International Journal of Drug Development & Research
| Oct-Dec 2010 | Vol. 2 | Issue 4 | ISSN 0975-9344 |
Available online http://www.ijddr.in
Covered in Official Product of Elsevier, The Netherlands

A TYPICAL ANTIPSYCHOTIC: A REVIEW

Mukesh Ratnaparkhi *[1], Guru Prasad Mohanta [2], Lokesh Upadhyay[3]

1. Marathwada Mitra Mandal's College of Pharmacy, Thergaon (Kalewadi), Pune-411033, India.
2. Annamalai University Annamalai Nagar Annamalai-608002, India.
3. CARISM, Sastra University, Tanjavur -613402, India.

ABSTRACT

Recent advances in understanding the pathophysiology of underlying psychotic disorder and subsequent development of new antipsychotic drugs to treat these diseases have altered clinicians' pharmacological approach. It has also helped researcher to produce a new generation antipsychotic agents (NGA) which could show better clinical results. However methodical approach as well as in-depth research in this area has provided several potent atypical antipsychotic agents. Now days all the atypical antipsychotics agents are FDA approved and being frequently used for pharmacotherapy of schizophrenia, acute mania, bipolar mania, psychotic agitation, bipolar maintenance, and other indications. Atypical antipsychotics are associated with the numbers of clinical benefits such as higher rate of responders, efficiency in patients with refractory disease, lower risk of suicides, better functional capacity and an improved quality of life and thus, have showed their efficacy against previous modes of treatment. The present review highlights the advantages, disadvantages as well as risk factors associated with novel antipsychotic agent with a view to outline their future scope.

Key Words: *Schizophrenia, atypical antipsychotic, extra pyramidal side effect.*

Introduction

Psychiatric illnesses are major disorder of organic or emotional origin and always associated with serious distortion of thought, behavior, capacity to recognize reality as well as deficient perception leading to delusion & hallucination and are the results of neurochemical imbalance in the brain[1]. Now it is well known that neither neurotransmitters such as nor adrenaline & dopamine plays a crucial role in the pathogenesis of these diseases. Further metabolic abnormalities of these amines in the brain may interfere with the neuronal functioning which could influence the vital centers of brain responsible for controlling the different neurophysiological activities. In fact metabolic imbalance between these two amines has been found associated with the psychosis process.

Schizophrenia is a chronic disabling illness, caused by abnormal amounts of certain neurotransmitters in the brain. The neurotransmitters controls our thought processes as well as emotions which has a wide range of symptoms. These include hallucinations (often hearing voices), delusions (false ideas that do not respond to reasoned argument), muddled speech and thoughts, and, very rarely catatonia (prolonged rigid postures or outbursts of repeated movement). The patients suffering from schizophrenia may also experience 'flattening' of their moods, which means that

For Correspondence:
E-mail: mukeshparkhi@yahoo.co.in
Telephone: +91 9960865355

they don't have any strong emotions, don't feel motivated to do anything and become detached from their social situation. Further, schizophrenia can follow a 'relapsing and remitting course', which means that symptoms comes and goes, or it can be 'chronic and progressive', which means that symptoms are persistent (are present all the time) and get worse over time. The schizophrenia can occur at any age, but it is rare before puberty and most common in late adolescence and the early twenties. It affects about 2 to 10 people in every 1000 in the general population and slightly more common in men than in women[2-4].

Pharmacotherapy of schizophrenia

In the past, schizophrenia has been treated with antipsychotic medicines that block the action of dopamine in the brain and these medicines were helping to control the abnormal thinking of people with suffering from this disease. Unfortunately, prolong use of these medicines have been found to decreases the person's ability to show emotion and also cause stiffness in the muscles. Apart from this, the medicines can cause other unpleasant side effects, like unusual movements of the tongue and face known as tardive dyskinesia. Further a dangerous syndrome, neuroleptic malignant syndrome (NMS) can develop in people using these medicines. A person with NMS may have rigid muscles or a very high body temperature and may even face coma [5].

The antipsychotic agents are being used for the treatment of psychiatric disorder such as schizophrenia, mania, and organic psychosis. Antipsychotic drugs are believed to work by influencing the metabolic status of neuro chemicals that transmit messages in the brain. Antipsychotics are the drugs that ameliorate mental aberration which is one of the major characteristics of the psychoses [6-7]. Now days different antipsychotic drugs are being used for the proper treatment of these diseases and has been divided into following groups:

a) Neuroleptic drugs
b) Major tranquilizers
c) Antischizophrenic drugs.

Classification of antipsychotic agents [8]

Phenothiazine typical antipsychotics:

Chlorpromazine, Fluphenazine, Mesoridazine, Perphenazine, Prochlorperazine, Promazine, Thioridazine, Trifluoperazine

Other typical antipsychotics: Chlorprothixene, Droperidol, Flupentixol, Haloperidol, Loxapine, Molindone

Atypical antipsychotics: Amisulpride, Aripiprazole, Clozapine, Melperone, Olanzapine, Quetiapine, Risperidone, Paliperidone, Sertindole, Sulpiride, Ziprasidone, Zotepine[8]

Mechanism of action

There are different types of DA-receptors[9] and it appears that antipsychotic drugs probably owe their therapeutic effects mainly by blocking the D_2 receptors. The main groups, phenothiazines, thioxanthines and butyrophenones, show preference for D_2 over D_1 receptors. Some newer agents (e.g. remoxipride) are highly selective for D_2 receptors, whereas clozapine is relatively non-selective between D_1 and D_2, but has high affinity for D_4 dopamine receptor. The naturally occurring agonist interacts with D_1 and D_2 receptors, and both receptors are found in high density in the corpus striatum and nucleus accumbens. It has been observed that mostly striated neurons exhibit D_1 responses whereas accumben neurons exhibit D_2 responses[10].

These drugs basically affect (1) mesocortical DA system as well as (2) mesolimbic DA system, and thus reflect antipsychotic and sedative actions. Extrapyramidal effects are caused by the inhibition of D_2 receptor of the nigrostriatal system (4). It is now known that the secretory inhibition of prolactin is caused by blocking the DA synthesis in the hypothalamus and hypophysis system[3]. In addition,

these drugs could inhit the action of central histamine and serotonin receptors.

Although D-receptor blockade occurs rapidly after initial antipsychotic drug treatment, a therapeutic response is not usually observed for several weeks. The time it takes for the clinical response to be manifested is thought to correlate with the delayed induction of depolarization blockade of mesolimbic DA neurons. Induction of depolarization blockade also correlates with a reversal of initial increase in the concentration of DA metabolites in cerebrospinal fluid[8].

Side effects and limitations of typical (conventional) antipsychotics:

1) Extra pyramidal side effects such as, akathisia (Restlessness, fidgeting, pacing, rocking, irritability), dystonia (Torsions and spasms of muscle groups), pseudo parkinsonism (Stiffness, shuffling, mask-like face, tremor, rigidity), rabbit syndrome (Trembling of lower lip), pisa syndrome leaning to one side (geriatric patients at higher risk), tardive dyskinesia (Facial signs of TD: smacking, licking of lips, chewing movements, rolling or protrusion of tongue, Spastic facial distortions, 'tics') are common. Further limited efficacy against negative and affective symptoms as well as cognitive deficits are also common[11].

1) Negative symptoms
2) Affective symptoms
3) Cognitive deficits

1. Negative symptoms: Diminution of normal mental activity.

Blunted (or flat) effects, catatonic behavior, alogia i.e. reduced speech, avolition i.e. lacking motivation.

2. Affective symptoms: Mood disorder with psychotic features.

3. Cognitive deficits: Executive function, attention, memory[11].

Atypical antipsychotics

The atypical antipsychotics (also known as second generation antipsychotics) are a class of special class of medications which is being frequently, used for the treatment of different psychiatric disorders in better safe manner. Now days all the atypical antipsychotics, which is used for the treatment of schizophrenia, are FDA approved. Some of the drugs carry FDA approved indications for acute mania, bipolar mania, psychotic agitation, bipolar maintenance, and other indications. The currently available atypical antipsychotics are clozapine, olanzapine, quetiapine, risperidone,. ziprasidone, aripiprazole, amisulpride, sertindole, zotepine, etc[12].

Pharmacological action of atypical antipsychotic

The exact mechanism of action of these drugs are still unknown but it has been worked out that these drugs may affect the receptor sites of different neurotransmitters and can block the over expression of a particular neurotransmitter. But it differs greatly from drug to drug and it may be due to the variation in the receptor binding profile which is common for exhibiting antipsychotic effect. All the antipsychotics work on the dopaminergic system but vary in regards to the affinity of the dopamine receptors[13]. There are 5 types of dopamine receptors in humans which are similar in structure and drug sensitivity[14]. The "D_2-like" groups include dopamine receptors 2, 3 & 4 and have a very similar structure but greatly differ in sensitivities to antipsychotic drugs. It has been proved that the "D_1-like" receptors never participates in the antipsychotic action of these drugs and thus least important for clinical relevance and therapeutic benefits [14].

The "D_2-like" group of dopamine receptors are classified together based on the structure but not on the drug sensitivity. It has been shown that D_2 receptor blockade is necessary for the antipsychotic action [13]. Generally all the antipsychotic block the D_2 receptors to some extent but the affinity of the antipsychotic vary from drug to drug and it has been hypothesized that it is the main reason that leads a change in the efficacy of

the drug[15]. Regarding mechanism of action of atypicals antipsychotics the "fast-off" theory has been propounded. According to this theory it was suggested that the AAP have low affinities for the D_2 receptor and only binds loosely to the receptor and rapidly released. In fact the AAP bind more loosely to the D_2 receptor than dopamine itself [13] and effectively interfere with the phasic release of endogenous dopamine. Further the AAP transiently bind and rapidly dissociate to the D_2 receptor to allow the normal dopamine transmission [15]. This transient binding keeps the prolactin levels normal on one hand and spares cognition and obviates EPS on the other hand. From a historical point of view, there has been interest in the role of serotonin in the pathogenesis of these diseases and their interaction with the use of antipsychotics. Experience with LSD suggests that 5-HT_2A receptor blockade may be a promising method of treating schizophrenia. One problem with this is the fact that psychotic symptoms caused by 5-HT_2 receptor agonists differs substantially from the symptoms of schizophrenic psychoses. The promising factor is that 5-HT_2A receptors are located on hippocampal and cortical pyramidal cells of the brain and have a high density in the fifth neocortex layer where the inputs of various cortical and subcortical brain areas are integrated. This makes that the blocking of this receptor may be of grate interest in relation to treatment of schizophrenia[15] and underline an area of research that could provide convincing results. Evidences pointout the fact that alone serotonin is not sufficient enough to produce an antipsychotic effect but serotonergic activity in combination with D_2 receptor blockade may be very much effective. Regardless of the neurotransmitters, these AAP antipsychotic drugs appears to work by restructuring the neuronal networks and capable enough to induce structural changes[14].

The side effects

The side effects associated with the different atypical antipsychotics vary and are medication-specific. Generally speaking, atypical antipsychotics are associated with fewer extrapyramidal side effects and less propensity for the development of tardive dyskinesia as compared with typical antipsychotics[16]. In 2004, the committee for the safety of Medicines (CSM) in the UK issued a warning that olanzapine and risperidone should not be given to elderly patients with dementia, because of an increased risk of stroke. Sometimes atypical antipsychotics can cause abnormal shifts in sleep patterns, and extreme tiredness as well as weakness. It is natural that schizophrenic patients typically try several antipsychotics before settling on one. "There's no question that atypical antipsychotics works, but it is also clear that they don't fulfill all the "expectations". Also the cost of atypical antipsychotics is 10 times higher as compared with older drugs and amongst all only zotapine is the least expensive than any other atypical antipsychotics. The percentage of substantial weight gain and metabolic disturbances are found higher in those who were treated with olanzapine. The mechanism of weight gain is unknown, but it was suggested that the blockage of histamine-1 receptors by novel antipsychotics disrupts the regulation of appetite. Others suggest that the involvement of central neurotransmitter mechanisms such as serotonin, dopamine, and norepinephrine receptor antagonism. Cortisol elevation, alterations in fat cell metabolism, gastric misperception of satiety, and better appetite associated with improvement in psychosis are other theories. Ziprasidone is less effective in relation to weight gain and thus safe as compared with clozapine and olanzapine. The product monographs and other available literature suggest a weight gain of approximately 2.3-to 8 kilograms in patients taking atypical antipsychotics. It has been concluded that respiridone treatment causes weight gain slowly over a longer period of time, so it does not become evident as quickly. In addition, it is now

suspected that they may promote the development to Type 2 diabetes, excessive salivation and may not work as quickly as typical antipsychotics. The second-generation (atypical) antipsychotics adverse effect includes metabolic abnormalities, diabetes, ketoacidosis, hyperglycaemia as well as lipid dysregulation[17].

Pharmacokinetics

Most neuroleptic drugs are highly lipophilic, bind avidly to proteins, and tend to accumulate in highly perfused tissues. Oral absorption is often incomplete and erratic, whereas IM injection is more reliable. With repeated administration, variable accumulation occurs in body fat and possibly in brain myelin. Half-lives are generally long, and so a single daily dose is effective.

Also esterifies derivate of fluphenazine requires dosing only once every week for few weeks. After long-term treatment if the drug administration is stopped, therapeutic effects may outlast due to significant decrease concentrations of the drug. This may result from tight binding of parent drug or active metabolites in the brain[17]. The most common route of administration of AAP is oral and it can also be injected but this method is not common [19].

Conclusion:

There have been tremendous advances in the development of the atypical antipsychotics since last decade. There's no question that there is a growth in the use of atypical antipsychotic agents compared to conventional antipsychotic agents may be due to following reasons:

a) They improve the social withdrawal and lacks of emotion that make people with schizophrenia seems to be different even when they are not having hallucinations or delusions.

b) Have fewer side effects than typical antipsychotic agents and have a seemingly additional effect on the 'negative symptoms' of schizophrenia.

c) Due to lower incidence of extrapyramidial side effects, but they don't fulfill all expectations, as some of these agents cause adverse effects such as, weight gain and metabolic disturbances that can cause diabetes. Product monographs and available literature suggest a weight gain of 2.3-8 kilograms in patients taking atypical antipsychotics, type 2 diabetes, excessive salivation and may not work as quickly as typical antipsychotics and metabolic side effects such as**,** diabetes, ketoacidosis, hyperglycaemia and lipid dysregulation in patients treated with second-generation (or atypical) antipsychotics, yet they have a more favorable side effect profile when compared with traditional drugs.

Moreover the third generation antipsychotics has emerged as aripiprazole (marketed at Abilify) creating hope for patients with schizophrenia and other psychotic disorders.

Acknowledgements:

The authors are thankful to the Vice Chancellor, Sastra University, Tanjavur & Principal Dr. Manohar Patil Marathwada Mitra Mandal's College of Pharmacy, Pune for encouragement.

Table 1: Data on NGA (New generation antipsychotic agents)

Generic name	Brand name	Dosage form	Common side effects	Manufacturer	Year of Approval by FDA.
Clozapine (dibenzodiazepine class) 8-chloro-11-(4-methyl-1-piperazinyl)-5H-dibenzo (b,e)(1,4)diazepine.[3]	Clozaril ®	Oral tablets	Sedation, agranulocytosis, weight gain and sialorrhoea	Novartis	1990
Olanzapine (thiobenzodiazepine class) 2-methyl-4-(4-methyl-1-piperazinyl)-10H-thieno[2,3-b][1,5]benzodiazepine.[3]	Zyprexa ®	Oral and dissolving tablets, and intramuscular injection	Drowsiness and excessive appetite with weight gain	Lilly	1996
Quetiapine (dibenzothiazepine class) 2-(2-(4-dibenzo [b,f][1,4]thiazepine-11-yl-1piperazinyl)ethoxy)ethanol. [3]	Seroquel ®	Oral tablets	Somnolence, orthostatic, hypotension	AstraZeneca	1997
Zotepine (Dibenzethiepine class) [3]	Zoleptil ®	Oral tablets	Weight gain, somnolence, dizziness, drowsiness and headache	Orion Pharmaceuticals	Not approved by FDA for use in the USA
Risperidone (benzisoxazole class) 4-[2-[4-(6-fluorobenzo[d]isoxazol-3-yl)-1-piperidyl] ethyl]-3-methyl-2, 6-diazabicyclo [4.4.0]deca-1,3-dien-5-one. [3]	Risperdal ®	Oral tablets	Headache, sedation anxiety and nausea	Janssen	1993
Ziprasidone (benzisothiazole class) 6-chloro-5-[2-[4-(7-thia-8-azabicyclo [4.3.0] nona-1,3,5,8 -tetraen-9-yl)piperazin-1-yl]ethyl]-1,3dihydroindol-2-one. [3]	Geodon ®	Oral capsules and intramuscular injection	Somnolence, nausea and orthostatic hypotension	Pfizer	2001
Aripiprazole (quinolinone class) 7-[4-[4-(2, 3-dichlorophenyl) piperazin-1-yl]butoxy]- 3,4-dihydro-1H-quinolin-2-one. [3] It is Dopamine partial agonist	Abilify™	Oral and dissolving tablets	Headache, anxiety insomania	Bristol-Myers Squibb Company	2002
Amisulpride (benzamide class).[3]	Solian ®	Oral tablets	Endocrine effects, insomania, anxiety and agitation	Lorex Synthelabo	Not approved by FDA for use in the USA
Sertindole (phenylindole derivative class).[3]	Serlect ®	Oral tablets	Rhinitis, reduced ejaculatory volume, nasal congestion	Abbott Laboratories	Not approved by FDA for use in the USA

References:

1) *F.S.K Barar. Essentials of pharmacotherapeutics. S Chand publication..2006.*
2) *Michael R et al. Current and Novel Approaches to the drug treatment of scizhophrenia. J. Med. chem. 2001;4: 478-501*
3) *Harsh Mohan, Text book of Pathology. Jaypee Publication.2010*
4) *Pathak Devender et al. New generation antipsychitics-a review, Indian journal of pharmaceutical education and research. 2006; 40: 2: 77-84.*

5) *John H. Block, John M. Beale Jr. Textbook of organic medicinal & pharmaceutical chemistry. Edited by Lippincotts Williams & Wilkins, A Wolters Kluwer Company. 2007*

6) *Turner T. ABC of mental Health- Schizophrenia. British Medical J. 1997; 315:108-111.*

7) *Mueser KT and Mcgurk SR. Schizophrenia. Lancet. 2004; 363: 2063-2072*

8) *Goodman G. A. The Pharmacological basis of therapeutics. McGraw hill Publication. 2006*

9) *Baldersseran et al. do central adrenergic action contribute to the atypical properties of clozapine. Br. J Pscchitry suppl. 1992;17:12-16*

10) *Daly SA and Waddington JL. Two directions of dopamine D_1/D_2 receptor interaction in studies of behavioural regulation a finding generic of four new selective dopamine D_1 receptor. Eur J Pharmacol. 1992;213:251-258*

11) *Sibley DR, Monsma FJ. Molecular Biology of dopamine receptors. Trends Pharmacol Sci. 1992; 13, 61-69.*

12) *Katzung, B.G. Basic and Clinical Pharmacology, Lange Medical Publisher. 2010*

13) *Horacek, J. et al. Mechanism of Action of Atypical Antipsychotic Drugs and the Neurobiology of Schizophrenia. CNS Drugs. 2006; 20(5): 389-405*

14) *Seeman, P. Atypical Antipsychotics: Mechanism of Action. Canadian Journal of Psychiatry. 2002; 47(1): 27.*

15) *American Diabetes Association; American Psychiatric Association; American Association of Clinical Endocrinologists; North American Association for the Study of Obesity (February 2004). "Consensus development conference on antipsychotic drugs and obesity and diabetes". Diabetes Care 27 (2): 596–601.*

16) *Sharpe JK, Hills AP. Atypical antipsychotic weight again major clinical challenge Aus N J Psychatry. 2003; 37:705-709.*

17) *Nasrallah H. A review of the effect of atypical antipsychotics on weight. Psychophneuroendocrinology 2003; 1:83-96.*

18) *Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology, Churchill Livingstone. 2003*

19) *McKim, W. Antipsychotics in Drugs and Behavior: An Introduction to Behavioral Pharmacology. Upper Saddle River, NJ. Pearson Prentice Hall. 2007.*

Article History:----------
Date of Submission: 20-09-10
Date of Acceptance: 23-11-10
Conflict of Interest: NIL
Source of Support: NONE