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Review Article

Antipsychotics - a key line treatment for various psychotic symptoms

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ABSTRACT

'Psychosis' is the state of mental disorder characterized by loss of contact with reality followed by delusions, hallucinations, disorganised thoughts etc. which mainly occurs because of the imbalance of neurotransmitters like dopamine, serotonin or glutamate. About 5-8% of people suffer from mental disorders in the whole world. In the earlier time it was difficult to treat such psychotic patients. So, when antipsychotics came in the market the treatment of such serious mental conditions became possible. Mainly two categories of antipsychotics are prescribed, out of which second generation are commonly prescribed because of their less adverse effects.

Keywords: Dopamine, Psychosis, Delusions, Hallucinations

INTRODUCTION

Psychosis is the mental state in which the person becomes unsure about what is reality and results in hallucinations, delusions like symptoms. This mainly happen due to imbalance of neurotransmitters like dopamine, serotonin or glutamate. The major consequences of psychiatric illness are imbalance or hyper or hypoactivity of dopamine (DA). The negative and positive symptoms of schizophrenia are also the result of dopamine imbalance.

Psychosis is one of the most common disorders, among central nervous system (CNS) disorder with an annual estimated prevalence of 5 to 8% of all the world population.[1] The prevalence of psychosis is most common in women as compared to men. In India, prevalence rate of psychosis, ranged from 9.54 to 370 per 1000 population.[2]

Approximately 1 percent population suffers from psychiatric disorders. It is most commonly found in people in their late teens to early thirties. People who have family history are more likely to develop psychiatric disorders than those who have no family history of it.

The various types of psychotic disorders are described below.

SCHIZOPHRENIA

Among the several types of psychosis, 'schizophrenia' is distinguished by three clusters of symptoms. The first cluster consists of "positive" symptoms, which are symptoms that are "added on" as a person becomes unwell. Positive symptoms include hallucinations (perception problems, such as hearing, seeing, tasting, smelling, or feeling something that isn't there) and delusions (fixed beliefs not based in fact). The second cluster consists of "negative" symptoms, which are "taken away" when a person becomes unwell.

Loss of enjoyment, ambition, and initiative, feeling indifferent, displaying little emotion, and avoiding social contact are all negative signs. The third cluster of symptoms are cognitive symptoms, which include memory loss, reasoning and calculating ability. These three clusters of symptoms must have persisted at least six months for a person to be diagnosed with schizophrenia.

Schizoaffective disorder

The patients with this disorder have symptoms of both mood disorder (depression) and schizophrenia.[3]

Schizophreniform disorder

When the schizophrenia symptoms last fewer or less than six months, the patient is diagnosed with schizophreniform disorder.

Brief psychotic disorder

When a patient has short or sudden episodes of psychotic behaviour due to stress usually that last less than a month.

Delusional disorder

Patients have false beliefs that isn't true or based on reality. These delusions usually involve mistaken perceptions or experiences.

Substance induced psychotic disorder

Substances like alcohol, amphetamine withdrawal can cause delusions and hallucinations, which is known as substance induced psychotic disorder.

Psychotic disorder due to medical condition

Psychotic symptoms that may result due to brain illness such as brain tumour are termed as psychotic disorder due to medical condition.

The various psychotic disorders have various psychotic symptoms. The most seen symptoms of psychotic disorders are described in Table 1.

Hallucinations

Hallucinations are noises or other sensations that are perceived as real even if they exist only in the person's mind. While hallucinations can affect any of the five senses, auditory hallucinations (hearing voices or other sounds) are the most prevalent in schizophrenia. Visual hallucinations are also rather prevalent.

According to research, auditory hallucinations develop when people perceive their own inner self-talk as originating from an outside source.

DELUSIONS

Delusion of persecution

Belief that others, usually a misty they, are trying to get him or her. Persecutory delusions can feature strange concepts and schemes (e.g., John is trying to kill me).

Delusion of reference

A neutral environmental occurrence is seen to have a specific and personal significance. For example, a schizophrenia patient assumes that a person on television is delivering him a message.

Delusion of grandeur

Belief in oneself as a great or famous character, such as Einstein. Delusions of grandeur also include the assumption that one possesses extraordinary abilities that no one else possesses or a fantasy (e.g., ability to swallow a person).

Delusion of control

Belief that outside, foreign forces are controlling one's thoughts or behaviour. Mind broadcasting, thought insertion, and thought withdrawal are all common delusions of control.

Disorganized speech

It may be seen in the way a person speaks. The patients frequently struggle to concentrate and retain a stream of thought. They may react to questions with unconnected answers, begin sentences with one topic and conclude with another, speak incoherently, or utter irrational things.

Disorganised behaviour

Psychosis impairs goal-directed activities, impairing a person's ability to care for himself or herself, work, and communicate with others. It appears as- a worsening in basic everyday functioning, unforeseeable or improper emotional responses, strange and purposeless behaviours, and attention and impulsive behaviour deficits.

ANTIPSYCHOTICS

First-generation antipsychotics (typical antipsychotics)

Examples include haloperidol, chlorpromazine, and fluphenazine.

These drugs primarily block dopamine receptors in the brain, helping to reduce the positive symptoms of psychosis (hallucinations, delusions).

They often have a higher risk of extrapyramidal side effects (movement disorders) like dystonia and tardive dyskinesia.

Second-generation antipsychotics (atypical antipsychotics)

Examples include aripiprazole, risperidone, olanzapine, and quetiapine.

These drugs also affect dopamine receptors but have a broader spectrum of action, impacting other neurotransmitters like serotonin.

Second-generation antipsychotics are often preferred due to a lower risk of extrapyramidal side effects but may have metabolic side effects, such as weight gain and increased risk of diabetes.

Long-acting injectable antipsychotics

Some antipsychotic medications are available in long-acting injectable formulations. These are administered every few weeks or months, providing a more consistent blood level of the drug.

Examples include paliperidone palmitate, aripiprazole lauroxil, and risperidone long-acting injection.

Adjunctive therapies

In some cases, antipsychotic medications are combined with other treatments such as psychotherapy, psychosocial interventions, and supportive care.

These adjunctive therapies aim to address the broader aspects of the patient's condition, improve functioning, and enhance overall well-being.

Personalized treatment

The choice of antipsychotic medication is often personalized based on the individual's specific diagnosis, symptom profile, and response to previous treatments.

Genetic testing and other biomarker assessments may also be used to guide treatment decisions.

Monitoring and side effects

Regular monitoring of patients on antipsychotic medications is essential to assess treatment efficacy and manage potential side effects.

Patients may undergo routine blood tests to monitor metabolic parameters and other potential adverse effects.

For the management of psychosis or psychotic disorders, antipsychotics were introduced. Antipsychotics are mainly of two types. First generation or typical antipsychotics and second generation or atypical antipsychotics. First generation antipsychotics (FGAs) were developed in 1950s. The increased extrapyramidal side effects (EPS) have introduced the second-generation antipsychotics (SGAs) in 1990s.[4]

FGAs are named or classified as chlorpromazine, prochlorperazine, thioridazine, haloperidol, fluphenazine, trifluoperazine, and thiothixene whereas SGAs are clozapine, asenapine, iloperidone, lurasidone, olanzapine, quetiapine, risperidone, aripiprazole, and amisulpride. SGAs have lower EPS as compared to FGAs. That's why SGAs are more prescribed than FGAs. Extrapyramidal side effects (EPS) are acute dystonia, akathisia, parkinsonism and tardive dyskinesia.[5,6]

The first-generation antipsychotics are D2 antagonists while second generation are 5-HT, D2, D3 antagonists and drugs such as aripiprazole, brexpiprazole and cariprazine are considered as partial D2 agonists.[7] The usual dose of various antipsychotics is considered in the table while it may vary according to the symptoms, disorder or other demographic factors.

Apart from schizophrenia, antipsychotic drugs are also given in conditions like acute mania, major depressive disorder with psychotic features, delusional disorder, severe agitation, tourette disorder, borderline personality disorder, dementia, delirium, substance induced psychotic disorder, mental retardation, childhood schizophrenia, autism spectrum disorder, obsessive compulsive disorder, and attention-deficit/hyperactivity disorder (ADHD) which are also prescribed in case of symptoms like aggression, agitation, irritation, hyperactivity apart from psychotic symptoms.

Antipsychotics may be used as the first line treatment medication for mania even when psychosis is not present.8 When there is antidepressant treatment failure in obsessive compulsive disorder or depression than treatment is often augmented with antipsychotics.[9,10] In Autism spectrum disorder (ASD) Antipsychotics are frequently used to treat aggressiveness or agitation. Risperidone and Aripiprazole are approved by FDA in 2006 and 2009 in ASD for agitation, aggression, irritation communication, restricted repetitive and stereotype behaviour like symptoms.[11] In case of ADHD, disruptive, impulse control and conduct disorders, hyperactivity, aggressive symptoms are controlled by antipsychotics. In conditions such as conduct disorders or depression, antipsychotics are usually given for adjunctive treatment of severe behavioural symptoms like aggression rather than psychosis.

The post-traumatic stress disorder (PTSD) refers to non-psychotic symptoms that follow a traumatic experience such as a violent assault. The affected person relives the event, is preoccupied with it, avoids situations associated with it and may have flashbacks (visual and auditory recollections of the event) that are impossible to distinguish from the hallucinations of a psychotic illness. Females were more prone to develop PTSD symptoms when exposed to a traumatic event. They may also be prescribed for mood instability or off-label in variety of other conditions.[12]

MECHANISM OF ACTION

Typical or first-generation antipsychotics have high affinity towards all DA receptor types of both D1 (D1 and D5) and D2 subfamily (D2, D3 and D4) found in the

different neuronal pathways of brain.[13] Antagonistic activity of FGAs at mesolimbic dopaminergic pathway relieves positive symptoms of psychosis. However, due to over D2 receptors at mesocortical pathway, FGAs are not as effective in relieving negative symptoms. These drugs also block the dopaminergic action in the nigrostriatal and tuberoinfundibular pathways. Dopamine (D2) receptor occupancy of over 80%, as presented by FGAs, is associated with the various motor side effects like EPS. D2 receptors of tuberoinfundibular dopaminergic (TIDA) pathway causes hyper elevation of prolactin hormone (hyperprolactinemia) due to their higher affinity towards dopamine receptors. Hyperprolactinemia which is a major consequence of FGAs treatment further manifested in various endocrine disorders including sexual dysfunction.[14] FGAs show minor antihistaminic (H1) and anticholinergic properties, hence causes less weight gain, sedation and low blood pressure like problems.

Table 1: Various symptoms of psychotic disorders.

Variables	Symptoms
Behavioural	Disorganized behaviour, agitation, hyperactivity, aggression, hypervigilance, repetitive movements, restlessness, self-harm, social isolation, repetition of words or actions.
Cognitive	Thought disorder, confusion, disorientation, slowness in activity, suicidal thoughts, unwanted thoughts, difficulty thinking and understanding, false belief of superiority, belief that thoughts aren't one's own
Mood	Anger, anxiety, apathy, excitement, feeling detached from self, general discontent, limited range of emotions, loneliness or nervousness
Psychological	Fear, hearing voices, depression, manic episode, paranoia, persecutory delusion, religious delusion or visual hallucinations
Speech	Deficiency of speech, excessive wordiness, incoherent speech, or rapid and frenzied speaking
Others	Memory loss, nightmares or tactile hallucination

Table 2: Pharmacokinetic parameters of antipsychotic drugs.

Drugs	Bioavailability	Half-life (hours)
Chlorpromazine	10-30	8-35
Fluphenazine	20-50	14-24
Haloperidol	40-70	12-36
Perphenazine	20-25	8.1-12.3
Aripiprazole	87	48-68
Asenapine	<2 orally	13-39
Clozapine	12-81	11-105
Iloperidone	96	18-33
Lurasidone	10-20	18
Olanzapine	80	20-70
Paliperidone	28	23
Quetiapine	9±4	6.88
Risperidone	68	3-24
Ziprasidone	59	4-10

Atypical or new/second generation antipsychotics show specific binding towards dopamine receptors of D2 subfamily (D2, D3, D4 receptors). Moreover, SGAs are also reported to have higher affinity for D3 and D4 than D2 receptors.[15] Besides their effectiveness against positive symptoms, SGAs also show relief from negative psychotic symptoms in case of schizophrenia. This is due to lower mesocortical DA occupancy by SGAs, they maintain the proper dopaminergic action at this pathway. SGAs showed less DA antagonism at nigrostriatal pathway and associated with extremely low typical side effects such as EPS. SGAs work by blocking D2 receptors as well as serotonin receptor antagonist action.[16]

PHARMACOKINETIC PARAMETERS OF ANTIPSYCHOTIC DRUGS

The average plasma half-life of the atypical antipsychotics as a family is approximately 20 to 24 hours.[17] Some drugs have shorter half-lives (e.g., quetiapine: 6 to 12 hours; ziprasidone: 4 to 10 hours).[18]

LONG-ACTING INJECTION (DEPOT) MEDICATIONS

Long-acting depot antipsychotics were developed in the 1960s to improve symptoms in people suffering from severe psychiatric disease. They generally contain antipsychotic drug in oily or in solution form that is injected 1-6 weeks intramuscularly. The use of antipsychotic long-acting injections (LAIs) (also known as depots) is recommended when a patient have preference for this treatment or when there is non-adherence with other oral medications. The LAIs treatment ensures that the clinicians can know when a patient has taken medication or when they should stop it. It remains to be clearly established that LAIs are more effective than oral antipsychotic medication. There are LAI formulations of SGAs, namely risperidone, paliperidone, olanzapine and aripiprazole; and FGAs depot medications, namely haloperidol, flupentixol/flupenthixol and fluphenazine.[19]

PSYCHOTHERAPY

Along with antipsychotic drugs counselling can also help to manage psychosis.

Cognitive behavioral therapy (CBT) can support you in diagnosing psychotic episodes It also helps you in

determining if what you see and hear is genuine or imagined. This type of therapy also emphasizes the significance of taking antipsychotic drugs and following to your treatment plan.

Supportive psychotherapy helps you understand to deal with and overcome psychosis It also develops healthier ways of thinking.

Cognitive enhancement therapy uses computer exercises and group work to help you think and understand better.

Family psychoeducation and support involves family members or closed ones. It helps you to bond and improve the way you solve problems together.

Coordinated specialty care (CSC) creates a team approach in treating psychosis when it's first diagnosed. CSC combines medication and psychotherapy with social services and work and education support.[20]

CONCLUSION

With the introduction of antipsychotic drugs, the treatment of schizophrenia like other psychotic disorders have become possible. The antipsychotics have shown a tremendous change in the treatment pattern with their efficacy. Cognitive-behavioural therapy (CBT) and other forms of psychotherapy can be beneficial in helping individuals with psychotic disorders manage their symptoms, improve insight, and develop coping strategies. Psychosocial interventions, such as family therapy and social skills training, can also play a crucial role in the treatment of psychotic disorders. Apart from the FGAs and SGAs tablet formulation, these injectables have seen to be most effective because of their long-term effect. The psychotherapy also helps these patients along with medications in their recovery.

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