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REVIEW ON ATYPICAL ANTIPSYCHOTICS: AN APPROACH TOWARDS A BETTER TREATMENT OF PSYCHOSIS

Aryendu Kumar Saini *, Hemendra Pati Tripathi
Student, Pharmacy Department, Pranveer Singh Institute of Technology, Kanpur, UP, India

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***Corresponding author**
E-mail: aryendu77@gmail.com

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ABSTRACT

Psychosis is a mental disorder which is associated with impaired relationship with reality. It can be an indication of serious mental disorders like Alzheimer's disease, some types of epilepsy, infection in the brain, tumor in the brain and many more. Delusion and hallucinations are experienced with the people having the psychosis. One of the major psychoses is Schizophrenia from which a lot of people with psychosis suffer today. The antipsychotic agents or drugs are the first line drugs for the treatment of schizophrenia. They are also used for other complications such as acute mania and bipolar disorder. This article is about the atypical drugs, their comparison with the typical antipsychotics on the premise of safety and adverse effects. This article also encompasses the aspects like haloperidol induced apoptosis, which are sufficient to certify that why atypical antipsychotics are used more and are better than typical antipsychotics despite having different side effects.

Keywords: Psychosis, Schizophrenia, Dopamine, Antipsychotics, Extrapyramidal, Neuroleptics

INTRODUCTION

Psychosis is a psychiatric disorder in which patient is not aware of his illness (insight is absent) and refuses to take the treatment. Major psychoses are schizophrenia and mood disorders like mania, depression and bipolar disorder[1]. Psychotic persons have an impaired relationship with the reality. The most common and the most important psychosis is schizophrenia[2]. The most recommended drugs which are used to treat psychosis are called as antipsychotic medications that include typical and atypical antipsychotics. However worthy typical antipsychotics may be; they are not better and safer than atypical antipsychotics. With the approval and introduction of atypical antipsychotics in the market, typical use is getting diminished and going into pharmaceutical dustbin. This has led to the increased price of atypical antipsychotics and has become a ground reality as well as the reason why typical antipsychotics are more prescribed to the poor people by the physicians in spite of knowing that the typical antipsychotics risks outweigh its benefits. Atypical antipsychotics have tremendous benefits over typical antipsychotics like they are capable of treating both positive and negative symptoms of schizophrenia that lacks with typical antipsychotics. They don't interfere with the endocrine process. Patients suffer from neurolepsis which is described by the features like psychomotor slowing and emotional quitting, when they are given typical antipsychotics. What will schizophrenic people will do if he suffers a lot from side effects rather from the disease he or she is suffering? The most recognized benefit associated with atypical antipsychotics is their less or no potential to cause Extrapyramidal side effects or symptoms that is most troublesome and people suffers more from these symptoms than the symptoms of disease itself. Moreover, atypical antipsychotics are neuron protective while typical antipsychotics cause apoptosis. Atypical drugs prevent progressive tissue loss which is associated with schizophrenia and at the same time stimulate the extension of axon and dendrite, promote neurogenesis and cell survival[3]. It may be a lot easier to treat the patients of psychosis when the scientists will find the exact cause of psychosis.

This article is not only about atypical antipsychotics, but also about the symptoms associated with psychosis, different available antipsychotics, their mechanism of action, assessment of benefits and limitations related to typical and atypical antipsychotics and the reasons why atypical antipsychotics are still safer and used more than typical antipsychotics despite having metabolic and other side effects. The integration of all these is important to justify that atypical antipsychotic use is a better and safer approach for the treatment of psychosis than typical drugs.

Symptoms Associated With Schizophrenia

Schizophrenia (one of the psychosis) is characterized by marked thinking disturbance in which thinking, ability to perceive, communication, social functioning and attention get altered. Symptoms of Schizophrenia are positive, negative and cognition dysfunctions. Positive symptoms are those that are normally many times experienced by the individual, but they are persistent in the people with schizophrenia. In the positive symptoms, there are delusions, disorganized speech, racing thoughts, hallucinations (tactile, olfactory, auditory, visual and gustatory) while in the negative symptoms; there is alteration of normal human behavior, thought pattern, disorganized thoughts, lack of emotion or flat expressions, lack of motivation, lack desire to form relationships, inability to experience pleasure. Cognitive dysfunction is the core characteristic of schizophrenia and the schizophrenic person has less ability to comprehend and acquire the knowledge. Different cognitive capabilities like learning, perception, memory, ability to solve problems, attentiveness get affected in the schizophrenia. Some of the affected cognitive areas become apparent even before the appearance of positive symptoms related to schizophrenia. According to severity, dysfunctions in the cognition processes

get to appear and they get more prominent with the first episode of schizophrenia and attainment of middle age.[4]

Causative Factors

Psychosis and schizophrenia are not one and the same thing. There are different types of psychosis like bipolar illness, organic psychosis, delusional disorder, schizoaffective disorder, etc. and schizophrenia is one among them. Psychosis is a collective term which is used to describe psychotic symptoms. Different conditions like cerebrovascular accident (CVA), brain tumors, brain infections or the use of drugs like cocaine, amphetamine etc., can also lead to psychotic symptoms.

The etiology is still unknown, but there are proposals on the genetic, environmental and neuronal developmental factors[5].

Psychoses can be organic and caused due to risk factors like central anti-cholinergic drugs, N-methyl D-aspartate receptor antagonists like phencyclidine, a definite disease process like dementia or it can be idiopathic[6]. Its exact cause is not known, but the basic flaw seems to involve the hyperactivity of the dopaminergic neurons in the mesolimbic pathway[7]. Other neurotransmitters like 5-HT (5-hydroxytryptamine) and NA (Nor-adrenaline) also probably play a role in this disorder. Although there are many hypotheses behind schizophrenia, but DA (Dopamine) hypothesis is the most recognized. This can be understood from the fact that the drugs which enhance the dopaminergic neuronal transmission such as levodopa, amphetamines (DA releaser) and apomorphine (DA agonist), increase or exacerbate the schizophrenia[8]. However, there too are the defects in the DA hypothesis like decrease in the symptoms of psychosis by blocking the activity of 5-HT_2 and alpha receptor that may not involve blocking of dopamine activity in the mesolimbic system. Dopamine hypothesis does not explain the cognitive deficits (meso-cortical dysfunction) and psycho mimetic effects of activation of other pathways (example: D-lysergic acid)[9]. D-lysergic acid is a 5-HT_{2A} agonist that can produce psychotic symptoms.

Treatment of Psychosis

At present, there is no drug in any system of medicine that can prove to completely cure the psychosis. They can only help to manage the disease and the symptoms associated with it. In modern medical science, there are therapies like psychotherapy, mood stabilizing drugs, counseling and support from the health care professionals and family, etc. Before the treatment, proper medical diagnosis is necessary to find whether it is schizophrenia or any other psychosis. The drugs in the traditional system of medicines like Ayurveda may be able to treat the disease, but their pharmaceutical studies in the terms of 'pharmacokinetics', 'pharmacodynamics' and 'efficacy' need to be found out. However, this article has nothing to do with the other systems of medicines except Allopathy. The drugs that are used for the treatment of psychosis are called as Antipsychotic drugs. These drugs are of great importance for relieving the symptoms of psychosis and helping to prevent further episodes of psychotic illness[10, 11].

Antipsychotics are classified as 'Typical' and 'Atypical' Antipsychotics. They are shown in the table 1.

Mechanism of Action of Typical and Atypical Antipsychotics

Dopamine was discovered and categorized as a neurotransmitter in the late 1950s by the Swedish Neuropharmacologist- Arvid Carlsson[12]. There exist four pathways or systems of dopaminergic receptor in the central nervous system. These systems or pathways include Mesolimbic pathway, Mesocortical pathway, Nigrostriatal pathway and Tuberoinfundibular pathway.

These four pathways are relevant to the mechanism of action and adverse effects of antipsychotic drugs[13]. All of these pathways influence the cognitive behavior, coordination of voluntary movement, thinking and learning. Over firing of dopamine in these pathways produces different symptoms of schizophrenia. Typical antipsychotics are the drugs which mainly act by blocking the D2 receptor effectively. They bind tightly to D2 receptor, which means the affinity for binding is high. They can block H1 (histamine), M1 (muscarinic) and α_1 (alpha) receptors. They increase the dopaminergic transmission in dopamine pathways. Atypical antipsychotics are those which yet bind with D2 receptor, but loosely as the affinity of atypical antipsychotic for D2 receptor is less. They get dissociated from the dopamine receptor easily due to this. They have a very good affinity for 5HT_{2A} receptor[14]. Some of the atypical antipsychotics are 5HT_{1A} agonist like Clozapine and Ziprasidone. In addition to this, atypical antipsychotic or second generation antipsychotics have α_1, H_1, 5-HT_{2C} and M_1 antagonist activity.

Adverse Effects and Limitations of Typical Antipsychotics

By the 1970, it was clearly recognized that the key pharmacological property of all Neuroleptics was their ability to block the D2 receptors in the mesolimbic pathway. This action has been proved to be responsible not only for the antipsychotic activity, but also for the side effect that is neurolepsis[15]. Typical antipsychotics or traditional antipsychotics are classically called as neuroleptic drugs. Neurolepsis is characterized by psychomotor slowing or decreased motor activity, emotional quitting and indifference to the surroundings. This is the reason why they are also named as neuroleptic drugs. Sleep may occur, but the person can be aroused and can respond to commands. As we know that Schizophrenia is manifested as positive symptoms, negative symptoms and cognitive dysfunction. The conventional or typical antipsychotics treat only positive symptoms, negative and cognition dysfunctions of schizophrenia are not treated by the typical antipsychotic which is a limitation of them.

When significant numbers of D2 receptors are blocked by the typical antipsychotics in the nigrostriatal pathway, then EPS (Extra pyramidal symptoms) get to appear[16]. The extra pyramidal symptoms are the major limitations due to which typical antipsychotics are not preferred over atypical antipsychotics. The extra pyramidal system regulates posture and skeletal muscle tone. Extrapyramidal symptoms (also called extrapyramidal side effects) have got their name because they are the symptoms of disorders in this system. They are the drug induced movement disorders[17]. Extrapyramidal side effects are the neurological disorder. Neurological disorders can be classified into "Acute" and "Tardive" syndromes. Acute movement disorders are Akathisia (motor restlessness), Dystonia (continuous spasm and muscle contractions) and Pseudo Parkinsonism (characteristic symptoms due to rigidity) and they appear within weeks or hours of initiation of treatment or by increasing the dose of typical antipsychotic[18]. Tardive dystonia is a kind of Tardive dyskinesia. It is a movement disorder that is marked by involuntary muscular contractions that is caused due to potent dopamine receptor blocker like typical antipsychotics[19]. Extrapyramidal symptoms and their clinical features are shown in the Table 2.

They possess anti-cholinergic effects like blurred vision, constipation, etc., in the body due to their potency to block cholinergic (muscarinic) receptors. These side effects are more seen with thioridazine, which is a typical antipsychotic. Due to their alpha 1 blocking activity, they interfere with the adrenergic functions and show the effects like postural hypotension and difficulty in ejaculation (in males) which can be problematic in adults. As they block the H1 receptors, so they also produce sedation. Low potency drugs like chlorpromazine are highly sedative whereas high potency drugs cause less sedation. Both the typical and atypical antipsychotics can decrease the seizure threshold and can precipitate convulsions in an epileptic patient. However, seizures are more common with the low potency typical antipsychotic drugs[20]. Thioridazine can cause arrhythmia (prolongation of the QT interval). Retinal damage limits the long term administration. In case of typical antipsychotics; the more is the potency, more is the extra pyramidal symptoms and low is the anticholinergic activity. Low potency drugs like chlorpromazine has significant α blocking activity.

Moreover, their prolonged use can lead to weight gain (with all except haloperidol). Interference with the dopaminergic transmission in the pituitary and hypothalamus leads to 'Amenorrhea', 'Galactorrhoea' and 'Gynecomastia' as the level of prolactin hormone gets increased which is not a problem in the case of atypical antipsychotics. Clinical consequences which are associated with hyperprolactinemia are well documented in women on antipsychotics, in whom the prevalence of symptomatic hyperprolactinemia reaches fifty percent or more, the most common symptoms being the galactorrhoea and irregularities in the menstruation[21].

The combination of all these side effects that have been mentioned above are very likely to affect the patient's qualities of life adversely and their desire to continue with and adhere to typical antipsychotic therapy.

Adverse Effects of Atypical Antipsychotics and Limitations

The word 'atypical' has been most often used to describe the action of Clozapine, and in fact this compound has been regarded as the prototype for a new class of antipsychotic drug[22]. All atypical antipsychotics (except ziprasidone) cause metabolic side effects like weight gain, hyperlipidemia and Type II diabetes. Atypical antipsychotics on the basis of their potential to cause metabolic side effects are shown in Table 3. They cause metabolic disorders rather neurological disorders as compared to typical antipsychotics. Despite their benefits outweigh their risks, but there too are some serious adverse effects with the use of atypical antipsychotic like weight gain, Type II diabetes mellitus, hyperlipidemia, QT interval prolongation, sexual side effects. Overall, weight gain and obesity are more troublesome with atypical antipsychotics than with typical antipsychotics. Of the atypical antipsychotics, Clozapine and Olanzapine have the most significant effect on weight. The incidence of weight gain with Clozapine is regarded to be the most significant and ranges from 4% to 31%. Olanzapine follows Clozapine in significant weight gain with an incidence of 5% to 40%. A meta-analysis by Allison and colleagues suggested that olanzapine was associated with a mean weight gain of 4.15 kg, while the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) trial indicated 30% of patients taking olanzapine experienced a weight gain of more than 7% from baseline (mean increase of 9.4 kg)[23]. Ziprasidone and Aripiprazole have a very less incidence on weight gain. There are many evidences from the case reports of patients that clearly suggest that new onset type 2 diabetes mellitus have been noted with clozapine and Olanzapine. Quetiapine and Risperidone showed no effect like this. Clozapine does not seem to cause hyperprolactinaemia, but it shows the same spectrum of anticholinergic and antiadrenergic side effects as with the typical antipsychotic[24], but it causes agranulocytosis that limits its use.

Partial agonist action on 5-HT_{1A} receptors can give deprivation of weight gain for an antipsychotic; this is very much relevant for Ziprasidone but it enhances the risk of prolonged QT interval and must be less used in the patients having cardiac diseases. Ziprasidone causes QT interval prolongation. Opposite to this, the blockade of the 5-HT_3 receptor removes the risk for prolonged QT interval but then it has a higher risk of weight gain. Relation to the 5-HT_3 receptor increases glucose uptake and this is more seen with atypical antipsychotic drugs like Clozapine and Olanzapine.

However, patients who have to be treated with atypical antipsychotic drugs like Sertindole and Ziprasidone should receive a baseline ECG (Electrocardiogram) before the treatment is started, if any of the following mentioned cardiac risk factors are present: personal history of syncope, known cardiac disease, a family history of sudden death at under age of 40 years (especially if both the parent had sudden death) or congenital long QT syndrome. A subsequent ECG is indicated if the patient presents with symptoms that are associated with prolonged QT interval (e.g. syncope) [25]. Besides, Clozapine is associated with myocarditis; it is contra-indicated in patients with severe heart diseases. Quetiapine can cause cataract. Hyperprolactinemia has most commonly seen with the use of Risperidone than with the other atypical antipsychotics. Its active metabolite which is Paliperidone has less risk of metabolic side effects.

Benefits of Atypical Antipsychotics Due To Which They Are Better and More Preferred Than Typical Antipsychotics despite Having Side Effects

The most important reason for using atypical antipsychotics despite having metabolic and other adverse effects is their low potential to cause extra pyramidal side effects or the neurological side effects burden on the patient. Unlike typical antipsychotic, they have very less risk of tardive dyskinesia and other extra pyramidal related side effects. Typical antipsychotics like chlorpromazine exhibit the property to cause neurolepsis which is not found in the case of atypical antipsychotics. Neurolepsis is characterized by slowness or the absence of motor movements and behavioral indifference that is not tolerated by the schizophrenic patient. Atypical antipsychotics have also been found to treat the negative symptoms of schizophrenia as compared to typical antipsychotics.

We all are quite aware about the treatment resistant schizophrenia in which the patient does not respond to the treatment or in which at least *two* adequate trials of classical or typical antipsychotics have been done and the patient has residual persistent moderate to severe positive symptoms, negative symptoms and poor work function. So in that case clozapine is a good drug as it can treat this condition. It also suppresses the positive as well as the negative symptoms of schizophrenia[26]. Not only this, clozapine which is an atypical antipsychotic is the first drug which is FDA approved for use as an anti-suicide.

The typical antipsychotics of phenothiazine category are very well associated and established causes of liver injury arising within one to four weeks of treatment. During the 1960s and early 1970s, chlorpromazine was one of the most common and

recognized cause of liver diseases. Although some of the atypical antipsychotics are also associated with liver disease, but clinically apparent liver injury with jaundice from these atypical agents is very rare[27]. Decrease of the dose leads to normalization of enzymes of liver, particularly in the cases of Risperidone and Clozapine.

Most of the adverse effects of the atypical antipsychotics can be prevented if the proper therapeutic dose monitoring is done as many of them are dose dependent e.g. Clozapine induced convulsions are purely dose dependent[28]. Another great justification of this statement can be seen in a survey that was done on diabetes associated with clozapine, it was found that glycemic control got improved when clozapine was stopped in the 78% of individuals who developed diabetes. 62% of these patients did not require hypoglycemic drug[29]. For olanzapine associated diabetes, Koller and Doraiswamy presented that 78% of patients had improved glucose level once the olanzapine dose was decreased[30].

The treatment and management become a lot easier when the 'Diabetologist' and 'Psychiatrist' work together to monitor impaired glucose tolerance and to lessen the risk of cardiovascular diseases in the schizophrenic people.

Neurogenesis, which we all know is the process of formation of neurons. They are continuously formed in some specific regions of the adult brain (in the human, neurogenesis continuously occurs in two regions throughout the adulthood which is the sub-angular zone and the striatum) which is contrary to the popular belief that neurogenesis does not take place in the adult brain.

Atypical antipsychotic enhance the neurogenesis and counteract the effect of haloperidol and reverse the effects of haloperidol induced toxicity by inverse agonist action on 5HT receptors, especially those which are the subset of 2A.

Typical antipsychotics cause apoptosis of neurons in the brain. When haloperidol, which is a typical antipsychotic, was found to cause apoptosis, the implications were serious. There is loss of gray matter in schizophrenia in the frontal cortex and due to this there is expansion of lateral ventricle and third ventricle. Dendrite length is reduced by 50%. The loss of gray matter is much more progressive during the course of disease that exacerbates the condition towards worst. So the drug that causes the loss of grey matter cannot be a good treatment. Different experiments have been done to validate this fact of 'haloperidol induced apoptosis'. On the basis of those, it was found that there was increase of the oxygen reactive species or free radicals, which arise from mitochondria and free radicals cause DNA damage which is a very well known fact. Opposite to this, the second generation or the atypical antipsychotics cause less injury to neuronal cells. They enhance the cell survival and neurogenesis[31]. So from these entire one can very well understand that still atypical antipsychotics are of greater importance than typical antipsychotics.

Table 1: Classification of antipsychotics[32]

Typical Antipsychotics	Atypical Antipsychotics
• **Phenothiazine** 1. Chlorpromazine 2. Thioridazine 3. Trifluoperazine 4. Fluphenazine • **Thioxanthenes** 1. Flupenthixol 2. Thiothixene • **Butyrophenones** 1. Haloperidol 2. Droperidol 3. Penfluridol • **Miscellaneous** 1. Pimozide 2. Loxapine 3. Molindone	• Clozapine • Olanzapine • Quetiapine • Iloperidone • Risperidone • Paliperidone • Ziprasidone • Lurasidone • Aripiprazole • Brexipiprazole • Asenapine • Sertindole • Zotepine • Cariprazine

Table 2: Extrapyramidal symptoms and their associated clinical features

Extrapyramidal symptoms	Clinical features
Acute muscular dystonia	Torticollis, Locked jaw, Oculogyric crisis or Spasm of other muscles.
Pseudo-parkinsonism	Parkinsonian gait, Tremor, Instability.
Tardive dyskinesia	Purposeless involuntary movements like chewing of cheeks or puffing of cheeks.
Akathisia	Repetitive motions, Agitations or irresistible desire to move in the absence of anxiety

Table 3: Atypical antipsychotics as per their potential to cause metabolic side effects

Potential	Atypical Antipsychotic Drugs
High potential	Olanzapine and Clozapine
Intermediate potential	Quetiapine
Low potential	Risperidone and Paliperidone
Least potential	Ziprasidone, Aripiprazole, Iloperidone and Asenapine

CONCLUSION

A number of different atypical antipsychotics have superior efficacy when it comes to treatment of positive, negative, cognitive symptoms of schizophrenia with typical antipsychotics. The typical antipsychotic drugs were the reliable treatment for the treatment of psychosis until the introduction of clozapine but now they are replacing the typical antipsychotics very fast and this can be justified from their high cost price. Although the treatment of schizophrenia got revolutionized by typical antipsychotics, but the imperfection or the drawbacks caused due to these drugs is decreasing their use. All atypical antipsychotics have less risk of extra pyramidal side effects as compared to typical antipsychotics, which is a major significant factor for the patients. They also have less risk to cause hyperprolactinemia, which is more associated with typical antipsychotic. It cannot be overstated that atypical antipsychotics are free of adverse effects, but most of the time it has been found that side effects are dose dependent and can be managed by the health care professional if the treatment is done properly.

Moreover, the benefits of atypical antipsychotics outweigh the risks associated when compared to typical antipsychotics. By considering all of the factors above, it can be said that atypical

antipsychotic drugs use is a better approach for the treatment of psychosis.

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