerning relapse time, this new medicine promises a longer time of disease recurrence. Brexpiprazole is administered orally once a day, with or without food, dose titration can start from 1 mg/day, in psychosis it is recommended that the dose should be increased to 2 mg/day from day 5 to day 7 and up to 4 mg/day from day 8 [16-18].

For its effects on negative symptoms, this novel compound is also recommended in major depressive disorder. These antidepressant effects could be explained by the partial agonism of 5-HT_{1A} and the antagonism of 5-HT_7 receptors similar to aripiprazole. It is used as supplementary to the antidepressants treatment, especially for patients who present with irritability and anxiety in need of a certain level of sedation and it helped improve sleep disturbances. Target dose is 2 mg per day, dosage can be adequately increased at weekly intervals [19].

The most common side effect that was observed in brexpiprazole treatment was: weight gain. Although it is a more potent histamine H_1 receptor antagonist than aripiprazole, it has a lower affinity for this receptor by comparison to the D_2 and 5-HT_{1A} receptors, resulting in a lower risk for sedation and weight gain. Other studies discovered that the most frequent side effect was akathisia and other found that akathisia and extrapyramidal syndrome were more common when higher doses were administered. These adverse effects could be linked and reduced due to a more potent 5-HT_{1A} partial agonism, 5-HT_{2A} antagonism and noradrenaline α_1 receptor than aripiprazole. Headache, nausea, dyspepsia, diarrhea, agitation and sedation were also observed. Compared to other second generation antipsychotics, glucose intolerance and high levels of lipids were less frequent and also, high prolactin levels and effects on the QTc interval [19].

Due to the fact that brexpiprazole is being metabolized by hepatic enzymes such as CYP2D6 and CYP3A4, it has multiple drug interactions with their inhibitors and inducers. Therefore, when combined with strong CYP3A4 or CYP2D6 inhibitors, the serum concentration of brexpiprazole is increased and only a half of the usual dose should be administered [20].

It is expected in the next years to be given to children and adolescents and perhaps being officially recommended as former and more used medicine, aripiprazole, as brexpiprazole has antipsychotic, antidepressant and antimanic effects similar to the previous, but a better tolerability. For now, it still has to be tested in adults as new indications may arise as well as side effects that were less studied [14].

Cariprazine

Cariprazine has been approved for use in adults in the United States by the FDA in 2015 for the acute and maintenance treatment with schizophrenia and for the acute treatment of manic or mixed episodes associated with bipolar I disorder. In 2019, cariprazine became FDA-approved as a monotherapy for bipolar I depression. In the European Union it has only been authorized by the EMA in 2015 for the acute and maintenance treatment of schizophrenia in adults [21-23]. It is a dopamine D3-preferring D3/D2 receptor partial agonist. Small doses have been described to be sufficient to reach maximal D3 receptor blockade which could have pro-cognitive, antidepressant effects and potential impact on negative symptoms of schizophrenia. The binding affinity of cariprazine for the D3 receptor, which is higher than for the D2 receptor, but also higher than dopamine's affinity for the D3 receptor, gives cariprazine a unique pharmacological profile [24, 25].

Cariprazine also acts as a partial agonist for 5-HT1A receptors and antagonist for 5-HT2A and 5-HT2B receptors. Furthermore,

in vitro studies have recorded it to have moderate affinity for histamine H1 receptors and low affinity for 5-HT2C receptors and α1A-adrenergic receptors. It has no significant affinity for cholinergic muscarinic receptors. Moreover, some studies regarding long-term treatment with cariprazine have reported increased levels of 5-HT1A and AMPA receptors and decreased levels of NMDA receptors [26].

The pharmacokinetic properties of oral cariprazine are characterized by the existence of two major metabolites (desmethyl cariprazine and didesmethyl cariprazine). Following the administration of a single dose, peak plasma concentration is reached in 3 to 6 hours. With multiple doses a steady state is reached in 1 to 2 weeks for cariprazine and desmethyl cariprazine and around 4 to 8 weeks for didesmethyl cariprazine. If the treatment is discontinued, the terminal half-life of cariprazine is 31.6–68.4 hours, of desmethyl cariprazine is 29.7–37.5 h, and of didesmethyl cariprazine is 314–446 h [22, 26].

The effectiveness of cariprazine in schizophrenia is characterized by a high impact on cases with predominant negative symptoms during the acute or maintenance phase. It can also be a choice for patients with predominant positive symptoms during the acute phase, without having the same troublesome adverse events as other antipsychotics. However, if positive symptoms are very severe, adjunctive medication may be necessary for the acute phase of the treatment. Cariprazine may also have a clear impact on cognitive impairment and reduce hostile behaviour.

During the trials for acute treatment with cariprazine of manic or mixed episodes associated with bipolar I disorder the overall improvement of manic symptoms has not been reported to be associated with worsening depressive symptoms or emerging depressive symptoms. The highest impact observed was on the irritability component [24, 25].

Throughout the treatment evaluation of bipolar I depression with cariprazine a reduction of total depressive symptoms has been ascertained. Additionally, improvement of both anhedonia and cognitive dysfunction was also noted [27, 28].

Cariprazine is administered orally once daily, with or without food, the recommended starting dosage for the treatment of schizophrenia being 1.5 mg/day, with titration possible up to 6 mg/day, depending on clinical response and tolerability. For the treatment of acute/mixed mania the starting dose is 3 mg/day going up to 6 mg/day, while in bipolar depression the starting dose is 1.5 mg/day with a maximum dose of 3 mg/day [22, 29].

Cariprazine is cleared by hepatic metabolism, primarily by CYP3A4 (and CYP2D6 to a lesser extent). These aspects should be taken into account because of multiple possible drug interactions, especially with CYP3A4 and CYP2D6 inhibitors which could increase the plasmatic concentrations and require dose adjustments of cariprazine. Co-administration of cariprazine and a CYP3A4 inducer (e.g. rifampin, carbamazepine) is not recommended [26].

Overall, cariprazine was well tolerated with the exception of elderly patients with dementia-related psychosis. Although cariprazine has not been approved for use in this category of recipients, it is worth noting this type of patients can be at an increased risk of all-cause death during the treatment with cariprazine. The most commonly reported side effects were EPS and akathisia. Small increases in body weight were also observed. Cariprazine has a low tendency to cause sedation or somnolence, it does not modify prolactin levels and it does not prolong the QTc interval [23, 27].

Lurasidone

Lurasidone is an atypical (second-generation) antipsychotic. It was approved by the European Medicines Agency in 2014 for the treatment of schizophrenia in adults. In the United States it is indicated for the treatment of schizophrenia in adults (approved by the Food And Drug Administration – FDA - in 2010) and adolescents aged 13 and older (since 2017), depressive episode associated with bipolar I disorder in adults, in either monotherapy or in combination with lithium and valproate (since 2013), and bipolar depression in adolescents aged 10 and older as monotherapy (approved by the FDA in 2018).[1] Off-label uses include irritability and anger in autism specter disorder and acute mania [30-32].

Lurasidone is part of the benzisothiazole class of atypical antipsychotic drugs. It acts as a full antagonist at serotonin 5-HT_{2A} and 5-HT_7 and dopamine D_2 receptors. In addition, out of all the atypical antipsychotics, Lurasidone is proved to have the highest binding affinity for the 5-HT_7 receptor. Lurasidone is also a partial agonist at serotonin 5-HT_{1A} receptors [33,34]. The blockage of dopamine D_2 and serotonin 5-HT_{2A} receptors is responsible for reducing positive symptoms and stabilizing affective symptoms, as well as reducing motor side effects. Antagonism at serotonin 5-HT_7 receptor contribute to alleviate negative symptoms, mood, sleep, cognitive impairment in schizophrenia, bipolar disorder and major depressive disorder. The partial agonism at 5-HT_{1A} receptors may be beneficial for mood, anxiety and cognition [32]. Lurasidone has low binding activity on histamine H_1, muscarinic M_1, $alpha_1$ and $alpha_{2A}$ adrenergic receptors, which minimizes the risk of sedation, orthostatic hypotension and weight gain associated with other antipsychotic agents [33, 34].

Lurasidone pharmacokinetic profile is consistent with once per day administration, considering its half-life of 18-31h. It reaches peak serum concentration in 1-3 hours and it plateaus in 7 days [32]. In a comparison of administration with food vs. administration while fasting, mean C_{max} increases by three times and the area under the curve doubles when administered with a meal, regardless of the fat content. Thus, the recommendation is to take lurasidone once daily, in the evening, with a meal [35].

Lurasidone is metabolized primarily by cytochrome P450 enzyme, CYP3A4, therefore caution is needed when administered in the presence of strong inducers or inhibitors of CYP3A4. When used at the same time with moderate CYP3A4 inhibitors (such as fluvoxamine, verapamil, diltiazem), it is recommended to decrease the dose of lurasidone by half. In contrast, when used concomitantly with moderate CYP3A4 inducers (modafinil), the lurasidone dose should be increased accordingly. CYP1A2 does not metabolize lurasidone, therefore smoking does not affect its pharmacokinetics [36]. Excretion of lurasidone is primarily in the feces (80%), with 9.2% being excreted in urine, thus making monitoring necessary for patients with renal and hepatic, moderate and severe impairment [30, 32].

The starting dose for schizophrenia patients is 40 mg/day in adults and adolescents, the maximum dose being 160 mg/day in adults and 80 mg/day for adolescents. In bipolar depression, the starting recommended dose in adults and pediatric patients is 20 mg/day, with a maximum of 120 mg/day in adults and 80 mg/day in pediatric patients [30].

In terms of adverse reactions, lurasidone has a better safety profile when compared to other second-generation antipsychotics. When compared to risperidone, quetiapine or olanzapine, lurasidone has a less significant risk of weight gain, hyperlipemia, hyperglycemia or hypercholesterolemia. The most common side effects in patients with schizophrenia and in patients with bipolar

depression are Parkinsonism, sedation, somnolence, akathisia, nausea [32].

Lurasidone has been clinically proven to be beneficial for patients with depressive episodes associated to bipolar I disorder and patients with schizophrenia. Studies show that a majority (80%) of patients with schizophrenia treated with lurasidone achieve optimal response within a dose range of 37-148 mg/day. Patients with bipolar depression benefit from doses of 20-60 mg of lurasidone per day [36, 37].

In terms of efficacy and safety of lurasidone in the pediatric and adolescent population suffering for schizophrenia, studies demonstrate that lurasidone administered at fixed doses of 40-80 mg/day provide significant improvements in quality of life and functional ability, with a high tolerability and minimum effects on weight and metabolic parameters [38]. Similarly, another study conducted on children and adolescents with bipolar depression treated with lurasidone at 20-80 mg/day, flexibly dosed, showed a significantly decrease of depressive symptoms, anxiety, and overall illness severity, and improved measures of quality of life and global functioning [39].

CONCLUSIONS

As we depicted in these research, hopes are high for the pharmaceutical treatment of schizophrenia, major depressive disorder or bipolar disorder. We can only look forward to see these medications being studied and used in children and adolescent populations also. Since then, a close study at side effects and other possible therapeutic uses must be a priority.

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