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Review On: Recent Trends in Antipsychotic Formulations

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ABSTRACT: Psychiatric illness typically necessitates long-term therapy, and like with most chronic illnesses, Antipsychotics are neuroleptic drugs that belong to the class of psychotropic medications which are used majorly to manage a condition like paranoia. D2-like receptors are majorly involved in the antipsychotic action of the drug. Antipsychotics were introduced in the 1950s with the oral route of administration. Such formulations caused a variety of undesirable side effects, encouraged Rhône-Poulenc to develop an antihistamine with central nervous system effects, and utilized chlorpromazine to treat inpatients, with the name antipsychotic only appearing in the 1960s. This reflected the 1950s mechanisms for drug research and regulation, also known as first-generation antipsychotics and formerly known as major tranquilizers, Conventional antipsychotics have proven a powerful tool in the psychiatrist's arsenal against psychotic diseases, and other adverse effects can occur in any system of the body. Antipsychotics of the first generation function by blocking dopaminergic neurotransmission. The clinical effects of antipsychotic drugs have been widely examined and documented. Atypical antipsychotics are more likely to cause adverse metabolic effects. The atypical antipsychotics integrate with the serotonin. They have similar or even higher affinity to 5-HT2A 2C. The presented artile describes in detail the about recent trends in the formulation aspects of antipsychotic formulations and their mode of action.

KEYWORDS: Atypical antipsychotics, Dopamine, chlorpromazine, clozapine, liquid antipsychotics.

I. INTRODUCTION:

Psychiatric illness typically necessitates long-term therapy, and like with most chronic illnesses, poor treatment compliance is a common occurrence due to human nature, which can be exacerbated by disease, treatment, and patient-related factorsPartial and complete non-compliance with long-term therapy is caused by a number of factors, including disease, treatment, and patient-related issues, with the relative importance of each element varies depending on the underlying illness (e.g. depression, bipolar disorder, schizophrenia). Antipsychotics are neuroleptic drugs that belong to the class of psychotropic medications which are used majorly to manage a condition like paranoia, hallucination, delusion, schizophrenia, etc.[1] Based on the neurotransmitter activity and affinity, antipsychotics are further classified as a Antipsychotics of the first generation, also known as typical antipsychotics, and second generation, also known as atypical antipsychotics.[2] The phenothiazines(e.g. chlorpromazine), thioxanthenes (e.g. chlorprothixene), butyrophenones (e.g. haloperidol), diphenylbutylpiperidines (e.g. pimozide), and dihydroindolones (e.g. molindone) are all examples of typical antipsychotic drugs. On the other hand, clozapine, Resperidone, Paliperidone, Zotepine, Cariprazine, Asenapine, etc are atypical antipsychotic drugs. Antipsychotic drugs, work by inhibiting dopamine receptors in the neurological system. There are total of 5 types of Dopamine receptors found in the human body of which Type 1 and Type 5 are similar in structure, named D1 like group while Type 2, Type 3 and Type 4 are similar in structure, named D2 like a group. D2-like receptors are majorly involved in the antipsychotic action of the drug.[3] Antipsychotics were introduced in the 1950s with the oral route of administration. Such formulations caused a variety of undesirable side effects, including involuntary movement difficulties, gynecomastia, impotence, weight gain, and metabolic syndrome. Long-term use can cause tardive dyskinesia, tardive dystonia, and tardive akathisia. Thus, poor adherence to the oral formulations leads to the development of long-acting injectables and the incidence of side effects was reduced.[4]

HISTORY:

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Chlorpromazine was developed by the French pharmaceutical company Rhône-Poulenc in 1950, but it was not intended to be a psychiatric medicine at the time. Antihistaminergic medicines were being developed for a variety of illnesses, including nausea and allergies. Henri Laborit, a French surgeon and researcher, encouraged Rhône-Poulenc to develop an antihistamine with central nervous system effects, believing it might be useful as a pre-anesthetic drug before surgery. Chlorpromazine was one of several chemicals discovered, and it was chosen for human testing after laboratory tests in rats proved its central nervous system effects. When given to patients before surgery, Laborit saw that chlorpromazine induced tranquility without sedation, which prompted him to believe it could be useful in psychiatry. As a result, two psychiatrists at St Anne's Hospital in Paris, Jean Delay and Pierre Deniker, utilized chlorpromazine to treat inpatients, including those suffering from mania and schizophrenia. They concluded that chlorpromazine was quite successful, and they released a series of papers, the first of which was published in 1952. They highlighted chlorpromazine's potential to moderate agitation and excitation in particular. This helps to explain why these drugs were first referred to as "major tranquilizers" in the United States, with the name "antipsychotic" only appearing in the 1960s. Psychiatrists in Europe and North America were widely prescribing chlorpromazine by 1956. Its rapid adoption in the United States was aided by a comprehensive marketing campaign by Smith Kline & French, the company that owned the license. The discovery of chlorpromazine's psychiatric effects is frequently referred to as serendipitous,' implying that it happened by coincidence or good fortune. Chlorpromazine was approved for use in the clinic without any prior clinical trials. This reflected the 1950s' mechanisms for drug research and regulation, which were vastly different from current practice.[5]

To address the critical challenges, several novel dosage formulations and delivery mechanisms have been developed and reported. The benefits of technological developments in terms of drug release, tolerance, efficacy, and compliance are highlighted in this review article.

TYPICAL ANTIPSYCHOTICS:

First-generation antipsychotics, commonly referred to as typical antipsychotics and formerly known as major tranquilizers, are a family of antipsychotic medicines first discovered in the 1950s and used to treat psychosis, notably schizophrenia. Conventional antipsychotics have proven a powerful tool in the psychiatrist's arsenal against psychotic diseases, but their side effect profile is concerning. Photosensitivity, jaundice, convulsions, blindness, agranulocytosis, malignant syndrome, and other adverse effects can occur in any system of the body. Antipsychotics harm the majority of physiological systems. These side effects, in particular, have an impact on the central nervous system, causing movement disorders, sedation and seizures. Other adverse effects, such as those affecting reproductive function, might be particularly bothersome for individuals.[6] These are more likely to cause EPS i.e Extrapyramidal symptoms. As a side effect of such antipsychotics, there is a chance of developing a dangerous condition known as tardive dyskinesia. The chance of developing tardive dyskinesia after taking a standard antipsychotic for a long time depends on several factors, including age and gender, as well as the antipsychotic consideration. The annual incidence of TD among younger patients is typically reported to be around 5%. There have been reports of incidence rates as high as 20% per year among elderly patients. The prevalence rate is around 30% on average.[7] First-generation antipsychotics work by obstructing dopaminergic neurotransmission; they are most effective when they obstruct around 72% of the brain's D2 dopamine receptors. Additionally, they function by blocking the cholinergic, histaminergic, and noradrenergic receptors.[8]

ATYPICAL ANTIPSYCHOTICS :

Atypical antipsychotics are characterized by either reduction in extrapyramidal side effects or increased therapeutic efficacy following improvement in positive, negative and cognitive symptoms. Atypical antipsychotics are differentiated from typical antipsychotics based on the dose-response separation between particular pharmacologic function, pharmacological activity and neurotransmitter interactions. The clinical effects of antipsychotic drugs have been widely examined and documented, but the mechanism of action that underpins them is still unknown. Antipsychotic medicines are thought to interact with central dopamine (DA) and specifically D2 receptor neurotransmission, but they may also have therapeutic benefits by affecting other neurotransmitter systems and receptor types.[9] The substantial discrepancies in the clinical and preclinical activity of clozapine, the prototype atypical antipsychotic, and other antipsychotic medicines suggest that these drugs may be

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classified into two distinct classes, atypical and typical antipsychotic drugs, respectively. Atypicals are more prone to have negative metabolic consequences like weight gain and a higher risk of type II diabetes. The atypical antipsychotics integrate with the serotonin (5-HT), norepinephrine (α, β), and dopamine (D) receptors to effectively treat psychotic disorders. They have similar or even higher affinity to 5-HT2A/2C, 5-HT1A/1C, α-1, and/or α-2 adrenergic receptors than D2 receptors. Atypical antipsychotics can change the excitability of 5-HT neurons by targeting these receptors. At the cellular level, D1 receptors interact with D2 receptors, and so D1 receptor antagonism may have a direct impact on psychotic illnesses via D2 receptor regulation.[10]

Typical Antipsychotics and Atypical Antipsychotics	
A) Butyrophenones 1. Haloperidol 2. Droperidol Penfluridol	1. Clozapine 2. Olanzapine 3. Quetiapine 4. Resperidone 5. Paliperidone 6. Ziprasidone 7. Asenapine 8. Zotepine 9. Cariprazine 10. Lurasidone
B) Thioxanthenes 1. Flupenthixol 2. Thiothixene	
C) Phenothiazine 1. Chlorpromazine 2. Thioridazine 3. Trifluperazine	

Table 1: Classification of typical and atypical antipsychotics.

RECENT TRENDS IN ANTIPSYCHOTIC FORMULATIONS:

Short-acting Intramuscular formulations:

Ziprasidone and olanzapine are two atypical antipsychotics that come in short-acting intramuscular (IM) forms. This method of administration offers significant advantages in terms of speed of the effect, making it particularly useful for treating acute psychotic episodes in which patients are agitated and aggressive symptoms must be controlled quickly. Peak plasma concentrations for ziprasidone and olanzapine in short-acting IM formulations are obtained in 30 to 45 minutes for ziprasidone and 15 to 30 minutes for olanzapine, compared to about 8 hours for ziprasidone and 3 to 6 hours for olanzapine following an oral dose.[11]

Short-intermediate acting Intramuscular formulations:

In acutely psychotic inpatients, IM ziprasidone has been tested in one open-label and two short-term (24-hour) double-blind investigations. The open-label study (n=132) compared this drug to IM haloperidol over seven days. Patients were given flexible-dose IM ziprasidone or IM haloperidol for up to three days. For the duration of the study, all patients were switched to oral ziprasidone or haloperidol after 3 days. In terms of overall and agitation item scores on the Brief Psychiatry Rating Scale, as well as CGI-S scores, ziprasidone outperformed haloperidol considerably. At all trial visits, patients treated with ziprasidone had considerably lower rates of EPS or akathisia than those treated with haloperidol.[12]

Injectable-depot antipsychotic formulations:

Rethinking the timing of the introduction of such long-acting agents in the treatment of schizophrenia is warranted in light of the current availability of a long-acting injectable formulation of risperidone and the potential future availability of long-acting formulations of other atypical antipsychotics (such as paliperidone). Patients with chronic schizophrenia who are at a high risk of noncompliance are currently only allowed to take long-acting formulations, in particular traditional antipsychotics (depots). Long-acting risperidone appears to be associated with good efficacy and tolerability, leading to high patient acceptance and treatment continuation rates that are higher than those seen with oral antipsychotics, according to recent and growing evidence from other patient groups, such as those with first-episode psychosis.[13]

Liquid antipsychotic formulations:

Two open-label trials have been conducted to examine the risperidone oral solution. Both studies involved patients who had just developed acute psychosis. In the first research, patients were given the option of receiving 5 mg IM haloperidol or 2 mg risperidone oral solution (with 2 mg IM lorazepam) (with 2 mg of oral lorazepam). The five agitation-related PANSS subscales (excitement, hostility, hallucinatory behaviour, uncooperativeness, and poor impulse control), as well as the CGI-S scores, showed equal improvements in both treatment groups at 30, 60, and 120 minutes. 14 Only one patient who received haloperidol intramuscularly (IM) suffered acute dystonia, and only one person who took risperidone oral solution needed further haloperidol therapy.[15]

Rapidly dissolving antipsychotic formulations:

The olanzapine tablet or wafer is made as a lyophilizate, which dissolves when it comes into contact with saliva. In addition, open-label research was released. This study involved 85 critically sick schizophrenic patients who failed to comply with

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their medication. For up to 6 weeks, patients were given 10 to 20 mg of fast dissolving olanzapine. Based on the PANSS total scores ($p<0.001$ against baseline at all time points), the results demonstrated a substantial improvement in psychopathology beginning Week 1 and continuing throughout the trial.[16] The olanzapine tablet, which dissolves quickly, was also found to increase patient compliance, attitudes toward prescribed medication, and acceptance of prescribed medication. After displaying considerable improvement in psychosis and medication compliance, 24 patients were moved to normal olanzapine tablets on a milligram-for-milligram basis. Despite being provided the normal pills, most patients chose to go with the rapidly dissolving tablets. Agitation, anxiety, dry mouth, headache, sleeplessness, somnolence, and weight gain were among the side effects observed.[17]

Osmotic-controlled release oral delivery system (OROS formulations):

The OROS technology has been used to develop paliperidone extended-release (paliperidone ER), a novel psychotropic medicine that is currently being studied in the treatment of schizophrenia. Paliperidone ER, at three distinct daily doses of 6 mg, 9 mg, and 12 mg, has recently been shown to be useful and generally well tolerated in the treatment of patients with acute schizophrenia. Furthermore, paliperidone ER had a significant improvement in overall PANSS score as early as Day 4 of treatment in the paliperidone 12 mg treatment group ($p<0.01$). The formulation has been developed to enable a slow increase in paliperidone blood levels, with a median t_{max} of 24.1 hours. Paliperidone ER is expected to have smoother plasma levels than IR antipsychotic formulations, with less peak to trough variability over 24 hours and thus be associated with a lower risk of side effects and improved tolerance. There is anticipated to be a good influence on compliance, as with other OROS formulations. This drug is now undergoing Phase III clinical studies.[18,19]

II. CONCLUSION:

From this brief analysis, it is clear that various available and emerging dosage forms of Atypical antipsychotics are of great importance in the management and treatment of psychotic disorders as compared to conventional antipsychotics. Such primary data would help and contribute to the scientific community in the pace of development of more formulations for psychotic disorders with minimal adverse effects.

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