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SCHIZOPHRENIA: A REVIEW WITH EMPHASIS ON ATYPICAL ANTIPSYCHOTICS

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ABSTRACT

This review describes schizophrenia and underlying pathological mechanisms, use and safety of atypical antipsychotics and how adverse effects are effecting the medication adherence in patient population. Schizophrenia is a chronic psychiatric illness with disabling symptoms, where the causes are multifactorial leading to the pathological changes in neurotransmitters. Pharmacological management includes treatment with typical and atypical antipsychotics. Typical antipsychotics are effective in treating schizophrenia but due to extrapyramidal side effects (EPS), there are not prescribed in recent times. Atypical Antipsychotics (AAP) due to their higher efficacy and safety profile, are more preferred. Both the class of drugs acts on dopamergic pathways to reduce symptoms in patients. The incidence of extrapyramidal side effects are lesser with atypical antipsychotics but the other side effects such as weight gain, metabolic disorders and dyslipidemia are leading to decrease in medication adherence among patients.

KEYWORDS: Schizophrenia, Antipsychotics, Dopamine, Extrapyramidal Side Effects, Weight Gain, Medication Adherence.

INTRODUCTION

Psychiatric illness are major disorder of organic or emotional origin and always associated with serious distortion of thought, behaviour, capacity to recognize reality as well as deficient perception leading to delusion and hallucination and are results of neurochemical imbalance in the brain.[1] Mental illness affects 1% of the world's population and causes debilitating social and occupational impairment.[2]

Schizophrenia is one of the most serious and frightening of all mental illness.[3] This disabling illness is caused by abnormal amounts of certain neurotransmitters in the brain.[1] Schizophrenia affects about 2 to 10 people in every 1000 in the general population[1,4,5] and accounts 1.1 % of the total disability adjusted life years worldwide.[3] The incidence of schizophrenia is about 0.20/1000/year[6] and males have higher lifetime risk of developing schizophrenia than women.[1,6] Schizophrenia can occur at any age, but it is rare before puberty and most common in late adolescence and the early twenties.[1] Urban residents have shown higher prevalence of schizophrenia compared to mixed urban – rural population and rural areas have lesser incidence of schizophrenia.[5,7]

Vulnerability to schizophrenia is likely to be related to genetic and environmental factors that influence early brain development, the disorder is minimally expressed until adolescence or young adulthood. Untreated psychosis may be related to the severity of illness, illness duration causally influences treatment responsivity and outcome.[8]

Risk factors

Schizophrenia is a multifactorial disorder, and the greatest risk factor is a positive family history.[3] Monozygotic twins (40 – 50%) are at higher risk than compared with dizygotic twins (10 – 15%).[2] Recent genome – wide association studies have identified 22 risk loci and thousands of genetic changes (single-nucleotide polymorphism) that contribute to one's risk of developing this mental illness.[9] Variant forms of genetic risk factors for schizophrenia includes dysbindin, neuregulin 1, DAOA, COMT and DISC1.[4] Various obstetrical difficulties may increase the risk by 2 – fold.[2,4] The different types of birth complications are complications of pregnancy (bleeding, diabetes, rhesus incompatability, preeclampsia), abnormal fetal growth and development (low birth weight, congenital malformations, reduced head circumference) and complications of labor (uterine atony, asphyxia, emergency caesarean section).[6] Some studies associate upper respiratory infections during the second trimester of pregnancy with a higher incidence of schizophrenia.[10] The factors of risk for developing schizophrenia is illicit drug use like cannabis and traumatic brain injury specifically if it leads to frontal and temporal lobe damage.[2] Stimulants like cocaine and amphetamines can induce a picture clinically identical to paranoid schizophrenia. It may be because of genetically determined vulnerability to the environmental stressor, a gene – environmental stressor, a gene-environment interaction.

Indeed, variations in the dopamine metabolising COMT (catechol-O- methyltransferase) gene affect the propensity to develop psychosis in people who use cannabis.[3]

Complete recovery from a first psychotic episode, relapse risk remains very high. More than 90% of patients experience a relapse within 5 years of initial treatment response, and maintenance antipsychotic treatment is a strong predictor of relapse risk in most. The confounding factors includes chronological age, age at illness onset, age at first hospitalization, sex, premorbid functioning, mode of onset, diagnosis, education, marital and socioeconomic status, family history of psychiatric illness, ethnicity, and duration or continuity of antipsychotic treatment.[8]

Pathophysiology

Neurotransmitters plays a crucial role in the pathogenesis of the disease.[1] The pathological neuronal abnormalities observed in brain structure of schizophrenia patients are.[2]

- Bilateral enlargement of ventricles reflects on underlying loss of tissue in CNS
- Synaptic and dendritic deficits in the cerebral cortex and hippocampus
- Reduced grey matter volume and 40% reduction in volume of CA2 region in hippocampus.

These changes appear to be consistent with brain asymmetry. The ventricular enlargement being most pronounced in the left temporal horn, and the decreased cortical size being most obvious in the left temporal lobe.[11,12] Decreased cortical thickness and increased ventricular size in the brains of many patients with schizophrenia, this occurs in the absence of widespread gliosis.[11] Gliosis, or the proliferation of glial cells, is thought to occur as a compensatory change in degenerative diseases of the brain that is reflected in schizophrenia too.[13] The molecular changes in the brain also contributes to the schizophrenia symptoms. Gross impairment in autophagy related gene expression in brains from schizophrenia patients, particularly BA22 of the superior temporal cortex, a region already hypothesized to be involved in pathogenesis of schizophrenia. It is the result of complex interactions between genetic and environmental factors that predispose to abnormalities in CNS. The cellular process of autophagy may be an important contributor to pathophysiology of psychiatric diseases. Autophagy, the process of degrading intracellular components in lysosomes. Autophagy failure has been linked with neurological dysfunction and lead to various neurodegenerative disorders. In recent studies it has revealed that this autophagy degeneration has a role in mental illness namely schizophrenia.[2]

First-episode schizophrenia (but not other psychosis) groups had reduced (left) hippocampal volume. Changes in hippocampal volume may correspond with impairment in neuropsychologic testing, and these patients may have poorer response to first-generation antipsychotics (FGAs).[12]

Brain abnormalities, including increased glucose metabolism in the caudate nucleus, and decreased blood flow and glucose metabolism in the frontal lobe and left temporal lobe. This can indicate dopaminergic hyperactivity in the head of the caudate nucleus and dopaminergic hypofunction in the frontotemporal regions. PET (Positron Emission Tomography) studies using Dopamine-2 (D2)-specific ligands suggest increased densities of D2 receptors in the head of the caudate nucleus with decreased densities in the prefrontal cortex.[14] Assessing Dopamine-1 (D1) function suggest that subpopulations of schizophrenics may have decreased densities of D1 receptors in the caudate nucleus and the prefrontal cortex. Hypofrontality can be associated with lack of volition and cognitive dysfunction, core features of schizophrenia. Descending glutamatergic tracts interact with dopaminergic tracts directly as well as through GABA interneurons. Glutamatergic deficiency produces symptoms similar to those of dopaminergic hyperactivity and possibly those seen in schizophrenia.[14]

Clinical presentation

Symptoms in schizophrenia are divided into following: It is believed that different brain regions play distinct role in positive and negative symptomatology.[2] Positive, negative and cognitive symptoms; among these positive symptoms are worse and need attention towards patient which accounts Lack of insight (97%), auditory hallucinations (74%), ideas of reference (70%), delusions of reference (67%), suspiciousness (66%), flatness of affect (66%), (64%), delusional mood (64%), delusions of perception (64%), thought alienation (52%), thoughts spoken aloud (50%).[3]

Table. 1: schizophrenia symptoms cluster.[14]

Positive symptoms	Negative symptoms	Cognitive symptoms
Suspiciousness Unusual thought content (delusions) Hallucinations Conceptual disorganization	Affective flattering Alogia Anhedonia Avolition	Impaired attention Impaired working memory Impaired executive function

Patients with negative symptoms may exhibit blunted or flattened affect, alogia, avolition, and anhedonia.[15]

Diagnostic criteria

The diagnosis of disease is done by ICD 10 (International Classifications of disease) diagnostic criteria which defines.

At least one symptom should present most of the time for a month

- Thought echo, insertion or withdrawal or thought broadcast
- Delusions of control referred to body parts, actions or sensations
- Delusional perception
- Hallucinatory voices giving a running commentary, discussing the patient, or coming from some part of the patient's body
- Persistent bizarre or culturing inappropriate delusions

Or at least two symptoms should present most of the time for a month

- Persistent daily hallucinations accompanied by delusions
- Incoherent or irrelevant speech
- Catatonic behaviour such as stupor or posturing
- Negative symptoms such as marked apathy blunted or incongruous mood.[3]

Another diagnostic criteria for schizophrenia include presence of two or more positive symptoms such as hallucinations and delusions – or negative symptoms – such as blunted emotional responsiveness, poverty of speech, and amotivation [DSM – 5(Diagnostic and statistical Manual)]. Positive symptoms represent an exaggeration of normal processes that result in a distortion of reality, often manifested as auditory hallucinations and paranoid delusions. Disorganized speech and behaviour are also hallmarks of schizophrenia and encompass findings such as tangential speech, derailment, neologisms, and incoherence. Negative symptoms, on the other hand, are conceptualized as an absence or diminution of normal processes, or deficit symptoms. Patients with negative symptoms may exhibit blunted or flattened affect, alogia, avolition and anhedonia.[2]

Pharmacotherapy

The management of schizophrenia includes psychotherapy and pharmacological therapy.

Psychotherapy: Psychotherapy includes psychosocial rehabilitation programs. These programs such as case management, psychoeducation, targeted cognitive therapy, basic living

skills, social skills training, basic education, work programs, supported housing, and financial support will help to improve patient condition.[14,16]

Cognitive behaviour therapy (CBT)

CBT can be used as the supportive or adjuvant treatment to mainstay of pharmacological management, CBT helps in reducing the severity of disease symptoms when treated with 4 – 9 months duration. Controlled studies have shown that individuals with schizophrenia who have persistent psychotic symptoms despite adequate pharmacotherapy have shown benefits in reducing the severity of delusions, hallucinations, positive symptoms , negative symptoms and overall symptoms and in improving social functioning. CBT is given by psychotherapist and the intensity and duration of the therapies that have been studied vary from 6 to more than 50 sessions, weekly or biweekly sessions over a treatment period of 4 – 9 months is the most typical treatment duration.[16,17]

Pharmacological therapy

Drugs used for treating schizophrenia are divide into two classes.[1]

Typical antipsychotics: Chlorpromazine, Fluphenazine, Mesoridazine, Perphenazine, Prochlorperazine, Promazine, Thioridazine, Trifluoperazine, Chlorprothixene, Droperidol, Flupentixol, Haloperidol, Loxapine, Molindone Atypical antipsychotics should start in next line: Amisulpride, Aripiprazole, Clozapine, Melperone, Olanzapine, Quetiapine, Risperidone, Paliperidone, Sertindole, Sulpiride, Ziprasidone, Zotepine.

Table. 2: Classification, dose, bioavailability and t ½ of antipsychotics.[14]

Name of the drug	Dose (mg/day)	Bioavailability (%)	Half-life (t ½ in hours)
Typical antipsychotics			
Chlorpromazine	100 – 800		
Fluphenazine	2 – 20	10 – 30	8 – 35
Haloperidol	2 – 20	20 – 50	14 – 24
Loxapine	10 – 80	40 – 70	12 – 36
Molindone	10 – 100		
Perphenazine	10 – 64		
Thioridazine	100 – 800	20 – 25	8.1 – 12.3
Thiothixene	4 – 40		
Trifluoperazine	5 – 40		
Atypical antipsychotics			
Aripiprazole	15 – 30	87	48 – 68
Clozapine	50 – 500	12 – 81	11 – 105
Olanzapine	10 – 20	80	20 – 70
Paliperidone	3 – 9	28	23

Quetiapine	200 – 500	9 ± 4	6.88
Resperidone	2 – 8/ 25 – 50 mg every 2 weeks	68	3 – 24
Ziprasidone	40 – 60	59	4 – 10

There are 5 types of dopamine receptors in human beings: type 1 and 5 are similar in structure and drug sensitivity, and these two receptors are referred to as the "D1like" group or class of receptors. Dopamine receptor types 2, 3, and 4 are also similar in structure and are, therefore, grouped together as the "D2like" group. Dopamine receptors 2, 3 and 4, however, have significantly different sensitivities to antipsychotic drugs. In particular the clinical efficacy of antipsychotics is associated with a blockade of 60 % to 80 % of D2 receptors in the brain.[18] The blockage of D2 receptors in the auditory and auditory-visual association cortices reduces the hallucinatory behaviour in schizophrenia.[2]

“Typical” antipsychotics are characterized by undesirable side effects such as extrapyramidal symptoms (EPS), hyperprolactinaemia, tardive dyskinesia and possible neuroleptic malignant syndrome. These symptoms are specific to the group as a whole and generally associated with high doses but in some cases also at clinically effective dosages. The second-generation or “atypical” antipsychotic drugs can be differentiated from traditional antipsychotics by their low or negligible levels of these unwanted side effects, by effectiveness and in general supposed increased safety. The multiple clinical and adverse effects of different antipsychotics depend on the combination of receptors occupancy, but the dopamine pathway is still considered the primary common target for all antipsychotic drugs.[18]

The most pressing clinical uncertainty arising from recent advances in the management of schizophrenia is the role of atypical antipsychotics. The term “atypical” was originally used to predict antipsychotic effects but do not produce catalepsy—most notably clozapine. It is also applied to drugs that are potentially more effective (particularly against depressive, negative, or cognitive symptoms) or better tolerated (especially causing fewer extrapyramidal side effects) than conventional anti-psychotics or have a different pharmacological profile (such as blockade of serotonin 5-HT2 receptors).[19]

The atypicals bind more loosely than typical antipsychotics to the dopamine D2 receptor, with dissociation constants higher than that for dopamine. Rapid dissociation from D2 receptors is one explanation for the improved EPS profile of atypical antipsychotics, and one that is also consistent with the theory of a lower affinity for D2 receptors for these drugs. The dopamine-serotonin antagonism theory generally predicts a separation between typicals and

atypicals.[18] Atypical antipsychotics defined as drugs showing a higher affinity for 5HT2A receptors than for D2 receptors and a lower affinity for D2 receptors than conventional antipsychotics.[20] Blockade of 5HT2A receptors leads to increased output of dopaminergic neurons into the striatum leading to displace the antipsychotic drug from its binding to D2 receptors. This could decrease the risk of EPS development.[21,22]

The newer agents appear more efficacious than conventional drugs in reducing negative symptoms (e.g. lack of emotion, interest and expression), possibly owing to the absence of extrapyramidal symptoms. Atypical drugs induce weight gain and alter glucose and lipid metabolism.[23]

Texas medication Algorithm project recommends antipsychotic monotherapy for the first three stages [stage 1, a second-generation antipsychotic (SGA); stage 2, a SGA not tried in stage 1 or 2 first-generation antipsychotic (FGA); stage 3, clozapine] and proposes the use of antipsychotic polypharmacy at stage 4 (clozapine plus SGA, FGA or electroconvulsive therapy).[24] Antipsychotic polypharmacy results in increases of total number of doses of antipsychotics. Multiple antipsychotics drugs is expected to lead dose dependent increase of antipsychotic side effects. The better symptom control with clozapine plus another antipsychotic and a reversal of metabolic side effects with a concomitant use of aripiprazole. Second generation antipsychotic polypharmacy to have increased from 3.3% in 1999 to 13.7% in 2004. Polypharmacy cost up to three times more per patient than monotherapy.[24]

The most common reason for the use of antipsychotic polypharmacy was reducing positive symptoms (60%), followed by reducing negative symptoms (20%), decreasing total amount of medication (9%) and reducing extrapyramidal side effects (5%).[24] Antipsychotic polypharmacy results in increases of total doses of antipsychotics. Therefore, in theory, the use of multiple antipsychotic drugs is expected to lead to a dose-dependent increase of antipsychotic side-effects.[24,25]

PORT (Patient Outcome Research team) recommendations for psychopharmacological treatment.[16]

- Patients with acute positive symptoms should be prescribed with antipsychotic medications other than clozapine. Antipsychotic medication dose approved by FDA includes the daily dosage of first-generation antipsychotic medications should be in the range of 300–1000

chlorpromazine (CPZ) equivalents. The daily dosage of second-generation antipsychotic medications for an acute symptom episode should be: aripiprazole: 10–30mg; olanzapine: 10–20 mg; paliperidone: 3–15 mg; quetiapine: 300–750 mg; risperidone: 2–8 mg; and ziprasidone: 80–160 mg. Treatment trials should be at least 2 weeks, with an upper limit of 6 weeks to observe optimal response.

- Patients with first acute positive symptoms with first - episode of schizophrenia should be prescribed with antipsychotic medications other than clozapine and olanzapine. Antipsychotic treatment should be started with doses lower than those recommended for multiepisode patients (first-generation antipsychotics: 300–500 mg CPZ equivalents; risperidone and olanzapine: lower half of recommended dosage range for multiepisode patients). An important exception is with quetiapine, which often requires titration to 500–600 mg/day. The therapeutic efficacy of low-dose aripiprazole or ziprasidone has not been evaluated in people with first-episode schizophrenia.

- Pharmacotherapy for maintenance antipsychotic dose includes first-generation antipsychotics in the range of 300–600 CPZ equivalents per day. The maintenance dosage for aripiprazole, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone should be the dose found to be effective for reducing positive psychotic symptoms in the acute phase of treatment.

- Long-acting injectable (LAI) antipsychotic medication should be offered as an alternative to oral antipsychotic medication for the maintenance treatment of schizophrenia when the LAI formulation is preferred to oral preparations. The recommended dose range for fluphenazine decanoate is 6.25–25 mg administered every 2 weeks and for haloperidol decanoate is 50–200 mg administered every 4 weeks, although alternative dosages and administration intervals equivalent to the recommended dosage ranges may also be used. The recommended dosage range for risperidone long-acting injection is 25–75 mg administered every 2 weeks. LAIs are often used in attempt to improve medication adherence in people with schizophrenia.[26]

Clozapine augmented with another antipsychotic drug may be beneficial for symptom control.[24] Clozapine's low dopamine D2 blockade could be augmented by adding an antipsychotic, especially in the case of strong and specific D2 blockers such as the benzamides. Superior efficacy may also be explained by the fact that combining two

antipsychotics leads to a higher overall dose of chlorpromazine equivalents.[27,28] Aripiprazole may reverse metabolic side-effects caused by ongoing antipsychotic treatment. aripiprazole also resulted in significantly greater reductions in total and low-density lipoprotein (LDL) cholesterol. These results demonstrated that combining aripiprazole and clozapine resulted in significant weight, body mass index (BMI) and fasting cholesterol benefits for patients treated with clozapine. Resperidone decrease serum prolactin level than other antipsychotic drugs. Quetiapine used as *prn* was associated with agitation (75%), followed by insomnia (9%) and agitation/anxiety (8%).[24]

Adverse drug reactions

An association between a greater degree of exposure to antipsychotic drugs and a higher risk for sudden cardiac death has been reported for both typical and atypical antipsychotic drugs.[29] Antipsychotic drugs are associated with adverse effects that can lead to poor medication adherence, stigma, distress and impaired quality of life.[30]

Table. 3: Adverse of few atypical antipsychotics.[3]

Olanzapine	Resperidone	Amisulpiride	Quetiapine	Clozapine
Weight gain Sedation Glucose intolerance Hypotension	Hyperprolactemia Hypotension EPS on higher doses Sexual dysfunction	Hyperprolactemia Insomnia EPS	Drowsiness Dyspepsia Hypotension	Sedation Hypersalivation Constipation Weight gain Glucose intolerance Tachycardia

Weight gain

One of untoward effect of many antipsychotic drugs is weight gain. The extent of weight gain apparently varies by drug, which may be because of the drugs' differing degrees of action on the serotonergic, dopaminergic, cholinergic, histaminergic, and other neurotransmitter systems.[31] Treatment with typical and atypical antipsychotics contributes to weight gain. The mean weight gain in patients receiving standard doses of antipsychotics over a 10-week period: the mean increases were 4.45 kg with clozapine, 4.15 kg with olanzapine, 2.92 kg with sertindole, 2.10 kg with risperidone, and 0.04 kg with ziprasidone. Data on quetiapine have been variable, but it seems that the weight gain liability on this drug may be similar to that of risperidone. Weight gain with olanzapine at the commonly used dose of 15mg/day may exceed 10 kg during the first year of treatment.[22]

Diabetes mellitus

The prevalence of type-2 DM in people with schizophrenia is more than twice higher than in general population.[32] Concomitant weight gain and dyslipidemia, which are known diabetic risk factors are seen in schizophrenia patients. Increased abdominal obesity, especially visceral obesity, can increase insulin resistance and contribute to hyperglycemia and diabetes.[22]

Hyperlipidemia

dibenzodiazepine- derived atypical antipsychotics (i.e., clozapine, olanzapine, quetiapine) have higher serum trigliceride levels. Both risperidone and ziprasidone are non-dibenzodiazepine AAP, and appear to have minimal effects on serum lipids.[33]

Prolongation of QTc interval

Sertindole in the amount usually administered in a clinical dose was found to increase the QTc interval by 22 msec, and the increase was dose dependent. The mean increase in the QTc interval were as follows: Ziprasidone 20.3 ms, risperidone 11.6 ms, olanzapine 6.8 ms, quetiapine 14.5 ms, thioridazine 35.6 ms, and haloperidol 4.7 ms.[22]

Myocarditis

Clozapine is associated with an increased risk of myocarditis Eighty percent of cases occurred within 6 weeks of the patient's starting clozapine, and the mortality rate approached 40%. Myocarditis should be suspected in clozapine-treated patients who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs or symptoms of heart failure, or ECG findings such as ST abnormalities and T wave inversions.[22]

Sexual side effects

Antipsychotic-induced sexual dysfunction is related to the effects of the drugs on alpha-1 and alpha-2 adrenergic, H1 histamine and dopaminergic receptors, in particular to the blockade of D2 receptors in pituitary lactotroph cells, which leads to an excess of prolactin secretion.[34,35] Risperidone, which results in a prolactin increase similar to that associated with first-generation antipsychotics. Prolactin levels in patients who were taking 2-16 mg/day of risperidone were similar to those in patients taking 20 mg/day of haloperidol, while those of patients taking 1-16 mg/day of risperidone were significantly higher than those of patients receiving 10 mg/day of haloperidol.[22]

Extrapyramidal side effects

AAP are used at recommended doses, they are associated with significantly lower rates of extrapyramidal side effects compared with (generally high-potency) conventional antipsychotics. Some AAP (e.g., risperidone and olanzapine) have a dose response relationship for extrapyramidal side effects.[22]

Adherence

Antipsychotics are used in treatment of schizophrenic patients to improve QOL and to avoid untoward happenings. Adherence to medication is essential to maximizing outcomes for individuals with schizophrenia. The medication adherence is questionable in these patients, the possible reason for non-adherence are side effects caused by antipsychotics, disease state.[26]

Relapse of disease symptoms is commonly seen in schizophrenia with poor medication adherence. Choosing the right choice of drug based on individual requirement and proper assessment can improve the compliance. Maintenance of the compliance can be done with few simple techniques such as pill counting technique which can be done by patient representatives and improvement of symptoms on medication use is other sign to judge patient adherence. For the objective evidence, analysis of blood samples for drug concentration can be done.[36]

Use of antipsychotics in combination may or may not have beneficial effects. On the other hand, side effects associated with antipsychotic polypharmacy as well as increased treatment cost have consistently been reported, leading to decreased compliance.[24]

CONCLUSIONS

AAP are safe and effective in patients with schizophrenia and has less side effects compared with typical antipsychotics. These drugs has showed its efficacy in positive, negative and cognitive symptoms and improved QOL in schizophrenic patients.

Choosing ‘’Right drug for right patient’’ will have positive treatment outcome and will help to avoid unwanted effects and cost effective treatment can be provided, thus improving in patients Quality of Life.

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