INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES
[ISSN: 0975-4725; CODEN(USA):IJPS00]
Journal Homepage: https://www.ijpsjournal.com

OPEN ACCESS

Review Article

Review Of The Pharmacology, On Antipsychotic's Drugs

Aishwarya B. Shewale *[1], Vishal C. Chavan[2], Sakshi K. Shinde[3], Siddhi M. Sharma[4]

[1,3,4]Students,KBHSS Trust's Institute of Pharmacy, Malegaon, Nashik, 423203
[2]Assistant Professor- KBHSS Trust's Institute of Pharmacy, Malegaon, Nashik, 423203

ARTICLE INFO

Received: 12 Sep 2024
Accepted: 16 Sep 2024
Published: 24 Sep 2024
Keywords:
Schizophrenia Dopamine Serotonin Typical antipsychotics Atypical antipsychotics.
DOI:
10.5281/zenodo.13835172

ABSTRACT

Antipsychotics are a cornerstone in managing psychotic disorders, including schizophrenia, bipolar disorder, and major depressive disorder. This review provides an overview of the mechanism of action, types, and efficacy of antipsychotics, including both typical and atypical agents. We discuss common side effects, safety concerns, and clinical applications, highlighting the importance of individualized treatment emerging research and future directions in antipsychotic development. Our review aims to provide a comprehensive update for clinicians, researchers, and healthcare professionals involved in the management of psychotic disorders.

INTRODUCTION

A complicated, long-term mental illness, schizophrenia is marked by a wide range of symptoms, such as delusions, hallucinations, disordered speech or behaviour, and diminished cognitive function. For many patients and their families, the condition is incapacitating due to its early start and chronic nature.Since schizophrenia is intrinsically diverse, opinions on its aetiology, pathophysiology, and standards for diagnosis are divided, Schizophrenia patients have a considerable 15–20 year loss in life expectancy and are more likely than the general population to have physical comorbidities such as diabetes, obesity, cancer, and cardiovascular disorders [3]. An estimated 24 million people worldwide suffer from schizophrenia, a serious mental illness with a prevalence rate of 1 in 300 (0.32%). Chronic schizophrenia is linked to significant personal and societal hardship [4,5]

Classification of Antipsychotic drugs

First generation of Antipsychotic drugs

Typical antipsychotics, or first-generation antipsychotics, are dopamine receptor antagonists (DRA). These comprise butyrophenones (haloperidol), thioxanthenes (thiothixene,

***Corresponding Author:** Aishwarya B. Shewale
Address: *Students , KBHSS Trust's Institute of Pharmacy, Malegaon, Nashik, 423203*
Email ✉: aishwaryashewale24@gmail.com
Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

chlorprothixene), dibenzoazepine's (loxapine), dihydroindoles (molindone), and diphenylbutylpiperidines (pimozide). Phenothiazine's (trifluoperazine, perphenazine, prochlorperazine, acetophenazine, triflupromazine, mesoridazine) are among them.[6,7]

Second generation of Antipsychotic drugs:

Atypical antipsychotics, another name for second-generation antipsychotics, are serotonin-dopamine antagonists. As of 2016, the Food and Drug Administration (FDA) had authorised twelve atypical antipsychotics. They are asenapine, lurasidone, iloperidone, cariprazine, brexpiprazole, clozapine, olanzapine, quetiapine, ziprasidone, aripiprazole, palpations, and asenapine.[8]

Brief history of antipsychotic development

Schizophrenia has a lengthy historical background. Scripture and classical literature both contain references to individuals who are obviously insane. For example, Mark 5 describes the Gerasene Demoniac, who "would howl and gash himself with stones among the tombs and in the mountains all day and all night." Indeed, the earliest known account of a mental disorder such as schizophrenia comes from Egypt's Ebers Papyrus, which goes back to 1550 BC.1. Literature from the 17th century begins to describe moments of lunacy that include hearing voices, seeing visions, and acting erratically and uncontrollably. Interestingly, even back then, people believed that lunacy was a medical condition rather than the result of evil spirits possessing people, despite the fact that they were

Mechanism of Action

First-generation antipsychotics impede dopaminergic neurotransmission; they are most effective when they block roughly 72% of the brain's D2 dopamine receptors. Moreover, they disrupt histaminergic, cholinergic, and noradrenergic pathways. Second-generation antipsychotics function by obstructing both the serotonin receptor antagonist and D2 dopamine receptors. The most often involved subtype of the serotonin receptor is 5-HT2A

Dopamine receptor antagonism

Dopamine's work at its receptors is blocked as part of the Mechanism of function (MoA) of dopamine receptor antagonism, namely:

1. **D2 receptor antagonism*:**

The majority of antipsychotics inhibit D2 receptors, which lessens the excitatory effects of dopamine and lessens positive symptoms of psychosis (delusions, hallucinations).

2. **D1 receptor antagonism*:**

A few antipsychotics also block D1 receptors, which may have a beneficial effect on patients but may have a negative impact on their cognitive function.

3. **D3 and D4 receptor antagonism*:**

Blocking these receptors may help some antipsychotics work as therapeutic agents, especially when it comes to improving cognition and stabilising mood.

Dopamine receptor antagonists work by preventing dopamine from entering receptors.

Diminish the excitatory effects of dopamine – Reduce psychotic symptoms (delusions, hallucinations) – May enhance mood and cognitive abilities – May have adverse consequences such as weight gain, extrapyramidal symptoms (EPS), and

Serotonin Receptor modulation

The term "serotonin receptor modulation" describes a substance's capacity to affect the brain's serotonin receptors' function. One neurotransmitter that is essential for controlling mood, hunger, sleep patterns, and other bodily functions is serotonin.

Modulators of serotonin receptors can:

1. _Activate_ serotonin receptors to simulate serotonin's effects

2. _Block_ serotonin receptors to lessen serotonin's effects.
3. _Partial agonism_, which activates receptors less strongly than dopamine
4. Several outcomes of this modulation include:
5. _Mood regulation_: Managing mood, lowering anxiety and depressive symptoms
6. _Appetite and satiety_: Controlling hunger, which affects weight
7. _Slumber-wake cycle_: Adjusting sleeping habits
8. _Pain modulation_: Modifying how one perceives pain
9. _Inflammation reduction_: Lowering bodily and mental inflammation

Glutamate and GABA modulation

The term "glutamate and GABA (gamma-aminobutyric acid) modulation" describes how the brain regulates the activity of these two neurotransmitters. Neurotransmitters that are excitatory include glutamate and inhibitory neurotransmitters like GABA.

Modulation of Glutamate:

1. NMDA receptor antagonists: Reduce excessive brain activity by blocking the excitatory effects of glutamate.
2. AMPA receptor potentiators: Boost the excitatory effects of glutamate, enhancing cognitive performance.
3. mGluR modulators: Control the effects of glutamate on glutamate receptors that are metabotropic.
4. GABA Stimulation:
5. GABA receptor agonists: Strengthen the inhibitory effects of GABA, which lower anxiety and encourage relaxation.
6. GABA receptor antagonists: Increase alertness and energy by obstructing GABA's inhibitory effects.

Applications in Therapy:

- **Anxiety disorders:**

Benzodiazepines and other GABA modulators lessen anxiety.

- **Depression:**

a. Glutamate modulators exhibit quick antidepressant effects; ketamine is one example.
b. Glutamate modulators, such as NMDA receptor antagonists, may alleviate the symptoms of schizophrenia.

- **Epilepsy:**

a. GABA modulators, such as barbiturates, lessen the frequency of seizures.
b. GABA modulators, such as zolpidem, help with sleep disturbances [9]

Adverse effects

Extrapyramidal side effects are a serious concern linked with first-generation antipsychotics, or FGAs. Low potency dopamine receptor antagonists such as chlorpromazine and thioridazine may cause anticholinergic side effects such as dry mouth, constipation, and urine retention. Sedation results from first-generation antipsychotics' inhibition of H1 histamine. The most sedative drugs include chlorpromazine; fluphenazine, haloperidol, and pimozide are less sedative. The seizure threshold can also be lowered by first-generation antipsychotics, and some drugs are more epileptogenic than others, such as thioridazine and chlorpromazine. If administered intravenously, haloperidol injections can result in torsades de pointes, ventricular arrhythmia, irregular heart rhythms, and even sudden death. Additional FGAs may result in various cardiac conduction problems, prolonged atrial and ventricular contraction, and prolonging of the Etc. interval. The FDA has backed a warning for sudden cardiac death with thioridazine. Orthostatic effects are often caused by low-potency FGAs, such as thioridazine or chlorpromazine[10]

Efficacy

Treatment for schizophrenia (both acute and ongoing)

Furukawa et al. Performed a meta-analysis to investigate how baseline severity of positive and negative symptoms affected antipsychotic medication efficacy[11] There isn't any solid proof that antipsychotic medication used at doses greater than the maximum permitted amount works better than recommended dosages.[12] First, there was just one study on patients who were resistant to treatment and just six studies on patients who had experienced their first episode. Since longer times may be needed to correctly predict final nonresponse in patients who are treatment resistant or who are[13] experiencing their first episode, this diagnostic test is best suited for patients who have experienced multiple episodes. Numerous independent investigations indicate that the response's time course in the first episode[14] In fact, at least for patients participating in clinical trials, the near-maximal effective dose (i.e., the threshold dose required to cause all or nearly all of the clinical responses for each treatment) for many antipsychotics is lower than the maximum approved dose[15] Crucially, clozapine proved to be the most effective oral antipsychotic to prevent hospitalisation and treatment failure, outperforming both first- and second-generation antipsychotics in a real-world, extensive national database trial from Sweden.[16] There are two extensive RCTs that looked into patients' switching tactics when they hadn't responded well to antipsychotic medication early on. The results were not yet available when this article was written. Antipsychotics have not shown much promise in treating schizophrenia; therefore, a number of psychotropic drugs have been combined to antipsychotics in an effort to increase their efficacy. We call this combination or augmentation therapy. This method is frequently used in clinical practice for combinations that include adding a nonantipsychotic drug to an antipsychotic as well as for antipsychotic cotreatment, which involves combining two antipsychotics. For instance, a median prevalence of 19.6% was found in 147 research that combined data from 1970 to 2009 on antipsychotic polypharmacy, or the concurrent use of at least two antipsychotics[17]

Clinical Application of Antipsychotic drugs

Clinically speaking, second-generation antipsychotic medications are expected to offer a wider range of therapeutic activity in schizophrenia, addressing symptoms such as negative and cognitive symptoms, and to cause less motor adverse effects. Lower dosages of these medications typically alleviate the latter symptoms, whereas greater dosages are most effective in treating positive (psychotic) symptoms. One possible distinction between the second-generation antipsychotics and the first-generation ones is their ability to exhibit varying degrees of neuroprotective benefits, frequently in a dose-dependent fashion. [18]It turned out that clozapine was the actual forerunner of atypical antipsychotic medications. Despite the fact that preclinical research did not support the drug's "neuroleptic" effect, it was launched in Europe in the 1970s. However, the clinical action of clozapine was observed to be in contradiction with the prevailing notion at the time, which was that extrapyramidal symptoms should accompany an antipsychotic effect.[19

CONCLUSIONS

Antipsychotic medications significantly reduce symptoms and enhance quality of life, making them an essential therapy choice for psychotic diseases. Although they have drawbacks and adverse consequences, risks can be reduced with cautious selection and oversight. Personalised treatment techniques, decreased side effects, and increased efficacy are the goals of ongoing research. Antipsychotic medications will remain essential for treating these crippling disorders,

improved patient outcomes, and improving lives as our knowledge of the intricate mechanisms underlying psychosis develops.

REFERENCE

1. Cognitive Theory, Research, and Therapy in Schizophrenia, Beck AT, Rector NA, Scholar N, Grant P. Guilford Press, New York, NY, New York, 2009. Contributions from Biology, pages. 30-61.
2. Crismon L, Argo TR, Buckley PF. Schizophrenia. In: DiPiro JT, Talbert RL, Yee GC, et al., editors. 1Pharmacotherapy: A Pathophysiologic Approach. 9th ed. New York, New York: McGraw-Hill; 2014. Pp. 1019–1046.
3. Correll C.U., Solmi M., Croatto G., Schneider L.K., Rohani-Montez S.C., Fairley L., Smith N., Bitter I., Gorwood P., Taipale H., et al. Mortality in people with schizophrenia: A systematic review and meta-analysis of relative risk and aggravating or attenuating factors. World Psychiatry. 2022;21:248–271. Doi: 10.1002/wps.20994.
4. Charlson F.J., Ferrari A.J., Santomauro D.F., Diminic S., Stockings E., Scott J.G., McGrath J.J., Whiteford H.A. Global epidemiology and Burden of Schizophrenia: Findings From the Global Burden of Disease Study 2016. Schizophr. Bull. 2018;44:1195–1203.
5. Stein D.J., Shoptaw S.J., Vigo D.V., Lund C., Cuijpers P., Bantjes J., Sartorius N., Maj M. Psychiatric diagnosis and treatment in the 21st century: Paradigm shifts versus incremental integration. World Psychiatry. 2022;21:393–414. Doi: 10.1002/wps.20998
6. Faden J, Citrome L. Resistance is not futile: treatment-refractory schizophrenia – overview, evaluation and treatment. Expert Opin Pharmacother. 2019 Jan;20(1):11-24.
7. Drummond N, McCleary L, Freiheit E, Molnar F, Dalziel W, Cohen C, Turner D, Miyagishima R, Silvius J. Antidepressant and antipsychotic prescribing in primary care for people with dementia. Can Fam Physician. 2018 Nov
8. Haddad PM, Correll CU. The acute efficacy of antipsychotics in schizophrenia: a review of recent meta-analyses. Ther Adv Psychopharmacol. 2018 Nov
9. Crouse EL, Alastanos JN, Bozymski KM, Toscano RA. Dysphagia with second-generation antipsychotics: A case report and review of the literature. Ment Health Clin. 2017 Mar;7(2):56-64
10. Lozupone M, La Montagna M, D'Urso F, Piccininni C, Sardone R, Dibello V, Giannelli G, Solfrizzi V, Greco A, Daniele A, Quaranta N, Seripa D, Bellomo A, Logroscino G, Panza F. Pharmacotherapy for the treatment of depression in patients with alzheimer's disease: a treatment-resistant depressive disorder. Expert Opin Pharmacother. 2018
11. Furukawa TA, Levine SZ, Tanaka S, et al. Initial severity of schizophrenia and efficacy of antipsychotics: participant-level meta-analysis of 6 placebo-controlled studies
12. Royal College of Psychiatrists. CR190 Consensus statement on High-dose Antipsychotic medication
13. Gallego JA, Robinson DG, Sevy SM, et al. Time to treatment response in first-episode schizophrenia: should acute treatment trials last several months
14. Emsley R, Rabinowitz J, Medori R. Time course for antipsychotic treatment response in first episode schizophrenia.
15. Davis JM, Chen N. Dose response and dose equivalence of antipsychotics. J Clin Psychopharmacol 2004
16. Tiihonen J, Mittendorfer-Rutz E, Majak M, et al. Real-world effectiveness of antipsychotic treatments in a nationwide cohort of 29 823 patients with schizophrenia

17. Gallego JA, Bonetti J, Zhang J, et al. Prevalence and correlates of antipsychotic polypharmacy: a systematic review and meta-regression of global and regional trends from the 1970s
18. Chen A.T., Nasrallah H.A. Neuroprotective effects of the second generation antipsychotics. Schizophr Res. 2019;208:1–7. Doi: 10.1016/j.schres.2019.04.009
19. Stille G., Fischer-Cornelssen K. Die Entwicklung von Clozapin (Leponex)—Ein Mysterium? In: Linde O.K., editor. Pharmakopsychiatrie im Wandel der Zeit. Tilia Verlag. Mensch und Medizin; Klingenmünster, Germany: 1988. Pp. 333–348
20. Amsler H.A., Teerenhovi L., Barth E., Harjula K., Vuopio P. Agranulocytosis in patients treated with clozapine. Acta Psychiatr. Scand. 1977;56

HOW TO CITE: Aishwarya B. Shewale Vishal C. Chavan , Sakshi K. Shinde , Siddhi M. Sharma , Review Of The Pharmacology, On Antipsychotic's Drugs, Int. J. of Pharm. Sci., 2024, Vol 2, Issue 9, 1295-1300. https://doi.org/10.5281/zenodo.13835172